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Dietary Factors in Lung Cancer Prognosis

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A hypothesis-generating analysis of the role of diet on survival was conducted among a sample of 463 men and 212 women with histologically-confirmed lung cancer. Interview information was obtained from two population-based case-control studies of lung cancer conducted on the Island of Oahu, Hawaii, between 1979 and 1985. The interview consisted of a quantitative dietary history to assess the usual intake of foods 1 year prior to diagnosis, a complete tobacco history, and other demographic and lifestyle information. Records from the Hawaii Tumor Registry were reviewed for data on stage, histology, and follow-up status of these patients. A food group analysis showed a significant reduction in the risk of death with increasing consumption of all vegetables combined among women (*P* for trend = 0.03), but not among men. The covariate-adjusted median survival times for women from the highest to the lowest quartiles of vegetable intake were 33, 21, 15, and 18 months, respectively. The results also suggested an association of fruit intake and survival among women (*P* for trend = 0.02), although a similar effect was not found among men. Increased consumption of certain foods, such as tomatoes and oranges among men, and broccoli and, perhaps, tomatoes among women, appeared to improve survival. This exploratory analysis provides mixed indications that certain components of vegetables and fruits may prolong survival in lung cancer patients.
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INTRODUCTION

A NUMBER of studies have suggested that dietary factors are important in the pathogenesis of human cancer, and that the carcinogenic process can be blocked both *in vitro* and *in vivo* by dietary supplementation [1]. Studies in human populations have shown that the dietary intake of micronutrients, such as vitamin A and beta-carotene, as well as the consumption of certain vegetables and fruits, reduce the risk of lung cancer [2]. Two recent studies of the effects of etretinate (a synthetic vitamin A derivative), folate, and vitamin B_{12}, on the regression of bronchial metaplasia among tobacco smokers, provide preliminary evidence that vitamin supplementation can reduce the risk for potentially premalignant lesions of the lung [3, 4]. However, the role of dietary intervention or vitamin supplementation to enhance the prognosis in lung cancer patients is largely unexplored. This is unfortunate, since factors that block tumour promotion may be similar to those that reduce cancer recurrence.

The current study is an outgrowth of several previous investigations of the influence of diet on the risk for lung cancer in Hawaii [5–7]. Two case-control studies showed a negative association between dietary vitamin A, beta-carotene [5, 7], and vegetable consumption [7], and the risk for this disease. The objective of the present analysis is to merge this interview data with information from a population-based cancer registry to examine the potential for certain dietary micronutrients, vegetables, and fruits to prolong survival in lung cancer patients. This exploratory analysis might generate hypotheses to be used in future clinical research of dietary intervention in lung cancer patients.

PATIENTS AND METHODS

Two case-control studies of risk factors for lung cancer incidence were conducted among residents of Oahu, Hawaii, between 1 September 1979 and 14 March 1983 [5] and between 1 March 1983 and 30 September 1985 [7]. These studies had similar designs and questionnaires, which made it possible to merge the data for this analysis. Patients with primary lung cancer were identified through the pathology logs and admission records in each of the seven major civilian hospitals on the island. Hawaii Tumor Registry data indicate that more than 84% of lung cancer cases on Oahu were admitted to one of these hospitals during the study period. Cases were restricted to

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individuals 30–84-years-old who were residents of Oahu for at least 6 consecutive months prior to interview, and who belonged to one of the five major ethnic groups: Japanese, Chinese, Hawaiian/part-Hawaiian, white, and Filipino. Patients with multiple primary tumours were not included in either study.

Interviews were completed for 872 (65%) of the 1333 eligible cases. Reasons for non-participation included patient refusal (7%), patient moved or was psychologically unable to be interviewed (9%), patient died or was too ill to be questioned and no proxy was available (15%), and physician refusal (4%).

Subjects were interviewed in their homes regarding their usual diet during the year prior to diagnosis, use of vitamin supplements, lifetime history of tobacco use, and other factors of interest. 184 surrogate interviews were sought from next-of-kin for patients who were either deceased or too ill to be interviewed directly. We have shown that smoking, drinking, and dietary histories obtained from such persons are highly reliable [8].

The diet history method has been described previously [9]. In brief, over 130 food items or categories were selected to provide an estimate of 85% or more of the intake of vitamin A, beta- and other carotenes, and vitamin C for individuals in the five major ethnic groups included in the studies. Sources of these nutrients and appropriate serving sizes were derived from measured food records of a random sample of the population. Colour photographs, illustrating the three most representative serving sizes, were used to assist subjects in estimating amounts consumed. For most items, the respondent indicated the usual frequencies consumed per day, week, or month, with yearly frequencies for particular seasonal foods such as mangoes. Amounts consumed were selected from the photographs in any combination of serving sizes. Vitamin A and C supplement use during the reference period was also recorded. This method has been shown to be reproducible [10, 11] and valid [12] when compared with food record data.

Records from the Hawaii Tumor Registry, a component of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) programme [13], were reviewed for information on histologic type, stage of the tumour at diagnosis, and follow-up status. The closing date for patient follow-up was 1 August 1987. All cases were histologically-confirmed. Histologic categories chosen for the analysis included adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and "other" cell types. Staging categories used were: "localised" for restriction to the lung, "regional" for spread by direct extension to immediately adjacent tissues or organs and/or spread into regional lymph nodes, and "distant" for spread of the tumour beyond immediately adjacent tissues or organs or regional lymph nodes. Cases were classified according to their follow-up status as alive, dead, or lost. The lost cases were treated in the analysis as "withdrawn alive" at the time they were lost.

We analysed the dietary data using a food composition database compiled largely from US Department of Agriculture tables [14, 15], and supplemented with data from Japan [16] and other publications [17, 18]. Recipes of local ethnic dishes were also included. The carotenoid contents of foods were estimated using the approach recommended by a Food and Agriculture/WHO Expert Group [19], with conversion to amounts of the specific vitamin A components from formulas published by the National Research Council [20]. The quantity of each food item consumed on a daily basis was calculated as the product of the frequency and serving size. The food composition database was then used to obtain the intakes of dietary vitamin A, beta-, and other carotenes, and vitamin C.

The survival experience of lung cancer patients was compared by consumption level of micronutrients, foods, and food groups, using a proportional hazards regression model [21]. Survival time was estimated from the date of lung cancer diagnosis. We assumed that the ratio of hazard rates and the effect of each prognostic variable were constant over time. A base model was created consisting of age at diagnosis, stage, and histologic type, which were found to be important prognostic variables from an earlier examination of these data [22]. We also adjusted the risks associated with nutrient and food intake by a body mass index (kg/m^2). Smoking status (ever vs. never smoked cigarettes) was included as a covariate when it significantly improved the fit of the model. Other methods of smoking adjustment were tried, such as the duration and intensity of smoking, but none of these alternatives provided a discernible improvement in fit or meaningful differences in the relative risks. An indicator variable for the two case-control studies was included in all of the proportional hazards equations to control for possible confounding due to subtle differences between the investigations. To simplify statistical adjustment, we excluded 44 subjects who smoked pipes or cigars, 76 subjects who had incomplete information on tobacco use, and 77 subjects who had missing information on histology and stage at diagnosis.

The appropriateness of the proportionality assumption was examined graphically by checking for parallelism of log–log survival curves when plotted against survival time. Relative risks and 95% confidence intervals were computed for the nutrients and foods divided into quartiles, or tertiles where appropriate. Linear trend in the risk of death was tested by including a trend variable in the model that was assigned the median value of the quantiles of the independent variable. A covariate-adjusted survival curve was calculated as the predicted curve of the average individual. Covariate-adjusted median survival time was calculated as the follow-up month where the proportional hazards model predicted a cumulative survival rate of 50%.

RESULTS

The distribution of the 675 lung cancer patients by selected demographic and clinical characteristics is presented in Table 1. The effects of these variables on the risk of death from lung cancer are described in detail in an earlier paper [22]. Briefly, most cases smoked cigarettes at the time of diagnosis, with only 5% of men and 25% of women classifying themselves as never smokers. There was a significant effect of ever smoking on survival among women, but not men. Subjects with small cell carcinoma or more advanced stages of lung cancer had a significantly poorer prognosis than did other subjects. No significant differences in the risk of death were found by ethnic group. A total of 538 cases (80%) had died and 14 cases (2%) were lost to follow-up at the time of this analysis. The median survival time among patients who died was 13 months for men and 19 months for women.

Table 2 shows little effect of micronutrient intakes on lung cancer survival after adjustment for age at diagnosis, stage at diagnosis, histologic type, body mass index, and study. Survival was slightly better among women in the highest compared with the lower quartiles of vitamin C consumption, but the relative risks were not suggestive of a trend. There was no effect on the risk of death for consumption of vitamin A or beta-carotene in

Table 1. Frequency distribution of lung cancer patients by selected demographic and clinical characteristics, Oahu, Hawaii, 1979–1985

	Men Cases (%)	Women Cases (%)
Total	463 (100)	212 (100)
Age (years)		
<55	83 (18)	31 (15)
55–64	146 (32)	76 (36)
65–74	175 (38)	71 (33)
75+	59 (13)	34 (16)
Ethnic group		
Japanese	160 (35)	48 (23)
White	143 (31)	80 (38)
Chinese	27 (6)	26 (12)
Filipino	55 (12)	12 (6)
Hawaiian	78 (17)	46 (22)
Smoking history		
Never	25 (5)	53 (25)
Ever	438 (95)	159 (75)
Histological type		
Adenocarcinoma	170 (37)	107 (50)
Small cell	67 (14)	30 (14)
Squamous cell	153 (33)	39 (18)
Other	73 (16)	36 (17)
Stage at diagnosis		
Localised	115 (25)	76 (36)
Regional	172 (37)	71 (33)
Distant	176 (38)	65 (31)

Table 2. Relative risks of death among lung cancer patients by quartile of micronutrient intake†, Oahu, Hawaii, 1979–1985*

	Men (n = 463)			Women (n = 212)		
Intake quartile	Vitamin A	Beta-carotene	Vitamin C	Vitamin A	Beta-carotene	Vitamin C
IV (high)‡	1.0	1.0	1.0	1.0	1.0	1.0
III	1.2	1.2	1.4§	1.3	1.3	1.7§
II	1.4	1.4	1.1	1.0	1.2	1.6
I (low)	1.1	1.0	0.9	1.4	1.5	1.2
P for trend	0.08	0.15	0.07	0.38	0.30	0.02

* Calculated by proportional hazards regression adjusting for age at diagnosis, stage, histology, body mass index, and study.
† The interquartile ranges (25th–75th percentile) for daily nutrient intakes were as follows: vitamin A from foods—men 6000–14250 IU, women 6000–13750 IU; beta-carotene—men 2000–5500 μg, women 2250–5750 μg; vitamin C from foods—men 75–225 mg, women 100–225 mg.
‡ Reference category for all models.
§ Confidence interval does not include unity.

either sex. Additional adjustment for patient smoking status did not alter the fit of any of the models significantly.

Recent case-control investigations have found that certain foods, such as carrots and tomatoes, particular food groups, including cruciferous vegetables, and fruits high in beta-carotene were protective against lung cancer [7, 23]. Table 3 shows the effects of selected foods and food groups on the relative risk of death among lung cancer patients. Of the individual foods,

Table 3. Relative risks of death among lung cancer patients by quartile of food intake†, Oahu, Hawaii, 1979–1985*

Food and Food Groups	Quartile of intake IV (high)‡	III	II	I (low)	P for trend
Men (n = 463)					
Tomatoes§	1.0	1.5††	1.5††	1.3††	<0.01
Broccoli	1.0	1.0	1.3††	1.0	0.37
Spinach	1.0	1.1	1.0	1.0	0.48
Carrots§	1.0	1.4	1.2	1.1	0.07
Oranges§	1.0	1.5††	1.5††	1.8††	<0.01
Cruciferous vegetables ‖	1.0	1.2	0.8	0.8	0.93
All vegetables§ ¶	1.0	1.4††	1.2	1.2	0.04
All fruits§ **	1.0	1.1	0.9	0.8	0.50
Women (n = 212)					
Tomatoes	1.0	1.4	1.4	2.0††	0.14
Broccoli	1.0	1.7††	2.0††	2.2††	<0.01
Spinach	1.0	1.7††	1.3	1.6††	0.03
Carrots	1.0	1.4	1.2	1.3	0.19
Oranges	1.0	1.7††	1.2	1.5	0.09
Cruciferous vegetables	1.0	1.4	1.6††	1.0	0.09
All vegetables	1.0	1.6	2.2††	1.9††	0.03
All fruits	1.0	2.0††	1.6	2.0††	0.02

* Calculated by proportional hazards regression adjusting for age at diagnosis, stage, histology, body mass index, and study.
† The interquartile ranges (25th–75th percentile) for daily intakes of foods and food groups (grams) were as follows: tomatoes—men, 6.5–50.0; women, 6.5–42.0; broccoli—men, 0.0–10.01; women, 1.0–8.0; spinach—men, 0.0–6.5; women,0.0–6.0; carrots—men, 0.0–7.5; women, 0.0–8.5; oranges—men, 0.0–120; women, 0.0–128; cruciferous vegetables—men, 6.0–36.0; women, 5.5–32.5; all vegetables—men, 75.0–230; women, 70.0–210; all fruits—men, 135–485; women, 180–500.
‡ Reference category for all models.
§ Includes juices of these items.
‖ Broccoli, chinese cabbage, mustard cabbage, head cabbage, pak choy.
¶ All vegetables in food group column, and green beans, peas, asparagus, zucchini, head lettuce, sweet potatoes, and mixed vegetable dishes.
** All fruits in food group column and papayas, and mangoes.
†† Confidence interval does not include unity.

increased consumption of oranges among men and broccoli among women showed significant, monotonic trends. The relative risks by quartile of tomato consumption were also suggestive of a relationship for this fruit and survival in women. There was no relation of survival to other foods high in carotene, such as sweet potatoes, mangoes and papaya (data not shown).

Among the food groups, all vegetable consumption showed a significant, although not monotonic, trend for survival among women (P = 0.03). The covariate-adjusted median survival times for women from the highest to the lowest quartiles of vegetable intake were 33, 21, 15, and 18 months, respectively. The intake of fruit was also a survival determinant among women (P for trend = 0.02), with an average improvement in survival of 15 months over the interquartile range. A similar benefit of vegetable and fruit intake was not found for men. There was no evidence for a dose–response by decreasing level of consumption for the other food groups investigated, including yellow–orange, green-leafy, and dark-green vegetables (data not shown).

Since we found that survival time varied by the histologic type of lung cancer [22], we examined the histologic-specific

Table 4. Relative risks of death among lung cancer patients by tertile of micronutrient and food intake, and histologic type, Oahu, Hawaii, 1979–1985*

Tertile of micronutrient or food intake	Men			Women		
	Adenocarcinoma (n = 170)†	Small cell (n = 67)	Squamous cell (n = 153)	Adenocarcinoma (n = 107)	Small cell (n = 30)	Squamous cell (n = 39)
Vitamin C						
High‡	1.0	1.0	1.0	1.0	1.0	1.0
Medium	0.9	1.9	1.7‖	1.6	3.5‖	0.9
Low	0.8	1.1	1.3	1.1	4.7‖	1.8
P for trend	0.68	0.12	0.05	0.15	0.02	0.90
Tomatoes						
High	1.0	1.0	1.0	1.0	1.0	1.0
Medium	1.0	2.1‖	1.2	1.2	3.2	1.3
Low	0.9	1.5	1.0	1.4	2.1	1.3
P for trend	0.94	0.06	0.53	0.63	0.09	0.58
Broccoli						
High	1.0	1.0	1.0	1.0	1.0	1.0
Medium	1.0	1.5	1.0	1.1	2.5	2.6
Low	0.8	1.8	1.1	1.6	2.7	5.6‖
P for trend	0.62	0.30	0.93	0.53	0.08	0.24
Oranges						
High	1.0	1.0	1.0	1.0	1.0	1.0
Medium	0.8	2.4‖	1.1	1.6	1.1	0.8
Low	0.8	2.6‖	1.3	1.1	1.5	0.8
P for trend	0.31	0.02	0.45	0.27	0.81	0.62
All vegetables §						
High	1.0	1.0	1.0	1.0	1.0	1.0
Medium	1.0	3.2‖	1.0	1.2	4.3‖	1.3
Low	1.0	1.8	0.9	1.3	1.7	2.7
P for trend	0.95	0.02	0.93	0.57	0.06	0.64
All fruits §						
High	1.0	1.0	1.0	1.0	1.0	1.0
Medium	1.2	1.6	1.4	1.2	2.1	0.8
Low	1.2	0.9	0.9	1.1	2.4	2.6
P for trend	0.56	0.29	0.22	0.52	0.26	0.91

* Calculated by proportional hazards regression adjusting for age at diagnosis, stage, smoking status, body mass index, and study.
† Number of cases.
‡ Reference category for all models.
§ See Table 3 for composition of all vegetable and all fruit categories.
‖ Confidence interval does not include unity.

findings for the micronutrients and foods of interest from Tables 2 and 3. The effects of food consumption on survival were stronger among subjects with small cell carcinoma than among subjects with other histologic types of cancer (Table 4). Among small cell carcinoma cases, there was a statistically significant dose–response gradient in the hazard of death by decreasing consumption of oranges in men, and by decreasing consumption of vitamin C in women.

In an earlier analysis of these data, we found that women who smoked had significantly poorer survival times than did never smoking women, although no association was found for men [22]. For this reason, we examined the joint effects of cigarette smoking, and vegetable and fruit consumption on the risk of death among women. We calculated relative risks, adjusted for age, stage, histology, body mass and study, for ever/never smokers and fruit or vegetable consumption, using subjects who were never smokers with high intake levels as the reference category. The results for vegetable consumption are shown in Table 5. There was no evidence of an interaction between smoking and vegetable consumption on survival time (P = 0.68). Among ever smokers below the 50th percentile of vegetable intake, we found an increased risk of death compared with the reference group (RR = 1.9; 95% CI: 1.0–3.4). There was a difference of 14 months in the covariate-adjusted median survival time between the two groups. Similar effects were found for fruit intake on the risk of death for smokers and never smokers of cigarettes (results not shown).

We examined the interrelation of measures of body size (height, weight, body mass), micronutrients and foods on the hazard of death among lung cancer patients and found that body mass, and to some extent weight, but not height, modified the effect of diet on the risk of death. Table 6 shows that the effect of all vegetable consumption on survival was limited to the less obese subjects of both sexes, although the interaction between body mass and vegetable consumption was not statistically significant for either men (P = 0.08) or women (P = 0.08). The results of additional analyses showed no significant interaction between any micronutrients or food intakes and body mass on survival (data not shown).

Stratification by the stage at cancer diagnosis showed similar

Table 5. Relative risks (RR) of death, 95% confidence intervals (CI), and median survival times among female lung cancer patients by smoking status and all vegetable consumption, Oahu, Hawaii, 1979–1985*

	All vegetable consumption†					
	Upper 50%			Lower 50%		
Smoking status	RR	95% CI	Median survival time (months)‡	RR	95% CI	Median survival time (months)
Never	1.0 §		32	1.5	0.7–3.0	21
Ever	1.5	0.8–2.7	21	1.9	1.0–3.4	18

* Calculated by proportional hazards regression adjusting for age at diagnosis, stage, histology, body mass index, and study.
† See Table 3 for composition of all vegetable category.
‡ Median survival time in months adjusted for age at diagnosis, stage, histology, body mass index, and study.
§ Reference category.

Table 6. Relative risks (RR) of death, 95% confidence intervals (CI), and median survival times among lung cancer patients by body mass index and all vegetable consumption, Oahu, Hawaii, 1979–1985*

		All vegetable consumption†					
		Upper 50%			Lower 50%		
Sex	Body mass index‡	RR	95% CI	Median survival time (months)§	RR	95% CI	Median survival time (months)
Men	<23.5	1.0‖		17	1.5	(1.1–2.0)	11
	≥23.5	1.2	(0.8–1.6)	14	1.2	(0.8–1.6)	14
Women	<22.7	1.0‖		30	1.9	(1.1–3.2)	17
	≥22.7	1.7	(1.0–2.8)	18	1.7	(1.0–2.9)	18

* Calculated by proportional hazards regression adjusting for age at diagnosis, stage, histology, smoking status, and study.
† See Table 3 for composition of all vegetable category.
‡ Dichtomised at the median.
§ Median survival time in months adjusted for age at diagnosis, stage, histology, smoking status and study.
‖ Reference category.

effects of diet on survival in each stage category among men (data not shown). Among women, trends tended to be somewhat stronger for regional compared with localised and distant stages, although these differences were not large, and none of the trend statistics was significant. Because of the powerful influence of stage on survival, residual confounding within the three broad stage categories defined for this analysis could have biased our survival analysis. To evaluate the potential for this effect, mean intakes of the micronutrients and foods were compared between stage groups for each sex, after adjusting for age, histology, smoking status, body mass, and study. No significant differences between the covariate-adjusted means were found, nor were there any distinct patterns in intake by stage.

DISCUSSION

There have been few reports concerning nonclinical prognostic variables for lung cancer, presumably because of the poor survival for this disease. Among our study subjects, the median survival time for men was a little more than 1 year, and for women less than 2 years from the time of diagnosis. Because of the short time to death, investigations of survival among patients with lung cancer are difficult, especially if data collection is carried out after cancer diagnosis. This is the first analysis, to our knowledge, of the dietary determinants of lung cancer prognosis.

The results of the exploratory analysis provide some tentative evidence for a relationship between survival in persons with lung cancer and their diet prior to diagnosis. Investigations of diet and lung cancer aetiology have shown that particular foods and food groups are more strongly associated with the incidence for lung cancer than are specific micronutrients in the diet [7, 23]. In addition to beta-carotene, other carotenoids without provitamin A activity, such as lycopene and lutein, as well as compounds abundant in cruciferous vegetables, such as indoles, phenols, and flavones, may play a role in reducing the risk of lung cancer among smokers. In a recent analysis, we found that the greatest reduction in the risk for lung cancer was associated with the level of intake of all vegetables combined, rather than with any specific micronutrient, food, or food group [7]. Consistent with investigations of cancer aetiology, these data suggest that some of the foods that have shown protective effects against lung cancer, such as tomatoes, broccoli, and all vegetables combined, were also associated with longer survival among patients with this disease.

Other foods, such as papaya, sweet potato, mango, and yellow–orange vegetables, that are rich in beta-carotene, had little influence on survival in our analysis. This is consistent with the lack of a clear association of beta-carotene and survival, and suggests that the intake of beta-carotene before diagnosis does not affect the progression of lung cancer. In contrast, tomatoes, which contributed only 8% of the beta-carotene content of the diet among the cases, showed a stronger positive relationship with survival, particularly in women.

Cruciferous vegetables have been shown to be protective against epithelial cancers [7, 23], but this food group was not associated with the risk of death in our analysis. However, broccoli, a vegetable that is common to both food groups, was related to survival among women. In addition to beta-carotene, broccoli is high in lutein and epoxy carotenoids. Unfortunately, there are no food composition data yet available to better define the role of these carotenoids in survival.

Several epidemiological studies of the association of vitamin A and carotene with the risk for lung cancer have shown that the protective effect of these micronutrients was limited to squamous cell and small cell lung cancers [23, 24]. We found that the intakes of vitamin C and of certain vegetables and fruits enhanced the prognosis among women diagnosed with small cell cancer, but not with adenocarcinoma of the lung. Thus, our results are somewhat consistent with investigations of diet and lung cancer aetiology. A weaker, but not inconsistent, relation was found between the intake of vegetables and fruit to the risk of death by histologic type among men compared with women. This is perhaps the result of a more modest role of diet or generally shorter survival times among men than women.

The present analysis suggests that body mass and smoking may modify the relationship of diet to prognosis among lung cancer patients. Vegetable consumption appeared to improve

survival among subjects with low body mass, but not high body mass. Unfortunately, because we did not have complete dietary information on these subjects, we were unable to adjust for energy consumption in our analysis. The data suggest that smoking may not only increase the hazard of death among lung cancer patients, but may also attenuate the benefits of a vegetable- and fruit-rich diet (perhaps through some physiological mechanism, such as increased oxidation). This is consistent with the observation that smokers have lower plasma vitamin C and carotenoid levels than non-smokers, even after adjustment for the dietary intake of carotenoids [25, 26].

One biologically plausible mechanism for an inverse association of vegetable or fruit consumption and survival in lung cancer patients would be through modulation of tumour infiltration or invasion. Although our results showed no significant differences in the mean dietary intake of micronutrients or foods by the stage at diagnosis, other factors, such as delay in seeking treatment, might be more important determinants of extent of disease when first diagnosed. Carotenoids have been shown to influence immune responsiveness through enhancement of T and B lymphocyte proliferation, stimulation of cells with tumoricidal activity, and increased cellular communication [27]. In addition to tumoricidal activity, increased immunocompetence in the lung cancer patient would decrease the likelihood of complications and death due to infectious agents. Nutritional deficiency might also be prevented in patients with high fruit and vegetable intake.

A strength of this analysis was the use of a personal interview with the patient or closely related proxy to gather dietary and non-dietary information for a large, multi-ethnic, population-based sample of lung cancer patients. All lung cancers were histologically confirmed and staged, enabling us to examine the effects of these factors on the association of diet and survival. Follow-up was very complete, with only 2% of cases lost according to Hawaii Tumor Registry records.

Unfortunately, because of the rapidly lethal nature of lung cancer, 383 (29%) of eligible patients died before we could interview them. A surrogate interview was not possible for 199 (52%) of these deceased cases, thus leading to a case sample that was biased toward longer survival. Indeed, after adjusting for age at diagnosis, stage, and histologic type, the median survival time for eligible patients who were not included in the analysis was 6 months, compared with 15 months for patients who were included in the analysis. Therefore, our study results would be biased if those subjects who were not interviewed because of a rapid demise had different dietary consumption patterns than those who survived longer.

Although surrogate interviews introduce the potential for error in dietary measurement, they provide the assurance of a more representative case sample. Mean nutrient and food intakes reported by surrogates in this study were very similar to those reported by directly interviewed lung cancer cases. To investigate the bias that may have been introduced through the use of surrogate interviews, we repeated the main analyses of Tables 2 and 3 excluding surrogate respondents. We found excellent agreement between the results of the two analyses.

A further limitation of these data is that the dietary history, although obtained after diagnosis, assessed intake prior to the diagnosis of lung cancer. Therefore, we do not know whether the dietary habits of the lung cancer patients remained the same subsequent to that time. It is possible that cases would modify their dietary behavior somewhat after the diagnosis of lung cancer, although there are no direct means for us to investigate the effects of this source of bias. One might anticipate that cases with more advanced disease at diagnosis would be less likely to tolerate their normal diet than cases with localised or regional lung cancer. We found no significant differences in the effect of diet on survival by tumour stage. Since survival times for lung cancer cases are short, it may be that diet prior to diagnosis is a stronger predictor of prognosis than diet subsequent to diagnosis. Nonetheless, a diet history is regarded as the most satisfactory method to obtain past diet, especially when dietary patterns may have been modified because of the patient's disease or treatment [28].

The issue of multiple comparisons and its effect on overall significance levels is important. As a result of the large number of comparisons we made for the evaluation of diet and lung cancer survival, it is not surprising that a few comparisons would achieve marginal significance. However, we chose not to adjust for the possibility of chance associations in the analysis, since this study was exploratory in nature and not meant to address a specific *a priori* hypothesis.

In summary, this exploratory analysis provides mixed indications that certain components of vegetables and fruits may prolong survival in patients with lung cancer. We were unable to identify a specific component in foods that enhances prognosis, and there was incomplete consistency of the results by sex. Further studies will be necessary to explore the relation of diet to prognosis in persons with lung cancer.

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Breast Cancer, Blindness and Melatonin

Michel P. Coleman and Russel J. Reiter

The hypothesis is advanced that blindness from an early age may lead to a reduced risk of breast cancer through altered patterns of melatonin secretion by the pineal gland. The available experimental evidence in animals and *in vitro* is consistent with this hypothesis. The hypothesis can be tested in humans by a simple observational study in which the breast cancer risk in blind women is compared with that of all women. The effect of age at onset, duration and degree of blindness could also be assessed, after adjustment for known risk factors for breast cancer. Melatonin might prove to be a natural oncostatic agent of practical value in cancer prevention.
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INTRODUCTION

WE ADVANCE the hypothesis that blind women, particularly those blind since childhood, may have a low risk of breast cancer due to increased melatonin secretion from the pineal gland. The rôle of melatonin in human cancer remains controversial, but this hypothesis can be tested in a simple observational study.

Melatonin is a hormone produced by the pineal gland in response to diurnal variations in light exposure. Visual perception of the light–dark cycle (the photoperiod) is required for control of pineal melatonin synthesis. The pineal thus acts as a neuroendocrine transducer, translating stimulation of the retina by light into hormonal signals. Neural pathways run from the retina via the retinohypothalamic tract to the suprachiasmatic nuclei, and thence, via descending axons to spinal nuclei in the upper thoracic cord, to pre- and eventually postganglionic fibres which innervate the pineal gland [1]. Light suppresses melatonin secretion, and the diurnal secretion cycle peaks during darkness, around 0200–0400 h [2]. Melatonin alters the firing rate of the gonadotropin-releasing hormone (GnRH) pulse frequency generator in the hypothalamus, thus reducing pituitary secretion of gonadotropins and of prolactin and, indirectly, the secretion of oestrogen by the gonads [3]. In mammals, melatonin has been shown to delay puberty, suppress ovulation and reduce gonadal steroidogenesis [4].

Light suppresses the nocturnal peak of melatonin secretion in humans [5], too, although a higher light intensity is required than for some mammals [6]. Seasonal variation in the photoperiod and in the diurnal rhythm of melatonin secretion may produce endocrine effects in humans which are similar to those in animals. Thus, in Oulu, northern Finland (65°N), where there is 20–22 h of daylight in May–June but only 3–4 h of daylight in November–January, melatonin secretion in women increases and ovarian activity decreases in the dark season [7], and reduced conception rates during the dark season have been

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