The Geographical Distribution of Cancer

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This article indicates the aims, methods and some results of geographical studies of the distribution of cancer. It must be remembered that such work relies on routine data, the quality of which needs to be carefully considered before it is used or interpreted[1].

Aims

There are four rather different aims:

1. Descriptive: where is there variation in the incidence, prevalence, survival, or mortality from malignant disease?
2. Hypothesis generation: what might be the factors related to the observed distribution of cancer? (For example, why is lung cancer more common in urban rather than rural locations?)
3. Hypothesis testing: do specific aetiological factors influence the risk of a particular cancer? (For example, does alcohol intake influence the risk of oesophageal cancer?)
4. The evaluation of medical care: is a particular campaign controlling the disease? (Is variation in uptake of cervical cytology in different locations influencing the incidence of mortality from the disease?)

Historical Review

In 1864 the first Decennial Supplement on Area Mortality was published by the General Register Office for England and Wales. In this, Farr[2] pointed out that it had 'been compiled to show in detail from the consecutive records of ten years the causes of deaths and the comparative salubrity of every part of the country'. At that time malignant disease was presented as a single condition; further analyses were presented at ten-yearly intervals; more limited material was presented annually. An enquiry, fostered by the Medical Congress in 1884 and supported by the British Medical Association, was published by Owen in 1889[3]. A questionnaire had been sent to every medical practitioner in the UK asking: 'Are the following diseases common in your district?' The diseases included cancer. More than 3,000 completed returns were analysed (the report gives no details of the sample size or exact response); they were sorted into localities and transferred on to maps which showed towns and villages with positive, doubtful and negative responses to the questions (where there was a disagreement in the responses of individual practitioners the result was coded according to the two-thirds majority). It was suggested that cancer was in general spread from end to end of the island, with a tolerably uniform distribution, apart from some suggestion of more negative responses in the south of Scotland than in the north. There was no evidence of the cancer following the sea coast, mountains, rivers, plains or other geographical features of the country. Owen concluded: 'on the whole one cannot claim to have made much out of the distribution of cancer'.

Hoffman[4], in a major statistical study of cancer throughout the world, devoted a chapter to its geographical incidence. He indicated the evidence suggesting there was geographical variation in incidence, and suggested that the conditions or methods of living which typify modern civilisation might be responsible for higher levels of cancer. He discussed various specific aetiological factors that might be influential, including genes, diet and occupation.

Veitch Clark[5] provided a general survey of the incidence of cancer and drew attention to an appreciable variation in mortality for specific sites of cancer in different countries. In 1923 the health committee of the League of Nations began to review the available mortality statistics for certain sites in different countries, using data from long-established vital statistics systems. Examining data for breast and cervical cancer, they found that sources of error existed which seriously affected the proper comparison between countries. They also concluded that it was impossible to assess the influence of race on mortality from cancer[6].

At this time the Registrar General's Annual Report only had limited data by area; deaths from all cancers together were presented by age and sex down to the level of county boroughs[7]. The Decennial Supplement of 1931 did not appear until 1952, but this gave data for 27 sites of cancer by age and sex for 12 subdivisions of the country, and also data for 'all cancers' for individual local authority districts[8]. However, an extended analysis was provided by Stocks[9-11], who utilised deaths from malignant disease in England and Wales for 1921-30 and population estimates from the censuses of 1921 and 1931. There were over half a million deaths from malignant disease in this period and the data were examined for a range of sites for both sexes with age and locality standardised rates. The data were presented for the counties of the country, with a commentary on each of the sites studied. For stomach cancer Stocks drew attention to the significant excess in Wales and the adjacent English counties; the diagnostic and certification practices were discussed, but it was suggested that these could not

explain the social class variation found with stomach cancer; the influence of dietary habits was discussed, in particular the ingestion of irritant foods or preventive foods such as fresh milk and vegetables.

Methods

Mapping

Once the geographical distribution of the cancer has been identified, the material may be presented in a variety of ways. One facet to consider is the geographical level at which the comparisons are made—between one country and another or, within a country, between one region and another, or within regions between particular localities. There are various problems in using international comparisons such as whether the validity of mortality statistics differs in the different countries, which can influence the statistics used; regions within a country may have statistics based on large numbers, but the use of data at this level may obscure contrasting mortality in small areas. In some studies the distribution of cancer may even be plotted at ward or another local level. Another aspect to be considered is whether conventional maps are used, with boundaries and shapes that the reader is used to, which have the disadvantage that sparsely populated areas may create a major visual impact due to their relative size on the map. An alternative is a 'demographic based map', on which the area plotted for each locality is proportional to the resident population. This distorts the boundaries and may confuse the reader, limiting his immediate reaction to the environmental differences that may be associated with spatial distribution of the disease.

An alternative to actually plotting the data on maps is to provide lists of localities with high and low incidence or mortality. These may be easier to produce, but have the major disadvantage of providing less stimulus to thought than a map.

Collation of Data

Data can be collated either graphically or statistically to examine the interrelationship between various environmental factors and the distribution of cancer. Localities (regions or counties) can be plotted by their incidence of, or mortality from, a particular cancer and the associated per capita intake of particular dietary nutrients. For example, various aspects of diet and breast cancer have been examined; the linear relationship, with an increase in mortality for higher levels of fat intake, has been one of the pointers to the aetiology of this disease. Instead of examining the data graphically, it is possible to calculate the statistical association between a wide range of variates and the frequency of disease; the geographical level selected will depend on the availability of the environmental material: many studies have been carried out on a national level. These may explore a wide range of dietary and comparable information in relation to the distribution of different sites of malignancy in both males and females. An alternative to this general exploratory study is the more specific probing of a particular hypothesis, such as the examination of the relationship between varying measures of alcohol intake and the risk of cancers such as those of the oesophagus, liver, pancreas, or large bowel. There are obvious major pitfalls in such studies; the quality of both the mortality and the environmental data have to be carefully considered. Again, when using data from many different countries, the differences may reflect the quality of the data rather than the direct relationship between a particular variate and the disease. In such studies the number of comparisons made can be very large (in one study on diet and cancer over 4,000 correlation coefficients were calculated[12]); there is then the problem of distinguishing the genuine positive from the positives that result purely from the large number of comparisons made.

A more powerful probe is examination of the trends of the disease in relation to trends of the environmental factor in several countries over as long a period as the data allow. McMichael used this technique in studying alcohol intake and various sites of malignancy[13,14].

Migrant Studies

If routine statistics provide counts of the population by place of birth and counts of deaths by cause and place of birth, it is feasible to generate analyses of migrant mortality for particular sites of malignancy. Such studies have been carried out for groups of migrants into America during the past 30 years, looking in particular at cancer mortality in the Japanese and Chinese, but also in migrants from European and other countries. Other studies have been done on migrants into Israel, Australia, England and Wales. If there is a long history of migration and appropriate population statistics exist, it may be possible to look not only at the mortality of those born abroad who migrate and then die in another country, but also at the mortality of the second generation (i.e., those born to parents who had migrated from other countries). Comparison of the age-adjusted mortality of males and females for particular cancers can then be made, comparing US whites with first and second generation migrants and also with the mortality in the countries from which the migrants came. Some interesting studies of this nature have looked at mortality from cancer of the stomach, colon and breast in the Japanese.

Clustering Studies

At the beginning of the century a limited amount of work was done on the distribution of cancer between different houses in a given locality; Pearson[15], using appropriate statistical techniques, sought to discover whether there were cancer houses in which a higher than expected proportion of residents died from malignant disease. A major extension of such work occurred in the 1960s when improved statistical techniques facilitated examination of the distribution of cancers by locality and also by time[16,17]. An early application looked at clustering in leukaemia and found some positive evidence of this. Subsequent studies did not confirm these findings. Similarly, for Hodgkin's disease, a degree of clustering has

been reported but not substantiated by repeat studies in other localities or of larger numbers of events.

The statistical technique for clustering may be an inefficient examination of the topic, if the contact between one case and another did not occur in the place of residence. The approach was refined by looking not only at the residence of children with leukaemia, but at the place and date of birth of the children[18], but even with this refinement there was no evidence of clustering[19]. The contact between one case and another need not necessarily relate to the place of residence of the mother during her pregnancy, or the child during its early life. A further development of this technique was to examine the network of contacts between cases; this was studied in Oxford for subjects with Hodgkin's disease[20].

Specific Sites of Malignancy

Some of the key findings for sites of malignancy on which various aspects of geographical pathology have had a considerable impact are given below. The material is arranged in the order of the International Classification of Diseases, though not every site of malignancy is covered. Table 1 shows the variation in age-adjusted incidence in a selection of sites in 16 localities throughout the world[21].

Digestive Tract

Oesophagus. There is a huge variation (at least 200-fold) between the highest and lowest rates of incidence of oesophageal cancer in different countries. In addition, the incidence varies strikingly between localities separated by only a few hundred kilometres. There is a broad band of high incidence covering the eastern and southern regions of Africa south of the Sahara, Iran, Afghanistan, Soviet and Central Asia, Siberia, Mongolia and the north and west of China[22]. Results of the first three years of cancer registration for the Caspian littoral indicated no source of bias in the material, and the incidence showed a 30-fold variation for women across the region and at least a tenfold variation for men[23]. These findings stimulated a series of epidemiological studies which have clarified but not finally resolved the aetiological factors of this malignancy[24].

Stomach. This cancer also shows appreciable international variation; during the past 30 years there has been a decline in mortality in many countries from the previous high rates[25,26]. This is one of the sites in which studies of migrants have been of value; the mortality rates for England, Scotland, Ireland, Poland, Yugoslavia, Greece and Italy were compared with the rate for migrants from those countries to Australia[27]. All seven countries of origin had higher stomach cancer rates than Australia, and the migrants' rate decreased with increased duration of residence.

Colon. Examining colon cancer mortality for 37 and incidence for 27 countries, Doll observed that the range of variation (about tenfold) was less than for oesophageal or stomach cancer, and no very high rates were observed in any country[28]. This is one of the sites for which collation studies have been done, using mortality or incidence for different countries and indices of nutrient intake. Several studies have shown an association with fat intake[29-31], but the relative contributions of meat and fat, which are interrelated, have not been clearly shown. The regional pattern of cancer of the colon in Great Britain in 1969-73 showed a significant negative correlation with the pentose fraction of dietary fibre[32].

Liver. There are clusters of high risk of liver cancer in eastern South Asia, areas south of the Sahara Desert, and southern and eastern Europe[33]. There is great difficulty in examining this topic because the localities thought to have a high incidence or mortality are those major tracts of the world in which statistics are limited. Examination of the distribution of liver cancer in China suggested that

Table 1. Malignant disease of various sites: age-adjusted incidence rates for 16 localities throughout the world by sex, 1969–73.

Area/Population	Oesophagus		Large intestine	Lung	Breast	Ovary	Prostate	Kidney	All sites (except skin)	
	Male	Female	Male	Male	Female	Female	Male	Male	Male	Female
Bulawayo (Black)	63.8	2.2	7.0	70.7	13.8	8.1	32.3	1.2	345.9	147.4
Hawaii (Hawaiian)	8.0	1.6	14.1	71.3	66.2	11.6	19.8	6.8	288.2	272.1
Alameda (White)	3.6	1.5	25.3	55.5	76.1	13.5	40.4	7.1	277.7	267.8
Saarland	4.9	1.0	15.5	67.7	50.6	9.3	21.1	6.0	257.6	234.5
Ayrshire	5.9	1.9	16.6	68.8	50.1	9.9	19.2	6.1	242.3	172.2
Saskatchewan	2.5	0.7	17.8	35.6	62.8	11.0	39.0	8.5	237.0	204.8
Norway (Urban)	4.0	0.8	15.0	33.0	49.6	15.0	36.3	8.6	228.0	199.9
Denmark	3.1	1.4	16.2	40.2	49.1	15.1	21.8	7.2	216.3	219.1
Israel (Europe/US born)	2.6	2.0	12.9	30.3	60.8	14.7	12.6	7.2	209.9	236.8
Osaka	9.7	2.9	6.3	23.5	12.1	2.8	2.7	2.0	207.1	142.6
Cracow	3.0	0.7	6.0	45.7	19.6	9.1	8.0	3.6	196.8	143.1
Zaragoza	4.0	0.8	6.5	23.5	30.6	3.6	17.7	3.6	186.0	133.2
Puerto Rico	14.8	5.4	6.0	15.4	25.4	5.3	21.4	2.2	174.0	146.7
Cuba	5.7	2.4	6.9	44.7	28.0	4.6	18.0	1.6	169.9	147.0
New Mexico (Spanish)	2.2	1.1	8.7	16.7	32.4	10.4	34.3	5.0	157.9	177.1
Bombay	15.2	10.8	4.6	13.5	20.1	4.8	8.0	1.2	141.0	120.5

the new lands on the shores of the Yellow Sea had a high incidence compared with neighbouring zones; geographical examination suggested that a major difference was the source of water supply, the high zone having limited fresh water and relying on water from ditches, stagnant streams and ponds.

Pancreas. There appears to be a steady increase in pancreatic cancer in many of the developing countries[34]. In the USA there was a much higher mortality among non-white males in the north-west, which might be due to the particular environment in which the individuals lived. Japanese residents dying in California in 1949-62 had a considerably lower mortality than the US whites, but the rates were above those found in Japan[35].

Respiratory Tract

Nose. The geographical variation in cause-specific mortality was examined for 1,366 local authority areas of England and Wales for the period 1968-78[36]. Using these very local levels, where the number of deaths for any given cause is obviously relatively small, it was possible to identify a number of excesses that aligned with earlier knowledge. For example, there was an excess of nasal cancer in some of the localities in which there was evidence of occupational hazards, e.g. from furniture manufacture and the production of boots and shoes.

Larynx. McMichael drew attention to the recent rise in laryngeal cancer mortality in Britain and Australia which particularly affected younger people[13]. He examined the time trends of sex-specific mortality in relation to estimated per capita consumption of cigarettes and alcohol and concluded that there was a causal association with alcohol consumption.

Lung. Stocks presented a map of London which showed an appreciable difference in age-standardised lung cancer mortality in males from different metropolitan boroughs in 1946-49[37]. There was an excess in the East End of London; Stocks remarked that it could hardly be supposed that the people in North-East London smoked 50 per cent more tobacco than those in South-West London, though they might tend to smoke different brands. The patterns of mortality in the 61 largest boroughs of England and Wales in 1948-54 and 1958-64 were related to 80 socio-economic variables. Lung cancer in both sexes was highly correlated with domestic air pollution[38].

Bone and Connective Tissue

Bone. The validity of mortality statistics for deaths from bone tumours registered in England and Wales in 1951-53 was checked. The data on the geographical distribution of these tumours throughout the country showed variation from county to county in the age-adjusted figures, but there was no indication that this variation was related to the levels of background radiation in the country[39].

Melanoma. Lancaster collated melanoma mortality data from different countries and populations within countries against latitude[40]. In Australia, New Zealand, South Africa and the USA, whites had the highest mortality in those parts of the countries with the lowest latitude. This showed also in comparisons between different countries, though Norway and Sweden seemed to have somewhat higher rates than neighbouring countries to the south. Examination of mortality in migrants to Australia showed that native-born Australians have the highest incidence, while British migrants have higher rates than those from other countries[41].

Skin. In general, skin cancer (other than melanoma) has a higher incidence in rural areas and in countries or regions of low latitude. However, this relationship is not straightforward; the incidence of lip cancer was higher in Finland than in the other Nordic countries and highest in the north of the country. It was suggested that this inverse relationship with measured solar radiation was due to a relationship between smoking, the standard of living, and working out of doors[42].

Female Reproductive Organs

Breast. It has long been recognised that there is an appreciable variation in breast cancer mortality throughout the world[4]. A number of studies have related differences in mortality to dietary and other environmental factors[12,31]. In addition, the relationship with reproduction has been examined; a significant negative correlation was shown between the proportion of women first married at 15-19 and the incidence of breast cancer in different provinces in Canada[43].

Cervix. Examination of the change in mortality from cervical cancer in various provinces in Canada, in relation to the proportion of the female population thought to have had cervical smears showed a negative correlation between these two indices (the greater the proportion of women who had smears examined, the lower the mortality). On the basis of this and other evidence, an official Canadian committee concluded that the Canadian Cytology Screening Programme was reducing mortality from cancer of the cervix[44].

Body of Uterus. A decline in the mortality from uterine cancer in successive generations in 20 countries has occurred, with a limited pause in the declining mortality in most countries shortly after the Second World War[45]. Migrant studies have further contributed to this topic; for example, Jews migrating to Israel from Europe and Egypt had a higher rate of endometrial cancer than the indigenous Israeli population[46].

Ovary. Mortality from ovarian cancer does not vary greatly from one country to another, though developed countries tend to have higher rates than developing countries. The main anomaly is Japan, which has relatively low rates compared with Europe and America. Ovarian cancer increased in first and second generation Chinese migrants to the USA[47].

Male Reproductive Organs

Prostate. Identification of patients with cancer of the prostate may vary widely, particularly when one considers *in situ,* or microinvasive cancer. Data on patients in the USA and Nigeria indicate that cancer is common in both US and Nigerian blacks, and that the Nigerian patients have less well differentiated tumours with more numerous foci of cancer and lesions that are at a later stage of presentation[48]. The mortality of prostatic cancer in Japanese residents in the USA was intermediate between the higher rates in US whites and the lower rates in Japan itself [35].

Testis. A number of authors have pointed to a recent increase in mortality from testicular cancer in young adults and a decrease in the elderly. This has been shown for Denmark[49], England and Wales[50], Japan[51], and the USA[52].

Penis. Data from pathology laboratories serving the populations of Uganda and Kenya showed that penile cancer was the commonest cancer in males in Uganda, although relatively rare in Kenya. It was thought that this might be due to major differences in the prevalence of circumcision in these two countries, a view supported by differences in the proportion of patients from tribes in Kenya who did and did not practise circumcision[53].

Urinary Organs

Bladder. For a long while it has been known that bladder cancer is relatively common in Egypt. This identification of variation in the Middle East led to further studies which suggested that bladder cancer is common in communities affected by schistosomiasis[54].

Kidney. Some studies of renal cancer in migrants have shown that individuals coming from Europe to Israel had raised rates for this malignancy, whereas those from Africa and Asia had lower rates. There was a tendency for the difference in these subgroups to diminish in the overall period of residence in Israel[55].

Central Nervous System

Little attention has been paid to international variation in the incidence or mortality of central nervous system tumours. Migrant studies show some evidence of an environmental factor; the mortality of those coming from Europe and America to Israel was higher than for those coming from Africa and Asia[46,55].

Thyroid Cancer

Several authors have drawn attention to the relatively limited international variation in incidence or mortality of thyroid cancer[56,57]. It was concluded that the international differences could be due to random variation coupled with some systematic effects hidden within the data[58].

Lymphatic and Haematopoietic Malignancies

Hodgkin's Disease. The incidence of Hodgkin's disease in 32 locations throughout the world showed an inverse association between the rates in childhood and in those aged 15-39 or over 40[59]. The authors suggested that this was compatible with an infection occurring in childhood. This is a malignancy in which clustering has been examined; using a mapping technique, it was suggested that micro-clusters occurred in Denmark[60]. Work in the USA and England showed no clear evidence of clustering in this condition[61,62]. Subsequent work on this topic has used rather different techniques, from examining the geographical or mathematical distribution of disease, e.g. a case-control technique, to examining contacts between young patients[20].

Leukaemia. Doll drew attention to the extraordinary constancy of international figures for deaths of persons aged 15-39 from leukaemia, and the wider variation in deaths in the older age ranges[63]. He concluded that the great variation could not be accounted for merely by differences in health care systems and certification. Using a technique for detecting space-time clustering of disease, there was evidence of a low grade epidemicity of leukaemia in North-East England[16,17], but further studies have not shown any clear evidence of consistent positive findings[64].

Children's Tumours

In a review of the epidemiology of children's tumours, the incidence of 10 types of tumour was compared for 9 countries[65]. The rates were roughly similar, and did not show the geographical variations that exist for many malignancies in adults.

Distribution of Carcinogens

A rather different approach has been to look at the distribution of carcinogens, and test whether the incidence and mortality from malignancy in general or for specific sites of malignancy varies in relation to the environment. As with other work, this may be exploratory or to test a specific hypothesis. The following comments amplify those made when discussing the various sites of malignancy.

Diet

Limited results have been presented for collation studies of dietary items against stomach cancer; these suggest a negative association with fat, sugar and animal protein—findings that have not been substantiated in more specific studies[12,31,66,67].

A number of studies on breast cancer have shown a positive association with the intake of fat, sugar, and animal protein[12,31,66-68]. The studies on the body of the uterus have produced conflicting findings, with one study of mortality and incidence showing a positive association with fat, sugar, animal protein and calorie intake[31] which was not found in two other

studies[66,68]. More consistent findings occur for ovarian cancer, four studies showing significant positive associations with fat intake[31,66-68].

There is a close relationship between time trends in alcohol consumption in Australia and the UK and mortality from oesophageal cancer[14,69]. A strong correlation between beer intake and rectal cancer was found for US states; examination of international data showed the same relationship[70]. The time trends for male rectal cancer in Australia, England and Wales, New Zealand and the USA followed very closely the preceding changes in beer consumption[14]. Rather surprising have been the high correlations between breast cancer and beer intake[12,70].

Environment

Reference has already been made to the relationship between atmospheric pollution and lung cancer. A number of other studies have shown that stomach cancer is related to atmospheric pollution in the UK[38,71] and the USA[72]. Other studies have related temperature indices to variation in mortality, though this may be a reflection of confounding with other factors[73].

Background Irradiation

The geographical variation of leukaemia mortality in Scotland was examined in relation to background irradiation in 1939-56[74]. Though the variation was not random, background radiation was unlikely to account for more than about 1 per cent of the observed differences. Examination of data in northern France also showed no clear relationship to risk of malignancy[75].

Occupation

Following the production of county mortality rates from various cancers in the USA for 1950-69, it was simple to relate these data to demographic, socio-economic and occupational indices. Excess rates of lung cancer were found in counties in which paper, chemical, petroleum, and transportation industries were located; there were no other obvious confounding factors associated with these relationships[76]. Male residents of counties where the petroleum industry is most highly concentrated were found to have higher rates for lung, nasal cavity and skin cancer[77].

A rise in lung cancer was observed in a Scottish town; mapping of the patients identified clustering downwind from an iron foundry. No other reason for the clustering could be found and it was concluded that it was due to environmental contaminants from the foundry[78].

Water Constituents

Asbestos. One of the variable constituents of public water supplies is asbestos fibres. There was no relation between levels of fibres and cancer mortality in two studies in the USA[79,80]. A highly significant association of chrysotile levels with cancer of the gall-bladder, pancreas, peritoneum and lung in both sexes showed in the San Francisco Bay area from 1969-71[81].

Chlorine. A number of studies in America have related the water levels of chloroform and other trihalomethanes to the cancer mortality of the population drinking such waters; there were positive correlations with bladder and brain cancer in both sexes and with renal cancer and lymphoma in males[82]. A recent review of these studies suggested that there might be slightly increased risks of colonic, rectal and bladder cancer, but that these seemed negligible compared with the problems of abandoning chlorination[83].

Fluoride. A number of authors have claimed that fluoridation of public water supplies increases the risk of cancer. Cook-Mozaffari and her colleagues examined data for the UK in some detail and reviewed other material[84,85]. They concluded that there is no evidence from England and Wales or elsewhere in the world of the addition of fluoride to water supplies increasing the risk of dying from cancer.

Conclusions

The study of the geographical variation in disease can lead to speculation about aetiology, but it is unlikely to reveal the cause of a particular disease[86]. The way ahead may be by focussing on a finer degree of variation—such as mapping at local authority level (recently begun for the 1,366 localities in England and Wales[36]) or by use of postcode or grid reference to study distribution of individuals with malignant disease[87].

Recently, the role of the geographer in helping to study the association of human biology, environment, life-style, and health care has been advocated[88]. A variety of disciplines are required for the careful analysis of routine data in collation and migrant studies. The difficulty of interpretation of such material must be borne in mind[89]. Such studies may then continue to provide leads for further exploration using other epidemiological and/or laboratory methods.

Acknowledgements

The major source of data for the study of geographical pathology is routine cancer incidence and mortality statistics; both these rely upon the activity of clinicians, who are the originators of the primary diagnostic material. Continued interest in improving the quality of the basic information (e.g. through the Report on Death Certification[90] and the implementation of its recommendations) should improve the quality of the statistics. Epidemiologists and other users of these statistics depend on this vital input from the clinician.

I am most grateful to Mrs J. Folwell for help in the preparation of this article.

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