Value of a Multinational Approach in Determining the Causation of Cancer

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MacMahon and Pugh define epidemiology as the use of knowledge on the frequency and distribution of disease to search for determinants [1]. This paper demonstrates that a multinational approach in cancer epidemiology can be of great value in at least four circumstances: namely, the compilation and standardization of data, the assessment of risk, the pooling of study populations to obtain interpretable results, and the provision of resources for specific epidemiologic investigations. One or two examples are given for each category—the determination of international cancer incidence patterns, the evaluation of the risk posed by chemicals to man, assessment of the effects of low doses of ionizing radiation, determination of the long-term effects of exposure to asbestos substitutes, and studies on the influence of diet on esophageal cancer.

MEASURING CANCER

Epidemiology, like any other science, is based on measurement: it is the differences in frequency, whether incidence, mortality, or proportion, that give rise to hypotheses [1]. (The reader may care to reflect on the problems of studying cancer etiology in a world where the risk was uniform.) While intranational differences in cancer incidence [2] and mortality occur, they are not usually as large as those observed between countries. International data on cancer incidence are thus of great value for hypothesis building and verification.

Following the publication of international cancer mortality figures in 1960 by Segi [3], the UICC assembled similar data for incidence, publishing a monograph in 1966 entitled Cancer Incidence in Five Continents, containing data from 35 registries [4]: Volumes III [5] and IV [6] of the series were published jointly by the International Agency for Research on Cancer and the International Association of Cancer Registries. Volume V, to appear in 1986, will contain material for 1978–1982 for 140 populations collected by 110 registries throughout the world. This resource, widely quoted in the literature, is the fruit of international collaboration.

The spectrum of risk is very large, ranging from five- to 100-fold for many cancers. It could be argued that such differences reflect purely genetic influences. The change of risk observed for many populations on migration to a new environment suggests otherwise, however; a migrant does not change his genes in his lifetime. Kennaway [7] was the first to realize the significance of migrant studies, writing, “the very high incidence of primary cancer of the liver found among negroes in Africa does not appear in negroes in the United States, and is therefore not of a purely racial character. Hence, the prevalence of this form of cancer in Africa may be due to some extrinsic factors which could be identified.” The existence of populations at contrasting risk not only serves as a source of hypotheses but also as a means of verification. If the observed...
distribution is not consistent with the hypothesis, the latter is either incomplete or wrong [8].

As data accumulate, time trends become available for examination [9]. These, like urban/rural differences in incidence, acquire a new dimension when examined internationally (Table 1). The absence of an urban/rural differential in lung cancer in Japan, when one exists in most other countries, and the existence of such differentials for breast cancer in Zaragoza, Spain, and for prostate cancer in the northwest region of England [10] larger than those reported elsewhere must give rise to etiological speculation.

**MONOGRAPHS ON CHEMICAL RISK**

Although there are about 4 million known chemical compounds and perhaps 60,000 new substances being synthesized each year, relatively few are manufactured in quantities greater than 500 kg each year. As several are very widely used in industry as food additives and as therapeutic agents, it becomes imperative to have an assessment of their carcinogenicity. National assessments, however, are frequently made in the context of political pressures, thus compromising the objectivity of these scientific analyses.

The need for an impartial weighing of evidence is thus evident. The International Agency for Research on Cancer therefore embarked on such a program nearly 20 years ago and has now examined over 700 chemical compounds, publishing the findings in a series of monographs entitled *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans* [11]. These monographs represent a truly international effort: experts are commissioned to write a draft on the basis of published work which is then subject to peer scrutiny at the Monograph meeting. A typical monograph gives the structure, physical properties, production, use, occurrence, and methods of chemical analysis of the substance under consideration. This information is followed by an evaluation of carcinogenicity studies in animals, mutagenicity and other short-term tests, and case reports and epidemiological studies of carcinogenicity in humans. A list of chemicals for which there is sufficient evidence of carcinogenicity is given in Table 2. Recently, the Monograph program has extended its sphere of activity to include habits such as smoking [12] and the use of so-called smokeless tobacco [13].

**TABLE 1**

Urban/Rural Differentials in Age-Adjusted Cancer Incidence for Lung, Prostate, and Breast Cancer Around 1975*

| Cancer Registry         | Lung Cancer        |             | Prostate (M)/Breast (F) |             |
|-------------------------|--------------------|-------------|-------------------------|-------------|
|                         | Urban              | Rural       | Urban                  | Rural       |
| Fukuoka, Japan          | 25.2               | 7.9         | 24.3                   | 6.0         |
| Finland                 | 80.9               | 7.1         | 68.7                   | 4.1         |
| Bas-Rhin, France        | 59.2               | 4.7         | 50.6                   | 4.1         |
| Norway                  | 34.3               | 6.9         | 18.6                   | 3.9         |
| Zaragoza, Spain         | 41.5               | 3.9         | 18.0                   | 3.0         |
| NW Region, England      | 91.2               | 17.2        | 38.4                   | 6.8         |
|                         |                    |             | 20.8                   | 54.2        |

*Data from [10]
### TABLE 2

Chemicals, Groups of Chemicals, Complex Mixtures, or Industrial Processes Associated with Cancer in Humans (Group 1) or Highly Probably Associated with Cancer in Humans (Group 2A)

| **Group 1** | **Associated Cancer Sites** | **Group 1** | **Associated Cancer Sites** |
|-------------|-----------------------------|-------------|-----------------------------|
| 4-Aminobiphenyl | Bladder                     | Combined chemotherapy for lymphomas (including MOPP, procarbazine, nitrogen mustard, Vincristine, prednisone) |
| Analgesic mixtures with phenacetin | Renal                       | Chlorambucil | Non-lymphocytic leukemia |
| Arsenic and arsenic compounds | Lung, skin, liver            | Chromium (hexavalent) | Lung, nasal cavities |
| Asbestos      | Lung, gastrointestinal tract | Coal tar     | Respiratory tract, scrotum  |
| Azathioprine  | Non-Hodgkin's lymphoma      | Coal tar pitch | Respiratory tract, scrotum  |
| Benzene       | Squamous skin, hepatobiliary | Conjugated estrogens | Corpus uterus (post-menopausal) |
| Benzidine     | Leukemia                    | Cyclophosphamide | Non-lymphocytic leukemia |
| Betel quid with tobacco    | Bladder                     | ortho-Toluidine | Bladder |
| N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine) | Pharynx, esophagus      |                         |                  |
| Bis (chloromethyl) ether, technical chloromethyl methyl ether | Bladder                     |                         |                  |
| 1,4-Butanediol dimethanesulphonate (Myleran) | Lung                       |                         |                  |

**Chemicals, Groups of Chemicals, and Complex Mixtures**

**Industrial Processes**

| **Group 1** | **Associated Cancer Sites** | **Group 1** | **Associated Cancer Sites** |
|-------------|-----------------------------|-------------|-----------------------------|
| Auramine manufacture | Bladder                     | Isopropyl alcohol manufacture (strong acid process) | Nasal cavity, larynx |
| Boot and shoe manufacture and repair | Nasal cavity, paranasal sinus | Nickel refining | Nasal cavity, paranasal sinus |
| Coal gasification (older processes) | Respiratory tract            | Rubber industry | Bladder |
| Coke production | Respiratory tract            | Underground hematite mining (with exposure to radon) | Lung |
| Furniture manufacture (wood dust) | Nasal cavity                 |                         |                  |

| **Group 2A** | **Associated Cancer Sites** | **Group 2A** | **Associated Cancer Sites** |
|--------------|-----------------------------|--------------|-----------------------------|
| Iron and steel founding | Lung                        | Mustard gas     | Lung, larynx                |
| Magenta manufacture | Bladder                     | 2-Naphthylamine | Bladder                     |
| Diethylstilbestrol | Vagina (in utero exposure)  | Shale oils     | Scrotum, squamous skin      |
| Melphalan     | Corpus uterus (post-menopausal) | Smokeless tobacco products | Pharynx                  |
| Methoxalen with ultraviolet A therapy (PUVA) | Non-lymphocytic leukemia | Soots          | Scrotum, squamous skin      |
| Mineral oils  | Squamous skin               | Tobacco smoke  | Lung, upper GI tract, bladder, pancreas, kidney |
|              | Respiratory tract, nasal cavity, scrotum, squamous skin | Treosulphan | Non-lymphocytic leukemia |
|              |                             | Vinyl chloride | Liver, lung, brain          |
These monographs evaluate the risk; they do not attempt to suggest limits or advise on regulatory action, as this is the prerogative of each country. They do, however, represent a balanced international opinion.

LOW DOSES OF RADIATION

There is widespread public concern about exposure to ionizing radiation, and debate on the effects of low doses continues. While proponents of hormesis [14] maintain that exposure to small quantities of harmful agents results in selective induction of appropriate defense mechanisms, this view is not universally held. Hence there is a continuing need to obtain data on the risk to humans after such exposures. It is arguable whether large-scale human studies of low-dose exposures will provide useful information; not only are these very expensive, but it is unlikely that other important risk factors, such as cigarette smoking, can be controlled for sufficiently. There are, moreover, statistical reasons why large studies of low statistical power may be misleading. It is thus important to evaluate special groups of individuals given high doses of ionizing radiation directed to an organ with malignant diseases in whom, by operation of the inverse-square law, other organs experience doses which can be classed as low to medium. The problem is to obtain large numbers of such persons; only international collaboration can do so.

Boice et al. [15] recently reported on the numbers of second cancers, notified to 15 cancer registries in eight countries, occurring among 182,000 women treated for cervical cancer, 83,000 of whom received radiation therapy. (At current rates, to accumulate this number in the entire continental U.S. would require 16 years: the SEER [Surveillance, Epidemiology and End Results] registries supported by the U.S. National Cancer Institute would need well over 100 years [16].) Compared to the numbers that would have been expected, had the same risk obtained in these 182,000 women as obtained in the general pooled populations, a small excess of second cancers was observed: 5,146 against 4,736 expected, arising one or more years after treatment. The large radiation doses experienced by nearly 83,000 women did not dramatically alter the risk of developing a second cancer: at most, about 162 of 3,324 second cancers occurring in these women could be attributed to radiation. The relative risk for developing cancer in organs close to the cervix, in particular bladder, rectum (Fig. 1), uterine corpus, ovary, small intestine, bone and connective tissue, and multiple myeloma increased with time since treatment. No similar increase was seen in these organs for the 99,424 women treated by means other than radiation.
Only a slight excess of acute and non-lymphocytic leukemia was found among irradiated women (Fig. 1), the relative risk being 1.3; many fewer cases were observed than expected on the basis of current radiation risk estimates published by the National Academy of Sciences [17]. This rather small excess risk of leukemia may be due to low doses of radiation delivered to bone marrow outside the pelvis; it may be assumed that the pelvic girdle marrow was destroyed or rendered inactive by the very large doses given.

Despite substantial doses, there was little evidence of a radiation effect for cancers of stomach, colon, liver, and gall bladder, for malignant melanoma and other skin cancers (Table 3). There was, however, an excess of thyroid cancer and a lower breast cancer risk (Fig. 1), with a relative risk of 0.7 (0.6 for those under 40 years of age and 0.8 for other women), probably the consequence of ovarian radiation damage. There was a large, highly significant excess of lung cancers (Fig. 1), relative risk 3.7, perhaps due to misclassification of metastases and, more likely, the confounding influence of cigarette smoking. A similar excess was observed in those not given radiation, relative risk 2.9.

While in no way changing the need to minimize exposure to radiation, these results, which could only have been obtained by international collaboration, help set the problem in perspective.

ARE ASBESTOS SUBSTITUTES SAFE?

Asbestos is one of the most useful minerals extant; however, it provokes mesothelioma and, in combination with cigarette smoking, relative risks for lung cancer on the order of 60 occur. Carcinogenicity is related to fiber profile. Glass fiber and rock wool...
have been and are extensively used as replacement materials, but they, too, have length/diameter ratios which make them a priori potentially carcinogenic.

As users of these insulating materials are also likely to have been exposed to asbestos, it was decided to examine the mortality, and when possible incidence, of those working in the production industry. As is usual in epidemiology, it was considered desirable to conduct studies in Europe in parallel with those under way in the United States to see whether the same result would be obtained.

Manufacture of these products is characterized by relatively small plants, the use of differing processes, and a high initial turnover of labor, considerations which in Europe demanded a multinational collaborative study to yield a sufficient number of exposed persons for follow-up. From an initial list of 72 plants, 13 in seven countries met the study criteria, namely, (a) in operation for 20 or more years, (b) ability to follow the workforce to incidence or death from cancer (and other diseases), (c) completeness of the cohort, (d) no significant exposure to asbestos, and (e) ability to count fibers at various points of the plants.

Follow-up of the pooled cohorts of 24,609 persons was excellent: 2.2 percent were lost to view and 3.0 percent were known to have emigrated but could not be further traced.

The results have public health significance: a twofold excess of lung cancers for the period thirty years or more since first employment [18,19]. Similar findings were obtained for the U.S. (20 cases for 17,000 production workers). In a further five-year follow-up, some 2,719 deaths occurred in the cohort compared to the 2,459 expected—a statistically significant difference with a standardized mortality ratio (SMR) of 111, most of the excess being due to violence (accidents). In the absence of this cause, the SMR fell to 102.

For lung cancer there was a significant excess for glass wool, continuous glass filament, and rock wool process workers when compared to national rates with a trend for the SMR to increase with time from first exposure. Using "local" lung cancer mortality experience for comparison modified the results (Table 4). Furthermore, the excess for glass wool and continuous filament production was no longer significant, but that for rock wool remained unchanged. For rock wool the excess was concentrated in the production and pre-production areas.

However, there was no pattern of lung cancer mortality in relation to duration of employment, and there is evidence that the three- to fourfold excess risk was mainly
TABLE 4
Standardized Mortality Ratio (SMR) for All Causes of Death and Lung Cancer among Those Exposed to Man-Made Mineral Fibers, by Years of Follow-up: Effect on Lung Cancer SMR of Comparison with “Local” Rather than National Mortality

| Causes of Death | SMR Based on National Mortality | SMR Based on “Local” Mortality |
|-----------------|---------------------------------|-------------------------------|
| All causes      | 111                             | —                             |
| All causes except violence | 102                             | —                             |
| All cancer      | 111                             | —                             |
| Lung cancer     |                                 |                               |
| 0–9 years       | 107                             | 96                            |
| 10–19 years     | 127                             | 112                           |
| 20–29 years     | 119                             | 105                           |
| 30+ years       | 173*                            | 153*                          |
| Total           | 129*                            | 111                           |

*Significant difference at 5 percent level

Based on data in [18] and personal communication from Saracci

concentrated among workers starting their exposure to rock wool some 40 or more years ago, when dust-suppressive agents and resin binders were not used and batch production methods prevailed, a process no longer used in the countries studied.

One case of mesothelioma occurred in an individual who died 13 years after employment for less than one year.

In such studies an increase in lung cancer due to smoking is difficult to exclude, as the smoking habits of the cohort members are usually not known. However, several features of the results point against smoking as the sole explanation; namely, (a) the three- to fourfold excess in risk, (b) persistence of excess when “local” populations, which presumably would have somewhat comparable smoking habits, were used for comparison, and (c) the mortality from other tobacco-associated disease did not follow suit.

NUTRITIONAL DEFICIENCY AND ESOPHAGEAL CANCER

Esophagus cancer is usually a disease of males. This is true in Occidental populations in which the risk is high and the disease mainly due to alcohol and tobacco. But in those countries where the incidence in males is below 5/100,000 per year, the sex ratio is usually 1.5 [6].

In the Asian esophageal cancer belt, which crosses from eastern Turkey to the north of China, passing through Iran, Iraq, southern Soviet Union, and Afghanistan, rates can be very high in females, on the order of 100 per 100,000 or more and, on occasion, exceed those in males [21]. In Iran, at least, alcohol and tobacco cannot explain more than a minute fraction of the cancer, particularly in women. Correlation and case-control studies have shown that dietary factors, notably deficiency of riboflavin, are likely to be of importance [22,23] although unlikely to cause cancer in the absence of a carcinogen (see below).

ALCOHOL—TOBACCO

The reasons for the high levels of this esophageal cancer in northwest France have been examined systematically by Tuyns and his colleagues. Here, over 90 percent of
the disease can be attributed to alcohol and tobacco. While each habit is independently carcinogenic, as the risks are probably multiplicative, reduction of one habit can have a large effect on the overall level of risk [24]. Tuyns has shown that the influence of tobacco is least in the middle third of the organ, where alcohol is more potent, and vice versa for the upper third, findings which are physiologically plausible [25].

Tuyns has also shown that in northwest France consumption of certain foodstuffs is protective, particularly those containing vitamins A and C [26]. In U.S. blacks a poor diet has been held to explain part of the disease, due mainly to alcohol consumption [27]. In India, an excess risk of esophageal cancer is seen in betel quid chewers who incorporate tobacco in the chew [28].

DIETARY EXPOSURES

In recent years, interest has focused upon esophageal cancer in Iran [21] and northeast China [29], where incidence rates in each sex exceed 100 per 100,000 people. In Iran, comparison of high- and intermediate-risk areas (the provinces of Mazanderan and Guilan, respectively) showed that diet in the high-risk area was more monotonous, more restricted, and deficient in fresh fruit and vegetables, the staple being wheat rather than rice. Levels of aflatoxin, polycyclic aromatic hydrocarbons, and nitrosamines were not significantly different [22,23]. Alcohol consumption was very low in men and non-existent in women. Case-control studies, in the form of a case-household control-household comparison, showed that even in an area of great poverty, cases came from the lower end of the socioeconomic scale and consumed less fresh fruit and vegetables.

Riboflavin deficiencies were shown to be widespread in the high-risk areas. An endoscopic survey, with biopsy, showed a series of esophageal mucosal changes denoted “esophagitis,” which was considered to be pre-cancerous [30,31]. These changes closely resembled those seen in non-human primates treated with 1-methyl 1-nitrosourea before squamous cell carcinoma appeared [32].

Opium used in the form of Sukteh was significantly more common in high- and very high-risk areas than in those with a low risk. Sukteh is a mixture of fresh opium and dross (pyrolyzed opium) widely used by both sexes and at all ages in the region [33]. It has been shown to be strongly mutagenic due to the presence of a class of hitherto unknown compounds (e.g., 2-methyl-3H-phenanthro [3,4-d] imidazol-10-ol) which transform Syrian hamster embryo cells in culture and which are probably carcinogenic for mice and hamsters [34]. It is quite possible that other risk factors also operate in this region [35]. O’Neill et al. [36] suggest that silica spicules in seeds may be important; this hot tea hypothesis has never been adequately tested.

In China, comparison of high-risk (Linxian) and low-risk (Jiaxian) populations showed that low levels of riboflavin, retinol, and zinc were widespread, but riboflavin deficiency was more widespread in Linxian [37]. It was thus decided to ascertain whether combined treatment of retinol, riboflavin, and zinc would lower the prevalence of pre-cancerous lesions. Following consultation with and the agreement of the population, some 305 males and the same number of females, aged 35 to 64, were randomized to receive weekly either a placebo, or a mixture of 15 mg of retinol, 200 mg riboflavin, and 50 mg zinc. Subjects were examined at entry to the study and at its close, 13½ months later. The final examination of 567 (93 percent) of those in the investigation included esophagoscopy and at least two biopsies [38].

The study was outstanding with regard to its design. The capsules used for treatment were packed individually in blister packs. On the reverse side of the blisters was a
self-adhesive label for each weekly dose with the individual’s study number and the week number printed thereon. These capsules were held by barefoot doctors, who, on giving a weekly treatment, removed the label, stuck it to the participant’s follow-up form, adding their signatures. The follow-up forms and remaining capsules were inspected every two months by field supervisors. Neither participants, barefoot doctors, nor field supervisors were aware of the treatment assignment. Two months after the start of the trial, compliance was assessed by measuring blood vitamins, from a sample of 100 participants stratified by age, sex, and production brigade. This showed that blood levels of those on placebo and on the vitamin capsules were as expected when compared with samples taken at the beginning of the study. This is probably the first strictly controlled nutritional intervention study in cancer epidemiology.

It was found that this treatment regime had no effect on the esophagitis. The results cannot be explained by bias or by confounding, as this was a randomized double-blind study. The lack of effect of the vitamin intervention may be interpreted in several ways:

a. The treatment period was not long enough or the dose was not sufficiently large. As angular stomatitis and cheilosis disappeared after three weeks with a dose of 50 mg of riboflavin, this seems unlikely. The retinol dose could not have been larger without continuous clinical monitoring.

b. Riboflavin and retinol may not induce regression of the esophagitis because of the persistence of other factors but may prevent the induction of pre-cancerous lesions. The natural history of chronic esophagitis may be like that of chronic atrophic gastritis, a precursor of gastric cancer, which seems to be irreversible. This hypothesis would be difficult to test if these lesions have been shown to begin early in life.

c. The original hypothesis may have been wrong.

It is evident that this cohort of persons needs to be followed for many years, but, even in such a high incidence area, no more than ten cases could be expected to arise from a population of 300 persons in ten years. The search for the carcinogens responsible continues; among those suggested to date are nitroso compounds from pickled vegetables [35] or from fusarium-contaminated wheat [39].

It is clear that to realize the full potential of these high levels of esophageal cancer requires not only an international but also a multidisciplinary approach.

**DISCUSSION**

Many problems of environmental carcinogenesis can best be solved by international collaboration. The work mentioned above typifies four distinct categories.

*Compilation and Standardization of Data*

Here scientists entrust their data to a central body—frequently supranational—which engages to produce these in a standard format useful to a wide spectrum of investigators and, implicitly, exercise a measure of quality control. Those publishing such data must make it clear that the endeavor reflects a collaborative effort.

*International Assessment of Risk*

Here, removed from the regulatory arena, scientists assess all available *published* evidence and give a scientific opinion on the carcinogenicity of the compound, process, or exposure under consideration.
Pooling of Study Populations to Obtain Interpretable Results

The work involved in mounting, coordinating, and analyzing such studies is such that they are not to be embarked upon lightly. Their major justifications are: (i) to escape from the tyranny of small numbers so that a statistically robust result is obtained, and (ii) when numbers in a given country are sufficient, to determine whether the result is consistent and of the same magnitude in each country and population studied—a type of study well exemplified and conducted by MacMahon et al. [40] on risk factors in breast cancer.

Provision of Resources for Individual Investigations

Many of the most interesting cancer problems occur in countries which are unable to exploit them to the full. Yet the study of such areas frequently can throw light on the genesis of the same cancer in countries where the disease is less common. The studies on nasopharynx cancer in China and North Africa [41], of Burkitt’s lymphoma in Uganda and Tanzania [42], and of esophageal cancer in Iran and China exemplify this approach.

To study the influence of nutrition in China and Iran on esophageal cancer in very high-incidence areas required epidemiological and statistical expertise, experienced endoscopists and pathologists, and a wide range of specialized biochemical and biological investigations.

Much of this panoply of investigations was beyond local resources and the relevant samples had to be sent abroad. One is thus faced with situations in which the study cannot be done without external expertise or without the collaboration of local scientists and populations. In these circumstances, it is axiomatic that every effort should be made to share knowledge. The resulting publications must be fair to both parties in terms of authorship. IARC has a rule that primary data must remain in the country of origin for local scientists to rework should they so desire; copies are sent abroad.

The examples chosen in this paper reflect the work and coordinating role of IARC, an institution which by vocation and mandate is particularly suited for such endeavors. Many comparable studies have of course been conducted by others, frequently ad hoc groups. International collaboration is likely to be increasingly used in the solution of problems of environmental carcinogenesis.

SUMMARY

Several of the circumstances under which a multinational approach can be of great value in cancer epidemiology are examined. The examples given include:

a. the collation of data and their publication in a standard format to assess international cancer patterns,
b. evaluation of the cancer risk posed by certain chemicals to man,
c. pooling of populations to obtain numbers sufficiently large for study, exemplified by investigations assessing the effect of low doses of ionizing radiation and the long-term consequences of exposures to the asbestos substitutes rock wool and glass wool, and,
d. the provision of resources for specific epidemiologic investigations illustrated by a dietary intervention study in a high-risk area for esophageal cancer in China.

In conducting multinational studies, particularly those involving the developing
countries, it is axiomatic that every effort should be made to share knowledge and that the resulting publications be fair to all parties. Primary data should remain in the country of origin, and copies sent to the study coordinator. International collaboration is likely to be increasingly used in the solution of problems of environmental carcinogenesis.

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