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A Cross-national Investigation of Diet and Bladder Cancer

J.R. Hebert and D.R. Miller

The existence of a large unexplained portion of attributable risk, and the marked variation in bladder cancer rates globally, have stimulated an interest in the role of nutrition in cancer of the urinary bladder. For this cross-national comparison study, we had complete data available for 50 countries. Using stepwise regression followed by general linear modelling, age-truncated (45–74 years), world-standardised, sex-specific bladder cancer mortality rates were regressed on an array of nutritional and socioeconomic independent variables in an effort to identify important predictors of bladder cancer mortality. Separate principal components analyses were used to summarise the nutritional and the socioeconomic (SES) variables. In the stepwise analyses, using food scores expressed in kcal/day per capita (as opposed to the nutritional components), total fat consistently entered the model first, and explained the greatest share of variability (R^2) for both males and females. General linear models were fitted that included total fat, tobacco, alcohol, the three SES components (comprising seven socioeconomic predictors) and two food categories found significant in stepwise modelling, roots/tubers and vegetable oil. The R^2 values were 0.84 for male rates and 0.77 for female rates, meaning that these study factors account for 84% of bladder cancer mortality in men and 77% in women. Substitution of the nutritional components for the foods resulted in general linear models with slightly higher R^2 values (0.85 for males, 0.77 for females), but with attenuated fat effects. Results are discussed in light of biological plausibility.

Key words: bladder neoplasms, epidemiological studies, animal fat, economic factors
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INTRODUCTION

IN RECENT years, a profound interest in the role of diet and nutrition on cancers of several organ sites has emerged [1–3]. Evidence for an association between specific nutritional factors and cancer comes from a number of sources: ecological studies [4–6], analytic epidemiological studies [1, 2, 7], and laboratory animal experiments [2, 8, 9]. There is a widening view that bladder cancer may be linked with diet [10, 11].

The most important known risk factor for bladder cancer is tobacco smoking. It is estimated that approximately 25–50% of bladder cancers occurring in the U.S.A. can be attributed to smoking [12]. Other known risk factors, such as occupational exposure, can account for only a small additional fraction of bladder cancer cases. The large unexplained portion of attributable risk, as well as the marked variation in bladder cancer rates globally, argue for the examination of alternative environmental hypotheses, such as those related to diet [1, 12–14].

Therefore, in order to examine the role of nutritional factors in bladder cancer, a cross-national ecological study to identify dietary variables associated with male and female bladder cancer mortality rates was undertaken. We were motivated partly by

Table 1. Age-standardised bladder cancer mortality rates for persons aged 45 to 74 years for 50 countries included in the analysis

	Male	Female		Male	Female
Argentina	18.7	2.7	Italy	24.8	3.9
Australia	11.8	3.9	Japan	5.6	1.9
Austria	16.5	5.4	Korea	5.2	0.9
Bahamas	3.5	0.0	Malta	27.8	6.2
Barbados	9.9	6.3	Maritius	8.6	2.4
Belgium	23.3	5.3	Mexico	3.5	1.1
Bulgaria	13.3	2.9	Netherlands	18.9	4.2
Canada	11.8	3.5	New Zealand	11.5	4.0
Chile	6.7	3.1	Panama	3.1	2.2
Costa Rica	5.9	1.3	Paraguay	4.2	1.3
Cuba	12.0	3.3	Poland	21.1	3.0
Czechoslovakia*	20.9	4.1	Peru	2.1	0.7
Dominan Republic	1.7	1.2	Portugal	12.7	3.1
East Germany†	21.8	4.7	Romania	13.7	3.9
Ecuador	2.9	1.3	Singapore	8.8	3.1
England	19.9	6.4	Spain	20.1	3.1
France	19.0	3.5	Surinam	4.0	2.0
Greece	18.0	3.7	Syria	1.5	0.1
Guatemala	0.9	0.3	Thailand	1.5	0.3
Honduras	0.0	0.6	Trinidad	6.9	2.9
Hong Kong	10.9	4.2	United States	10.8	3.5
Hungary	19.4	3.9	Uruguay	19.3	3.3
Iceland	9.9	4.3	Venezuela	5.1	2.7
Ireland	12.9	4.3	West Germany†	18.8	3.2
Israel	3.8	3.8	Yugoslavia‡	12.6	3.2

Number of cases per year per 100 000 people, aged 45 to 74 years, standardised to the world age distribution by decade, 1980–1986. *Data compiled before the division into the Czech and Slovac Republics. †Data compiled before the unification of Germany. ‡Data compiled before the break-up of Yugoslavia.

the large variability in cancer rates observed in these data (25-fold here as opposed to non-occupationally exposed inter-group differences within populations of only around two-fold). As much as possible, we adjusted for aggregate tobacco disappearance data, per capita alcohol disappearance data and relevant socioeconomic variables. All analyses were weighted by the mortality data-specific sex-specific mid-period populations.

MATERIALS AND METHODS

Data sources

National data were obtained from a number of United Nations specialised agencies. Complete data were available for 50 countries which were included in all analyses (Table 1). These countries excluded those with senility and ill-defined causes accounting for > 15% of total mortality [5]. For each country, bladder cancer mortality rates for 1980 to 1986 were computed from bladder cancer mortality and population estimates specific for gender and decade of age. Rates for ages 45 to 74 years were further standardised for decade of age, by the direct method, to world population estimates for 1980 to 1986, and combined, yielding gender- and country-specific age-standardised bladder cancer mortality rates for ages 45 to 74 years.

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Nutritional (i.e. nutrients and food items) variables were obtained from the *Food Balance Sheets* 1979–1981 *Average*, cumulated and published by the Food and Agriculture Organization of the United Nations [15]. These data are based on the sum of imports and production minus exports, with adjustments made for non-food uses, losses during storage and transport, food fed to livestock and used for seeds, and in manufacture for food and non-food uses. For this analysis, we used data from 1979–1981. This time-lagging reflects the belief that dietary factors primarily affect promotional (i.e. late) stages of carcinogenesis [16–19]. These data probably represent good approximations for diet in the periods corresponding to the preceding data available, 1965 [20] until 1979 [21–23]. Data are pro-rated on a per capita basis. Nutrient scores were also derived from this source. The nutritional variables consisted of total calories and calories from total fat, animal fat, vegetable fat, alcohol and animal protein. Food categories included all vegetable foods, meat, milk, fish, vegetable oils, cereals, pulses, nuts, roots and tubers, cabbages, fruit and sugar.

All food variables were expressed in terms of daily average calorie intake. A calorie-adjusted alcohol score was derived from linear regression as follows: alcohol calories were regressed on total calories, and a residual was obtained by subtracting the actual value of alcohol disappearance from the value predicted from the total calorie score, based on the linear regression equation. Therefore, the residual is that portion of alcohol disappearance that is unexplained simply by the variation in total number of calories [24].

Information on basic sanitation (i.e. proportion of the population without safe water and without excreta disposal facilities) were obtained from the World Health Organization [25]. Basic economic indicators, infant mortality rates and life expectancy figures were obtained from World Bank compilations [26]. Statistics on numbers of physicians per unit population (physicians/10 000) and hospital bed availability (beds/10 000) were obtained from the World Health Organization [27].

Per capita tobacco use by each country was estimated from tobacco disappearance data averaged from 1958 to 1963 [28, 29] and population estimates corresponding to the same years [30]. Time-lagging tobacco data by approximately 20 years was based on current thinking about tobacco's role as a cancer initiator and its requisite latency [6].

Statistical analyses

Exploratory analyses were performed on all variables to identify any drastic departures from the assumptions of standard statistical procedures, i.e. normality, linearity and independence [31]. Pearson correlation coefficients were calculated to determine bivariate relationships between sex-specific bladder cancer mortality rates and nutrient predictors, alcohol consumption, per capita tobacco use based on disappearance data and socioeconomic predictors. All correlations were weighted by the sex-specific population across countries for the 45–74 year age range.

Because of the high intercorrelation among nutritional and socioeconomic predictors, component scores were initially computed from principal components to summarise these sets of variables into a smaller set of variables while reducing intercorrelations. One set each of nutritional and socioeconomic components were computed using PROC FACTOR (principal components) with VARIMAX Rotation in SAS [32]. Twelve variables were included in the nutrition principal components analysis (PCA): calories from all vegetable sources, cereals, roots and tubers, pulses, nuts, cabbage, fruit, meat, fish, milk, vegetable oil, and simple sugars. Seven variables related to socioeconomic conditions were included in computing the socioeconomic (SES) principal components: gross national product per capita, life expectancy at birth, infant mortality rate, proportion of the population without safe water or excreta disposal facilities, and the number of physicians or hospital beds/10 000 population. The component scores for socioeconomic predictors were used in the analyses because they provided better explanatory ability in the general linear models (GLM) than did the individual SES variables. For the nutritional predictors, the use of individual variables, as well as the components computed from PCA, were used in analyses as both provided interpretable results and both yielded high levels of explanatory ability. Pearson correlation coefficients, weighted by the square root of mid-mortality data period country population, were computed for all candidate independent variables.

Male and female bladder cancer mortality rates were considered separately in all analyses. To compensate for differences in population size among the countries, weighting by the square root of the individual country mid-mortality data period population was applied in all analyses. Stepwise regression models were fitted with sex-specific bladder cancer rates as the dependent variables using Proc Stepwise in SAS [32]. Separate analyses were conducted using the nutritional variables and the nutritional components. Using the results of our stepwise modelling, general linear models were designed as a final step in our analyses. For these GLMs, tobacco consumption, SES principal components and the alcohol residual were forced into the models as independent variables in the first step. These "best fit" (i.e. highest R^2) general linear models were designed to reduce the risk of including intercorrelated predictors, to account to maximum variability in bladder cancer rates, and to allow for computation of interpretable and stable regression coefficients.

Several alternative models were examined in an effort to obtain a "best fit" (highest R^2 value). This approach was taken because nutritional variables tend to be highly intercorrelated and highly correlated with other potential predictors of bladder cancer. When fitted simultaneously into a general linear model, intercorrelated predicators may produce regression coefficients that are unstable and, therefore, uninterpretable [33]. The aim was to fit a model that accounted for maximum variability in bladder cancer mortality, whose regression coefficients were interpretable, and in which important covariates were controlled.

RESULTS

Substantial variation in bladder cancer mortality was observed among the 50 countries included in this analysis (Table 1). Rates ranged from over 20 per 100 000 per year for several European countries to less than one per 100 000 per year in several countries in Asia and Latin America. Male rates were generally higher than female rates.

Substantial variation was also observed in the nutritional variables investigated in this analysis. Many of these variables correlated significantly with bladder cancer mortality among the 50 countries (Table 2). Particularly high correlations were observed for total fat, animal fat, animal protein, meat, milk, alcohol and cereals (inverse).

Tobacco consumption was only weakly correlated with bladder cancer mortality. This is consistent with what we observed earlier for lung cancer [6]. Stronger correlations were observed for the socioeconomic variables, with the highest mortality rates in countries of great affluence, health care utilisation and hygiene.

Results from the PCA of the socioeconomic and nutritional variables are presented in Tables 3 and 4, respectively. The SES PCA produced three components, each of which accounted for at least 1% of the variance. The first component, SESPC1, is primarily a poor-sanitation high-infant mortality rate component. SESPC2 loads most heavily on access to medical care, while SESPC3 is an affluence component. The nutrition PCA yielded five components each of which explained at least 1% of the variance. The first component (NUTPC1) may be considered a measure of a diet composed of large quantities of meat, dairy products and sweets and low levels of pulses (high negative loading). The second NUTPC is apparently a vegetable/cereal factor. NUTPC3 had one high positive loading, fish, and one negative loading, fruit. NUTPC4 has only one high loading, roots and tubers, while NUTPC5 has two high loadings, nuts and fruit. All variables significantly associated in any stepwise regression model ($P < 0.1$) or ultimately fitted in the GLMs are shown in Table 5.

In the stepwise analyses with the nutritional variables (as opposed to the nutritional factors), total fat consistently entered the model first and explained the greatest share of variability (R^2) for both males and females. In fact, with total fat in the model, of the nutritional variables, only roots and tubers and vegetable oil entered using a P value of 0.20 for the F test of $B = \Phi$ as the inclusion criterion. When vegetable and animal fat were entered in place of total fat they both entered the models, but with much lower F values, and their coefficients were

*Table 2. Correlation of bladder cancer mortality rates with study variables among 50 countries**

	Mean value	Male	Female
Nutritional variables			
Total calories (kcal/day)	3042	0.75	0.65
Total fat (g/day)	104.6	0.74	0.78
Animal fat (g/day)	70.8	0.73	0.78
Vegetable fat (g/day)	33.8	0.46	0.46
Animal protein (g/day)†	49.3	0.65	0.67
Alcohol residual (g/day)†	139.4	0.46	0.37
Vegetable foods (kcal/day)	2305.1	0.20	−0.04
Cereals (kcal/day)	1048.8	−0.33	−0.53
Roots and tubers (kcal/day)	129.4	0.54	0.47
Simple carbohydrates (kcal/day)	367.2	0.38	0.54
Pulses (kcal/day)	38.6	−0.41	−0.38
Nuts (kcal/day)	42.2	−0.33	−0.24
Vegetable oil (kcal/day)	60.9	0.23	0.03
Cabbage (kcal/day)	6.5	−0.03	−0.11
Fruit (kcal/day)	98.6	−0.09	−0.05
Meat (kcal/day)	414.6	0.61	0.66
Fish (kcal/day)	38.1	−0.29	−0.25
Milk/milk products (kcal/day)	243.1	0.64	0.70
Non-nutritional variables			
Tobacco (kg per capita per year)	17.1	0.25	0.33
Gross national product ($1000 per capita per year)	4.88	0.32	0.53
Life expectancy (years)	70.4	0.57	0.65
Infant mortality (no./1000 live births)	27.4	−0.59	−0.68
Medical doctors (no./10 000)	12.2	0.82	0.69
Hospital beds (no./10 000)	64.6	0.64	0.68
Safe water (% households without)	13.2	−0.57	−0.67
Sanitary facilities (% households without)	16.5	−0.61	−0.63

*Pearson correlation coefficients. Correlations are statistically significant at $\alpha = 0.05$ if $r \geq 0.28$, at $\alpha = 0.01$ if $r \geq 0.36$, and at $\alpha = 0.001$ if $r \geq 0.45$. †Obtained by regressing out the effect of total calories with constant added to ensure no negative values.

virtually identical, indicating there was no differential effect according to type of fat. General linear models with total fat, roots and tubers, vegetable oil, tobacco, alcohol and the three SES PCs were then fitted. The food-related variables were included because they had entered the stepwise models. Results are shown in Table 6. The R^2 values were 0.84 for male rates and 0.77 for female rates using the food-related variables. Total fat was a strong independent predictor of bladder cancer mortality in both males and females. Tobacco consumption was also a marginally significant independent predictor for females, but not males, while SESPC1, the poor sanitation component, was negatively associated with bladder cancer in both sexes. SESPC2 was positively associated and SESPC3 was negatively associated in males only. No other variables increased the R^2 value of 0.02 or more when added to the models.

Table 3. Results of principal components analysis for socioeconomic variables, rotated component pattern

Variables	SESPC1	SESPC2	SESPC3
Gross national product	−0.207	0.306	0.903
Life expectancy	−0.495	0.568	0.463
Infant mortality	0.746	−0.427	−0.355
Per cent of households without safe water	0.869	−0.213	−0.142
Per cent of households without sanitation	0.914	−0.194	−0.145
Physicians per capita	−0.199	0.893	0.176
Hospital beds per capita	−0.301	0.798	0.324
Variance explained by each principal component	2.566	2.117	1.334

Subsequently, models were fitted substituting four NUTPCs found to be significantly associated in the stepwise models for the two food-related variables. These models had about equal R^2 values (0.85 for males and 0.77 for females; Table 6). Here, tobacco consumption was not even a marginally significant independent predictor of bladder cancer mortality for either males or females. The effect of total fat was reduced for both sexes. Of the nutrition principal components, only NUTPC5 was even marginally associated; as a protective factor, in men only. The SESPCs were related to bladder cancer in these models essentially the same way as we had observed them in the previous models.

DISCUSSION

Although it is well established that tobacco smoking and certain occupational exposures are important risk factors for bladder cancer [13, 34–37] most bladder cancer mortality within populations remains unexplained [13]. Discrepancies between bladder cancer rates and exposure to known risk

Table 4. Results of principal components analysis for nutrition variables rotated component pattern

Variables	NUTPC1	NUTPC2	NUTPC3	NUTPC4	NUTPC5
All vegetable sources	−0.079	0.879	−0.278	−0.058	−0.002
Cereals	−0.503	0.721	−0.051	−0.391	−0.083
Roots and tubers	0.120	−0.026	−0.046	0.940	−0.018
Simple carbohydrates	0.735	−0.152	−0.251	−0.170	−0.242
Pulses	−0.605	−0.067	−0.484	0.201	−0.333
Nuts	−0.202	0.169	0.081	−0.035	0.829
Vegetable oils	0.189	0.828	0.114	0.013	0.170
Cabbage	−0.011	0.722	0.409	0.148	0.075
Fruit	−0.178	−0.379	−0.537	0.190	0.448
Meat	0.862	0.100	0.050	0.282	−0.031
Fish	−0.099	−0.062	0.837	0.014	0.077
Milk/dairy	0.839	−0.002	0.022	0.133	−0.217
Variance explained by each principal component	2.745	2.715	1.558	1.266	1.1530

factors call into question the role of other lifestyle factors [38]. A number of dietary risk factors have been proposed in order to account for this unexplained risk. These include intakes of carotenoid-rich foods and dairy products [39], coffee drinking [40], specific beverage consumption and overall consumption of liquids [41, 42]. In a recent case–control study in Hawaii, there was a decrease in risk with increasing levels of vitamin C in women, and decreased risk with increasing levels of dark green vegetables among men [43]. Both of these parameters are strongly inversely correlated with dietary fat, which we found to be positively associated with bladder cancer mortality in our data. In a follow-up study of Seventh-Day Adventists in California, bladder cancer risk was shown to increase with increased consumption of meat, poultry and fish [44], foods strongly related to animal fat calories in this study. The possible role of selenium in bladder carcinogenesis [45] indicating a protective effect of antioxidants, is consistent with our findings in that diets high in fat tend to be low in antioxidant vitamins.

Previously, we have proposed that dietary fat could be related to bladder cancer mortality [13]. One ecological study previously demonstrated a correlation between dietary fat and bladder cancer mortality of 0.7 [5]. There are several plausible hypotheses whereby dietary fat consumption, in particular animal fats, could increase the probability of bladder cancer [16, 18, 19, 46]. These include cell membrane effects, increasing solubility of lipid-soluble carcinogens, and effects on cell-mediated immune response.

Although total fat consistently entered the stepwise models first and continued to be a significant predictor of bladder cancer mortality in most GLMs, several anomalous results should be pointed out. First, inclusion of the nutritional components, although producing an impressive overall R^2 value, attenuated the fat effect. This may be because several components, in

*Table 5. Correlation between selected variables among 50 countries**

Variables†	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Total calories	0.85	0.80	0.62	0.36	0.42	0.21	0.69	0.41	−0.24	0.27	0.10	−0.57	0.64	0.20	0.54
2. Total fat		0.95	0.71	0.43	0.14	0.30	0.87	−0.06	−0.24	0.31	0.18	−0.42	0.63	0.49	0.55
3. Animal fat			0.45	0.50	0.05	0.33	0.88	−0.09	−0.19	0.34	0.03	−0.38	0.63	0.43	0.53
4. Vegetable fat				0.11	0.30	0.11	0.50	0.05	−0.26	0.14	0.43	−0.33	0.36	0.41	0.38
5. Roots and tubers					−0.01	0.32	0.34	−0.02	−0.08	0.89	−0.21	−0.22	0.36	−0.04	0.12
6. Vegetable oil						0.04	0.04	0.83	0.25	0.11	0.45	−0.50	0.04	−0.03	0.05
7. Alcohol							0.22	−0.05	0.16	0.27	0.11	−0.10	0.51	0.13	−0.07
8. NUTPC1								−0.18	−0.39	0.08	0.17	−0.32	0.48	0.44	0.52
9. NUTPC2									0.20	0.10	0.10	−0.45	0.02	−0.33	0.00
10. NUTPC3										0.10	0.22	−0.22	−0.11	0.22	−0.15
11. NUTPC4											−0.11	−0.17	0.26	0.00	0.02
12. NUTPC5												−0.17	0.00	0.41	0.21
13. SESPC1													−0.25	−0.15	−0.41
14. SESPC2														−0.06	0.25
15. SESPC3															0.39
16. Tobacco															

*Correlations are statistically significant at $\alpha = 0.05$ if ≥ 0.28, at $\alpha = \geq 0.01$ if ≥ 0.36, and at $\alpha = 0.001$ if ≥ 0.45. †Variables shown are those entering at least one stepwise model with $P < 0.10$ or inclusion in the GLMs or both. They are in units as noted in the text.

*Table 6. General linear models for variation in bladder cancer mortality rates among 50 countries**

Variable	Male b	Male *P* value	Female b	Female *P* value
Using nutritional variables				
Intercept	2.550	0.35	2.084	0.003
Tobacco (kg/year)	−0.085	0.15	−0.027	0.07
Total fat (g/day)	0.092	0.001	−0.022	0.002
Roots and tubers (kcal/day)	0.013	0.12	0.001	0.53
Vegetable oil (kcal/day)	0.020	0.40	−0.014	0.02
Alcohol residual (g/day)	0.013	0.24	0.002	0.58
SESPC1	−1.837	0.03	−0.815	0.0003
SESPC2	2.320	0.03	0.193	0.45
SESPC3	−1.853	0.02	−0.047	0.80
Model R^2	0.84		0.77	
Using nutritional components				
Intercept	2.779	0.50	2.613	0.01
Tobacco (kg/year)	−0.064	0.30	−0.026	0.09
Total fat (g/day)	0.082	0.02	0.015	0.09
Alcohol residual (g/day)	0.017	0.11	0.002	0.52
NUTPC1	0.719	0.47	0.246	0.32
NUTPC2	−0.500	0.70	−0.066	0.84
NUTPC4	0.549	0.47	0.108	0.57
NUTPC5	−1.396	0.09	−0.094	0.65
SESPC1	−1.518	0.06	−0.816	0.003
SESPC2	2.427	0.02	0.245	0.34
SESPC3	−1.623	0.05	−0.020	0.92
Model R^2	0.85		0.77	

*All results shown are based on type III (orthogonal) sums of squares.

particularly NUTPC1 ($r = 0.87$), are highly correlated with fat. As these same components are related to the SESPCs as well (see Table 5), they also attenuated those effects in the second GLMs, shown in Table 6.

It is also of concern that the SESPCs were consistently predictive of bladder cancer mortality, even after accounting for total fat. These socioeconomic factors almost certainly are not having a direct effect on bladder cancer mortality, but they are good, indirect indicators for whatever other factors are having an effect. As all of the variables in the models are essentially economic, they all suffer from the same well-known deficiencies [47, 48].

Because mortality rates vary widely among the countries included in our analysis, we were able to examine environmental factors, such as diet. In addition to variability in cancer rates, we were able to exploit large interpopulation differences in diet, much larger than are generally found in study populations within individual countries [49]. Furthermore, both cancer rates and estimates of diet were based on relatively large populations and, therefore, they are largely unaffected by random error [24]. Other problems generally associated with ecological studies remain, including use of aggregate data resulting in potentially uncontrolled confounding. However, we have advanced beyond previously published analyses of this kind [5], in attempting to partially deal with the issue of confounding by using multivariable analysis to adjust for available information (albeit with aggregate data) on potential confounders [50]. It is known that a large amount of random error normally accompanies nutritional data [51]. An important component in the failure of dietary self-report is cognitive, or memory-related [52–54]. In addition, there is probably a very important psychological component related to social desirability, though it has only rarely been studied [55]. Despite these obvious drawbacks of self-report data, such information is regularly used in epidemiological studies without any way of assessing true underlying criterion validity. Given the potential of ecological studies to model linear relationships with data meeting regression model assumptions [56, 57], we believe these results merit careful consideration.

This study indicates a potentially important role for dietary fat in bladder carcinogenesis. The fact that we were able to account for approximately 75–85% of bladder cancer mortality across the countries we examined using variables, the most prominent of which was total fat consumption, should prompt further work both in laboratory animal models and in analytical epidemiological studies.

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