

ENVIRONMENTAL FACTORS AND CANCER INCIDENCE AND MORTALITY IN DIFFERENT COUNTRIES, WITH SPECIAL REFERENCE TO DIETARY PRACTICES

by

Bruce ARMSTRONG and Richard DOLL

Department of the Regius Professor of Medicine, Radcliffe Infirmary, Oxford OX2 6HE, England

Incidence rates for 27 cancers in 23 countries and mortality rates for 14 cancers in 32 countries have been correlated with a wide range of dietary and other variables. Dietary variables were strongly correlated with several types of cancer, particularly meat consumption with cancer of the colon and fat consumption with cancers of the breast and corpus uteri. The data suggest a possible role for dietary factors in modifying the development of cancer at a number of other sites. The usefulness and limitations of the method are discussed.

The correlation of incidence and mortality rates with the prevalence of environmental agents in various geographical areas has provided useful pointers for the study of environmental factors in the aetiology of cancer. Such studies may be conducted either within defined regions of a single country or across several countries. The former approach has the advantage of more uniform data sources, but is limited in that subdivision to allow sufficient observations for analysis may so reduce the size of the population in each region that the rates become unstable; moreover, differences within a country are likely to be less than those between countries. The correlation of cancer rates with the prevalence of environmental agents in different countries may therefore be a worthwhile exercise in spite of the fact that the apparent distribution of both the cancer and the agent may be significantly affected by differences in the quality of the data available.

Correlation studies of cancer incidence or mortality with various environmental agents have been reported previously over a wide range of

countries. Most were conducted before incidence figures became readily available (UICC, 1966, 1970) and before the usefulness was recognized of truncated age-standardized rates as descriptors of international variations (Doll and Cook, 1967). Most of the studies were restricted to a few selected cancers and environmental agents and the analyses limited to calculation of simple correlation coefficients. Only male rates have usually been used except where cancers of the female breast or genital organs have been studied, and often rates have been included for countries for which the mortality data were unreliable.

With the increasing interest in possible environmental causes of human cancer and the availability of incidence data and a wider range of mortality data, it seemed that a further international correlation analysis would be justified. In this study we have used cancer incidence data from 23 countries and mortality data from 32 countries and have correlated most discrete cancer sites in men and women with a wide range of dietary and other variables. The usefulness of

partial correlation analysis has been explored as a means of identifying the relationships most likely to be worthy of further study.

DATA AND METHODS

Cancer incidence data were taken from UICC, 1966 and 1970. The truncated age-standardized incidence rates for ages 35-64 years were used with the "world population" as a standard. The advantages of this age-range are that at these ages cancer is common enough to produce stable rates even in quite small populations; that the relationship between incidence and age is similar through this age range in nearly all countries; and that it reduces the inaccuracies introduced by using data from older age groups in which cancer registration may be very incomplete. The countries from which data were used and the years covered by these data are shown in Table I. All countries were included from which the data available might reasonably have been considered to be representative of the country as a whole. For countries in which data were available from two or more cancer registries, a mean incidence rate was calculated, weighted

for the population in the age-group 35-64 years in each registration area. The person/years of experience for the periods studied ranged from 0.17 to 16.2 million years for men and from 0.21 to 16.9 million years for women.

Cancer mortality data were taken from Segi *et al.* (1969) and WHO (1967-1969, 1970). Truncated age-standardized mortality rates for ages 35-64 years were calculated, using as a standard the same world population as was used for the incidence rates. The countries from which data were used, and the years covered by these data, are shown in Table I. Countries were included in the analysis only if less than 15% of the deaths in 1965 were attributed to senility or ill-defined causes. The person/years of experience for the periods studied ranged from 0.71 to 61.3 million years for men and from 0.71 to 65.0 million years for women.

The 27 types of cancer studied are shown in Table II. Data for each cancer were not available in all countries. Incidence data were available for cancer of the liver and cancer of the gall-bladder and biliary tract in only 21 out of the 23 countries. Mortality data were available for cancer of the

TABLE I
YEARS FOR WHICH CANCER INCIDENCE AND MORTALITY DATA WERE USED
IN THE COUNTRIES STUDIED

| Country | Incidence data | Mortality data | Country | Incidence data | Mortality data |
|-----------------------|----------------------|----------------|---------------------------------|----------------|----------------|
| Nigeria ¹ | 1960-65 ² | | German Fed. Repub. ¹ | 1963-66 | 1964-65 |
| Canada ¹ | 1963-66 | 1964-65 | German Dem. Repub. | 1964-66 | |
| Chile | 1959-61 | 1964-65 | Greece | | 1964-65 |
| Colombia ¹ | 1962-66 | 1964-65 | Hungary ¹ | 1962-66 | 1964-65 |
| Jamaica ¹ | 1964-66 | | Iceland | 1955-63 | |
| Puerto Rico | 1964-66 | | Ireland | | 1964-65 |
| USA ¹ | 1959-66 | 1964-65 | Italy | | 1964-65 |
| Taiwan | | 1965-66 | Netherlands ¹ | 1960-62 | 1964-65 |
| Hong Kong | | 1965-66 | Norway | 1964-66 | 1964-65 |
| Israel | 1960-66 | 1964-65 | Poland ¹ | 1965-66 | 1964-65 |
| Japan ¹ | 1962-64, 66 | 1964-65 | Portugal | | 1964-65 |
| Philippines | | 1965-66 | Rumania ¹ | 1967 | 1965-66 |
| Austria | | 1964-65 | Sweden | 1962-65 | 1964-65 |
| Belgium | | 1964-65 | Switzerland | | 1964-65 |
| Bulgaria | | 1965-66 | United Kingdom ¹ | 1963-66 | 1964-65 |
| Czechoslovakia | | 1964-65 | Yugoslavia ¹ | 1961-65 | 1964-65 |
| Denmark | 1958-62 | 1964-65 | Australia | | 1964-65 |
| Finland | 1962-65 | 1964-65 | New Zealand | 1962-66 | 1964-65 |
| France | | 1964-65 | | | |

¹ Incidence data available for only part of the country.
² 1960-65 etc. means all years in the inclusive range 1960 to 1965.

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TABLE II
SIMPLE CORRELATION COEFFICIENTS BETWEEN
MALE AND FEMALE RATES FOR CANCER
INCIDENCE AND MORTALITY AT VARIOUS SITES

| Cancer site ¹ | Incidence rates | Mortality rates |
|-----------------------------------|-----------------|-----------------|
| Oesophagus (150) | 0.93 | 0.41 |
| Stomach (151) | 0.97 | 0.95 |
| Small intestine (152) | 0.66 | — |
| Colon (Inc. 153; Mort. 152-3) | 0.98 | 0.94 |
| Rectum (154) | 0.90 | 0.93 |
| Liver (155.0) | 0.96 | — |
| Gall bladder etc. (155.1) | 0.76 | — |
| Pancreas (157) | 0.46 | 0.69 |
| Nose (160) | 0.84 | — |
| Larynx (161) | 0.10 | 0.12 |
| Lung (162-3) | 0.54 | 0.28 |
| Kidney (180) | 0.81 | 0.88 |
| Bladder (181) | 0.70 | 0.75 |
| Nervous system (193) | 0.94 | — |
| Thyroid (194) | 0.73 | — |
| Bone (196) | 0.75 | — |
| Connective tissue (197) | 0.42 | — |
| Lympho- and reticulosarcoma (200) | 0.85 | — |
| Hodgkin's disease (201) | 0.62 | — |
| Myeloma (203) | 0.93 | — |
| Leukaemia (204) | 0.49 | 0.90 |

¹ ICD 7th Revision rubrics in parentheses. Where no coefficient is given, mortality data for that cancer were not available in the sources used. Incidence and mortality rates for cancer of the breast (170), cervix uteri (171), and ovary (175) were studied in women and for cancer of the prostate (177) in men. Incidence rates only were studied for cancer of the corpus uteri (172) and other genitalia (176) in women and for cancer of the testis (178) and other genitalia (179) in men.

pancreas in 23 out of the 32 countries and for cancers of the ovary, kidney and bladder in 21 countries.

International *per caput* commodity consumption and other data were derived from various sources (Food and Agriculture Organization, 1959, 1960, 1971; Statistical Office of the United Nations Organization, 1960, 1970; Beese, 1972; Cartographic Department of the Clarendon Press, 1972). The variables studied are listed in Table IV. Except where specified otherwise, the figures used were measurements *per caput* in 1963-65. These data were available for all the countries studied except for tea consumption in Colombia, Puerto Rico and Iceland, coffee consumption in Nigeria and Taiwan and cigarette consumption in 1953-55 in Puerto Rico.

Product-moment simple and first-order partial correlation coefficients between the cancer rates

and the environmental variables were calculated using SPSS package programmes (Nie *et al.*, 1970) on the Oxford University ICL 1906A computer. Countries with missing data were excluded separately from the calculation of all correlation coefficients involving the missing variable. The product-moment correlation method was used in preference to a rank correlation method as it provides the most satisfactory partial correlation coefficients. Even when the variables being correlated are both normally distributed, the product-moment correlation coefficient is a useful measure of the association between them which, in contrast to ranking methods, makes use of all the information in the data.

Preliminary analyses

As an aid to interpreting the correlations between the cancer rates and the environmental variables, some preliminary analyses were performed. These are shown in Tables II-IV.

TABLE III
SIMPLE CORRELATION COEFFICIENTS BETWEEN
INCIDENCE AND MORTALITY RATES OF CANCER
AT VARIOUS SITES IN 18 COUNTRIES

| Cancer site | Men | Women |
|-----------------------|------|-------|
| Oesophagus | 0.89 | 0.96 |
| Stomach | 0.88 | 0.89 |
| Colon | 0.92 | 0.95 |
| Rectum | 0.77 | 0.62 |
| Pancreas ¹ | 0.70 | 0.64 |
| Larynx | 0.82 | 0.36 |
| Lung | 0.91 | 0.68 |
| Breast | — | 0.90 |
| Cervix | — | 0.53 |
| Ovary ² | — | 0.84 |
| Prostate | 0.57 | — |
| Kidney ² | 0.78 | 0.50 |
| Bladder ² | 0.56 | 0.59 |
| Leukaemia | 0.58 | 0.66 |

¹ 15 countries.

² 14 countries.

Table II shows the correlation between male and female incidence and mortality rates for the cancer sites common to both sexes. A low correlation between male and female rates may suggest either that different aetiological factors are responsible for the cancer in the two sexes, or that the ratio of male to female exposure or

TABLE IV
CORRELATION COEFFICIENTS BETWEEN ENVIRONMENTAL VARIABLES

| Environmental variables ¹ | GNP | Physician density | Cereals | Potatoes etc. | Sugar | Pulses etc. | Vegetables | Fruits | Meat | Eggs | Fish |
|--------------------------------------|---------------|-------------------|--------------------|---------------|--------|-------------|------------|---------------|----------------|----------|---------------|
| Liquid energy 1955-57 | 0.83 | 0.20 | -0.62 | -0.06 | 0.58 | -0.20 | 0.00 | 0.26 | 0.61 | 0.59 | 0.04 |
| Solid energy 1955-57 | 0.42 | 0.33 | -0.35 | 0.44 | 0.45 | -0.42 | 0.01 | -0.06 | 0.54 | 0.40 | -0.23 |
| Population density 1965 ² | -0.18 | -0.32 | 0.05 | -0.34 | -0.23 | 0.18 | -0.04 | -0.13 | -0.12 | -0.02 | 0.33 |
| Tea 1955-57 | 0.14 | -0.10 | -0.29 | 0.06 | 0.48 | -0.17 | -0.09 | -0.16 | 0.52 | 0.42 | -0.10 |
| Coffee 1955-57 | 0.69 | -0.03 | -0.64 | 0.32 | 0.46 | -0.36 | -0.31 | 0.11 | 0.19 | 0.23 | 0.25 |
| Cigarettes 1963-65 | 0.24 | 0.08 | 0.02 | -0.40 | 0.12 | 0.10 | 0.11 | 0.02 | 0.36 | 0.28 | -0.21 |
| Total fat | 0.82 | 0.39 | -0.72 | 0.34 | 0.76 | -0.55 | -0.03 | 0.35 | 0.81 | 0.74 | -0.16 |
| Total protein | 0.53 | 0.56 | -0.11 | 0.08 | 0.34 | -0.24 | 0.36 | 0.32 | 0.65 | 0.56 | -0.34 |
| Animal protein | 0.85 | 0.33 | -0.76 | 0.28 | 0.78 | -0.55 | 0.00 | 0.30 | 0.87 | 0.77 | -0.08 |
| Calories | 0.57 | 0.50 | -0.24 | 0.27 | 0.56 | -0.45 | 0.14 | 0.22 | 0.72 | 0.58 | -0.42 |
| Fats and oils | 0.64 | 0.44 | -0.59 | 0.39 | 0.55 | -0.46 | 0.08 | 0.41 | 0.52 | 0.62 | -0.06 |
| Fish | -0.01 | -0.31 | -0.14 | -0.06 | -0.24 | 0.27 | -0.02 | -0.12 | -0.35 | -0.11 | |
| Eggs | 0.69 | 0.60 | -0.61 | 0.08 | 0.63 | -0.24 | 0.21 | 0.46 | 0.72 | 0.74 | 0.70 |
| Meat | 0.75 | 0.38 | -0.59 | 0.10 | 0.71 | -0.48 | 0.08 | 0.26 | 0.72 | 0.91 | 0.72 |
| Fruits | 0.38 | 0.61 | -0.29 | -0.25 | 0.16 | 0.15 | 0.40 | | 0.69 | 0.82 | 0.61 |
| Vegetables | 0.03 | 0.42 | 0.24 | -0.30 | -0.28 | 0.52 | | 0.70 | 0.93 | 0.82 | 0.89 |
| Pulses etc. ³ | -0.34 | -0.10 | 0.51 | -0.56 | -0.67 | | 0.08 | 0.16 | 0.18 | 0.16 | -0.08 |
| Sugar | 0.66 | 0.22 | -0.80 | 0.43 | | -0.18 | 0.53 | 0.09 | 0.49 | 0.16 | 0.55 |
| Potatoes etc. ⁴ | 0.09 | -0.10 | -0.41 | | -0.30 | 0.40 | 0.35 | 0.25 | 0.42 | 0.40 | 0.06 |
| Cereals | -0.71 | -0.07 | | 0.08 | -0.16 | 0.38 | -0.17 | -0.28 | -0.16 | -0.31 | -0.11 |
| Physician density 1965 | 0.36 | | -0.13 | 0.25 | 0.10 | 0.20 | 0.50 | 0.33 | 0.43 | 0.46 | 0.46 |
| GNP 1965 ⁵ | | 0.20 | -0.13 | 0.15 | 0.57 | 0.28 | 0.58 | 0.32 | 0.65 | 0.34 | 0.38 |
| | Liquid energy | Solid energy | Population density | Tea | Coffee | Cigarettes | Total fat | Total protein | Animal protein | Calories | Fats and oils |

¹ Also total energy (1955-57), cigarettes (1953-55) and milk.

² Per square kilometre of land.

³ Pulses, nuts and seeds.

⁴ Potatoes, starchy and other staple foods.

⁵ GNP = Gross national product.

sensitivity to a common aetiological factor differs significantly from country to country; or that random factors are significantly affecting the rates. It is probable, therefore, that the most useful inferences can be drawn from data for cancers in which the male and female rates are highly correlated.

Table III shows the correlations between cancer incidence and mortality rates in the 18 countries for which both rates were available. Clearly, many factors may account for a low correlation between incidence and mortality rates, particularly when the case fatality rate for the cancer site in question is low. From an aetiological point of view, correlations between incidence rates and environmental variables ought to be the more revealing, provided that the incidence data are reliable.

Table IV shows the intercorrelations between all the environmental variables which were highly correlated with at least one of the rates over the 32 countries with mortality data. This Table is of the familiar triangular form produced when a set of variables are correlated with one another, except that the "tail" of the triangle has been inverted and placed beneath the diagonal line to save space; the columns beneath the diagonal should be read with the column labels at the bottom of the Table and the row labels to the right. From this Table, environmental variables may be identified which are highly correlated with one another. Thus other variables may be identified which could explain an association between one variable and a cancer rate.

TABLE V
SIMPLE CORRELATION COEFFICIENTS BETWEEN
INCIDENCE AND MORTALITY RATES OF CANCER
OF THE STOMACH AND ENVIRONMENTAL
VARIABLES

| Environmental variable | Incidence | | Mortality | |
|------------------------|-----------|------------------|------------------|------------------|
| | Men | Women | Men | Women |
| GNP | -0.38 | -0.42 | -0.44 | -0.54 |
| Meat | -0.43 | -0.51 | -0.47 | -0.58 |
| Animal protein | -0.18 | -0.28 | -0.43 | -0.57 |
| Total fat | -0.48 | -0.56 | -0.48 | -0.63 |
| F ratio | 2.1 | 3.0 ¹ | 3.6 ² | 6.1 ³ |

¹ $p < 0.05$.

² $p < 0.01$.

³ $p < 0.001$.

RESULTS AND DISCUSSION

The number of correlation coefficients produced in these analyses is very large and we are therefore reporting in detail only those data that relate to cancers which show a pattern of correlation coefficients unlikely to have occurred by chance and which are common in, or limited to, only one sex or whose incidence and mortality rates are closely correlated in both sexes (coefficient > 0.80 , Table II). The simple correlation coefficients for these cancers which are numerically greater than 0.50 are shown in Tables V to X with only the highest coefficients for cancers of the nose, cervix uteri and other genitalia in Table XI.

The assignment of statistical significance to individual correlation coefficients in this study is complicated by the large number of coefficients which has been calculated, making it likely that some extreme associations will have occurred by chance. We have, therefore, calculated an F ratio ($F_{4, \infty}$; see Appendix) for each set of simple correlation coefficients from which an estimate has been made of the probability that the pattern of coefficients observed might have occurred by chance on the null hypothesis that no real associations exist. The F ratios and probabilities referred to in Tables V-XI therefore relate not to individual coefficients but to the complete set of coefficients for the incidence or mortality of a particular cancer in one or other sex. We have, however, selected the numerically highest coefficients for detailed attention in the subsequent discussion because they are the coefficients most likely to provide useful information.

Although the incidence rates for lympho- and reticulo-sarcoma and for myeloma are highly correlated in both sexes, they show a pattern of coefficients which might have occurred by chance and these cancers are therefore not considered further. For those types of cancer which are not highly correlated between the sexes but show a pattern of coefficients for at least one of the rates which is unlikely to have occurred by chance, we give only the highest simple correlation coefficients in Table XI.

Some of the relationships between cancer rates and environmental variables are plotted in Figures 1-5. Examination of the graphed data is important, as it allows assessment of the contribution of extreme values to the size of the calculated coefficient.

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TABLE VI
SIMPLE CORRELATION COEFFICIENTS BETWEEN INCIDENCE AND MORTALITY RATES
OF CANCERS OF THE COLON AND RECTUM AND ENVIRONMENTAL VARIABLES

| Environmental variable | Colon | | | | Rectum | | | |
|------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------------------|-------------------|------------------|
| | Incidence | | Mortality | | Incidence | | Mortality | |
| | Men | Women | Men | Women | Men | Women | Men | Women |
| GNP | 0.81 | 0.82 | 0.77 | 0.69 | 0.74 | 0.64 | 0.58 | 0.44 |
| Cereals | -0.52 | -0.51 | -0.70 | -0.67 | -0.32 | -0.28 | -0.49 | -0.37 |
| Sugar | 0.55 | 0.56 | 0.63 | 0.65 | 0.48 | 0.34 | 0.53 | 0.41 |
| Meat | 0.85 | 0.89 | 0.85 | 0.84 | 0.83 | 0.68 | 0.67 | 0.57 |
| Eggs | 0.69 | 0.71 | 0.69 | 0.70 | 0.71 | 0.70 | 0.59 | 0.52 |
| Milk | 0.58 | 0.62 | 0.62 | 0.62 | 0.57 | 0.38 | 0.53 | 0.45 |
| Fats and oils | 0.49 | 0.53 | 0.67 | 0.60 | 0.54 | 0.41 | 0.68 | 0.62 |
| Calories | 0.60 | 0.66 | 0.63 | 0.62 | 0.75 | 0.56 | 0.64 | 0.59 |
| Animal protein | 0.74 | 0.80 | 0.86 | 0.84 | 0.71 | 0.53 | 0.68 | 0.59 |
| Total protein | 0.54 | 0.62 | 0.53 | 0.53 | 0.64 | 0.44 | 0.51 | 0.48 |
| Total fat | 0.74 | 0.78 | 0.85 | 0.81 | 0.76 | 0.60 | 0.74 | 0.64 |
| Cigarettes 1963-65 | 0.53 | 0.54 | 0.26 | 0.20 | 0.63 | 0.49 | 0.12 | 0.04 |
| Tea | 0.50 | 0.55 | 0.48 | 0.59 | 0.50 | 0.40 | 0.34 | 0.30 |
| Cigarettes 1953-55 | 0.40 | 0.41 | 0.22 | 0.24 | 0.51 | 0.35 | 0.03 | -0.02 |
| Total energy | 0.68 | 0.67 | 0.69 | 0.62 | 0.65 | 0.53 | 0.57 | 0.49 |
| Solid energy | 0.34 | 0.30 | 0.49 | 0.37 | 0.48 | 0.41 | 0.63 | 0.59 |
| Liquid energy | 0.59 | 0.63 | 0.63 | 0.66 | 0.43 | 0.32 | 0.30 | 0.20 |
| F ratio | 12.0 ¹ | 15.0 ¹ | 21.5 ¹ | 18.5 ¹ | 12.0 ¹ | 6.1 ¹ | 11.2 ¹ | 7.4 ¹ |

¹ p < 0.001.

TABLE VII
SIMPLE CORRELATION COEFFICIENTS BETWEEN INCIDENCE AND MORTALITY RATES
OF CANCERS OF THE FEMALE BREAST, CORPUS UTERI AND OVARY AND ENVIRONMENTAL VARIABLES

| Environmental variables | Breast | | Corpus uteri | Ovary | |
|-------------------------|-------------------|-------------------|-------------------|------------------|------------------|
| | Incidence | Mortality | Incidence | Incidence | Mortality |
| GNP | 0.83 | 0.72 | 0.82 | 0.44 | 0.64 |
| Cereals | -0.64 | -0.70 | -0.58 | -0.43 | -0.78 |
| Sugar | 0.70 | 0.74 | 0.62 | 0.43 | 0.78 |
| Pulses etc. | -0.43 | -0.46 | -0.62 | -0.41 | -0.53 |
| Fruits | 0.64 | 0.44 | 0.54 | 0.16 | 0.31 |
| Meat | 0.78 | 0.74 | 0.78 | 0.40 | 0.53 |
| Eggs | 0.71 | 0.80 | 0.68 | 0.28 | 0.51 |
| Milk | 0.66 | 0.73 | 0.64 | 0.47 | 0.66 |
| Fats and oils | 0.63 | 0.80 | 0.76 | 0.40 | 0.66 |
| Calories | 0.57 | 0.71 | 0.65 | 0.36 | 0.51 |
| Animal protein | 0.77 | 0.83 | 0.74 | 0.45 | 0.71 |
| Total protein | 0.49 | 0.57 | 0.50 | 0.32 | 0.33 |
| Total fat | 0.79 | 0.89 | 0.85 | 0.53 | 0.79 |
| Coffee | 0.42 | 0.37 | 0.43 | 0.50 | 0.50 |
| Total energy | 0.70 | 0.60 | 0.77 | 0.31 | 0.45 |
| Solid energy | 0.30 | 0.40 | 0.55 | 0.06 | 0.23 |
| Liquid energy | 0.70 | 0.62 | 0.55 | 0.43 | 0.53 |
| F ratio | 14.0 ² | 24.0 ² | 14.9 ² | 3.2 ¹ | 9.0 ² |

¹ p < 0.05.

² p < 0.001.

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TABLE VIII

SIMPLE CORRELATION COEFFICIENTS BETWEEN INCIDENCE AND MORTALITY RATES OF CANCERS OF THE PROSTATE AND TESTIS AND ENVIRONMENTAL VARIABLES

| Environmental variables | Prostate | | Testis |
|-------------------------|-----------|-------------------|------------------|
| | Incidence | Mortality | Incidence |
| GNP | 0.43 | 0.69 | 0.54 |
| Cereals | -0.50 | -0.60 | -0.50 |
| Sugar | 0.33 | 0.63 | 0.60 |
| Pulses etc. | -0.15 | -0.59 | -0.61 |
| Meat | 0.37 | 0.60 | 0.50 |
| Milk | 0.25 | 0.66 | 0.57 |
| Fats and oils | -0.04 | 0.70 | 0.76 |
| Calories | -0.05 | 0.61 | 0.54 |
| Animal protein | 0.25 | 0.67 | 0.59 |
| Total protein | -0.11 | 0.50 | 0.34 |
| Total fat | 0.20 | 0.74 | 0.76 |
| Coffee | 0.43 | 0.57 | 0.45 |
| Population density | -0.54 | -0.29 | -0.08 |
| Total energy | 0.30 | 0.60 | 0.43 |
| Liquid energy | 0.44 | 0.54 | 0.37 |
| F ratio | 2.0 | 12.9 ¹ | 6.9 ¹ |

¹ p < 0.001.

TABLE IX

SIMPLE CORRELATION COEFFICIENTS BETWEEN INCIDENCE AND MORTALITY RATES OF CANCER OF THE KIDNEY AND ENVIRONMENTAL VARIABLES

| Environmental variables | Incidence | | Mortality | |
|-------------------------|-------------------|-------------------|------------------|------------------|
| | Men | Women | Men | Women |
| GNP | 0.73 | 0.67 | 0.62 | 0.49 |
| Cereals | -0.57 | -0.41 | -0.71 | -0.62 |
| Sugar | 0.60 | 0.45 | 0.65 | 0.51 |
| Pulses etc. | -0.72 | -0.62 | -0.56 | -0.55 |
| Vegetables | -0.16 | -0.02 | -0.43 | -0.51 |
| Meat | 0.70 | 0.73 | 0.44 | 0.21 |
| Milk | 0.74 | 0.73 | 0.56 | 0.53 |
| Fats and oils | 0.68 | 0.57 | 0.64 | 0.56 |
| Calories | 0.55 | 0.64 | 0.37 | 0.18 |
| Animal protein | 0.81 | 0.83 | 0.59 | 0.44 |
| Total protein | 0.55 | 0.70 | 0.21 | 0.04 |
| Total fat | 0.77 | 0.74 | 0.69 | 0.53 |
| Coffee | 0.62 | 0.40 | 0.56 | 0.68 |
| Total energy | 0.62 | 0.43 | 0.44 | 0.19 |
| Liquid energy | 0.62 | 0.52 | 0.48 | 0.37 |
| F ratio | 11.9 ² | 10.3 ² | 6.2 ² | 4.1 ¹ |

¹ p < 0.01.

² p < 0.001.

Cancer of the stomach

A negative correlation with total fat consumption is the strongest association with gastric cancer (Table V). Controlling for total fat consumption reduces the partial correlation coefficients with meat consumption and GNP (gross national product) to negligible levels, but strengthens a positive association between incidence rates and fish consumption (r_0 , 0.43 and 0.37; r_1 , 0.60 and 0.58). r_0 refers to the simple (zero order) coefficient, and r_1 to a first-order partial correlation coefficient. Controlling for

TABLE X

SIMPLE CORRELATION COEFFICIENTS BETWEEN INCIDENCE RATES OF CANCERS OF THE LIVER AND NERVOUS SYSTEM AND ENVIRONMENTAL VARIABLES

| Environmental variables | Liver | | Nervous system | |
|-------------------------|------------------|------------------|------------------|------------------|
| | Men | Women | Men | Women |
| GNP | -0.42 | -0.53 | 0.59 | 0.54 |
| Physician density | -0.53 | -0.55 | 0.65 | 0.62 |
| Potatoes etc. | 0.71 | 0.69 | -0.44 | -0.37 |
| Sugar | -0.68 | -0.66 | 0.62 | 0.50 |
| Pulses etc. | 0.50 | 0.49 | -0.56 | -0.42 |
| Fruits | -0.38 | -0.46 | 0.52 | 0.52 |
| Meat | -0.40 | -0.47 | 0.50 | 0.37 |
| Eggs | -0.49 | -0.57 | 0.60 | 0.58 |
| Milk | -0.51 | -0.57 | 0.69 | 0.58 |
| Fats and oils | -0.47 | -0.57 | 0.65 | 0.56 |
| Calories | -0.53 | -0.60 | 0.56 | 0.41 |
| Animal protein | -0.59 | -0.67 | 0.69 | 0.59 |
| Total protein | -0.46 | -0.54 | 0.54 | 0.45 |
| Total fat | -0.49 | -0.59 | 0.71 | 0.58 |
| Cigarettes | -0.52 | -0.51 | 0.16 | 0.08 |
| Coffee | -0.17 | -0.23 | 0.52 | 0.51 |
| Liquid energy | -0.25 | -0.31 | 0.50 | 0.51 |
| F ratio | 6.1 ¹ | 7.7 ¹ | 8.5 ¹ | 5.8 ¹ |

¹ p < 0.001.

meat consumption reduces the partial correlation with total fat consumption to low levels in the same way (r_1 varies from -0.25 to -0.32). An examination of Figure 1 shows that extreme values weaken rather than strengthen the negative association with total fat consumption, whereas a similar plot for fish consumption (not shown) shows that the positive relationship is entirely dependent on the extreme values for Japan and

TABLE XI
SIMPLE CORRELATION COEFFICIENTS BETWEEN OTHER CANCER INCIDENCE AND MORTALITY RATES
IN EACH SEX AND THEIR MOST HIGHLY CORRELATED ENVIRONMENTAL VARIABLE

| Cancer | Sex/Rate ¹ | Environmental variable | Coefficient | F ratio |
|-----------------|-----------------------|------------------------|-------------|-------------------|
| Small intestine | MI | Sugar | 0.45 | 1.2 |
| | FI | Liquid energy | 0.73 | 5.9 ⁴ |
| Pancreas | MI | Eggs | 0.61 | 4.3 ³ |
| | MM | Animal protein | 0.80 | 9.1 ⁴ |
| | FI | Eggs | 0.56 | 2.0 |
| | FM | Sugar | 0.64 | 4.5 ³ |
| Nose | MI | Pulses etc. | 0.60 | 3.3 ³ |
| | FI | Pulses etc. | 0.61 | 2.7 ² |
| Larynx | MI | Fish | -0.54 | 1.1 |
| | MM | Vegetables | 0.52 | 1.4 |
| | FI | Potatoes etc. | 0.58 | 2.6 ² |
| | FM | GNP | -0.40 | 1.6 |
| Lung | MI | Solid energy | 0.69 | 4.3 ³ |
| | MM | Solid energy | 0.67 | 8.3 ⁴ |
| | FI | Tea | 0.60 | 3.3 ³ |
| | FM | Population density | 0.75 | 3.5 ³ |
| Cervix uteri | FI | Total protein | -0.66 | 3.8 ³ |
| | FM | Fruit | -0.42 | 1.3 |
| Other genitalia | MI | Total protein | -0.60 | 2.8 ² |
| | FI | Eggs | -0.59 | 3.2 ² |
| Bladder | MI | GNP | 0.59 | 3.8 ³ |
| | MM | Fats and oils | 0.66 | 2.2 |
| | FI | Cereals | -0.54 | 1.6 |
| | FM | Fats and oils | 0.67 | 3.6 ³ |
| Leukaemia | MI | Population density | -0.44 | 1.1 |
| | MM | Calories | 0.75 | 13.7 ⁴ |
| | FI | Sugar | -0.36 | 0.5 |
| | FM | Fats and oils | 0.72 | 11.3 ⁴ |

¹ MI = male incidence; MM = male mortality; FI = female incidence; FM = female mortality.

² $p < 0.05$.

³ $p < 0.01$.

⁴ $p < 0.001$.

Iceland; fish consumption is therefore unlikely to contribute significantly to international variation in gastric cancer rates.

Case-control studies have not produced a strong association between gastric cancer and any dietary variable. The most convincing finding has been a protective effect of raw vegetable consumption (Graham *et al.*, 1972; Haenszel *et al.*, 1972) but this is not seen in the correlation data (r_0 for vegetables from 0.12 to 0.20). What data there are on fat and meat consumption suggest a weakly positive rather than a negative relationship (Higginson, 1966).

Other geographical correlation studies have shown a positive association with cereal consumption (Hakama and Saxén, 1967) and a negative association with animal protein consumption (Gregor *et al.*, 1969). In our data, the former association is weak (r_0 from 0.37 to 0.48) and can be accounted for by the negative association with total fat consumption (r_1 from 0.05 to 0.12).

Cancers of the colon and rectum

The environmental variables most highly correlated with colon cancer rates are meat and animal protein consumption (Table VI). Control-

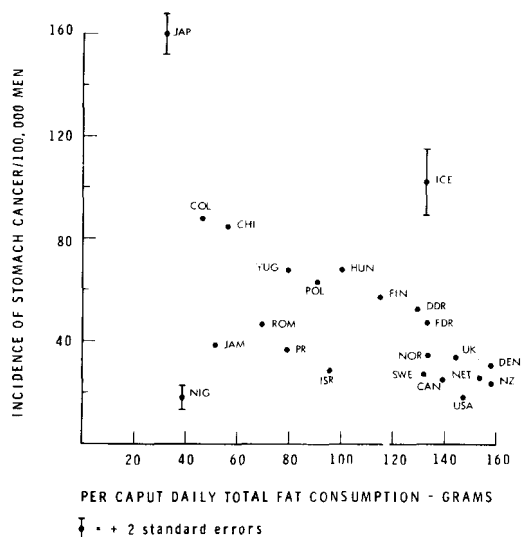


FIGURE 1

Correlation between incidence of cancer of the stomach in men and *per caput* total fat consumption in 23 countries. NIG = Nigeria; CAN = Canada; CHI = Chile; COL = Colombia; JAM = Jamaica; PR = Puerto Rico; USA = United States of America; ISR = Israel; JAP = Japan; DEN = Denmark; FIN = Finland; DDR = German Democratic Republic; FDR = Federal German Republic; HUN = Hungary; IRE = Ireland; NET = Netherlands; NOR = Norway; POL = Poland; ROM = Rumania; SWE = Sweden; UK = United Kingdom; YUG = Yugoslavia; NZ = New Zealand.

ling for one or other of these in the calculation of first-order partial correlation coefficients substantially reduces the correlation with all the other variables (*e.g.* r_1 for total fat varies from 0.11 to 0.24), whereas no other variable can reduce the correlation between meat consumption and incidence rates to less than 0.70. The pattern for rectal cancer is not quite as clear; total fat consumption is more highly correlated with the mortality rates (Table VI) but this correlation is substantially reduced by controlling for animal protein consumption (r_1 0.41 and 0.33). Total fat, meat and animal protein consumption are, of course, highly correlated with one another (Table IV). Figure 2 shows that the association between meat consumption and colon cancer is quite plausible.

Previous studies of colon cancer have emphasized the correlation with total fat consumption, although animal protein consumption has also

been mentioned (Gregor *et al.*, 1969; Drasar and Irving, 1973). As a result of these studies, the possible role of dietary fat in the production of potential faecal carcinogens has been extensively investigated (Drasar and Hill, 1972).

Until recently, case-control studies have not shown any association between meat or fat consumption and cancer of the colon and rectum (Higginson, 1966; Wynder and Shigematsu, 1967; Wynder *et al.*, 1969). Haenszel *et al.* (1973), however, have reported a positive association between meat consumption and large-bowel cancer in Hawaiian Japanese. A positive result may have been obtained in this study whilst the others were negative because of the considerable dietary heterogeneity in the Hawaiian Japanese population.

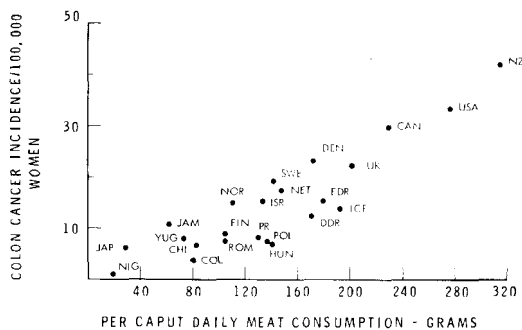


FIGURE 2

Correlation between incidence of colon cancer in women and *per caput* daily meat consumption in 23 countries.

One of the most publicized associations with colon cancer is the negative relationship with fibre consumption, cereal fibre generally being considered to be the most important (Burkitt, 1971). In our data, the negative correlation with cereal consumption is readily accounted for by the positive association with meat (r_1 for cereals, controlling for meat or animal protein varies from -0.10 to -0.20).

Cancers of the breast, corpus uteri and ovary

The correlation between breast cancer and total fat consumption is the best documented of any such association (Lea, 1966; Carroll, 1968; Drasar and Irving, 1973). This correlation is seen

here in the mortality data ($r_0 = 0.89$, Table VII) but not as strongly in the incidence data ($r_0 = 0.79$) in which GNP is more highly correlated and can explain the correlation with total fat consumption (r_1 for total fat controlling for GNP is 0.35). In this situation, GNP may reflect some other variable correlated with economic development (such as animal protein or total fat consumption with which it is highly correlated, $r_0 = 0.85$ and 0.82). Alternatively, it may suggest that the quality of the cancer incidence data is significantly affected by economic factors, particularly as controlling for any of the food consumption variables can reduce the correlation with GNP only to 0.52 (controlling for animal protein).

Total fat consumption is also the variable most highly correlated with cancers of the corpus uteri and ovary (Table VII). The association between total fat consumption and cancer of the corpus uteri is shown in Figure 3.

There is evidence from case-control and prospective studies that both cancer of the breast and cancer of the corpus uteri are associated with obesity (Marks, 1960; Mackay and Khoo, 1969;

Lin *et al.*, 1971; de Waard and Baanders van Halewijn, 1974). By implication, therefore, both may be associated with overnutrition. Recent experimental data have demonstrated an enhancing effect of a high-fat diet on 7,12 dimethylbenzanthracene induction of mammary cancer in rats (Chan and Cohen, 1974). This effect appeared to be mediated through alterations in circulating levels of prolactin.

Cancers of the prostate and testis

Mortality from cancer of the prostate is highly correlated with total fat consumption, whereas the incidence is not (Table VIII). In this case, the mortality rates are probably more reliable as the correlation between incidence and mortality rates is fairly low (0.57, Table III) and ascertainment of the true incidence of prostatic cancer is likely to be deficient, varying from country to country according to diagnostic practices. In this respect, it may be relevant that the incidence of latent cancer of the prostate in Japan and in Japanese in Hawaii may be quite similar whereas the mortality is very much lower in Japan (Akazaki and Stemmerman, 1973). Environ-

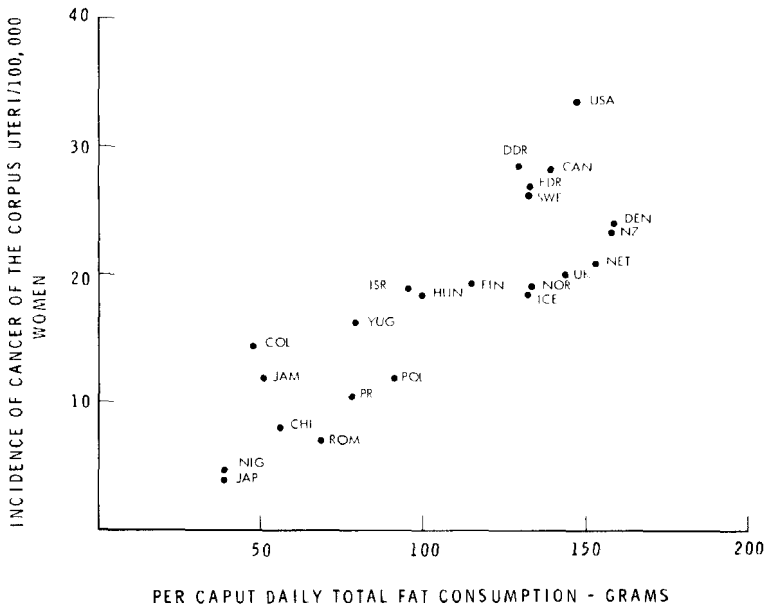


FIGURE 3

Correlation between incidence of cancer of the corpus uteri and *per caput* daily total fat consumption in 23 countries.

mental factors may therefore affect the rate of progression of the latent cancer.

A previous report has been made of the correlation between mortality from prostatic cancer and coffee consumption (Takahashi, 1964; see also Table VIII). This association may, however, be accounted for by the positive correlation with total fat consumption (r_1 coffee, total fat controlled, 0.32 and 0.31).

Cancer of the testis is also positively correlated with total fat consumption (Table VIII). It may be that cancers of the testis and prostate are influenced by hormonal factors which, as with breast cancer, may be affected by the level of dietary fat.

Cancer of the kidney

The positive correlation between renal cancer mortality and coffee consumption (Table IX) has been reported previously (Shennan, 1973). A similar correlation is seen with the incidence rates (r_0 0.40 and 0.62) but the variable correlated most highly with these rates is animal protein consumption (r_0 0.81 and 0.83). The correlation with animal protein consumption can explain the correlations with coffee consumption and with total fat consumption, which has the second highest correlations with the incidence rates (r_1 coffee 0.31 and -0.18 , r_1 total fat 0.00 and 0.18) and can itself be partly explained by the correlation with total fat consumption (r_1 0.42 and 0.55).

Apart from a weak association with cigarette smoking (Bennington and Laubscher, 1968), little is known of the aetiology of renal adenocarcinoma (the major component of renal cancer rates). From Figure 4, it appears that the association with animal protein consumption is plausible and warrants investigation by other methods.

Cancer of the liver

The common view that primary hepatoma is associated with nutritional deficiency (Wynder and Mabuchi, 1972) is supported by the significant negative correlation with consumption of calories, animal protein, total protein and total fat (Table X). The most strongly positive association is with potatoes, starchy and other staple foods (r_0 0.69 and 0.71). These and the other correlations must be interpreted with great care, however, as they are largely (and in the case of potatoes etc., entirely) dependent upon the extreme values for Nigeria, where the incidence of liver cancer in men is three times greater than the next highest rate (Figure 5).

Cancers of the nervous system

Cancers of the nervous system are a heterogeneous group which has seldom been studied epidemiologically. The highest correlations in this study (Table X) are with the major dietary variables (*e.g.* r_0 0.71 and 0.58 for total fat consumption). An interesting point is raised by

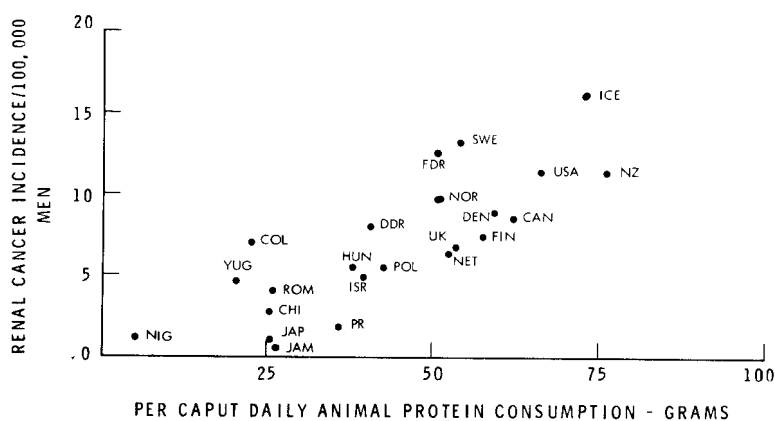


FIGURE 4

Correlation between incidence of renal cancer and *per capita* daily animal protein consumption in 23 countries.

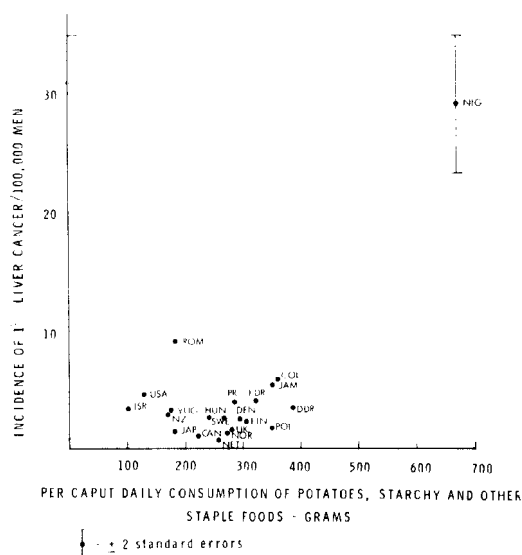


FIGURE 5

Correlation between incidence of primary liver cancer and *per caput* daily consumption of potatoes, starchy and other staple foods in 21 countries.

the positive correlation with the number of physicians per unit of population (r_0 0.65 and 0.62). This is in part due to the extreme position occupied by Israel on both axes (physician density, 24.5/10,000; incidence of cancers of the nervous system in men aged 35-64 years, 18.3/100,000), but it may be also that the positive correlation reflects the importance of adequate medical services in detecting these diseases.

Other cancers

Cigarette consumption is not, as might have been expected, the variable most highly correlated with male lung-cancer incidence rates (Table XI) and the coefficient is higher with the 1963-65 consumption figures ($r_0 = 0.44$) than with the 1953-55 figures ($r_0 = 0.38$). The correlation is substantially higher ($r_0 = 0.71$), however, when the incidence rates are correlated with cigarette consumption in 1925-29 in the 11 countries for which these data were available. This suggests that the rapid changes in cigarette consumption which occurred between 1925 and 1955 could have substantially altered the relative positions of the countries in relation to *per caput* cigarette consumption so as to obscure an

association with lung-cancer rates. Prolonged smoking is needed to produce a high incidence (Doll, 1971) and in these circumstances it may be that a closer association would be found with consumption figures for the more distant past than for the more recent. Other reasons for the low correlation of lung cancer rates with the recent cigarette consumption figures may be the inadequacy of total *per caput* cigarette consumption as a measure of separate male or female smoking habits, or the presence of substantial differences between countries in the methods of smoking (Doll, 1968). The failure of this study to show a strong correlation between cigarette smoking and lung cancer emphasizes the point that a weak or absent correlation between two variables in populations does not necessarily mean that they are not associated in individuals.

Stocks (1970) has previously reported the correlation between solid energy consumption (Table XI) and lung cancer mortality and has suggested that the association is through air pollution from burning solid fuels. He has also produced evidence of a direct association between air pollution and mortality from lung cancer (Stocks, 1960).

It is generally thought, however, that the contribution of air pollution to lung cancer is quite small (Waller, 1972).

Bladder-cancer rates are not highly correlated with either of the variables in our study which have been associated with bladder cancer by Cole and others (Cole, 1971; Cole *et al.*, 1971) in case-control studies (cigarette consumption, r_0 from -0.08 to 0.44; coffee consumption, r_0 from 0.17 to 0.39). The highest correlation in our data is between bladder-cancer mortality rates and consumption of fats and oils (Table XI). This is not seen with the incidence rates (r_0 , 0.25 and -0.12) and in view of the low correlation between incidence and mortality rates (0.56), no meaning can be readily attached to it.

Some of the other cancers listed in Table XI also show quite strong associations with environmental variables (*e.g.* leukaemia mortality rates). In most cases, however, the lack of consistency in the associations shown by incidence and mortality rates and the low correlation between male and female rates for these cancers makes them difficult to interpret in the absence of more specific hypotheses.

CONCLUSIONS

There are clearly ways in which these analyses might be improved; for example, the inclusion of environmental data recorded at various intervals before the period to which the cancer rates refer. Most of these data, however, are not readily available; moreover, there are seldom objective criteria for deciding the length of latent period to allow. If such analyses were performed, they might reveal other strong correlations which would nonetheless require confirmation by other means, as is the case with our analyses.

It is doubtful whether additional statistical analysis would clarify the associations further than is done by calculating simple and first-order partial correlation coefficients. We have calculated several higher orders of partial correlation coefficients and performed multiple regression analyses, but are not convinced of their value. In any case, with the limited number of observations available, it is possible that calculation of even one order of partial correlation coefficients is not statistically valid, much less the calculation of higher orders or the performance of multivariate regression (Finney, 1974).

The strongest points to emerge from these analyses are the suggestions of associations between cancers of the colon, rectum and breast and dietary variables—particularly meat (or animal protein) and total fat consumption. Examination of a large number of environmental variables and the calculation of partial coefficients increases the probability that these associations are not just secondary to an association with some other variable. In the case of colon cancer, this suggests that meat consumption may be more strongly associated than total fat consumption, which has received the greatest attention so far.

Given the many weaknesses of this method in terms of the quality of the data, allowances for latent periods and the uncertainty as to whether the most relevant environmental variables have even been included in the correlation matrices, it is clear that these and other correlations should be taken only as suggestions for further research and not as evidence of causation or as bases for preventive action. Nonetheless, we are impressed by the large number of strongly positive and negative relationships between cancer rates and dietary variables. While it is possible that all these relationships might be explained by

secondary associations with other environmental agents or by economic effects on the quality of the data, this seems unlikely, particularly as the economic variables are rarely as highly correlated as the dietary ones. It is possible, therefore, that diet may have an effect upon many cancers, perhaps by affecting the metabolism of various carcinogens, as has been suggested by McLean (1973), or by altering the body's capacity to deal with malignant cells. Animal data have been available for many years which demonstrate a general effect of diet upon tumour production (Tannenbaum and Silverstone, 1957). The subject warrants more attention in humans.

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APPENDIX

Overall test of association (by Richard Peto)

Suppose we have a given $n \times m$ matrix z_{ij} (dietary data) and a random $m \times 1$ vector y_j (cancer rates) where the elements of y are mutually independent with variance v and fourth central moment $v^2(3+k)$. Define $\bar{z}_i = \sum_{j=1}^m z_{ij}/m$, $ss_i = \sum_{j=1}^m (z_{ij} - \bar{z}_i)^2$ and p_{ck} ($c, k = 1, \dots, m$) as $\sum_{i=1}^n (z_{ic} - \bar{z}_i)(z_{ik} - \bar{z}_i)/n \cdot ss_i$. The regression coefficient b_i of y_j on z_{ij} is $\sum_{j=1}^m y_j(z_{ij} - \bar{z}_i)/ss_i$ and the variance, v_i , of b_i equals v/ss_i . The b_i will not in general be statistically independent of each other, and as a test of whether the set of b_i s differ significantly from zero, the statistic $B^2 = \frac{1}{n} \sum_{i=1}^n b_i^2/v_i$ may be examined. It has exactly unit expectation, and its distribution may reasonably be approximated by the F -distribution with the same mean and variance. This is the F -test with $\nu_2 = \infty$, $\nu_1 = 2/\text{var}(B^2)$. $\text{var}(B^2)$ can be shown to equal $2 \sum \sum p_{ck}^2 + k \sum p_{cc}^2$, which for our data is approximately $0.5 + 0.05k$, both for "all countries" and for the subset of countries with incidence data. We have therefore approximated the distribution of B^2 in our data by the distribution of $F_{4, \infty}$, and tests of significance based on this approximation are cited in Tables V-XI.

FACTEURS ÉCOLOGIQUES ET TAUX D'INCIDENCE
ET DE MORTALITÉ DE CERTAINS CANCERS
DANS DIVERS PAYS, PARTICULIÈREMENT
DU POINT DE VUE DES HABITUDES ALIMENTAIRES

Les taux d'incidence de 27 types de cancer dans 23 pays et les taux de mortalité concernant 14 types de cancer dans 32 pays ont été mis en corrélation avec une large gamme de variables alimentaires et autres. On a constaté une corrélation très nette entre les variables alimentaires et plusieurs types de cancer, notamment entre la consommation de viande et le cancer du côlon et entre la consommation de graisses et les cancers du sein et du corps utérin. Les statistiques conduisent à penser que les facteurs alimentaires jouent peut-être un rôle dans le développement d'un certain nombre d'autres types de cancers. Les auteurs analysent l'utilité et les limites de la méthode.

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