American Journal of Epidemiology

Vol. 146, No. 4
Printed in U.S.A.

Association of Soy and Fiber Consumption with the Risk of Endometrial Cancer

Marc T. Goodman,[1] Lynne R. Wilkens,[1] Jean H. Hankin,[1] Li-Ching Lyu,[1] Anna H. Wu,[2] and Laurence N. Kolonel[1]

The authors conducted a case-control study among the multi-ethnic population of Hawaii to examine the role of dietary soy, fiber, and related foods and nutrients on the risk of endometrial cancer. Endometrial cancer cases (n = 332) diagnosed between 1985 and 1993 were identified from the five main ethnic groups in the state (Japanese, Caucasian, Native Hawaiian, Filipino, and Chinese) through the rapid-reporting system of the Hawaii Tumor Registry. Population controls (n = 511) were selected randomly from lists of female Oahu residents and matched to cases on age (±2.5 years) and ethnicity. All subjects were interviewed using a diet history questionnaire that included over 250 food items. Non-dietary risk factors for endometrial cancer included nulliparity, never using oral contraceptives, fertility drug use, use of unopposed estrogens, a history of diabetes mellitus or hypertension, and a high Quetelet's index (kg/m^2). Energy intake from fat, but not from other sources, was positively associated with the risk of endometrial cancer. The authors also found a positive, monotonic relation of fat intake with the odds ratios for endometrial cancer after adjustment for energy intake. The consumption of fiber, but not starch, was inversely related to risk after adjustment for energy intake and other confounders. Similar inverse gradients in the odds ratios were obtained for crude fiber, non-starch polysaccharide, and dietary fiber. Sources of fiber, including cereal and vegetable and fruit fiber, were associated with a 29–46% reduction in risk for women in the highest quartiles of consumption. Vitamin A and possibly vitamin C, but not vitamin E, were also inversely associated with endometrial cancer, although trends were not strong. High consumption of soy products and other legumes was associated with a decreased risk of endometrial cancer (p for trend = 0.01; odds ratio = 0.46, 95% confidence interval 0.26–0.83) for the highest compared with the lowest quartile of soy intake. Similar reductions in risk were found for increased consumption of other sources of phytoestrogens such as whole grains, vegetables, fruits, and seaweeds. Ethnic-specific analyses were generally consistent with these results. The observed dietary associations appeared to be largely independent of other risk factors, although the effects of soy and legumes on risk were limited to women who were never pregnant or who had never used unopposed estrogens. These data suggest that plant-based diets low in calories from fat, high in fiber, and rich in legumes (especially soybeans), whole grain foods, vegetables, and fruits reduce the risk of endometrial cancer. These dietary associations may explain in part the reduced rates of uterine cancer in Asian countries compared with those in the United States. *Am J Epidemiol* 1997;146:294–306.

case-control studies; diet; dietary fiber; energy metabolism; fats; soybeans; uterine neoplasms

Similar to breast and ovarian cancers, rates for cancer of the uterine corpus are lower in Japan, China, and other Asian countries than in the United States and Europe (1). International differences in the incidence of uterine cancer may actually be underestimated because rates are not corrected for the high prevalence of hysterectomized women who are no longer at risk in western countries (2). Reproductive history is an important determinant of uterine cancer, as it is for cancers of the ovary and breast, and part of the reduced risk for this disease among Japanese women may be attributable to their later menarche and higher birth rate compared with white women in the United States (3). In addition to reproductive history, international variation in diet, body size, body fat distribution, and exogenous estrogen use may contribute to the observed global differences in the incidence of these hormone-dependent malignancies.

Epidemiologic data, including the increased risk of endometrial cancer associated with estrogen replace-

Received for publication July 30, 1996, and accepted for publication April 7, 1997.
[1] Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, Honolulu, HI.
[2] Department of Preventive Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA.
Reprint requests to Dr. Marc T. Goodman, Epidemiology Program, Cancer Research Center of Hawaii, University of Hawaii, 1236 Lauhala Street, Honolulu, HI 96813.

ment therapy and the reduced risk associated with combination type oral contraceptives, suggest that estrogen stimulation of the uterine lining plays a key role in endometrial carcinogenesis (4). Asian women have lower levels of urinary (5, 6) and plasma (7–10) estrone and estradiol than do white women in the United States. There is also some evidence that urinary estrogen concentrations among Asian-American women may be intermediate between those in Asian women and those in US white women (6). Accordingly, the incidence of uterine corpus cancer increases among Asian migrants to the United States, although their rates are still generally lower than those of other US ethnic groups (11).

A number of dietary hypotheses have been proposed for endometrial cancer, chief among them the possibility that dietary fat enhances risk (12, 13). Increased dietary fat might be indirectly associated with endometrial cancer through a positive relation to obesity, a well-established risk factor (14, 15), or fat may have a direct effect on circulating levels of estrogen (7, 16). Differences in the amounts and sources of dietary fat among populations could explain part of the international variation in uterine corpus cancer incidence. In addition to fat, the consumption of other dietary constituents, such as fiber, vegetables, and fruits, differs among populations. It has been proposed (17) that the reduced risk of breast cancer among Asians in Japan and China may be attributed to their high intake of dietary fiber and soy products. A similar rationale may apply to uterine cancer: reduced consumption of dietary fiber and soy products, and increased consumption of dietary fat on migration may explain the increase in uterine cancer among Asian-Americans. The objective of this analysis was to examine the role of dietary factors, especially soy, fiber, and related foods and nutrients, in the etiology of endometrial cancer among the multi-ethnic population of Hawaii.

MATERIALS AND METHODS

The eligible cases for this population-based, case-control study in Hawaii comprised all patients with histologically confirmed, primary endometrial cancer diagnosed between January 1, 1985 and June 1, 1993 in any of the major hospital centers on Oahu. We identified eligible cases and obtained histologic information through the pathology logs and admission records of the participating hospitals by the rapid-reporting system of the Hawaii Tumor Registry, part of the National Cancer Institute-sponsored Surveillance, Epidemiology, and End Results (SEER) Program (18). Eligible cases included women aged 18–84 years who were residents of Oahu and belonged to one of the five major ethnic groups in Hawaii: Japanese, Caucasian, Native Hawaiian, Filipino, and Chinese. Native Hawaiian was defined as any part Hawaiian while the other ethnicities were defined as having three of four grandparents of that ethnicity. Potential controls were selected randomly from lists of female Oahu residents who were interviewed by the Health Surveillance Program of the Hawaii Department of Health and were matched to each case on ethnicity and age (±2.5 years). Annually, the Department of Health identifies a 2 percent representative sample of all households in the state with a sampling procedure modeled after that of the National Health Survey (19).

Of the 540 endometrial cancer cases eligible for participation in the study, 356 (66 percent) completed the interview. Reasons for non-participation included physician refusal (1 percent), patient refusal (14 percent), and death, inability to locate, language barrier, or psychological reasons usually associated with the illness (19 percent). Of the 1,023 potential controls who were contacted to participate in the study, 18 percent refused to be interviewed, 8 percent had moved, were mentally incompetent, or had a language barrier, and 1 percent had died or were too ill to be interviewed. Thus, interviews were completed for 742 controls, representing 73 percent of women initially eligible. For the purpose of this report, we excluded cases (n = 15) with leiomyosarcoma, stromal sarcoma, and other miscellaneous tumors with morphology codes greater than 888 (20). We also excluded nine cases with missing information on one or more of the non-dietary variables included in this analysis. The remaining cases (n = 332) were diagnosed with adenocarcinoma (94 percent) or some other epithelial cancer (6 percent). The majority (88 percent) of these were localized malignancies. A total of 231 controls who were hysterectomized or matched to the excluded cases were also omitted, yielding a final sample of 341 cases and 511 controls.

The majority (>95 percent) of subjects were interviewed in their homes by trained interviewers. Occasionally, if requested by the participant, the interview was conducted at the worksite or the Cancer Research Center of Hawaii. The majority of interviews took 1-1/2 to 2-1/2 hours to complete. Our interviewers were trained extensively in taking diet histories to standardize data collection and coding techniques and to minimize inter-interviewer variation. The interviewing procedures were also monitored by periodic observation and evaluation in the field by supervisors.

We used a structured interviewing format for data collection. The questionnaire included information on diet, height, weight at various ages, use of exogenous estrogens, reproductive, menstrual and medical histories, and other life-style practices. The diet history

method has been described previously (21). In brief, over 250 food items or categories were selected to provide an estimate of 85 percent or more of major dietary components for the five ethnic groups included in this study. The food sources of these dietary components and common serving sizes for each item were derived from measured food records among a random sample of the major ethnic groups in Hawaii. Alcoholic beverage consumption was also assessed. For each food or beverage item, the respondent indicated the usual frequency consumed per day, week, or month, with yearly frequencies for particular seasonal items such as cantaloupe. Color photographs illustrating the three most representative serving sizes were used to assist subjects in estimating amounts consumed. Both combination and multiple servings could be selected. The dietary reference period was the year before diagnosis for the cases and the year preceding the interview for controls. The median time between diagnosis and interview was about 16 months for the cases.

The quantity of each food item consumed on a daily basis was calculated as the product of the frequency and serving size. For the nutrient analysis, a food composition database containing over 3,000 foods and 95 components was used to obtain the daily intake of nutrients from each food item. The specific nutrient intakes for each person were computed as the sum of that nutrient over all foods. The food composition database was compiled largely from the US Department of Agriculture tables (22) and supplemented with publications by Pennington (23), McCance and Widdowson (24), the Japan Dietetic Association (25), and other research and commercial publications. Recipes of local ethnic dishes were also included. Several different analytical methods were used to measure the fiber content of food. Crude fiber was estimated after the removal of soluble fiber and some insoluble dietary fiber (26). Values for dietary fiber, including all indigestible plant compounds, i.e., non-starch polysaccharides, lignin, and resistant starch, were derived largely through enzymatic-gravimetric methods (26). The enzymatic-chemical method according to Englyst (27) restricts fiber to non-α-glucan (non-starch) polysaccharides, which can be divided into the cellulosic and non-cellulosic fiber components. Unlike the other methods of fiber estimation, Englyst's method is unaffected by cooking. Both methods were included in our analysis because of controversy over the definition of fiber (28), and because there are no reliable food composition data available for lignin or resistant starch. Vitamin supplementation was not considered in this report. In addition to nutrient analyses, we created food groups as the sum of the daily grams consumed for foods that contributed to that group. (See Appendix for the food items in each of the food groups.)

In this article, we have focused on the association of legumes, dietary fiber, and related foods and nutrients with the risk of endometrial cancer. Other dietary and non-dietary factors were analyzed as potential confounders, but details of these analyses will be reported elsewhere. A preliminary examination of the data included comparisons of cases and controls with respect to several demographic characteristics and risk factors of interest. We used analysis of covariance to compare the mean, log-transformed intakes of nutrients and foods between cases and controls while adjusting for age and ethnicity (29). Partial Pearson correlations (r_p) of continuous dietary and non-dietary variables adjusting for age and ethnicity were calculated to evaluate colinearity. These means and correlations were used as a guide for subsequent regression analyses.

The risks associated with different levels of the exposure variables were evaluated by conditional logistic regression modeling case-control status, except in table 6, where an unconditional approach was used because the age-ethnicity match was broken (30). Odds ratios and 95 percent confidence intervals (CI) were computed by exponentiating the coefficients (and CIs) for the binary indicator variables representing the quartile (or tertile) levels of nutrient or food intake. The quantile cutpoints were based on the distribution for the combined population of cases and controls. Adjustment variables included age and Quetelet's index (kg/m^2) as continuous variables, ethnicity by indicator variables, and the following additional dichotomous variables: pregnancy history (ever vs. never pregnant), oral contraceptive use ($\geq$1 month/never), unopposed estrogen use ($\geq$1 month/never), and diagnosis of diabetes mellitus (yes/no). The addition of an indicator variable for hypertension diagnosis to the logistic models did not change the findings. We employed various methods of calorie adjustment including the standard method (31), the residual method (32), and the partition method (33). However, odds ratios were generally similar for each of the three methods so we have limited presentation of the results to the standard method in which calories were introduced as a model covariate. We also adjusted for fat calories or non-carbohydrate (fat + protein) calories (individually), instead of total calories, because these indices were less correlated than total calories with the nutrients and foods of interest. Log-transformed vitamin A (retinol + retinol precursors) intake from food was included as a continuous model covariate in major analyses with no significant change in fit. We performed a test for linear trend in the logit of risk by

comparing twice the difference in log likelihoods for models with and without a trend variable, based on a chi-square distribution with one degree of freedom. The trend variable was assigned the median for the appropriate quantile or category. The likelihood ratio test was also used to evaluate the interaction between variables on the risk of endometrial cancer. This test compared a no-interaction model containing main effect terms with a fully parameterized model containing all possible interaction terms for the variables of interest.

RESULTS

Cases were slightly older (58.5 years) than controls (57.1 years) on average, although the difference in age was not statistically significant (table 1). Over one-third of the subjects were Japanese, followed by Caucasian, Native Hawaiian, Filipino, and Chinese. A smaller percentage of cases (86 percent) than controls (94 percent) had been married. There was no difference between cases and controls in the level of education attained (mean of 12.7 years for both groups).

Table 2 shows odds ratios for several factors commonly associated with endometrial cancer after adjustment for age and ethnicity (column 4), and after adjustment for additional confounders (column 7). Pregnancy was inversely related to the risk of endometrial cancer: 25 percent of cases had never been pregnant compared with 12 percent of controls. Women who had been pregnant had a 54 percent lower risk of endometrial cancer than women who had never been pregnant. There was little association of age at menarche or age at menopause with the estimated risk of endometrial cancer. Menopausal status was also similar because cases and controls were matched on age. Oral contraceptive use was protective against endometrial cancer, with greater protection afforded with increased duration of use. A larger percentage of cases (5 percent) than controls (3 percent) had used fertility drugs. Unopposed estrogen use was strongly related to the development of uterine cancer in this population: risk among users was 2.6 times that among never users and odds ratios increased sharply with prolonged (>3 years) duration. Women with diabetes and hypertension were also at increased risk of endometrial cancer, but odds ratios were attenuated after adjustment for other risk factors. Tobacco and alcohol use were inversely related to risk, although the confidence intervals included unity. A strong, positive dose-response relationship of Quetelet's index to the odds ratio for endometrial cancer was found, with odds ratios among women in the highest quartile almost fivefold those among women in the lowest quartile. Additional covariate adjustment had little effect on the odds ratios shown in table 2.

TABLE 1. Sociodemographic characteristics of endometrial cancer cases and controls, Oahu, Hawaii, 1985–1993

	Cases (n = 332)		Controls (n = 511)	
	No.	%	No.	%
Age (years)				
<45	51	15	95	19
45–54	67	20	110	22
55–64	99	30	149	29
≥65	115	35	157	31
Ethnicity				
Japanese	125	38	203	40
Caucasian	84	25	117	23
Hawaiian	55	17	89	17
Filipino	40	12	63	12
Chinese	28	8	39	8
Married				
Never	45	14	29	6
Ever	287	86	482	94
Education (years)				
<12	79	24	120	23
12	91	27	138	27
>12	162	49	253	50

Energy intake from fat, but not from other sources, was positively associated with endometrial cancer (table 3). We also found a positive, monotonic relation of fat intake with the odds ratios for endometrial cancer after adjustment for calories, and a non-monotonic inverse gradient of risk with carbohydrate consumption. Among the complex carbohydrates, starch was unrelated to the development of endometrial cancer, but fiber was inversely related to risk. Similar inverse gradients in the odds ratios were obtained for crude fiber, non-starch polysaccharides, and dietary fiber. Increased consumption of fiber from cereals and fruits, but not vegetables, was also inversely related to the development of endometrial cancer, although gradients in estimated risk were monotonic only for fruit fiber. The intakes of vitamin A and vitamin C were associated with a decreased risk of endometrial cancer, although trends were not strong. No association with cancer was observed for α-tocopherol (vitamin E) consumption.

Several groups of phytoestrogen-rich foods were selected for analysis (table 4). We found a negative monotonic gradient of risk associated with increasing consumption of legumes, especially tofu and other soy products. The data also suggested an inverse association of dried peas and beans with the risk of endometrial cancer, although this relation was weak. The intake of whole grain foods, including whole grain cereals, was inversely related to the risk of endometrial cancer, although the gradient in risk was non-

TABLE 2. Odds ratios and 95% confidence intervals for the association of potential confounding variables with the risk of endometrial cancer, Oahu, Hawaii, 1985–1993

Variable	No. of cases	No. of controls	Odds ratio*	95% confidence interval	*p* for trend†	Odds ratio‡	95% confidence interval	*p* for trend†
Pregnant								
Never	84	60	1.00§			1.00§		
Ever	248	451	0.41	0.28–0.59		0.46	0.30–0.70	
Age (years) at menarche								
≤12	165	213	1.00§			1.00§		
13	68	123	0.73	0.51–1.04		0.89	0.60–1.33	
14	42	79	0.66	0.42–1.01		0.85	0.52–1.37	
>14	57	95	0.74	0.49–1.12	0.07	0.96	0.61–1.51	0.59
Menopausal status								
Premenopausal	99	176	1.00§			1.00§		
Postmenopausal	233	335	1.02	0.59–1.76		0.91	0.48–1.70	
Age (years) at menopause¶								
≤47	56	92	1.00§			1.00§		
48–50	68	100	1.12	0.69–1.83		1.05	0.62–1.79	
51–53	62	73	1.42	0.86–2.35		1.33	0.77–2.31	
>53	46	68	1.11	0.66–1.86	0.57	1.09	0.62–1.92	0.54
Oral contraceptive use								
Never	253	328	1.00§			1.00§		
Ever	79	183	0.55	0.38–0.80		0.66	0.43–1.01	
≤3 years	55	90	0.78	0.51–1.19		0.75	0.46–1.22	
>3 years	23	91	0.31	0.18–0.53		0.40	0.23–0.72	0.002
Fertility drug use								
Never	314	496	1.00§			1.00§		
Ever	18	15	2.20	1.08–4.49		1.78	0.77–4.14	
Estrogen use								
Never	167	344	1.00§			1.00§		
Ever	165	167	2.13	1.53–2.94		2.62	1.83–3.76	
≤3 years	70	82	1.82	1.20–2.78		1.98	1.24–3.14	
>3 years	67	50	2.51	1.59–3.98		3.62	2.18–6.03	0.0001
Diabetes mellitus								
Never	287	483	1.00§			1.00§		
Ever	45	28	2.47	1.50–4.07		1.44	0.83–2.53	
Hypertension								
Never	196	358	1.00§			1.00§		
Ever	136	152	1.65	1.22–2.23		1.13	0.80–1.60	
Tobacco use								
Never	211	300	1.00§			1.00§		
Ever	121	211	0.80	0.58–1.09		0.81	0.57–1.15	
Alcohol use								
Never	254	373	1.00§			1.00§		
Ever	78	138	0.75	0.52–1.06		0.90	0.60–1.36	
Quetelet's index (kg/m^2)								
≤21.1	55	156	1.00§			1.00§		
21.2–23.5	68	141	1.56	1.01–2.42		1.50	0.94–2.39	
23.6–27.3	84	125	2.25	1.46–3.48		2.30	1.45–3.65	
>27.3	125	89	4.70	2.98–7.40	0.0001	4.96	2.99–8.20	0.0001

* Matched on age and ethnicity.
† Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the categories.
‡ After additional adjustment for the following unmatched covariates (when appropriate): pregnancy history, birth control pill use, estrogen use, history of diabetes mellitus, and Quetelet's index (kg/m^2).
§ Reference category.
¶ Models include postmenopausal women only.

monotonic. Both vegetable and fruit consumption reduced the risk of uterine cancer substantially, with odds ratios in the lowest intake quartile almost twice those of the highest intake quartile. Increased consumption of seaweed, and perhaps beer, were also associated with lower odds ratios for endometrial cancer in our population.

We repeated all of the analyses shown in table 4 exchanging (individually) fat calories and noncarbohydrate (fat + protein) calories for total calories

TABLE 3. Odds ratios* (OR) and 95% confidence intervals (CI) for the association of selected dietary components with the risk of endometrial cancer, Oahu, Hawaii, 1985–1993

Dietary component	Quartile of intake†							p for trend§
	1 (low)‡	2		3		4 (high)		
	OR	OR	95% CI	OR	95% CI	OR	95% CI	
Source of calories								
Total	1.00	1.10	0.70–1.72	0.82	0.52–1.31	1.60	0.99–2.59	0.13
Fat	1.00	1.04	0.67–1.64	1.34	0.84–2.12	1.60	0.97–2.61	0.04
Protein	1.00	0.94	0.60–1.45	0.99	0.64–1.55	1.34	0.83–2.15	0.23
Carbohydrate	1.00	0.87	0.54–1.41	0.80	0.50–1.27	1.16	0.72–1.88	0.62
Alcohol	1.00	0.85	0.53–1.36	0.92	0.56–1.50	0.86	0.54–1.37	0.61
Macronutrients¶								
Fat	1.00	1.06	0.64–1.74	1.38	0.77–2.45	1.68	0.77–3.69	0.17
Protein	1.00	0.84	0.51–1.39	0.86	0.48–1.51	1.02	0.46–2.26	0.96
Carbohydrate	1.00	0.73	0.43–1.22	0.57	0.31–1.04	0.66	0.29–1.48	0.23
Plant polysaccharides¶								
Starch	1.00	0.91	0.56–1.47	0.87	0.51–1.49	1.65	0.85–3.18	0.20
Crude fiber	1.00	0.69	0.43–1.11	0.63	0.38–1.03	0.60	0.33–1.09	0.31
Non-starch polysaccharides	1.00	0.79	0.49–1.29	0.62	0.37–1.04	0.60	0.32–1.11	0.08
Cellulose	1.00	0.66	0.41–1.07	0.60	0.36–1.01	0.59	0.32–1.07	0.08
Non-cellulosic polysaccharides	1.00	0.84	0.51–1.37	0.68	0.40–1.14	0.62	0.34–1.15	0.10
Dietary fiber	1.00	0.70	0.44–1.11	0.72	0.44–1.18	0.47	0.25–0.86	0.02
Cereal fiber	1.00	1.43	0.89–2.30	0.93	0.57–1.53	0.55	0.33–0.92	0.001
Vegetable fiber	1.00	0.75	0.47–1.20	0.71	0.43–1.16	0.71	0.40–1.23	0.22
Fruit fiber	1.00	0.70	0.44–1.12	0.61	0.37–0.99	0.54	0.32–0.92	0.02
Micronutrients from food¶								
Vitamin A	1.00	0.52	0.32–0.86	0.66	0.40–1.10	0.65	0.37–1.14	0.22
Vitamin C	1.00	0.58	0.35–0.96	0.73	0.45–1.20	0.59	0.34–1.03	0.10
α-tocopherol	1.00	0.85	0.52–1.38	0.97	0.57–1.65	0.86	0.43–1.71	0.75

* After adjustment for the following unmatched covariates: pregnancy history, birth control pill use, estrogen use, history of diabetes mellitus, and Quetelet's index (kg/m^2).

† The quartile cutpoints for daily nutrient intakes were as follows: total calories, 1,416, 1,795, 2,332 kcal; fat calories, 420, 587, 847 kcal; protein calories, 202, 272, 366 kcal; carbohydrate calories, 750, 929, 1,206 kcal; fat, 46.7, 65.2, 94.1 g; protein, 50.6, 68.0, 91.4 g; carbohydrate, 187, 232, 302 g; starch, 93.9, 124, 160 g; crude fiber, 3.01, 4.34, 6.04; non-starch polysaccharides, 10.2, 14.6, 20.6 g; cellulose, 2.35, 3.54, 5.10 g; non-cellulosic non-starch polysaccharides, 7.27, 10.2, 15.0 g; dietary fiber, 12.3, 17.2, 23.9; cereal fiber, 0.01, 0.44, 2.51 g; vegetable fiber, 2.94, 4.45, 6.25 g; fruit fiber, 2.21, 3.92, 6.27 g; vitamin A, 4,979, 8,142, 12,418 IU; vitamin C, 93.3, 138, 202 mg; α-tocopherol 6.83, 9.31, 13.1 mg.

‡ Reference category for all models.

§ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the quartiles.

¶ After additional adjustment for total calories.

to see if either of these substitutions would change the results. The results were similar, although adjustment for non-carbohydrate calories tended to make the gradients in risk steeper. For example, the odds ratios for endometrial cancer associated with the three upper quartiles compared with the lowest quartile of legume consumption were 0.61, 0.56, and 0.49, respectively, after adjustment for non-carbohydrate calories. Similar results were found when we adjusted the data for the consumption of vitamin A.

The food group analyses were performed separately by ethnic group to examine the consistency of the dietary associations (table 5). Common tertile cutpoints for the foods were used for all ethnic groups to facilitate the comparison of risks. Only the data for Japanese, Caucasian, and Filipino women are presented because of sparse numbers in some risk categories for Chinese and Native Hawaiian cases. The majority of the associations were homogeneous across ethnic groups and all of the trends in risk were inversely related to food intake level. Several of the trends were strong enough to reach statistical significance despite the small number of cases.

We were interested in whether any of the non-dietary risk factors identified in our analysis influenced the association of the dietary variables with endometrial cancer risk, or whether the dietary factors cooperated in any way in producing malignancy. To do this, we looked at various combinations of the dietary and non-dietary variables, using the jointly "unexposed" or low-risk women as the reference group (e.g., soy intake ≥9 g/day or never used unopposed estrogen). The results for soy product intake are shown in table 6 as an example of our findings, because this legume is particularly high in the isoflavones (34). We found a positive (synergistic) statistical interaction (p = 0.02) between soy product consumption and pregnancy history: women who had

TABLE 4. Odds ratios* (OR) and 95% confidence intervals (CI) for the association of phytoestrogen-containing foods with the risk of endometrial cancer, Oahu, Hawaii, 1985–1993

Food	Quartile of intake†							*p* for trend§
	1 (low)‡	2		3		4 (high)		
	OR	OR	95% CI	OR	95% CI	OR	95% CI	
Legumes	1.00	0.63	0.39–1.02	0.61	0.37–0.99	0.51	0.31–0.86	0.009
Tofu	1.00	0.65	0.39–1.06	0.70	0.42–1.18	0.53	0.30–0.94	0.04
Tofu and other soy products	1.00	0.55	0.34–0.88	0.53	0.31–0.91	0.46	0.26–0.83	0.01
Other peas and beans	1.00	0.96	0.61–1.53	0.87	0.54–1.42	0.70	0.42–1.17	0.21
Whole grain foods	1.00	1.10	0.63–1.64	0.92	0.57–1.49	0.57	0.34–0.95	0.09
Whole grain cereals	1.00	1.20	0.77–1.87	0.71	0.43–1.17	0.48	0.29–0.79	0.009
Vegetables without juice	1.00	0.53	0.33–0.85	0.56	0.34–0.93	0.51	0.29–0.90	0.03
Fruits without juice	1.00	0.62	0.38–0.99	0.57	0.35–0.94	0.48	0.28–0.80	0.004
Beer	1.00	1.32	0.53–3.29	0.47	0.15–1.40	0.54	0.18–1.62	0.18
Seaweed	1.00	0.61	0.38–0.98	0.62	0.37–1.01	0.48	0.28–084	0.03

* After additional adjustment for the following unmatched covariates: pregnancy history, birth control pill use, estrogen use, history of diabetes mellitus, Quetelet's index (kg/m^2), and total calories.

† The quartile cutpoints for daily food intake were as follows: legumes, 8.52, 21.1, 39.0 g; tofu, 0, 10.0, 23.4 g; soy products, 0.05, 8.89, 22.0 g; peas and beans, 1.55, 6.53, 15.6 g; whole grain foods, 14.3, 45.1, 103 g; whole grain cereal, 0, 18.0, 57.9 g; vegetables, 132, 199, 272 g; fruits, 95.5, 183, 282 g; beer, 0, 23.7, 154 g; seaweed, 0, 0.09, 0.60 g.

‡ Reference category for all models.

§ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the quartiles.

never been pregnant and who consumed <9 g of soy products a day were at 4.52 times the estimated risk of endometrial cancer compared with women in the reference category. This compares to an estimated risk of 3.11 assuming an independent (additive) relation of pregnancy history and soy consumption on endometrial cancer. Among women who had never used estrogens, risk was increased (odds ratio = 1.80) for those who consumed <9 g of soy a day. Among estrogen users, however, the level of soy intake had little influence on the odds ratios for endometrial cancer. The data suggest a negative (antagonistic) statistical interaction ($p = 0.04$) between soy product consumption and unopposed exogenous estrogen use on the risk of endometrial cancer. Assuming an additive relation (main effects only), the odds ratios were 3.49 for women with low tofu intake who used estrogens, 2.58 for women with high tofu intake who used estrogens, and 1.35 for women with low tofu intake who had never used estrogens. This diminution in the effect of soy intake in the presence of estrogen use was found for other legumes, but not for other food groups.

DISCUSSION

Our data suggest that plant-based diets low in fat, high in fiber, and rich in legumes (especially soybeans), whole grain foods, vegetables, and fruits reduce the risk of endometrial cancer. This is the first study to show an inverse association of soy consumption with the risk of endometrial cancer. These associations were independent of other dietary risk factors (total calories, fat calories, non-carbohydrate calories, vitamin A) and most non-dietary risk factors (ethnicity, oral contraceptive use, history of diabetes mellitus, Quetelet's index) identified in our study population.

An inverse association of dietary soy and fiber with the risk of uterine cancer is biologically plausible. Diets in many parts of Asia include soybean-based foods that are rich in the isoflavones genistein and daidzein, and high-fiber foods such as legumes, whole grains, and cereals that contain substantial amounts of lignin, a non-polysaccharide component of dietary fiber (28). Such diverse foods as beer and seaweed contain precursors to the lignans enterolactone and enterodiol (35). Both isoflavones and lignans have a diphenolic structure, competing with endogenous (and synthetic) estrogen for receptor sites (34, 36). By binding to the estrogen receptor, phytoestrogens exhibit agonistic and antagonistic properties, because they compete with estrogen for the receptor and, as a consequence, can also regulate gene expression mediated by the estrogen response element. Studies conducted among premenopausal and postmenopausal women in Asia (8–10) and recent southeast Asian migrants to Hawaii (7) show that plasma estradiol levels are higher in whites than in Asians of similar ages and menopausal status. Urinary estrogen concentrations among Asian-Americans have been shown to be intermediate between the levels in Asian women and in US white women (6). An antiestrogenic effect of these plant compounds (phytoestrogens) may be relevant to the inhibition of endometrial carcinogenesis by lowering endometrial cell proliferation or reducing levels of ovarian steroids through down regulation of the hypothalamus and pituitary (37). While a phytoestrogenic mechanism is attractive, isoflavones

TABLE 5. Odds ratios* (OR) and 95% confidence intervals (CI) for the association of phytoestrogen-containing foods with the risk of endometrial cancer by ethnic group, Oahu, Hawaii, 1985–1993

Food (g/day)	All (n = 332; 511)†		Japanese (n = 125; 203)		Caucasian (n = 84; 117)		Filipino (n = 40; 63)	
	OR‡	95% CI	OR	95% CI	OR‡	95% CI	OR	95% CI
Legumes								
≤11.5§	1.00		1.00		1.00		1.00	
11.5–30.6	0.73	0.48–1.09	0.87	0.42–1.82	0.60	0.27–1.34	0.20	0.03–1.55
>30.6	0.59	0.38–0.92	0.80	0.38–1.68	0.36	0.14–0.98	0.11	0.01–0.97
p for trend¶	0.02		0.55		0.04		0.04	
Tofu								
0§	1.00		1.00		1.00		1.00	
0.1–17.8	0.64	0.40–1.01	0.64	0.24–1.71	0.58	0.23–1.50	0.07	0.01–0.91
>17.8	0.63	0.38–1.05	0.65	0.24–1.78	0.42	0.10–1.88	0.10	0.01–1.65
p for trend	0.05		0.48		0.13		0.03	
Whole grain food								
≤24.8§	1.00		1.00		1.00		1.00	
24.8–78.9	0.97	0.64–1.46	0.81	0.43–1.52	0.62	0.22–1.78	0.97	0.21–4.42
>78.9	0.65	0.42–1.01	0.57	0.30–1.11	0.46	0.15–1.38	0.39	0.07–2.30
p for trend	0.08		0.12		0.16		0.38	
Whole grain cereal								
0§	1.00		1.00		1.00		1.00	
0.1–28.6	1.08	0.71–1.63	0.92	0.48–1.76	0.97	0.39–2.45	1.67	0.35–8.00
>28.6	0.59	0.38–0.91	0.63	0.32–1.23	0.70	0.29–1.70	0.34	0.06–1.82
p for trend	0.02		0.18		0.41		0.28	
Vegetables								
≤152§	1.00		1.00		1.00		1.00	
153–248	0.72	0.48–1.09	0.45	0.23–0.89	0.56	0.22–1.44	0.59	0.12–2.85
>248	0.62	0.38–1.01	0.37	0.16–0.85	0.62	0.20–1.87	1.11	0.19–6.62
p for trend	0.04		0.01		0.38		0.99	
Fruits								
≤122§	1.00		1.00		1.00		1.00	
123–244	0.61	0.40–0.91	0.68	0.36–1.29	0.41	0.16–1.01	0.30	0.06–1.39
>244	0.52	0.33–0.82	0.55	0.26–1.14	0.41	0.15–1.09	0.20	0.03–1.35
p for trend	0.01		0.10		0.05		0.06	

* After adjustment for the following unmatched covariates: pregnancy history, birth control pill use, estrogen use, history of diabetes mellitus, Quetelet's index (kg/m^2), and total calories.
† Number of cases; number of controls.
‡ After additional adjustment for ethnic group.
§ Reference category for all models.
¶ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the tertiles.

such as genistein also have other properties, including the inhibition of tyrosine kinase and topoisomerase II, that might reduce endometrial cancer risk (34, 36).

Adlercreutz et al. (38, 39) have proposed that women on a high-fiber diet may be exposed to less of their own endogenous estrogen than women on a low-fiber diet because of decreased enterohepatic recirculation of estrogen. Women who consume high fiber diets have decreased concentration of intestinal β-glucuronidase, increased elimination of estrogen by the fecal route, and reduced intestinal reabsorption of estrogen (40, 41). Rose et al. (42) have shown that wheat bran supplementation decreases serum estradiol and estrone levels. In a study of omnivores and vegetarians in Finland (43), intake of dietary fiber was found to be positively associated with plasma levels of sex hormone-binding globulin (SHBG), resulting in lower levels of free estrogen. The nearly twofold in-

TABLE 6. Odds ratios* (OR) and 95% confidence intervals (CI) for the joint association of soy product consumption and other factors on the risk of endometrial cancer, Oahu, Hawaii, 1985–1993

Variable	≥9 g/day of soy products				<9 g/day of soy products				p value†
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	
				Non-dietary					
Pregnant									
Ever	117	226	1.00‡		131	225	1.13	0.74–1.72	
Never	40	35	1.37	0.76–2.50	44	25	4.52	2.25–9.06	0.02
Oral contraceptive use									
Ever	34	91	1.00‡		45	92	1.10	0.58–2.08	
Never	123	170	1.31	0.73–2.34	130	158	1.98	1.10–3.58	0.42
Estrogen use									
Never	73	188	1.00‡		94	156	1.80	1.12–2.94	
Ever	84	73	3.61	2.19–5.96	81	94	3.40	2.01–5.76	0.04
Diabetes mellitus									
No	130	240	1.00‡		157	243	1.30	0.87–1.94	
Yes	27	21	1.35	0.68–2.71	18	7	2.85	1.03–7.88	0.42
Quetelet's index (kg/m²)									
<23.6	59	147	1.00‡		63	149	1.35	0.79–2.29	
≥23.6	98	114	2.26	1.39–3.66	112	101	3.97	2.32–6.79	0.28
				Dietary					
Fat calories (kcal)									
≤587	69	121	1.00‡		80	151	1.15	0.69–1.94	
>587	88	140	1.16	0.66–2.05	95	99	1.87	1.01–3.45	0.92
Dietary fiber (g)									
>17.2	98	148	1.00‡		74	103	1.13	0.68–1.89	
≤17.2	59	113	1.01	0.61–1.65	101	147	1.55	0.93–2.57	0.36
Whole grain cereal (g)									
>18.0	199	159	1.00‡		73	101	1.26	0.82–1.96	
≤18.0	60	113	1.28	0.83–1.98	109	150	1.88	1.19–2.97	0.63
Vegetables (g)									
>199	88	155	1.00‡		77	101	1.45	0.87–2.42	
≤199	69	106	1.32	0.82–2.15	98	149	1.55	0.95–2.54	0.52
Fruits (g)									
>184	88	152	1.00‡		75	107	1.23	0.74–2.07	
≤184	69	109	1.34	0.83–2.17	100	143	1.86	1.11–3.11	0.28

* Adjusted by unconditional multiple logistic regression for age, ethnicity, and (when appropriate) pregnancy history, birth control pill use, estrogen use, history of diabetes mellitus, Quetelet's index (kg/m²), and total calories.
† Based on the likelihood ratio test comparing models with and without an interaction term.
‡ Reference category.

crease in the levels of SHBG among vegetarians was attributed to the increased consumption of phytoestrogens. These data suggest that women on a diet rich in fiber may be at reduced risk of endometrial cancer.

The role of diet in the etiology of endometrial cancer has been investigated in five other case-control studies (44–48) and one prospective study (49). La Vecchia et al. (44) conducted a hospital-based, case-control study in Milan, Italy, that included 206 cases and 206 hospital controls. Data were collected on the frequency of consumption of 12 broad dietary categories, including whole grain breads and pasta. Risks for endometrial cancer were reduced with more frequent intake of green vegetables, fruits, and whole grains, although trends were neither significant nor monotonic in multivariate analysis. In a second case-control study conducted among 274 cases and 572 hospital controls in Switzerland and Italy (45), the frequency of intake of 50 foods was considered. An inverse association was reported for the consumption of whole grain bread and pasta, as well as fresh vegetables and fruits. A reported positive association of the intake of peas and beans with risk is contrary to our finding, but may have resulted from the limited food list and lack of adequate control for energy intake. A study in Shanghai (46) of 268 cases and 268 population controls showed a positive association of fat and protein calories, as well as meats and eggs, with the risk of endometrial cancer, and a suggested inverse association with fruits, complex carbohydrates, and allium vegetables. These investigators did not report their findings for soybean products. Barbone et al. (47) used

the 116-item Willett questionnaire (50) to study 168 cases and 334 optometry clinic controls in Birmingham, Alabama. They reported a positive relation of protein and cholesterol to the risk of endometrial cancer, and an inverse relation with carotene, nitrate, and several vegetables, but no association with fiber. Potischman et al. (48) used the 60-item Block food-frequency questionnaire (51) to study 399 endometrial cancer cases and 296 community controls identified in five areas of the United States. They showed that fat calories, especially from saturated fat, were positively related to risk, and that dietary fiber was not associated with uterine cancer, although a food group analysis showed a nonsignificant reduced risk for endometrial cancer associated with the consumption of complex carbohydrates, cereals, and grains. Finally, in a prospective study of 23,000 postmenopausal Iowa women using the self-administered Willett questionnaire, Zheng et al. (49) reported an inverse association of endometrial cancer with the intake of energy from plant foods, although this finding was limited to women with $\geq$5 years of follow-up. The Iowa study also suggested a positive association of processed meat and fish consumption with risk.

Complex carbohydrates include digestible and indigestible (resistant) starch and indigestible dietary fiber. Fiber includes non-starch polysaccharides, such as cellulose, β-glucans, hemicellulose, pectin, and gum, as well as lignin. In the present analysis, we found an inverse association of dietary fiber (by several analytic methods) and fibrous foods (whole grain foods, vegetables, fruits), but not starch, with the risk of endometrial cancer. This is in agreement with the data from the two European case-control studies (44, 45). Neither the Shanghai study (46) nor the Alabama study (47) found a relation of dietary fiber or legumes with the risk of endometrial cancer, but the Chinese data showed that complex carbohydrates, fruits, and some vegetables may be protective. Although not specifically stated, the data of Potischman et al. (48) suggest that it is the starch component rather than the fiber component of complex carbohydrates that is relevant to endometrial cancer risk reduction in their population. The inconsistency in the findings between our study and theirs may result from problems in the current definition of dietary fiber, as well as in the assay methods used to measure the fiber content of foods (28). Starch that is resistant to digestion by enzymatic hydrolysis (resistant starch) contaminates analytical methods for dietary fiber and leads to inconsistencies in food values among laboratories using different systems of analysis. If the food table values for dietary fiber used by different investigators vary systematically, then comparisons of results for foods and food groups may be more reliable.

We found excellent correspondence between our food composition (nutrient) analyses and food group analyses. Foods such as bread and rice with a high starch content were unrelated to the risk of endometrial cancer. Interestingly, food groups comprised of all vegetables or all fruits appeared to be more strongly related to risk than were vegetable or fruit fiber. It is likely that other dietary factors, such as carotenoids, that are contained in fruits and vegetables may act independently (or synergistically) to reduce risk. Indeed, our data show an inverse association between dietary vitamin A level and endometrial cancer risk, although we found no statistical interaction of vitamin A with soy or fiber on cancer risk.

The risk estimates associated with the food groups of interest were generally homogeneous among the three main ethnic groups in Hawaii: Japanese, Caucasian, and Filipino. In particular, the association of the consumption of legumes and tofu with the risk of endometrial cancer was inverse for each of the ethnic groups examined. In addition to ethnicity, the association of soy product consumption with the risk of endometrial cancer was independent of the other risk factors identified in this population, with the exception of pregnancy and unopposed estrogen use: the association of soy products and other legumes with the risk of endometrial cancer was limited to never pregnant women and never users of unopposed estrogens. These interactions may be understood in the context of a hormonal mechanism for the protective effect of dietary soy and fiber on the risk of endometrial cancer. The biologic potencies of the isoflavones are much lower than those of animal or synthetic hormones. Genistein is the most uterotropic (estrogenic) isoflavone in the mouse uterus, but has only 1×10^{-5} the activity of diethylstilbestrol (52). The binding affinity of genistein to rat, rabbit, and sheep uterine cytosol is 1×10^{-2} that of 17β-estradiol, and other isoflavones have even less affinity than genistein to cytoplasmic estrogen receptors. Thus, phytoestrogens may not reach the concentrations necessary to prevent significant complexing of the synthetic estrogen with receptors, nor to further reduce endometrial cancer risk in pregnant or lactating women.

In considering the validity of our findings, it is reassuring that odds ratios for the association of obesity, reproductive history, and use of synthetic hormones with endometrial cancer are similar to those reported by other investigators (53). However, the dietary data are limited by the difficulties of accurate classification of eating patterns, recall bias, problems with food composition data, and lack of knowledge of

the critical time period of diet in cancer development. A further limitation in the interpretation of dietary analyses such as ours is the high colinearity between various nutrients, foods, and food groups, which makes it difficult to distinguish among effects, such as that between fat and fiber in which the correlation was 0.55. Such considerations aside, a strength of this study is the wide range of dietary intakes in our multi-ethnic population. For example, among controls, the percentages of calories from fat were 21.7, 27.3, 32.1, 37.4, and 41.4 percent in the 10th, 25th, 50th, 75th, and 90th percentile of consumption, respectively. Furthermore, there were sufficient numbers of Caucasians and Hawaiians who ate soy products on a regular (weekly) basis for comparison of endometrial cancer risk. Such regular exposure to dietary isoflavones and lignan is important because phytoestrogens may be more rapidly metabolized and excreted than steroidal estrogens (52).

We have focused considerable attention on validating our dietary assessment method against food records (54), and we have demonstrated that our dietary data are reproducible (55, 56). It is unlikely that cases would systematically over- or underestimate the consumption of the many foods included in our questionnaire, although we have no means of examining this possibility. Our interviewers were trained in probing methods that minimized inter-interviewer variation. Information was elicited on a large number of food items, and special questions concerning food preparation, seasonal items, and use of fresh foods were also included.

An advantage of this study was its population-based design. Cases were identified through the rapid-reporting system of the Hawaii Tumor Registry, which provided prompt access to the study subjects. Controls were selected randomly from lists of female Oahu residents who responded to the Hawaii Department of Health's annual survey, which is conducted under statutory provision. However, the validity of our findings may be somewhat limited by the less than optimal response rates in this study (66 percent for cases and 73 percent for controls). Nevertheless, these response rates compare favorably with those of other studies of diet and the risk of endometrial cancer that have been conducted in the United States (47, 48).

In summary, our data support the notion that diets low in calories and rich in legumes (especially soybeans), whole grain foods, vegetables, and fruits reduce the risk of endometrial cancer. Although it is difficult to distinguish among food constituents, plant-based cuisines that are low in fat and high in fiber typify the diet in countries such as Japan and China where uterine cancer rates are relatively low. Our dietary results offer at least a partial explanation for the international variation in uterine cancer incidence. These findings and those of other investigators suggest a practical strategy for the prevention of endometrial cancer: namely, weight control through a reduction in energy intake, especially from fat and protein, and an increase in soy and fiber, mostly from vegetables and fruits. Any large-scale dietary interventions should measure changes in plasma or urinary estrogens during the follow-up period to determine more precisely the interaction of diet and hormones in endometrial carcinogenesis.

ACKNOWLEDGMENTS

This investigation was supported in part by Public Health Service grant nos. P01-CA-33619, R01-CA-58598, R01-CA-55700, P20-CA-57113, and contract nos. N01-CN-05223 and N01-CN-55424 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

The authors thank the physicians, administrators, and cancer registrars at the following institutions for their support of this study: Castle Memorial Hospital, Kaiser Medical Center, Kapiolani Medical Center for Women and Children, Kuakini Medical Center, Queen's Medical Center, Straub Clinic and Hospital, St. Francis Hospital, Tripler Army Hospital, and Wahiawa General Hospital. They also gratefully acknowledge the programming assistance of Ms. Sau-Ling Hicks and Ms. Lucy Liu.

REFERENCES

1. Parkin DM, Muir CS, Whelan SL, et al, eds. Cancer incidence in five continents. Vol VI. IARC Scientific Publications no. 120. Lyon: IARC, 1992.
2. Marrett LD. Estimates of the true population at risk of uterine disease and an application to incidence data for cancer of the uterine corpus in Connecticut. Am J Epidemiol 1980;111: 373–8.
3. Hoel DG, Wakabayashi T, Pike MC. Secular trends in the distributions of the breast cancer risk factors—menarche, first birth, menopause and weight—in Hiroshima and Nagasaki, Japan. Am J Epidemiol 1983;118:78–89.
4. Key TJA, Pike MC. The dose-effect relationship between "unopposed" estrogens and endometrial mitotic rate: its central role in explaining and predicting endometrial cancer risk. Br J Cancer 1988;57:205–12.
5. MacMahon B, Cole P, Brown JB, et al. Urine oestrogen profiles of Asian and North American women. Int J Cancer 1974;14:161–7.
6. Trichopoulos D, Yen S, Brown J, et al. The effect of westernization on urine estrogens, frequency of ovulation and breast cancer risk. Cancer 1984;53:187–92.
7. Goldin BR, Adlercreutz H, Gorbach SL, et al. The relationship between estrogen levels and diets of Caucasian American and Oriental immigrant women. Am J Clin Nutr 1986;44:945–53.
8. Key TJA, Chen J, Wang DW, et al. Sex hormones in women in rural China and Britain. Br J Cancer 1990;62:631–6.
9. Shimizu H, Ross RK, Bernstein L, et al. Serum oestrogen levels in postmenopausal women: comparison of American whites and Japanese in Japan. Br J Cancer 1990;62:451–3.

10. Bernstein L, Yuan JM, Ross RK, et al. Serum hormone levels in pre-menopausal Chinese women in Shanghai and white women in Los Angeles: results from two breast cancer case-control studies. Cancer Causes Control 1990;1:51–8.
11. Miller BA, Kolonel LN, Bernstein L, et al, eds. Racial/ethnic patterns of cancer in the United States 1988–1992. Bethesda, MD: National Cancer Institute, 1996. (NIH publication no. 96–4104).
12. Kolonel LN, Hankin JH, Lee J, et al. Nutrient intakes in relation to cancer incidence in Hawaii. Br J Cancer 1981;44:332–9.
13. Prentice RL, Sheppard L. Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes Control 1990;1:81–9.
14. Schapira DV, Kumar NB, Lyman GH, et al. Upper-body fat distribution and endometrial cancer risk. JAMA 1991;266: 1808–11.
15. Austin H, Austin JM Jr, Partridge EE, et al. Endometrial cancer, obesity, and body fat distribution. Cancer Res 1991; 51:568–72.
16. Prentice R, Thompson D, Clifford C, et al. Dietary fat reduction and plasma estradiol concentration in healthy postmenopausal women. J Natl Cancer Inst 1990;82:129–34.
17. Adlercreutz H, Mousavi Y, Hockerstedt K. Diet and breast cancer. Acta Oncologia 1992;31:175–81.
18. Young JL Jr, Percy CL, Asire AJ, eds. Surveillance, Epidemiology, End Results: incidence and mortality data 1973–1977. Natl Cancer Inst Monogr 1981;57:1–1082.
19. Oyama N, Johnson DB. Hawaii Health Surveillance Program survey methods and procedures. (Research & Statistics report no. 54). Honolulu: Hawaii State Department of Health, Research and Statistics Office, 1986.
20. World Health Organization. International classification of diseases for oncology. Geneva: World Health Organization, 1976.
21. Hankin JH. 23rd Lenna Frances Cooper Memorial Lecture: A diet history method for research, clinical and community use. J Am Diet Assoc 1986;86:868–75.
22. US Department of Agriculture. Nutrient data-base for standard reference, release 10. Bethesda, MD: USDA Human Nutrition Information Service, 1992.
23. Pennington JAT. Bowes and Church's Food values of portions commonly used. 16th ed. Philadelphia: JB Lippincott Co, 1994.
24. Holland B, Welch AA, Unwin ID, et al. McCance and Widdowson's The composition of foods. 5th ed. Cambridge, UK: Royal Society of Chemistry, Ministry of Agriculture, Fisheries and Food, 1991.
25. Kagawa R. Standard tables of food composition in Japan. (In Japanese). Tokyo: Women's Nutrition University Press, 1995.
26. Southgate DAT. Determination of carbohydrates in foods. II. Unavailable carbohydrates. J Sci Food Agric 1969;20:331–5.
27. Englyst HN, Cummings JH. An improved method for the measurement of dietary fibre as the non-starch polysaccharides in plant foods. J Assoc Anal Chem 1988;71:808–14.
28. Bingham S. Definitions and intakes of dietary fiber. Am J Clin Nutr 1987;45:1226–31.
29. Snedecor GW, Cochran WG. Statistical methods. Ames, IA: Iowa State University Press, 1967.
30. Breslow NE, Day NE. Statistical methods in cancer research. Vol I. The analysis of case-control studies. (IARC scientific publications no. 32). Lyon: IARC, 1980.
31. Pike MC, Bernstein L, Peters RK. Re: "Total energy intake: implications for epidemiologic analyses." (Letter). Am J Epidemiol 1989;129:1312–13.
32. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
33. Howe GR, Miller AB, Jain M. Re: "Total energy intake: implications for epidemiologic analyses." (Letter). Am J Epidemiol 1986;124:157–9.
34. Messina M, Barnes S. The role of soy products in reducing risk of cancer. J Natl Cancer Inst 1991;83:541–6.
35. Thompson LU, Robb P, Serraino M, et al. Mammalian lignan production from various foods. Nutr Cancer 1991;16:43–52.
36. Setchell KDR, Adlercreutz H. Mammalian lignans and phytoestrogens. Recent studies on their formation, metabolism, and biological role in health and disease. In: Rowland IR, ed. Role of gut flora in toxicity and cancer. London: Academic Press, 1988:315–45.
37. Lu L-J W, Anderson KE, Grady JJ, et al. Effects of soya consumption for one month on steroid hormones in premenopausal women: implications for breast cancer risk reduction. Cancer Epidemiol Biomarkers Prev 1996;5:63–70.
38. Adlercreutz H, Hockerstedt K, Banwart C, et al. Effects of dietary components, including lignans and phytoestrogens, on heterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). J Steroid Biochem 1987;27:1135–44.
39. Adlercreutz H, Martin F. Biliary excretion and intestinal metabolism of progesterone and estrogens in man. J Steroid Biochem 1980;13:231–44.
40. Rose DP. Dietary fiber and breast cancer. Nutr Cancer 1990; 13:1–8.
41. Goldin BR, Adlercreutz H, Gorbach SL, et al. Estrogen excretion patterns and plasma levels in vegetarian and omnivorous women. N Engl J Med 1982;307:1542–7.
42. Rose DP, Goldman M, Connolly JM, et al. High-fiber diet reduces serum estrogen concentrations in premenopausal women. Am J Clin Nutr 1991;54:520–5.
43. Adlercreutz H, Mousavi Y, Clark Y, et al. Dietary phytoestrogens and cancer: in vitro and in vivo studies. J Steroid Biochem Mol Biol 1992;41:331–7.
44. La Vecchia C, Decarli A, Fasoli M, et al. Nutrition and diet in the etiology of endometrial cancer. Cancer 1986;47:1248–53.
45. Levi F, Franceschi S, Negri E, et al. Dietary factors and the risk of endometrial cancer. Cancer 1993;71:3575–81.
46. Shu XO, Zheng W, Potischman N, et al. A population-based case-control study of dietary factors and endometrial cancer in Shanghai, People's Republic of China. Am J Epidemiol 1993; 137:155–65.
47. Barbone F, Austin H, Partridge EE. Diet and endometrial cancer: a case-control study. Am J Epidemiol 1993;137: 393–403.
48. Potischman N, Swanson CA, Brinton LA, et al. Dietary associations in a case-control study of endometrial cancer. Cancer Causes Control 1993;4:239–50.
49. Zheng W, Kushi LH, Potter JD, et al. Dietary intake of energy and animal foods and endometrial cancer incidence: the Iowa Women's Study. Am J Epidemiol 1995;142:388–94.
50. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
51. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1:58–64.
52. Price KR, Fenwick GR. Naturally occurring oestrogens in food—A review. Food Addit Contam 1985;2:73–106.
53. Schottenfeld D. Epidemiology of endometrial neoplasia. Cell Biochem 1995;23(suppl):151–9.
54. Hankin JH, Wilkens LR, Kolonel LN, et al. Validation of a quantitative diet history method in Hawaii. Am J Epidemiol 1991;133:616–28.
55. Hankin JH, Yoshizawa CN, Kolonel LN. Reproducibility of a diet history in older men in Hawaii. Nutr Cancer 1990;13: 129–40.
56. Hankin JH, Nomura AMY, Lee J, et al. Reproducibility of a diet history questionnaire in a case-control study of breast cancer. Am J Clin Nutr 1983;37:981–5.

Appendix follows

APPENDIX

Food Groups Included in the Analysis

Soy products

Soybeans, tofu (soy bean curd), miso.

Peas and beans

White beans, red beans, azuki beans, kidney beans, pinto beans, lima beans, yellow beans, chickpeas, blackeyed peas, lentils, split peas.

Legumes

Soy products, and peas and beans.

Whole grain cereals

Cooked cereals such as oat bran, Wheatena, or seven grain, cold high fiber cereals and fortified cereals such as bran, natural grain, Muesli, Cheerios, Wheaties, Nutri-Grain, and Grapenuts.

Whole grain foods

Whole grain cereals, whole grain and mixed grain breads, dark breads, bran muffins, brown rice.

Vegetables

Asparagus, avocado, green beans, string beans, head cabbage, won bok (Chinese cabbage), celery, head lettuce, Romaine and butter (green leaf) lettuce, okra, peapods, peas, zucchini, bittermelon, broccoli, Brussels sprouts, head cabbage, cauliflower, pak choy (white stem cabbage), parsley, spinach, ong choy (water spinach), taro leaves, watercress, bittermelon leaves, sweet potato leaves, kai choy (green mustard cabbage), coriander, marungay (horseradish tree leaves), bamboo shoots, mung bean sprouts, eggplant, mushrooms, onions, yellow (sweet) pepper, green (sweet) pepper, red (sweet) pepper, chayote squash, summer squash, burdock, kanpyo (dried gourd strips), carrots, pumpkin, winter squash, sweet potatoes, tomato, corn.

Fruits

Cherries, figs, grapes, honeydew melon, papaya, pears, prunes, raisins, tamarinds, watermelon, grapefruit, oranges, tangerines, apricots, mango, cantaloupe, nectarines, peaches, bananas, apples, strawberries.