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# Comments and Critique

# The Burden of Cancer in Europe

IN THIS issue (p. 1167), much space is allocated to the estimation of the numerical burden of cancer and incidence rates in the member states of the European Community: the first time such estimates have been made.

Ascertainment of the cancer burden in a community, both in terms of the rate at which new cases appear (incidence) and die (mortality), has always been recognised as fundamental for cancer control, especially when assessing the impact of new treatment or prevention strategies in a given population. Mortality data, based on death certification, are available from routine vital statistics schemes over long periods and covering many national populations. Such data have provided an excellent resource for epidemiologists and have been used successfully to monitor and predict time trends (e.g. Case *et al.* [1]), to investigate differences in death rates between countries (e.g. Kermack *et al.* [2]) and to estimate the proportion of cancer deaths due to different environmental factors [3]. Despite several problems related to accuracy and interpretation [4], notably those associated with the correct recording of site [5] and selection of the underlying cause of death [6, 7], mortality data remain very useful.

Population-based cancer incidence data, available from cancer registration schemes, can give a better estimate of cancer occurrence than mortality data, particularly for those tumours that are not always lethal. However, incidence data are frequently only available for a restricted number of regions within a country and do not generally exist for such an extended period of time as do mortality data. While site specific mortality data are available from the 1950s for nearly the whole of Europe, including many countries outside the European Community, cancer registration schemes have, with a few notable exceptions, been more recent.

Several attempts were made before this century began to measure the prevalence of cancer in several parts of Europe [8]. The first attempt to register newly diagnosed cases covering a well-defined population began in Hamburg in 1929 and thus predates other well-known cancer registries, such as those in the province of Saskatchewan, Canada (1932) and Connecticut (1935). Data collection in Hamburg was interrupted in 1939 and did not resume until 1954. In 1942, cancer registration began in Denmark under the guidance of Dr Johannes Clemmesen, the first director of the Danish Cancer Registry. Within twelve months it was population-based. In 1936, in the United Kingdom, several registries began to collect cancer cases as part of a scheme initiated by the Radium Commission to follow up treated cancer patients, but this did not become population-based until about 1950 and registration has proved to be more effective in some regions than in others [9].

Much of the impetus for future developments in cancer registration came from a meeting on the geographical pathology and demography of cancer in 1950. This group, chaired by Prof. J.H. Maisin and including Johannes Clemmesen, Richard Doll, Harold Dorn and Percy Stocks among its members, made recommendations under three broad headings: (i) review of available information on variations in the incidence and behaviour of cancer and suggestions for future work; (ii) guidance on the presentation of statistical studies of geographical and other variations in incidence; and (iii) advice on the methods for the provision of a mechanism by which studies could be promoted, assisted and made more fruitful by cooperation [10].

The Union Internationale Contre le Cancer (UICC) established a committee on geographical pathology, initially under the chairmanship of Dr H.L. Stewart and subsequently of Dr John Higginson, who went on to become the first director of the International Agency for Research on Cancer (IARC). A meeting of this committee in Mexico in 1964 led to publication of the volume that was to become the first in the series *Cancer Incidence in Five Continents* [11]. The interest which the data contained in this publication aroused led to the creation of a UICC committee on cancer incidence under the chairmanship of Richard Doll. This committee took responsibility for publication of the second volume in the series [12]. Subsequent volumes [13–15] have been produced by the IARC and the International Association for Cancer Registries (IACR). It would be difficult to overestimate the influence that these monographs have had on the collection, standardisation and presentation of cancer incidence data.

As registration became better established, registries have become increasingly interested in data quality and comparability. At the same time, however, an increasing number of restrictions have been placed on the freedom of action of cancer registries in certain countries. The most important of these restrictions is the inability in many countries of the cancer registry to have nominal access to death certificates. Without such access, it is very difficult to know which of all the patients with cancer have died, and hence to calculate survival, or to determine the proportion of cancers that appear only on death certificates. This latter constraint deprives registries of one of their most valuable methods of checking on completeness of registration and, by identifying where defects lie, indicating where remedial action is needed. The same barrier effectively prohibits registry-bound cohort studies aimed at uncovering causal factors.

By 1980, there was national coverage for all the Nordic countries (Sweden, Norway, Finland, Iceland and Denmark). Of these, only Denmark is a European Community member state. The United Kingdom, the Netherlands and Belgium have population-based cancer registgration, but quality and completeness vary. Population-based cancer registration also exists in several regions of Spain (e.g. Navarra, Saragossa), France (e.g. Bas-Rhin, Calvados, Doubs, Isère), Italy (e.g. Parma, Ragusa, Varese), Germany (Saarland and the former German Democratic Republic) and the Irish Republic. Elsewhere in the Community, cancer registration is at an earlier

*Table* 1. *Estimated cancer incidence and rate per* 100 000 *in the European Community*, 1978–1982

| | No. of cases | | Age-adjusted rates | |
|---|---|---|---|---|
| | Males | Females | Males | Females |
| Oral cavity and pharynx | 27 328 | 4 994 | 13.7 | 1.9 |
| Oesophagus | 11 894 | 4 387 | 5.7 | 1.3 |
| Stomach | 55 125 | 37 797 | 25.1 | 11.1 |
| Colon | 42 255 | 50 657 | 19.2 | 15.8 |
| Rectum | 23 838 | 20 042 | 10.9 | 6.6 |
| Liver | 30 753 | 27 472 | 14.3 | 8.5 |
| Gallbladder | 3 294 | 8 603 | 1.5 | 2.5 |
| Pancreas | 16 131 | 14 679 | 7.5 | 4.4 |
| Larynx | 24 566 | 1 234 | 12.3 | 0.5 |
| Lung | 135 213 | 22 939 | 64.0 | 8.2 |
| Melanoma | 6 557 | 10 053 | 3.6 | 4.9 |
| Breast | | 135 403 | | 56.8 |
| Cervix uteri | | 22 054 | | 10.4 |
| Corpus uteri | | 24 390 | | 9.7 |
| Ovary | | 25 768 | | 11.0 |
| Prostate | 84 889 | | 35.2 | |
| Testis | 5 991 | | 3.9 | |
| Bladder | 41 596 | 11 051 | 19.2 | 3.5 |
| Kidney | 16 306 | 10 228 | 8.0 | 3.8 |
| Brain/CNS | 14 127 | 17 163 | 7.8 | 8.0 |
| Non-Hodgkin lymphoma | 10 373 | 7 789 | 5.4 | 3.1 |
| Hodgkin's disease | 3 754 | 4 000 | 2.2 | 2.2 |
| Multiple myeloma | 4 581 | 3 627 | 2.1 | 1.2 |
| Leukaemia | 16 557 | 13 003 | 8.4 | 5.3 |

stage of development and assessment of the total number of new cases of cancer from cancer registries in the European Community as a whole is thus not a simple task.

Thus, the article presented in this issue by Dr Jensen and his colleagues is of considerable importance in its provision of estimates of the numbers of cases of cancer of different forms which occur in the member states of the European Community. This work also represents a landmark in the development of cancer registration in Europe and the use to which the collected data can be put. In 1980, there were 730 000 deaths attributed to cancer in the European Community countries as a whole and Jensen and his colleagues have estimated that there were 1186 000 new (incident) cases in that year alone: these estimates exclude non-melanoma skin cancer which, although a rare cause of death nevertheless demands medical care. The total number of cases of the major cancer sites is outlined in Table 1 above.

Among males, lung cancer was the commonest form of cancer with an estimate that more than 135 000 new cases were diagnosed in that single year. The second commonest cancer was prostate cancer with nearly 85 000 new cases. Among females, it was estimated that there were over 135 000 new cases of breast cancer diagnosed in women. Colon cancer was the second commonest form of cancer in women and fourth in men. The variation in the rates of these cancers which are clearly displayed in the accompanying article indicate the possibilities which exist for cancer reduction within Europe and the importance of so doing.

Demographic factors alone, that is the increasing average age of the population, will result in an increasing number of cancers to be treated and diagnosed in the future unless serious attempts at prevention are made [16]. Although other risk factors for cancer have been identified, the obvious initial target for primary prevention is tobacco smoking: a reduction in cigarette smoking would not only reduce lung cancer incidence but would also serve to reduce the incidence of other important forms of cancer such as bladder, larynx, oesophagus, mouth, kidney and pancreas. Well designed and implemented national screening programmes for cervix uteri and breast cancer could reduce the mortality rates of both forms of cancer: examination of the likely efficacy of screening for prostate cancer is beginning to be undertaken in Europe.

As cancer prevention becomes an increasing focus of activity in many parts of Europe, it is important to have available estimates of the total cancer burden. Thus, the estimates provided by Jensen *et al.* can also serve as a basis for assessing the impact of cancer prevention activities. Given the increases in the average age of the population throughout Europe which continue to take place, and the consequent increases in the numbers of new cases of cancer, it now seems to be the time to be increasing cancer prevention research [17].

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# The Myelodysplastic Syndrome

THE MYELODYSPLASTIC syndrome (MDS) includes a range of haematological abnormalities in which a clonal population of haemopoietic stem cells arising from an initial genetic insult progresses to a preleukaemic state and ultimately to overt acute myeloblastic leukaemia (AML) [1, 2]. This probably develops as a sequence of events, over many years, in which the earliest stages may be difficult to detect by conventional techniques. It is likely that the mechanism of progression from a trivial haematological aberration to overt leukaemia involves successive genetic changes resulting in abnormal control of cell proliferation and differentiation. Expansion of an abnormal clone may be related to independence from normal growth factor control, insensitivity to normal inhibitory factors and suppression of normal haemopoiesis. In many cases clonal evolution is accompanied by increasing chromosome abnormalities, increasingly malignant characteristics in the bone marrow and eventually AML. Usually neither the nature of the genetic insult nor the lesion produced is known, though MDS may follow either chemical or radiation attack on the marrow. We are now beginning to define the molecular lesions in the genome that are associated with myelodysplasia and the development of leukaemia.

## CLINICAL PICTURE

MDS has been well defined since the study published by the French–American–British (FAB) group in 1982 [3]. The clinical manifestations vary from mild anaemia to incipient AML. Five categories of disorder have been defined on the basis of cellular morphology and the percentage of blast cells in the bone marrow [3]. The early stages of MDS may be associated with minimal haematological signs [4] and in practice many cases are discovered by accident after routine blood examination. The haematological picture includes peripheral blood cytopenias associated with a cellular bone marrow in which the cells appear dysplastic and have a high premature death rate. There are numerous functional abnormalities in progenitor cells, immature myeloid cells and in the end cells of all lineages. Although patients usually have a hypercellular bone marrow with a peripheral blood cytopenia, in many cases the marrow is hypoplastic [5] and difficult to differentiate from aplastic anaemia. The occurrence of MDS as a late event in well established cases of aplastic anaemia [6] suggests a common aetiology in some cases. Progenitor cell cultures are usually abnormal. We have found erythroid colonies in peripheral blood cultures to be reduced or absent in 79% of patients at diagnosis and myeloid colonies to be reduced in 45%.

The median age of myelodysplastic patients at diagnosis varies in different reports from about 60 to 75 years, presumably depending on referral patterns and methods of selection. The number of patients below the age of 50 years varies between 3 and 30% in different series. MDS appears to be uncommon in children, but when it occurs there is a high rate of leukaemic transformation to both acute lymphoblastic leukaemia (ALL) and AML. There are no specific symptoms or signs other than those of progressive haemopoietic failure.

## GENETIC ABNORMALITIES

It is generally accepted that any genes which code for proteins mediating the cellular response to growth factors may be potential "oncogenes", whether they code for growth factors, receptors, inner membrane or cytoplasmic proteins or nuclear-binding proteins. However, the full range of protein kinases, transcription factors, ribonucleases, cell cycle control proteins, suppressor proteins, matrix and adhesion molecules has hardly begun to be identified. Mutations in any of these could result in disordered proliferation contributing to the malignant process. The identity of the transformed stem cell in MDS is not known but it is often assumed that this is a totipotential cell. In a few cases all the haemopoietic lineages, including lymphoid cells, derive from the same clonal origin [7]; in others the origin is not so clear [8]. The sequential accumulation of genetic damage during leukaemogenesis may be located in the same target cell or in stem cells of varying lineage potential. The role of stromal cell damage is still undefined.

The progress of MDS, and therefore the patient's prognosis, is often measured in terms of haematological indices, such as the degree of anaemia or neutropenia or blast cell count. As the genetic lesions occurring in MDS become better understood it may be more appropriate to measure progression in terms of the burden of these lesions. While some lesions may occur early in the process and others, such as complex chromosome abnormalities, occur late, the total accumulation of lesions indicates the amount of genetic damage, which determines the severity of the haematological disorder.

### *Chromosome 5 haemopoietic genes*

Much of our knowledge of genetic changes in MDS has followed observations of cytogenetic abnormalities [9]. There is a particular concentration of genes relating to growth control and haemopoiesis on the long arm of chromosome 5 and these regions are commonly deleted in MDS [10]. The association of a specific deletion of a critical region of chromosome 5 with the development of an abnormal clone of premalignant haemopoietic stem cells suggests that the lesion is an essential part of the process, though the deletions are inconsistent and only one allele is affected. Growth factor genes can undergo the same pathological processes that result in the activation of proto-oncogenes, and abnormalities in the structure of the GM-CSF gene and its messenger RNA have been described in patients with AML in whom no structural abnormality of chromosome