# INCIDENCE AND PROGNOSIS OF CANCER IN THE NETHERLANDS:

## STUDIES BASED ON CANCER REGISTRIES

Incidentie en prognose van kanker in Nederland:
onderzoek met kankerregistraties

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*Aan mijn vader*

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CHAPTER 1

# INTRODUCTION

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# INTRODUCTION

Cancer comprises of a group of 50 to 150 diseases, the number depending on the degree of diagnostic refinement. About 3 of 4 male and 2 of 3 female patients ultimately die from cancer in the Netherlands and about 30% of all deaths are due to cancer. The prevalence, an indicator of the burden of care for society, is clearly rising. This trend exists in many industrialized countries and is expected to continue for the next decade.[1] Even with unaltered incidence rates, rising steeply with age, this follows firstly from the rising number of middle-aged and elderly inhabitants as well as from the gradually improving survival rates due in part to more effective treatment and in part to earlier diagnosis. Both incidence and survival rates can be biased 'upwards' by earlier detection of the more slowly growing, less malignant forms. Cancer mortality is the product of the risk of and death from cancer and can only be affected by changes in incidence of invasive forms and more effective therapy, also due to detection preceding metastasis. Though widely known and respected, the registry of causes of death, as reported by about 15,000 physicians to the Dutch Central Bureau of Statistics, suffers from inaccurate specification of cause of death, especially for the elderly who often suffer from more than one disease. Individuals over 75 years of age account for about 60% of all deaths and 40% of cancer deaths; within this age-group one out of 6 die from cancer. Thus cancer mortality is also affected by changes in the frequency and/or natural history of other diseases.

An accurate description of changes in the incidence of and survival rates for cancer in a population can be derived from surveys of morbidity. Special cancer registries became an established tool for this purpose in the second half of this century. However, point-prevalence surveys of cancer patients had already been carried out by physicians in Germany and the Netherlands in 1900[2]; later similar activities developed in other European countries. Starting in the 40's an international cancer registration 'movement' began to grow in most industrialized countries, including the Netherlands since 1953. This movement stagnated during the 60's and even stopped in the 70's for reasons explained in chapter 2, with one notable exception, the Eindhoven Cancer Registry.

If a registry is considered as a tool for acquiring knowledge that will lead to better disease management - the investment will only pay off in the long term if the information is used. Such registries generate primarily reference data on the risk of and population-based survival rates for cancer which can be of use

for clinicians, investigators, educators, teachers, providers, insurers or policy-makers in cancer control.

The aim of this thesis was to accomplish the primary task: assemblage and presentation of reference data, thereby generating ideas for specific studies. Various studies of (changes in) cancer incidence and survival in the last 15 years in the Netherlands were based on two registries:

*1* the regional Eindhoven Cancer Registry (ECR), which covers almost 7% of the Dutch population, has recorded all forms of cancer since 1955;

*2* the nationwide laboratory-based registry of leukaemia of the Dutch Childhood Leukaemia Study Group (DCLSG), a cooperative group of nearly all Dutch paediatricians, was initiated in 1972.

In chapter 2 an appraisal is given of the current state of cancer registration in the Netherlands, where interest in cancer control and registration revived in the 80's. The major characteristics of the two registries and their place in the health care system are presented in chapter 3.

In chapter 4 overviews are given of trends in the incidence of and survival rates for most cancers registered in the ECR; supplemental information is provided by an epidemiological review of cancer in the elderly: is ageing responsible for cancer incidence and death rather than exogeneous factors and treatment? The studies of incidence and survival also include analyses of changes in mortality due to cancer, that serves as an indicator of severity.

The tumour-specific studies described in chapter 5 focus on haematological malignancies, for children throughout the Netherlands by means of the DCLSG and for adults only in the ECR area. These studies can in part be considered as a confirmation of the health policy report on the future structure of intensive medical care for haematological patients.[3] The other ECR studies in chapter 5 cover common tumours, such as breast, ovarian, lung and non-melanoma skin cancer, that exhibited interesting changes in incidence or survival. About 15 regional specialists and some experts from outside the area were involved in interpretation of the changes. The studies in chapter 5 also suggest that a registry can be considered as a tree that carries only fruits when its roots are still functioning.

In chapter 6 the major results of these studies are discussed and the role of cancer registries for future clinical and aetiological research of cancer in the Netherlands is considered.

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CHAPTER 2

# CANCER REGISTRATION: HISTORY AND TRENDS

Chapter 2

# CANCER REGISTRATION: HISTORY AND TRENDS*


SUMMARY

A historical and functional review of the development of cancer registration as a world-wide phenomenon is presented in order to place the developments in the Netherlands in perspective. The roles of the International Agency for Research on Cancer and the International Association of Cancer Registries are seen as reference points. The development of cancer registries seems to follow a similar course in the diverse countries. From the beginning there appears to be a certain tension between the intended aims and the administrative set-up: ends and means. A registry which does not create a framework for using the data is doomed to fail. Moreover, the improved knowledge of cancer and the possibilities for treatment and prevention that result from that knowledge in turn give rise to changing demands with respect to the organization of the medical profession, epidemiological research and use of the cancer registry for these purposes. Nevertheless, the rather delayed developments in the Netherlands, the first steps were already taken in 1953, appear to show the same trend. However, the disadvantage of the late final start might turn into an advantage, if certain mistakes are avoided. There is no need for "more of the same". For example, a national approach to the registration of patients seems more suited for rare tumours than for common tumours; collection and evaluation of the latter can be performed better at the regional level. As of 1988, the Eindhoven registry can boast of the steadily increasing use of its data in a wide variety of fields, which would seem to justify its existence.


## INTRODUCTION

Cancer registration is a method for the systematic collection of data on all (in fact: as many as possible) new patients with cancer in a defined population, the course of their disease and treatment. Cancer registration is therefore a means of enlarging our knowledge about the occurrence of cancer, its spread, causes


* Coebergh JWW. History and trends in cancer registration. *T Med Inf* 1988;17:3:25-7 (suppl) (in Dutch)

and prognosis. A cancer registry can also be used as a register of "cases" which can be identified in relation to the need for estimates of the demand for care or a study on the risk of cancer. The most important results of registration are the incidence of and survival rates for the various types of cancer and the changes in these features with time. They are usually interpretated with respect to corresponding mortality figures (of the Central Bureau of Statistics, CBS) and data on the supply of specialized care as an indicator of access and the diagnostic process.

Cancer is a group of chronic diseases with a large diversity in localization, incidence and natural history. Depending upon the degree of precision, 50 to 200 different forms and types of cancer can be distinguished. The diagnosis cancer is made by a clinician, usually a specialist, on the basis of the case history, the physical examination - sometimes including endoscopy -, a radiological examination and cell and tissue studies; these findings are often supplemented with biochemical, immunological and cytogenetic investigations. Since cancer is generally characterized by a long latency period and often a prolonged course, the value of a registry increases with the duration of its existence. In the course of time the possibilities of application continue to multiply and to change, which is sometimes expressed as "moving targets".

## HISTORY

The phenomenon cancer registration in its present form developed in the 1930's after initial impulses at the start of the century, also in the Netherlands. It started in the city state of Hamburg in 1927, the state of Connecticut in the United States in 1935, the state of New York in 1940, Denmark in 1943, the province of Saskatchewan in Canada in 1944, southwest England in 1945, Finland and Norway in 1953, Sweden and England in 1958 and subsequently in a gradually increasing number of countries and regions. The last edition of Cancer Incidence in Five Continents[1] presents the results of 104 recognized cancer registries in 34 countries. It contains a contribution from national or regional registries from every country in Europe except Belgium, Austria, Greece, Turkey and Albania. At an international convention in Copenhagen in 1946, attended by representatives of 12 countries including the Netherlands, a resolution recommending the establishment of cancer registries throughout the world was adopted; it was later forwarded by the World Health Organization. The Netherlands has participated officially since 1973 first via the (isle of) Curaçao registry, established single-handedly by Dr. Freni and inoperative as of 1983, and since 1978 via the registry of the Cooperative Association of Hospitals in Oncology (SOOZ) in Eindhoven. This is a regional organization of specialists and hospitals in southeastern North Brabant and northern Limburg which has been part of the Comprehensive Cancer Centre South (IKZ) since 1983. Previous attempts, under auspices of the Queen Wilhelmina Fund (KWF), to set up a national registry in the fifties and regional registries in the

sixties met with failure in the seventies, except for this regional registry. As a matter of fact the hospital-based registries of the Antoni van Leeuwenhoek Hospital and the Rotterdam Cancer Institute, established in the fifties, are still functioning.

Generally cancer registries were started by a group of worried and interested physicians under the leadership of a key figure who was able to create space and perspective. The stimulus was usually an increase in the number of patients with cancer and the need for more insight into this problem, especially with respect to good care. In addition to primary attending physicians, pathologists and radiotherapists were usually involved in the setting up of a registry, because they were confronted daily with the increasing need for care in the various fields. In the later SOOZ-area close cooperation between the Radiotherapy Department and the various home care agencies also developed for this reason. It should be realized that knowledge about cancer was fairly limited and the patients visited the physician, as a rule, in a late stage, so that the possibilities of cure were limited. (Note: at the end of the fifties relative 5-year survival in the Netherlands, excluding skin cancer, was 16% for men and 33% for women; today it is about 30% for men and more than 45% for women.[2])

## METHODS OF OPERATION

The methods of operation of registries at that time, now often called documentation, varied from one country to the next depending on such local factors as distance, availability of population statistics, degree of organization of the physicians, oncological interest and relation with the government. The aspect of religion also may play a role: what led to unity in Scandinavia, probably resulted in dispersion in the Netherlands. In some countries the data were collected actively in the hospitals, thus decentralized, while others preferred central registration. However, in view of progress in diagnostics and treatment, the principle of multiple sources was always followed. Since the publication of the first edition of Cancer Incidence in Five Continents in 1966, considerable energy - internationally speaking - has gone into the realization of the most uniform possible method of operation as far as the major aspects related to diagnosis and treatment are concerned. The aim is to be able to get comparable results.[3]

### *Continuity*

After a number of years of operation most of the pioneering cancer registries have run into problems: the amount of data collected has increased faster than the ability and desire to do something with it. Some went into decline or deteriorated into "one-man shows". The question arises: Who does what, in whose name and for the benefit of whom? In the sixties inertia was tremendous because data compilation was not yet mechanized via the computer. Paralyzing discussions about the aim or the target (which in the meantime had changed)

and usefulness also took place in those registries already considered as well-established projects. The initially broad basis appeared to have become smaller which in turn had a negative effect on discussions about funding, whereby governments and organizations for the prevention of cancer passed the burden of responsability from one to the other. In the vacuum thus created, newly developed information systems in pathological laboratories and hospitals attempted to bring the cancer registry under their control (read: in large and expensive computers) for reasons of efficiency. The lack of trust in - or perhaps better, the lack of belief in - the usefulness of cancer registries increased; this also became apparent in the development of discussions about privacy. These problems were also encountered in the Netherlands, whereby the lack of interest of Dutch specialists (most of them in private practice) and their lack of confidence in (coordinating) organizations responsible for cancer control, such as the KWF and the national government, proved fatal. At that time not only did these organizations fail to provide leadership, but there was also few with sufficient authoritative clinical and epidemiological expertise to play an integrating role.

A review of a large number of publications indicates that the cancer registry in Finland in particular made most progress during this period. Presumably this is because its staff rapidly diversified and included both pathologists and epidemiologically trained biostatisticians and because automation was introduced gradually. The metamorphosis of the Danish cancer registry after 1978 is also striking: it has evolved into an Institute for Cancer Epidemiology. Also worthy of mention is the fairly active role in the production of survival statistics of the SEER programme (Surveillance, Epidemiology and End Results) developed by the National Cancer Institute for 10% of the American population.[4] This programme served incidentally as a stimulus for the development of diverse regional cancer registries, including that in Connecticut. Elsewhere in the country registries that are not part of the SEER programme have set up imitations. It appears that developments in most of the well-known registries are pointing in the same direction: reinforcement of the research staff mainly through cooperation with university departments and specialized institutes, enrichment of the work by means of research and clinical documentation projects, automation tailored to the needs with exchange of software and, finally, shared financial responsibility by health insurers, government and organizations for cancer control, such as QWF, which will be confronted with an increasing number of requests for project grants.

## INTERNATIONAL DEVELOPMENTS

The International Association of Cancer Registries (IACR) and the Unit for Descriptive Epidemiology of the International Agency for Research on Cancer (IARC), established in 1968, have played an important role by setting standards and facilitating communication. Every beginning registry can become an

associate member of the IACR; voting membership is granted when the data over a five-year period are deemed accurate enough to be included in Cancer Incidence in Five Continents. Whereas the annual IACR-meetings initially were devoted mainly to technical and organizational aspects (how do you run a registry, what are the rules for codification, what can you do with it, how does one approach automation, etc.), in recent years these meetings have acquired an increasingly scientific, epidemiological and even clinical accent. This development was described in a book "The Role of the Registry in Cancer Control"[5] in which various applications of the cancer registry in different fields are given: planning programmes for early diagnosis, longitudinal research into occupational risk factors for cancer, planning of specialized care, evaluation of effectiveness by means of population-based survival rates, occurrence of second tumours and information services to medical specialists. This is a logical development when considered against the background of the simultaneous increase in knowledge of cancer, the growing interest in cancer among the public and the providers of care, and the marked increase in and diversification of oncological care. This broadening of interest, knowledge and possibilities leads to more specific demands of the registries and the desire for more extensive documentation. Because (early) diagnosis and treatment of cancer are at present in the half-way phase of technological development, the need for evaluation of care remains considerable, more so than if simple and effective examination and treatment modalities ("end technologies") were available. The Scenario Committee on Cancer in the Netherlands considered it rather unlikely that drastic changes in this situation would appear before the year 2000.[6]

## RECENT EXPERIENCES IN THE NETHERLANDS

In about the same year when the subsidy for the cancer registration process (in 4 regions) was withdrawn, in 1974, the Dutch government became again more actively involved in cancer control and registration as a means towards that end. It was stimulated by the American government which delegated this responsibility by law to the National Cancer Institute. Motivation for this involvement, strongly supported by the Parliament, was usually expressed as "the need to know more, sometimes even everything, about the frequency and distribution of cancer because otherwise one can neither form nor pursue a policy". (In this respect it is interesting to note how little use was made at that time of the cancer mortality figures of the Netherlands Central Bureau of Statistics which clearly revealed for example, the unusually marked increase in mortality due to lung cancer; in addition the Atlas of Cancer Mortality in the Netherlands in 1969-78[7] elicited little in the way of policy or specific questions on regional differences, which were rather great for common cancers such as of stomach and lung.) In the past 10 years these intentions of government and Parliament have been the basis for the development of 8 regional Comprehensive Cancer Centres (CCC). Starting in 1979 new attempts were made to

establish a national registry within the framework of these CCC's and coordinated by the newly formed National Council of Comprehensive Cancer Centres, in which administrators were the leading persons. However, a potential coordinating agency on subject matter, the National Committee for Cancer Research, was dismantled in 1982. With regard to the development of registries the activities have gone into two directions since then, which have led to a certain amount of tension.

On the one hand the registration process in most of the CCC's is now gradually occurring in a systematic and respectable manner by means of decentralized collection in the hospitals via the clinical records (following the example of the Eindhoven Cancer Registry), using multiple sources such as pathological reports and records of radiotherapy ensure confirmation and completeness. As a result of automation of the archives of a growing number of pathological laboratories (guided by the National Computerized Archives for Pathologists, PALGA) the supply of data to regional cancer registries became easier. As part of an international process the number of people interested in the results and use of cancer registration has increased markedly, which a.o. appears from the marked growth of the number of registry-based epidemiological and clinical publications. Policy-making, e.g. by scientific societies, consensus meetings under the auspices of the Coordinating Agency for Medical Audit, the Health Council and the Steering Committee on Future Health Scenarios, is also based increasingly on data from these registries. Thus the usefulness of cancer registration has been demonstrated beyond any doubt. Diverse research projects in which the cancer registries will play a central role are in the planning stage: follow-up studies of diet and cancer, the occurrence of secondary cancer, the prognosis of cancer in the elderly, the prognosis of breast cancer classified according to morphometric methods, the influence of early diagnosis of breast cancer on the prognosis and population-based case-control studies e.g. of the causes of breast cancer in young women. For the management of patients with fairly common forms of cancer, such as lung, breast, prostate, large bowel, stomach, skin and bladder, regional collaboration (tumour study groups) has developed, often using the registry as a database. For rare tumours, however, which are encountered relatively more often in the young and exhibit steadily improving survival rates thanks to intensive and more refined treatment, national and international organizations are concentrating on protocols for diagnosis and treatment. In the Netherlands, for example, the Committee on Bone Tumours, the Dutch Childhood Leukaemia Study Group, Haemato-Oncology for Adults (HOVON) and a variety of special oncological study groups within the professional societies are active.

On the other hand, quite a few people were - and some still are - obsessed by the actual cancer registration process. An enormous amount of time has been spent in devising detailed regulations, a good example being the Specifications for Cancer Registration (Bestek, 1984), although the major guidelines had in fact already proved effective elsewhere for many years. This costly

learning process was a result from the the administrative responsibility which was more focussed upon means (read: computers) than at practical experience related to ends. The resulting drive to achieve perfection gave rise to substantial waste which, understandably, will be reacted upon by proposing far reaching technological solutions and staff cuts at a time when the work has really become worthwhile.

## WHAT IS NEXT?

The path that this intriguing phenomenon will follow in the 'Province' of the Netherlands before 1992 can easily be deduced from the above. And it is likely that things will change again even further after that year. The tendency toward increased internationalization of cancer management and research will continue (cancer after all does not stop at the borders), as will the demand for high quality data. However, relations between Dutch specialists and the government have been deteriorating steadily for a number of years and this will certainly have a negative effect on the cancer registration process. Discussions on costs, computers and privacy will, as a result, undoubtedly become more heated while technocratic attempts to find all-embracing solutions will become more frantic. Continued "privatization" and an increased demand for help in irregular and unregulated fields of "medicine" will presumably lead to enhanced opaqueness of the once so clearly structured field of specialized care for patients with cancer in the Netherlands.

Therefore, unless professional guidance of the cancer registry is installed its survival will remain doubtful.

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CHAPTER 3

# REGISTRIES IN THE NETHERLANDS

## Chapter 3.1

# Eindhoven Cancer Registry 1983-1987*

This regional registry began operations in 1955 as part of a programme for nationwide cancer registration. It started as a system of clinical documentation in 3 hospitals in Eindhoven, collecting data on new cancer patients during the consultants' weekly meetings and, subsequently, directly from pathology reports and patient records a.o. radiotherapy files. Registration activities expanded together with the decentralized consulting services of radiotherapists from Eindhoven, where megavoltage facilities were concentrated. More systematic registration procedures were developed according to international guidelines, especially since 1967 when a medical officer was appointed. In the early seventies the registry served 13 hospitals in a defined area, consisting of southeastern North Brabant and middle and northern Limburg. Registration activities were continued in 1974, when the other 3 remaining population-based registration projects were terminated. The growing interest for oncology was formalized in 1979 by the establishment of a regional organization, the Cooperative Association of Hospitals in Oncology (SOOZ). It enabled an evaluation of completeness and accuracy, which was carried out in the period 1980-83, also at the request of the Minister of Health. The data-base was computerized from 1974 onwards. Completeness could be assumed for most tumours from analyses of referral patterns and registration procedures as well as various comparisons of incidence, a.o. with cancer mortality. Additional data were collected on, directly referred, mainly younger patients with bone, head and neck, eye and brain cancer, leukaemia and lymphoma in various specialized centres elsewhere. The incidence rates could thus be determined in a core area, comprising 85% of the population covered by the registry. Inclusion was attained in Cancer Incidence in Five Continents, volume V, and the International Incidence of Childhood Cancer.

As of 1990, the registry is still functioning on a voluntary basis, but within a newly developing national scheme of cancer registration, which gradually evolved from 1984. On assignation of the government it is funded by social

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* Coebergh JWW, Verhagen-Teulings MTh, van de Boogaert-Masseling E, van der Heijden LH, Crommelin MA. Southeastern North Brabant and northern Limburg: Eindhoven Cancer Registry, 1983-87. In: *Cancer Incidence in 5 Continents*, Vol. VI, Parkin DM, Whelan Sh, (eds.) Lyon: IARC Scientific Publications (in press)
The corresponding data are presented in Annex A.

and private health insurance companies and administered by comprehensive cancer centres, which were set up since 1977.

The registry serves an area of about 2,500 $km^2$, lying 20 to 50 metres above sea level and comprising almost 1 million inhabitants or 7% of the Dutch population in 1985, with an average density of 400 per $km^2$, roughly the national average. Annual population data are derived from the Central Bureau of Statistics, which disposes of demographic data from municipalities. Forty-seven percent of the population-at-risk lived in urban, 41% in suburbanized and 12% in rural municipalities. Between 1965 and 1975 the (high) fertility rate of 3 dropped to 1.5, featuring the secularization of this Roman-Catholic population. As a consequence there is a pronounced ageing of the population, which is enhanced by an annual increase in the number of people over 55 years of about 2%, partly due to decreasing mortality rates for major causes of death. It will be reinforced by the post-war baby-boom that is now in its 4the decade. However the population was still relatively young in 1985, in part because of immigration related to economic development.

The prevalence of smoking among male adults decreased from about 90% in the fifties and sixties to about 40% in the eighties. In contrast women exhibited an increase to about 40% from about 20%, but reaching a plateau in the past few years. Alcohol consumption, mostly beer and wine, rose from a low level, in particular among females. Since 1965 about 50% of young women were taking oral anticonceptives. The proportion of females in the official labour market rose from - a relatively low level of - 25% in 1975 to almost 50% of male employment rates in 1986. In the last 20 years an intensive pig and poultry breeding industry developed, now contributing considerably to acid rain and a rising nitrate content in the ground water. The main industries generated electronical products, cars and trucks, copying machines, textiles and food products. The tobacco processing industry, important in the Eindhoven area, was declining since the 70's. Zinc factories, situated along the border with Belgium since 1900, caused marked pollution of the soil with cadmium. Monitoring of air pollution by the National Institute for Public Health and Environmental Hygiene showed rising and relatively high concentrations of ozone, lead, nitrogen monoxide and sulphur dioxide, largely originating from surrounding industrialized regions and the port areas of Antwerp and Rotterdam.

Access to medical care was easy as a result of the relatively short distances (always <30 km) to a hospital, ample supply of health services and a sickness insurance system without major financial obstacles. Some 60% of the people are covered by the Sickness Benefit Funds, a compulsory social insurance policy for people with lower incomes, while less than 1% of the population would be uninsured. Virtually all consultants work in hospitals, mostly on a fee for service system.

After correction for population growth and ageing the number of, increasingly specialized, consultants rose with about 30%. They can only be consulted through referral by a general practitioner, about one for every 2,500 persons. The community hospitals, most of which have been (re)built within the past 20 years, have been involved in mergers, the number of beds decreasing from 5 to 3.5 per 1,000 persons. On the other hand the number of beds in nursing homes increased markedly. About 35% of new cancer patients were treated at the regional Department of Radiotherapy in Eindhoven. Pathological diagnostics were carried out in 3 laboratories. In the absence of a regional cancer centre or university hospital younger patients with rare tumours were often referred directly to nearby specialized hospitals elsewhere, e.g. the departments of Paediatric Oncology, Haematology and Ear-Nose-Throat and Orthopaedic Surgery of the University Hospital in Nijmegen and the cancer centres in Amsterdam and Rotterdam. Patients with (suspected) tumours of the central nervous system were usually referred to neurosurgeons in Tilburg. An organized cervical cancer screening programme, carried out in the period 1974-82 was offered to 70% of women between 35 and 55 years of age, with exposure rates of about 50%. Screening for breast cancer was carried out in the nearby Nijmegen and Utrecht areas.

Registration procedures remained unchanged during the period 1983-87, but coding was refined by the newly developed national registration effort, which adopted the SOOZ collection methods. They encompassed multiple sources, varying according to local circumstances and consisted of:

- routine reports for all patients were provided by the Departments of Pathology and Radiotherapy;
- regular active and direct collection of data from patient records in all hospitals, in cooperation with the medical records office and also supported by regular contacts with secretariats of consultants and specific out-patient clinics including dermatology;
- annual cross-checks with data from the specialized departments and hospitals mentioned above and periodically with the Committee for the Diagnosis of Bone Tumours and the Dutch Childhood Leukaemia Study Group.

At the registration office data were coded according to ICD-9 and filed by name and tumour site, as of 1986 directly in a computer. Follow-up of date of death was feasible and consisted of systematic checks of the vital status of patients diagnosed since 1975 in municipal population registers as of 1988.

Regional mortality rates are derived from the causes of death register that is based on anonymous death certificates, administered by the Central Bureau of Statistics. For cancer of the oesophagus, stomach, pancreas and lung mortality rates were higher than incidence in the older age groups. Compared to national figures relatively high mortality rates existed for cancer of the lung, large bowel, prostate and haematalogical malignancies for men and low rates for cancer of

the cervix and upper digestive and respiratory tracts for women. Consequently rates for all sites were higher for men, and lower for women (see appendix B)

Compared to the period 1978-82 age-adjusted incidence rates for all sites in the period 1983-87 remained unchanged for men and rose by 7% for women. The crude rates increased by 10% for men and 20% for women. After age-adjustment clearly higher rates were found among men for cancer of the colon, bladder, skin (non-melanoma) and non-Hodgkin's lymphoma, and lower rates for cancer of the stomach, larynx and lung. Among women rates were higher for cancer of the head & neck, lung, skin, bladder and non-Hodgkin's lymphoma; they became lower for cancer of the stomach, gallbladder, cervix (only in women over 40) and mainly chronic leukaemias. These changes generally reflect the trends in cancer mortality in the Netherlands. With respect to population density the lowest incidence rates (both sexes) were found in rural communities and also for men in suburban communities; with respect to urban communities the difference in rate was about 10% for men and 15% for women. High rates were found in rural municipalities for cancer of the lip and rectum (men), cancer of the stomach (women) and leukaemia (both sexes) and low rates for cancer of the gallbladder, pancreas and head & neck (both sexes), breast and uterus (cervix and corpus) and kidney and bladder (men). In the cities high rates were found for cancer of the head & neck, oesophagus, stomach, lung, and cervix uteri. Incidence and regional mortality rates from most sites closely resemble those in Saarland (FDR) and mortality in eastern Belgium.[1]

Incidence rates obtained from this registry have formed the basis for an extensive policy analysis of cancer control in the Netherlands and the development of policy scenarios for the period 1985-2000.[2]

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2 Cleton FJ, Coebergh JWW, (eds.) *Cancer in the Netherlands; Scenarios on cancer, 1985-2000.* Boston: Kluwer Academic Publishers, 1988.

Chapter 3.2

# Dutch Childhood Leukemia Study Group (DCLSG), 1973-1982*

The DCLSG that was set up by the Dutch Paediatric Society in 1972 aims to optimize and coordinate treatment of childhood leukaemia in the Netherlands and to stimulate research. Almost all paediatricians (98%) participate on a voluntary basis. The DCLSG is responsible for a central laboratory, registration of patients and collection of data during treatment and follow-up, as well as distributing protocols for treatment, supportive care and follow-up. The DCLSG was financed by a grant from the Ministry of Health and Environmental Hygiene from 1972 to 1975 and from private funds, through the Queen Wilhelmina Cancer Foundation, from 1975 to 1980. Since 1980, health insurance has provided a stable source of funding.

New registrations and regular updates of clinical data are recorded in the central office. The data are analysed by the European Organisation for the Research and Treatment of Cancer (EORTC) in Brussels. Cytomorphological examination of bone marrow and blood smears and, recently, spinal fluid samples of every patient, is performed at diagnosis and regularly during treatment and follow-up. The French-American-British (FAB) classification has been used since 1975. Immunological phenotyping of leukaemia cells has been performed in collaboration with the Central Laboratory of the Red Cross Blood Transfusion Service in Amsterdam since 1979. Cytogenetic analysis of leukaemic cells has been carried out since 1984 through collaboration with specialized laboratories. Coordination of treatment has resulted in centralization of allogeneic bone-marrow transplantation in the Department of Paediatrics in the University Hospital in Leiden.

A nationwide childhood leukaemia register was established in 1973. Its coverage proved to be about 97% complete in an evaluation study performed in 1980. The number of new cases of childhood leukaemia has varied between 100 and 125 per year among a decreasing childhood population (0-14 years) of approximately 3.5 million. Incidence rates in urban areas are slightly higher than those in rural areas.

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* Coebergh JWW, van der Does-van de Berg A, van Wering ER, van Zanen GE. The Netherlands: Dutch Childhood Leukaemia Study Group (DCLSG), 1973-82. In: *International Incidence of Childhood Cancer,* Parkin DM, Stiller CA, Draper GJ, Bieber CA, Terracini B, Young JL, (eds.) Lyon: IARC Scientific Publications No.87, 1988: pp 263-5.

Access to medical care is excellent in all parts of the Netherlands. Patients are generally referred to paediatricians via general practitioners, of whom there were about one for every 3,000 inhabitants in 1975. The 70% of the population in the lower income bracket are insured through sickness funds; the other 30% are nearly all privately insured. The registry of the DCLSG covers the whole of the Netherlands, a densely populated country with about 400 inhabitants per square kilometer. Differences between urban and rural areas are, in general, not very large. They have been further reduced as a result of extensive migration out of the larger cities in the 60's and 70's. In the 70's about 600,000 people migrated to the Netherlands from the Mediterranean region and from the former colony of Suriname. Until about 1970, approximately 40% of the population was Roman Catholic by birth, and the same percentage was Protestant. A strong trend towards secularization has occurred since that time.

Several epidemiological studies have been carried out, descriptive as well as etiological, in collaboration with the Department of Epidemiology of the Erasmus University in Rotterdam.[1 2 3] These include a time trend analysis of incidence rates and a study of the geographical distribution. In addition to the leukaemia registration, a retrospective survey of children with malignant lymphoma has recently started.

## POPULATION

The population at-risk has been calculated from the estimates for the Netherlands of 1973, 1976 and 1980, which are available as a result of continuous registration of the population by the Central Bureau of Statistics.

**Average annual population in 1973-82**

| Age (yrs) | Boys | Girls |
|---|---|---|
| 0 - 4 | 495,949 | 478,508 |
| 5 - 9 | 583,102 | 557,012 |
| 10 - 14 | 624,532 | 596,623 |
| 0 - 14 | 1,703,583 | 1,632,143 |

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CHAPTER 4

# INCIDENCE, SURVIVAL AND MORTALITY: ALL SITES

Chapter 4.1

# Trends in incidence of cancer in southeastern North Brabant and northern Limburg in the period 1975-1986:

## Report from the Eindhoven Cancer Registry*


SUMMARY

In southeastern North Brabant and northern Limburg the incidence of cancer was determined for the period 1975-86, using the Eindhoven Cancer Registry. For men the age-adjusted incidence of cancer increased up until 1984 and then decreased. A similar trend was observed for cancer of the lung, prostate, head-neck region and kidney. The incidence of carcinoma of the large bowel and malignant melanomas increased, that of cancer of the stomach decreased. Among women the incidence of cancer increased gradually. The incidence of cancer of the lung, breast, bladder, head-neck region and kidney and melanoma increased; the incidence of cancer of the stomach and gallbladder decreased. The trend in the incidence of lung cancer differed between men and women; this is presumably the result of contrasting changes in tobacco consumption since the 1960's. The changes in incidence agreed in general with the mortality trends recorded by the Central Bureau of Statistics for the same region. Distortion of the results due to changes in the methods of collection and coding of the data is considered unlikely; some detection bias could have been caused by a lower barrier to specialized care related to the increased number of newly trained consultants.


INTRODUCTION

Since the turn of the century physicians have tried to record the increasing morbidity of cancer within given populations in specific disease registries.[1] Whereas these registries initially provided insight into the course of the disease in individuals, they later appeared - partially due to the process of automation - to be useful in many fields of investigation: follow-up studies of groups with


* Coebergh JWW, Verhagen-Teulings MTh, Crommelin MA, Bakker D, van der Heijden LH. Trends in incidence of cancer in southeastern Netherlands, 1975-86: report from the Eindhoven Cancer Registry. *Ned Tijdschr Geneeskd* 1990;134:754-60. (in Dutch)

a possibly enhanced risk for cancer, evaluation of prognosis and estimations of the demand for specific types of care.

In the Netherlands the initiative for a national cancer registry came from the Queen Wilhelmina Fund (KWF) in 1953. As of 1968 the only participating areas were the city of the Hague, the province of Friesland (except Leeuwarden), the city of Rotterdam and southeastern North Brabant. In 1974 financial support was discontinued because of insufficient completeness and perspective. However in the hospitals of southeastern North Brabant - together with those of northern and middle Limburg - registration continued, stimulated by the growing cooperation in the field of oncology, especially with respect to radiotherapy. For the purpose of international comparison, the incidence rates for the period 1978-82, supplemented by regional cancer mortality rates derived from the Netherlands Central Bureau of Statistics (CBS), were accepted by the editors of Cancer Incidence in Five Continents.[2] We now present the results of a study of changes in the incidence of and mortality from cancer among adults in southeastern North Brabant and northern Limburg in the period 1975-86.

## PATIENTS AND METHODS

### *Population and registration*

Registration began in the three Eindhoven hospitals in 1955; in the early 1970's the project encompassed a continuous region which included southeastern North Brabant and North and Middle Limburg. Since 1979 the registry has functioned within the framework of the Cooperative Association of Hospitals in Oncology (SOOZ)[3] which has been part of the Comprehensive Cancer Centre South (IKZ) since 1983. In an evaluation of the registry, totally automated as of 1975, completeness could be assumed for most tumours in about 85% of the area - the so-called nucleus comprising about 850,000 inhabitants (figure 1).[4] For some less common tumours with a supraregional referral pattern, this applied as of 1978.

### *Patient data*

This study covered all patients with cancer who were first diagnosed between January 1st 1975 and January 1st 1987: in total 11,961 women and 14,261 men. These patients were identified by means of reports of tissue examination in the pathological laboratories in Venlo and Eindhoven (Helmond since 1984) and the records of radiotherapists. In cooperation with the hospital medical records office and the secretariats of the diverse specialist groups the data were collected by special clerks from clinical and out-patient records in hospitals in Eindhoven, Geldrop, Helmond and Deurne, Horst (until 1979), Venlo and Tegelen (until 1983), Veghel, Venray, and Weert. Data were requested on patients from the nucleus who were initially referred to centres outside the area, such as to the Department of Neurosurgery of the St. Elisabeth Hospital in

Tilburg, the Departments of Haematology, Ear, Nose and Throat Diseases and Orthopedics of the Nijmegen University Hospital, specialized oncological centres in other academic hospitals and, via the medical registration services, the two major cancer institutes. Data were also checked with the national Bone Tumour Committee.

Coding took place under the direction of the registration physician according to the 8th (until 1978) and subsequently the 9th revision of the "International Classification of Diseases" (ICD). In this analysis we included only the invasive forms of cancer given by the code /3 of the ICD. In addition we combined tumours of the rectum and colon (ICD 153 and 154), head and neck region (ICD 141-149), leukaemia and lymphoma (ICD 200-208) and the groups undefined malignancies and metastasis with unknown primary localization (ICD 195-199). Not included were the various types of childhood cancer and tumours of the skin (ICD 173).

*Mortality*

As of 1970, the cause-of-death statistics of the CBS provided information about death due to cancer and other causes in COROP (an intraprovincial division) areas 36 and 37, which coincided with about 90% of the nucleus population of our registration area (figure 1).

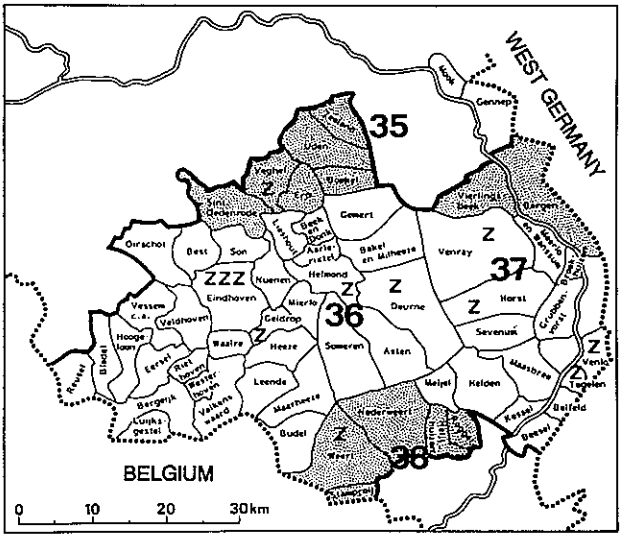


**FIGURE 1 Municipalities covered by the Eindhoven Cancer Registry in southeastern North Brabant and northern Limburg**
(white=nucleus, shaded=peel of registry area, numbers=COROP area,
z = hospital, ..... = national borders, ---- = provincial borders)

*Analysis*

The data were analysed with the "Statistical Analysis System" (SAS), version 5. The distribution of the population-at-risk for each year was obtained from the CBS, Department of Population Statistics. The incidence and mortality rates were calculated per 100,000 men and women per age group (5 and 15 year) per year and standardized for age using the European standard population[5] which resembled the Dutch population in the period 1980-85 (table 1).

TABLE 1 **Age distribution of the population in 1980 in southeastern North Brabant and northern Limburg, the European standard and the Dutch population in 1985**

| Age (yrs) | SOOZ area | Population European* | Netherlands |
|---|---|---|---|
| 0-14 | 23,700 | 22,000 | 19,500 |
| 15-29 | 26,600 | 21,000 | 26,000 |
| 30-44 | 21,700 | 21,000 | 22,000 |
| 45-59 | 15,900 | 20,000 | 16,000 |
| 60-74 | 9,000 | 12,000 | 11,500 |
| ≥75 | 3,100 | 4,000 | 5,000 |
| | 100,000 | 100,000 | 100,000 |

source: CBS
* ref 5

Incidence and mortality rates were calculated for the entire period and for 3-year periods: 1975-77, 1978-80, 1981-83 and 1984-86. The lethality or case fatality ratio per tumour per sex per 3-year period was calculated as follows: mortality:incidence x 100%. In the event of a high lethality, i.e. ≥75%, mortality is divided by incidence for the same period; when <75%, mortality is divided by the incidence for the previous period. Only those ratios that exhibit a pronounced difference are given.

RESULTS

The incidence of cancer in the middle-aged population was clearly higher for females than males; for the group over 55 years of age, the reverse applied. For men lung cancer was the most prominent type, for women breast cancer (figure 2). The incidence of cancer of the stomach, large bowel and bladder rose steeply with age, more for men than for women (figure 3). For men, the age-adjusted total incidence and mortality increased until 1980 and then gradually decreased. For females, the incidence increased during the entire period; the mortality decreased up until 1980 and subsequently remained constant (table 3). Per 15-year age group the incidence for the elderly (≥75 years) in particular continued to increase: approximately 1.5% for men and 2% for women per

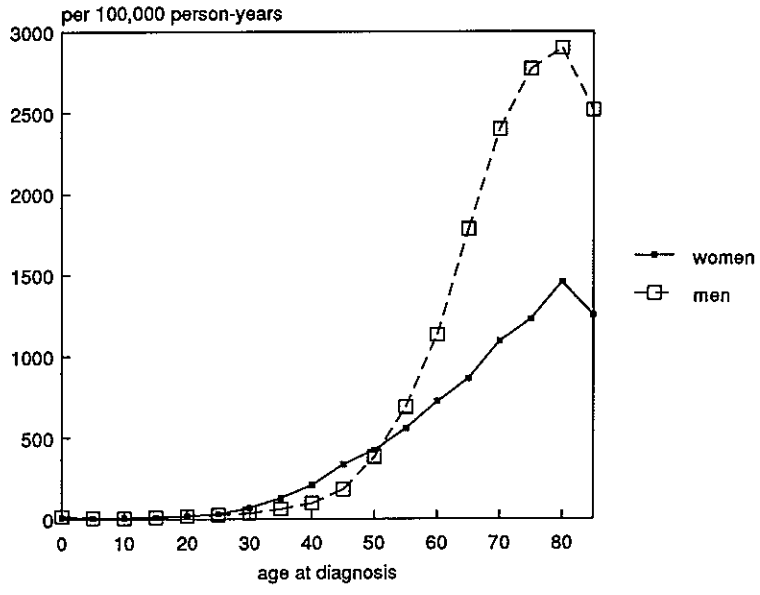


FIGURE 2 **Age-specific incidence of cancer in southeastern North Brabant and northern Limburg in the period 1975-86: per sex, per 100,000 person-years**

TABLE 2 **Incidence of cancer in southeastern North Brabant and northern Limburg in the period 1975-86: per 100,000 person-years, (listed in order of frequency)**

| Men Site | % | Inc* | no. | Women Site | % | inc* |
|---|---|---|---|---|---|---|
| Lung | 32.6 | 131 | 1 | Breast | 34.4 | 96 |
| Colorectal | 13.6 | 55 | 2 | Colorectal | 15 | 42 |
| Prostate | 11.2 | 45 | 3 | Ovary | 5.9 | 16 |
| Stomach | 7.7 | 31 | 4 | Stomach | 5.4 | 15 |
| Bladder | 6.6 | 27 | 5 | Endometrial | 5.4 | 15 |
| Kidney | 3.0 | 12 | 6 | Cervix | 3.2 | 8.8 |
| Non-Hodgkin's | 2.5 | 10 | 7 | Lung | 2.9 | 8.0 |
| Leukaemia | 2.3 | 9.4 | 8 | Melanoma | 2.3 | 6.5 |
| Pancreas | 2.2 | 8.9 | 9 | Pancreas | 2.3 | 6.4 |
| Laryngeal | 2.2 | 8.7 | 10 | Non-Hodgkin's | 2.2 | 6.1 |
| Brain** | 1.6 | 6.4 | 11 | Gallbladder | 2.2 | 6.1 |
| Gallbladder | 1.2 | 4.7 | 12 | Kidney | 2.2 | 6.0 |
| Melanoma (skin) | 1.1 | 4.6 | 13 | Leukaemia | 2.1 | 5.9 |
| Oesophagus | 1.0 | 3.8 | 14 | Bladder | 1.8 | 4.9 |
| Testicular | 0.8 | 3.0 | 15 | Myeloma | 1.2 | 3.6 |

source: Eindhoven Cancer Registry
* European standard population; ** only in period 1979-86

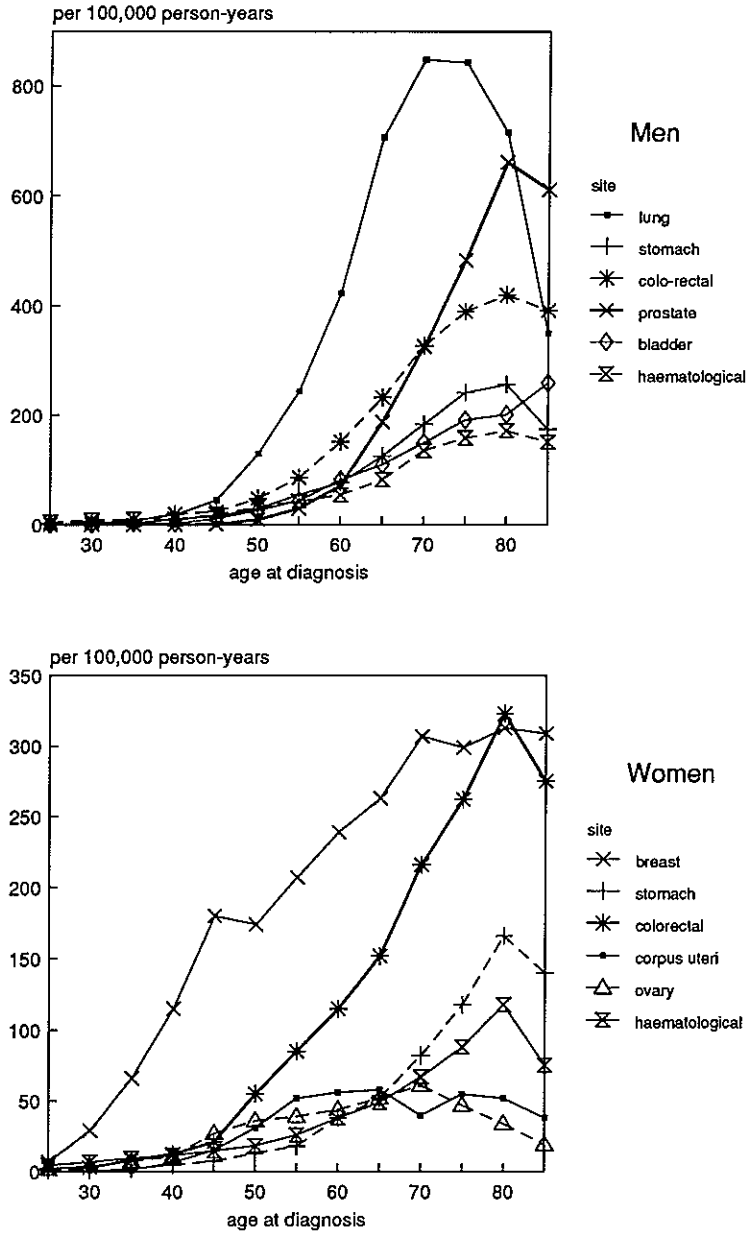


FIGURE 3 Age-specific incidence of the most common tumours in southeastern North Brabant and northern Limburg in the period 1975-86: per 100,000 person-years

TABLE 3 Age-adjusted* incidence of and mortality from cancer (all types) and all causes of death per 100,000 person-years, the lethality ratio and percentage of all deaths attributable to cancer in southeastern North Brabant and northern Limburg from 1975 to 1986, divided into 4 periods

| | Sex | 1975-77 | 1978-80 | 1981-83 | 1984-86 |
|---|---|---|---|---|---|
| Incidence of cancer (per $10^5$) | ♂ | 375# | 412 | 424 | 407 |
| | ♀ | 266# | 274 | 283 | 293 |
| Mortality from cancer (per $10^5$) | ♂ | 299 | 322 | 322 | 319 |
| | ♀ | 177 | 156 | 163 | 163 |
| Cancer lethality ratio (%) | ♂ | | 78% | 76% | 78% |
| | ♀ | | | 59% | 58% |
| Mortality all causes (per $10^5$) | ♂ | 1098 | 1102 | 1063 | 1033 |
| | ♀ | 665 | 629 | 600 | 602 |
| Cancer mortality/ | ♂ | 27% | 29% | 30% | 31% |
| total mortality (%) | ♀ | 27% | 25% | 27% | 27% |

* European standard population
\# some incompleteness possible

year. For the 60 to 74-year age group, there was little change in the percentages while the groups below 60 years of age exhibited considerable fluctuations.

The age-adjusted incidence of the different types of cancer varied considerably (table 4). Among men, the incidence of cancer of the lung, prostate, kidney, larynx and head & neck region increased in the first and/or second period but later decreased; up until 1984 an increase in melanomas of the skin and after 1978 cancer of the large intestine was seen. The incidence of stomach cancer decreased for men and women and that of gallbladder decreased for women. Among women, the incidence of cancer of the breast, lung, head-neck region, bladder increased in most periods; and temporarily, kidney as well as melanoma of the skin.

*Mortality*

The age-adjusted mortality due to cancer as percentage of the total mortality - which decreased markedly for women - remained constant for women at 27% and increased for men from 27% to 31% (table 3). The lethality ratio for men was almost 1.5 times higher than that for women and only changed for some types of cancer. In the course of time, mortality decreased with respect to the incidence of colorectal, endometrial, ovarian and kidney cancer as well as leukaemia and lymphoma in women and laryngeal, testicular and bladder cancer in men; the opposite was found for cervical cancer (table 5).

TABLE 4 Number of new patients and age-adjusted* incidence of cancer in southeastern North Brabant and northern Limburg in the periods 1975-77, 1978-80, 1981-83 and 1984-86, per 100,000 person-years

| Site | no. | 1975-77 | 1978-80 | 1981-83 | 1984-86 |
|---|---|---|---|---|---|
| **Males** | | | | | |
| Head & neck | 75 | 4.4# | 5.9 | 7.9 | 7.5 |
| Oesophagus# | 50 | 3.4 | 4.2 | 4.0 | 3.7 |
| Stomach | 300 | 34 | 33 | 29 | 28 |
| Colorectal | 500 | 53 | 51 | 57 | 58 |
| Gallbladder | 50 | 5.0 | 6.2 | 3.3 | 4.2 |
| Pancreas# | 50 | 6.8 | 9.8 | 10.2 | 8.9 |
| Larynx | 100 | 7.0# | 10.1 | 9.8 | 7.7 |
| Lung | 1200 | 122# | 139 | 136 | 128 |
| Melanoma | 50 | 3.2 | 3.9 | 6.2 | 4.9 |
| Prostate | 400 | 42 | 44 | 49 | 45 |
| Testis | 40 | 2.4 | 3.5 | 3.6 | 2.6 |
| Bladder | 250 | 26 | 26 | 26 | 28 |
| Kidney | 125 | 10.1 | 12.5 | 13.2 | 11.8 |
| Brain | 75 | 2.8# | 5.9 | 6.9 | 4.7 |
| Haematological | 300 | 22# | 26 | 28 | 28 |
| NOS/metastases | 175 | 12.2 | 15.1 | 16.8 | 18.4 |
| **Females** | | | | | |
| Head & neck | 30 | 1.3# | 3.0 | 2.5 | 3.0 |
| Oesophagus# | 20 | 0.8 | 1.1 | 1.3 | 1.4 |
| Stomach | 175 | 17.9 | 15.6 | 13.7 | 13.3 |
| Colorectal | 475 | 41 | 42 | 43 | 42 |
| Gallbladder | 75 | 7.5 | 6.6 | 5.2 | 5.1 |
| Pancreas# | 75 | 5.6 | 6.4 | 6.8 | 6.9 |
| Larynx | 10 | 0.2# | 0.7 | 0.8 | 0.9 |
| Lung | 90 | 5.9 | 7.2 | 8.7 | 10.2 |
| Melanoma | 75 | 3.9 | 6.4 | 8.1 | 7.2 |
| Breast | 1200 | 92 | 95 | 94 | 102 |
| Cervix uteri | 100 | 9.7 | 9.8 | 7.9 | 7.8 |
| Corpus uteri | 175 | 14.1 | 13.7 | 16.0 | 16.4 |
| Ovarium | 175 | 16.6 | 14.7 | 18.2 | 16.3 |
| Bladder | 75 | 3.8 | 4.2 | 4.5 | 7.3 |
| Kidney | 75 | 3.7 | 6.1 | 7.6 | 6.6 |
| Brain | 40 | 1.9# | 3.0 | 3.5 | 3.6 |
| Haematological | 225 | 17# | 16 | 18 | 19 |
| NOS/metastases | 125 | 12.5 | 10.2 | 11.6 | 14.6 |

# some incompleteness possible
* European standard population

TABLE 5 Number of deaths and age-adjusted* mortality due to cancer in southeastern North Brabant and northern Limburg in the periods 1975-77, 1978-80, 1981-83 and 1984-86, per 100,000 person-years (the lethality ratio of mortality and incidence in % is between parentheses)

| Site | no. | 1975-77 | 1978-80 | (%) | 1981-83 | (%) | 1984-86 | (%) |
|---|---|---|---|---|---|---|---|---|
| Males | | | | | | | | |
| Head & neck | 40 | 1.5 | 2.5 | | 3.4 | | 3.8 | |
| Oesophagus | 60 | 4.5 | 4.2 | | 3.6 | | 6.1 | |
| Stomach | 250 | 32 | 31 | (94) | 26 | (90) | 25 | (89) |
| Colon rectal | 325 | 35 | 33 | (62) | 34 | (66) | 37 | (65) |
| Gallbladder | 35 | 5.2 | 5.5 | | 2.7 | | 3.4 | |
| Pancreas | 120 | 11.4 | 11.5 | | 12.6 | | 12.4 | |
| Larynx | 35 | 3.3 | 3.4 | | 4.0 | (40) | 2.7 | (36) |
| Lung | 1200 | 123 | 136 | | 137 | | 130 | |
| Melanoma | 20 | 1.8 | 1.5 | (47) | 1.8 | (46) | 2.0 | (32) |
| Prostate | 225 | 21 | 26 | (62) | 22 | (50) | 26 | (53) |
| Testis | 8 | 0.6 | 1.1 | (46) | 0.9 | (25) | 0.3 | (8) |
| Bladder | 90 | 10.4 | 11.1 | (43) | 10.9 | (42) | 9.0 | (35) |
| Kidney | 75 | 6.0 | 6.6 | (65) | 8.9 | (42) | 6.6 | (48) |
| Brain | 60 | 3.9 | 5.3 | | 5.8 | | 4.7 | |
| Haematological | 210 | 16.3 | 20 | (77) | 22 | (79) | 22 | (79) |
| NOS/metastases | 150 | 11.1 | 12.3 | | 14.9 | | 14.8 | |
| Females | | | | | | | | |
| Head & neck | 15 | 0.6 | 1.1 | | 1.2 | | 1.1 | |
| Oesophagus | 20 | 0.9 | 1.6 | | 0.9 | | 1.6 | |
| Stomach | 150 | 20.1 | 13 | (84) | 11.9 | (86) | 12.4 | (93) |
| Colorectal | 300 | 29 | 27 | (66) | 25 | (60) | 25 | (58) |
| Gallbladder | 55 | 5.1 | 6.1 | | 4.9 | | 4.2 | |
| Pancreas | 110 | 7.5 | 9.6 | | 7.7 | | 9.6 | |
| Larynx | 4 | 0.2 | 0.2 | | 0.2 | | 0.5 | |
| Lung | 110 | 6.8 | 6.3 | | 9.4 | | 10.9 | |
| Melanoma | 20 | 1.2 | 0.8 | (21) | 1.2 | (19) | 1.9 | (23) |
| Breast | 450 | 44 | 34 | (37) | 40 | (42) | 37 | (39) |
| Cervix uteri | 45 | 4.1 | 3.6 | (37) | 4.1 | (42) | 3.6 | (46) |
| Corpus uteri | 40 | 3.7 | 4.4 | (32) | 3.4 | (25) | 3.6 | (23) |
| Ovarium | 125 | 14 | 11 | (76) | 11 | (62) | 10.3 | (63) |
| Bladder | 35 | 2.6 | 2.1 | (55) | 2.2 | (52) | 3.2 | (71) |
| Kidney | 60 | 3.0 | 3.2 | (86) | 5.1 | (84) | 4.8 | (63) |
| Brain | 35 | 2.8 | 2.2 | | 3.5 | | 3.1 | |
| Haematological | 180 | 13 | 12 | (75) | 12.6 | (70) | 12.3 | (65) |
| NOS/metastases | 100 | 10.6 | 9.9 | | 10.0 | | 9.2 | |

source: Central Bureau for Statistics
* European standard population

## DISCUSSION

So far studies on the occurrence of cancer in the Netherlands have been based on mortality data provided by the CBS and estimates derived from the diagnosis-upon-discharge register of in-patients admitted for the first time. On the whole the results agree with our studies. However, for the appraisal of trends, the results of a special cancer registry are to be preferred. The methods of collection and coding of data, based on international agreements, provide a more reliable basis for comparison. Not only completeness, but especially the uniform manner of registration is important, e.g. tumour type, stage at diagnosis and eventual occurrence of a second tumour.[6] Distortion of our results due to changes in methods of data collection is not very likely, since registration has taken place in a decentralized fashion in the various hospitals under supervision of the same physician since 1967. Another cause of the changes in incidence of cancer could be a change in medical management, for instance earlier diagnosis which increased and autopsy which decreased during the study period. Consider, for example, the introduction of new examination techniques such as mammography, echography, cytology, uroscopy and flexible endoscopy, which as a rule lead to higher rather than lower incidence rates of the tumours detected by means of these techniques. Although only screening for cervical cancer in about 50% of the female population was performed, we assume that a similar effect occurred in our population, partly due to the (almost) two-fold* increase in the number of specialists involved in the diagnosis and treatment of cancer patients. With the exception of ovarian and bladder cancer, we do not assume a virtual increase in the incidence of the cancers studied. The marked tendency towards earlier diagnosis of breast cancer occurred in the absence of screening.[7] Distortion of the incidence due to more intensive and more precise diagnostics appears to be insignificant, because the incidence of "unidentified" tumours and metastasis of unknown primary tumours increased in our study from 3.3% to 4.5% among men and from 4.5% to 5% among women, respectively. It should be noted that the marked increase in the incidence and survival demonstrated, for example, for cancer of the breast, prostate and uterus by the SEER programme (Surveillance, Epidemiology and End Results) in the United States in the seventies could have been in part due to this phenomenon. The investigation, carried out upon request of the Congress, into time trends and avoidability of the apparently increased cancer risks was therefore based mainly upon mortality rates.[8]

### *Trends of the individual types of cancer*

Our results clearly agree with the changes in national cancer mortality rates for the period 1969-81, i.e. cancer of the stomach, large intestine, lung, larynx and

* Adjusted for age distribution and population growth the increase would amount to about 30%.

head & neck region exhibited a steady increase among women - although the initial incidence was low - and an obvious turnabout was found in the incidence and mortality rates for these tumours for men in the 1980's.[9] Whereas we assumed some underregistration in the period 1975-77 for rare types of cancer, such as that of the brain and head & neck region and (certain types of) leukaemia and lymphoma, comparison of the incidence and mortality in all periods indicates that the same applies for cancer of the oesophagus, pancreas and lung. This is not entirely certain since in some (deceased) cases the diagnosis may have been based entirely on clinical findings.

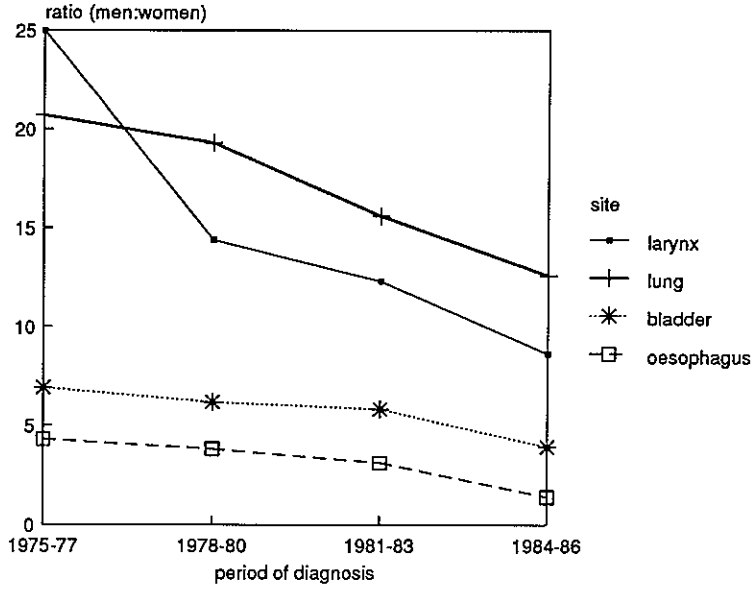


FIGURE 4 Male:female ratio for the incidence of tobacco-related types of cancer in southeastern North Brabant and northern Limburg in the period 1975-86

## *Influence of risk factors*

The decrease in the incidence of cancer of the airways, larynx and lung is presumably related to changes in smoking habits (J van Reek, written communication 1987); the male:female ratio, which was high in the sixties, has decreased (figure 4). However this area was also found to be part of a larger area with a relatively high mortality due to lung cancer among men: southeastern and western Netherlands, eastern Belgium, Saarland, Rhineland-Palatinate and Westphalia.[10] Presumably in addition to the use of tobacco, other risk factors related to environment and occupation may also have been important. Their influence on trend is unknown.

*Comparison within the Netherlands*

How representative are the results of an investigation that covers about 7% of the Dutch population? The incidences registered in the period 1968-72 in Friesland, the Hague and Rotterdam were in many respects lower - presumably also because of the incompleteness at that time.[11] If the survival rates per region are presumed equal, then the regional differences in cancer mortality can be considered primarily as indicators of differences in incidence. Mortality figures for the periods 1969-78 and 1979-82 revealed that, compared to the national average, mortality from and therefore the incidence of cancer of the stomach (men and women), large intestine (men and women), lung (men) and breast (women) was relatively high in southeastern North Brabant and northern Limburg; in contrast mortality from cancer of the oesophagus (men and women), pancreas (men and women), cervix and endometrium (women) and leukaemia and lymphoma (men and women) was relatively low.[12] Previously the strikingly high mortality due to lung cancer among European men had already been established. For an appraisal of the risk for many common forms of cancer within the Netherlands, regional contrasts in incidence or mortality may provide more insight than a national mean (see also appendix B).

*Conclusion*

The incidence of and mortality from cancer of all types did not change much in southeastern North Brabant and northern Limburg in the period 1975-86. For men the incidence increased until 1983 and then decreased, which may be explained largely by changes in smoking habits and thus in a lower incidence of tumours of the lower airways. Among women the incidence of such tumours increased. The incidence of cancer of the gastrointestinal tract also changed: a decrease of stomach cancer and an increase of cancer of the large intestine, only in males.

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Chapter 4.2

# Survival of cancer patients in southeastern Netherlands in the period 1975-1985:
## Report from the Eindhoven Cancer Registry*


SUMMARY

Relative survival was determined for all patients with cancer first diagnosed in the period 1975-85 in southeastern North Brabant and northern Limburg. Patient data were collected in community hospitals by the Eindhoven Cancer Registry, supplemented almost completely with information on date of death as of 31 December, 1987. Of the 22,744 patients 22% were over 75 years of age and 13% did not receive primary treatment of the tumour. The 5 and 10-year cumulative relative survival rates were 33% and 27% for men and 51% and 44% for women, respectively. The 10-year relative survival rate was more than 50% for Hodgkin's disease, melanoma and cancer of the testis, breast, larynx, thyroid, uterine cervix and corpus; it was less than 20% for multiple myeloma, cancer of the oesophagus, stomach, gallbladder, pancreas, lung and brain. Comparison with the 5-year relative survival rates for the various tumours reported in Finland, the Canton of Vaud and the United States revealed only small differences. The 5-year relative survival rate remained unaltered for men and increased for women from 50% in the period 1975-79 to 52% in 1980-85. Relative survival improved for children and for patients at age 30 to 44, while cancer mortality declined below age 45. Above age 60 survival improved for women and decreased for men and this was also confirmed by trends in cancer mortality and incidence.


INTRODUCTION

Estimates of the prognosis for patients with cancer can be derived from clinical studies, which usually focus on a group of selected patients, sometimes unselected from one hospital, but generally from a population-based survey. As a rule, the latter is based on a cancer registry and is especially suited for evaluation

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* Coebergh JWW, Crommelin MA, van der Heijden LH, Hop WCJ, Verhagen-Teulings MTh. Survival of cancer patients in southeastern Netherlands in the period 1975-85: report from the Eindhoven Cancer Registry. *Ned Tijdschr Geneesk* 1991; (in press) (in Dutch)

of changes with time. The question is often: does the management of cancer patients improve? Meinsma reported on the relative survival of cancer patients in the Netherlands who were listed in the, then national, registration scheme in the periods 1953-55 and 1956-58.[1,2] The aim of this study was to determine population-based survival rates for patients with cancer first diagnosed in the period 1975-85 in southeastern North Brabant and northern Limburg and recorded in the regional Eindhoven Cancer Registry. A comparison is made with equivalent data from cancer registries in some industrialized countries. For interpretation of changes in relative survival, trends in regional cancer mortality in the same period are considered[3] as well as changes in the supply of specialized care.

## PATIENTS AND METHODS

### *Patients and registration*

This study covered all patients living in southeastern North Brabant and northern Limburg, a region with almost 850,000 inhabitants served by the Eindhoven Cancer Registry. Included were all patients for whom a diagnosis of cancer was established for the first time between January 1, 1975, and January 1, 1986. Data on patients, disease and treatment were derived directly from clinical, and sometimes out-patient, records after notification by the pathology laboratories, the Department of Radiotherapy, medical records offices and secretariats of consultant groups; specialized clinics outside the registration area also supplied data on request. There were no cases known from death certificates only.

After exclusion of papilloma of the bladder, borderline tumours of the ovary and basal and squamous cell skin cancer, 23,685 tumours were registered among 22,833 patients in the period 1975-85. Per 31 December, 1987 we determined through municipal population registries whether each of the patients not known to be dead was alive on that date and if not, when death had occurred. Seventy-one (0.3%) patients were untraceable and 88 patients (0.4%) were lost to follow-up due to frequent changes of address. Tumours of the tongue, mouth and pharynx were combined into one group. No data are presented on either patient groups with less than 100 cases or leukaemias.

### *Estimation of survival*

The survival rates were calculated only for patients with first tumours according to the actuarial method.[4] In addition to the 71 untraceable patients, 18 patients (0.1%) were excluded because death preceded diagnosis. For comparison with other registries a separate calculation was carried out after exclusion of 1281 (5.6%) patients who died within one month of diagnosis.

The *observed* survival rate is based on death irrespective of the cause of death; the *relative* survival rate is the ratio of the observed survival rate for the patient group to the survival rate expected for a group similar in age distribution to the

group of patients at diagnosis.[5] It can be interpreted as the chance that the patient will not die of the disease. The expected survival rate is based upon age-specific mortality rates for other causes of death. Regional figures were derived from data from the Central Bureau of Statistics (CBS). For calculation of the relative survival rate heterogeneity in withdrawal was taken into account.[6] The special computer program of the Finnish Cancer Registry was used.[7] The standard error of relative survival was calculated according to Greenwood's formula.[8]

For the periods 1975-79 and 1980-85 relative survival rates were also computed for all cancers separately and combined according to 15-year age groups and sex starting with age 30. Tumour-specific data are only presented per period in the event of marked differences. Regional age-adjusted (European standard population[9]) and age-specific cancer mortality rates were computed per 100,000 person-years for the period 1975-86, which was divided into periods of 3 years each.

## RESULTS

This study included 22,833 patients with 23,685 tumours; after exclusion of 71 untraceable and 18 patients with a diagnosis before death 22,744 patients could be evaluated, of whom 88 were lost to follow-up. Table 1 presents an overview per tumour of the total number of patients and the percentage males, patients ≥75 years and those with an untreated tumour. On the average men were 64 at the time of diagnosis, women were 61. Although the percentage patients with an untreated tumour increased with age, 23% were over 75 years of age, the relation with old age was not consistent. Figure 1 shows the cumulative observed, expected and relative survival rates for all types of cancer: the 5 and 10-year relative survival rates were 33% and 27% for men and 51% and 44% for women, respectively. When cancer of the lung was excluded, the 5 and 10-year relative rates for men were 43% and 36%, respectively. In the first two years after diagnosis the annual relative survival rates were considerably higher for women than for men (figure 2). Annual excess mortality for women became less than 5% after 5 years and for men after 7 years. Tumour-specific data (table 2) revealed marked mutual differences. Compared to 5 years after diagnosis the difference between the observed and relative survival rates generally doubled after 10 years. The 10-year relative survival rate was more than 50% for patients with melanoma of the skin, Hodgkin's disease and cancer of the uterine cervix and corpus, testis, larynx, breast and thyroid and less than 25% for multiple myeloma and cancer of the oesophagus, stomach, gallbladder, pancreas, lung and brain.

Compared with the period 1975-79 the 5-year relative survival rates increased for women in 1980-85 from 50% to 52% and for most patients younger than 45 years (table 3). Survival of older men declined, while it improved for women. Five year relative survival rates increased for women with breast cancer

**TABLE 1 Number of patients with a first cancer, the percentages male, patients over 75 years and those untreated**

| Tumour site | Patients no. | Male % | ≥75 yrs % | Untreated % |
|---|---|---|---|---|
| Mouth/pharynx | 232 | 69 | 21 | 5 |
| Oesophagus | 163 | 73 | 24 | 18 |
| Stomach | 1520 | 62 | 31 | 23 |
| Colon | 1987 | 46 | 29 | 5 |
| Rectum | 1237 | 57 | 25 | 5 |
| Gallbladder | 364 | 37 | 37 | 19 |
| Pancreas | 510 | 54 | 26 | 27 |
| Larynx | 290 | 92 | 14 | 5 |
| Bronchus | 4248 | 93 | 19 | 20 |
| Soft tissue | 163 | 60 | 9 | 1 |
| Melanoma | 425 | 39 | 11 | 1 |
| Breast | 3395 | 0 | 15 | 1 |
| Cervix uteri | 329 | 0 | 12 | 1 |
| Corpus uteri | 520 | 0 | 16 | 1 |
| Ovary | 598 | 0 | 11 | 5 |
| Prostate | 1255 | 100 | 44 | 4 |
| Testis | 140 | 100 | 3 | 1 |
| Bladder | 1003 | 82 | 26 | 4 |
| Kidney | 561 | 61 | 22 | 13 |
| Brain | 318 | 61 | 5 | 30 |
| Thyroid | 113 | 30 | 10 | 4 |
| Non-Hodgkin's | 537 | 59 | 20 | 18 |
| Hodgkin's disease | 183 | 55 | 7 | 5 |
| Multiple myeloma | 275 | 51 | 29 | 16 |
| All | 22,744* | 55 | 22 | 13.3 |

source: Eindhoven Cancer Registry
* including other sites

(from 67% to 71%), ovarian cancer (from 30% to 45%), cancer of the stomach (from 17% to 22%), while decreasing of cervical cancer (from 65% to 60%). For men an increase was observed of melanoma of the skin (from 59% to 68%) and testicular cancer (from 78% to 90%), while it decreased of the colon (from 57% to 49%) and lung (from 13% to 11%). Survival rates increased of Hodgkin's disease (from 71% to 80%) and decreased of non-Hodgkin's lymphoma (from 47% to 41%).

Age-specific cancer mortality figures for children and young adults generally decreased; they increased among males older than 30 years until 1981, but have decreased since then, except among the elderly. Among women cancer mortality decreased until 1981 and has remained stable since then, again except for the elderly.

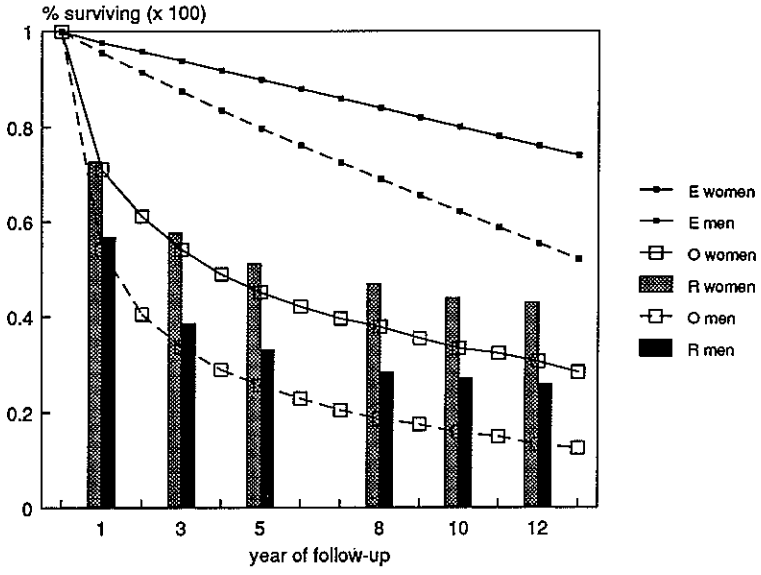


FIGURE 1 Cumulative survival of cancer patients (all sites) in southeastern Netherlands, 1975-85: observed (O), expected (E) and relative (R)

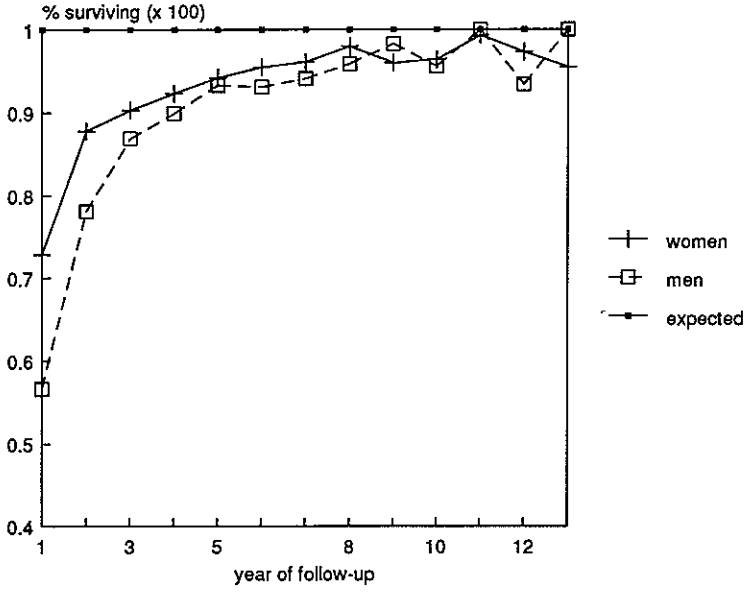


FIGURE 2 Annual relative survival rates for cancer patients (all sites) in southeastern Netherlands, 1975-85.

**TABLE 2 Five and ten year cumulative survival [observed (O) and relative (R)] of cancer in the period 1975-85**

| Tumour side | | year 5 O (%) | year 5 R (%) | year 5 SE# (%) | year 10 O (%) | year 10 R (%) | year 10 SE# (%) |
|---|---|---|---|---|---|---|---|
| Mouth/pharynx | | 38 | 47 | (4.1) | 29 | 43 | (5.4) |
| Oesophagus | | 7 | 9 | (2.6) | 3 | 4 | (3.0) |
| Stomach | | 17 | 21 | (1.3) | 11 | 19 | (1.7) |
| Colon | | 40 | 50 | (1.4) | 29 | 46 | (2.1) |
| Rectum | | 33 | 41 | (1.7) | 22 | 36 | (2.5) |
| Gallbladder | | 9 | 11 | (1.9) | 6 | 11 | (2.6) |
| Pancreas | | 4 | 5 | (1.0) | 1 | 2 | (1.4) |
| Larynx | | 59 | 71 | (3.6) | 40 | 62 | (6.5) |
| Lung | ♂ | 10 | 12 | (0.6) | 5 | 9 | (0.8) |
| | ♀ | 16 | 18 | (2.5) | 12 | 15 | (3.1) |
| Soft tissue | | 52 | 56 | (4.3) | 43 | 51 | (5.6) |
| Melanoma | ♂ | 59 | 65 | (4.4) | 48 | 58 | (5.7) |
| | ♀ | 78 | 84 | (2.9) | 65 | 77 | (4.9) |
| Breast | | 62 | 69 | (1.0) | 44 | 55 | (1.4) |
| Cervix uteri | | 58 | 63 | (3.0) | 48 | 57 | (3.8) |
| Corpus uteri | | 72 | 80 | (2.3) | 61 | 77 | (3.4) |
| Ovary | | 35 | 39 | (2.2) | 28 | 34 | (2.9) |
| Prostate | | 36 | 54 | (2.1) | 16 | 40 | (3.6) |
| Testis | | 81 | 84 | (3.6) | 75 | 81 | (4.8) |
| Bladder | ♂ | 50 | 66 | (2.4) | 29 | 53 | (4.2) |
| | ♀ | 37 | 46 | (4.8) | 22 | 36 | (7.7) |
| Kidney | | 38 | 45 | (2.5) | 26 | 38 | (3.5) |
| Brain | | 23 | 25 | (2.6) | 16 | 19 | (4.0) |
| Thyroid | | 65 | 70 | (5.0) | 54 | 65 | (7.8) |
| Non-Hodgkin's | | 37 | 43 | (2.5) | 22 | 31 | (3.6) |
| Hodgkin's disease | | 73 | 76 | (3.6) | 59 | 66 | (5.3) |
| Multiple myeloma | | 22 | 27 | (3.2) | 5 | 9 | (3.1) |

source: Eindhoven Cancer Registry
# standard error of R

## DISCUSSION

These population-based survival rates give an impression of the state of affairs for unselected patients with cancer diagnosed and treated in community hospitals in southeastern Netherlands. At first glance, the relative survival rates for the various tumours are not surprising: the 5-year relative survival rate of 42% is an aggregate figure. In a previous study of patients with Hodgkin's disease from the ECR-area in the period 1972-83 5-year survival in the ECR-area was about similar to that in Dutch specialized centers.[10] Further analyses, directed at the cause of these changes, will be tumour-specific or age-specific. Some examples are given. The increase of the 5-year relative

TABLE 3 Five year cumulative survival [observed (O) and relative (R)] of cancer in southeastern North-Brabant and northern Limburg in the periods 1975-79 and 1980-85: per age group and sex

| Age (yrs) | Sex | % of total number | 1975-79 O (%) | 1975-79 R (%) | 1975-79 SE# (%) | 1980-85 O (%) | 1980-85 R (%) | 1980-85 SE# (%) |
|---|---|---|---|---|---|---|---|---|
| 0-14 | ♂+♀ | 1 | 63 | 63 | (4.8) | 72 | 72 | (4.5) |
| 15-29 | ♂+♀ | 2 | 69 | 70 | (3.5) | 70 | 70 | (2.9) |
| 30-44 | ♂ | 5 | 44 | 44 | (3.2) | 52 | 53 | (2.7) |
| | ♀ | 12 | 60 | 61 | (2.3) | 69 | 69 | (1.9) |
| 45-59 | ♂ | 22 | 33 | 35 | (1.5) | 34 | 36 | (1.3) |
| | ♀ | 28 | 56 | 57 | (1.5) | 56 | 57 | (1.3) |
| 60-74 | ♂ | 48 | 23 | 30 | (1.1) | 23 | 28 | (1.0) |
| | ♀ | 36 | 40 | 44 | (1.4) | 43 | 47 | (1.3) |
| ≥75 | ♂ | 22 | 14 | 27 | (2.1) | 13 | 25 | (1.8) |
| | ♀ | 21 | 21 | 33 | (2.4) | 22 | 35 | (1.9) |
| All ages | ♂ | 100 | 26 | 33 | (0.8) | 26 | 33 | (0.7) |
| | ♀ | 100 | 44 | 50 | (0.9) | 45 | 52 | (0.8) |

source: Eindhoven Cancer Registry
# standard error of R

TABLE 4 Trends in age-specific mortality from cancer in southeastern North-Brabant and northern Limburg in 1975-86, divided in 4 periods: by sex

| Age (yrs) | Sex | Mortality per 100,000 person-years in: 1975-77 | 1978-80 | 1981-83 | 1984-86 |
|---|---|---|---|---|---|
| 0-14 | ♂+♀ | 4.7 | 4.1 | 3.8 | 3.0 |
| 15-29 | ♂+♀ | 8.5 | 5.0 | 4.8 | 6.2 |
| 30-44 | ♂ | 30 | 35 | 29 | 36 |
| | ♀ | 56 | 37 | 41 | 40 |
| 45-59 | ♂ | 242 | 253 | 244 | 228 |
| | ♀ | 210 | 171 | 197 | 178 |
| 60-74 | ♂ | 1120 | 1225 | 1269 | 1197 |
| | ♀ | 567 | 522 | 514 | 523 |
| ≥75 | ♂ | 2354 | 2884 | 2818 | 3001 |
| | ♀ | 1327 | 1250 | 1305 | 1345 |
| All ages | ♂ | 299 | 322 | 322 | 319 |
| | ♀ | 177 | 156 | 163 | 163 |

source: Central Bureau for Statistics

survival rate for patients with breast cancer is certainly related to earlier diagnosis.[11] The increased survival rate for patients with testicular cancer, accompanied by a decreasing mortality - not influenced by incidence - is almost certainly due to intensification of treatment.[12] According to a multivariate analysis, the improved prognosis for women with ovarian cancer - even after exclusion of borderline tumours - applied especially for those below 70 and was accompanied by a decreased mortality below age 60; despite increased application of more efficacious therapy, a more favourable stage distribution - despite stage migration and/or a more benign natural history - may have played a role.[13] For cervical cancer population-based screening from 1975-82 has led to a more favourable stage distribution also of invasive cancer and thus biassed survival rates. Lung and colon cancer as well as non-Hodgkin's lymphoma showed an increased incidence for elderly men.

For patients registered in 1956-58 in the national study, the 5-year relative survival rates were 16% for men and 33% for women.[2] The increase in survival may in part be caused by a different distribution of tumours, in part by improvements for specific tumours; tumours withmarked improvements are listed below with the figures for 1956-58 shown in parentheses, to be compared with the 5-year relative survival rates in table 2: cancer of the stomach (10%), colon (32%), rectum (32%), larynx (50%), lung (7%), melanoma (38%), breast (46%), ovary (18%), prostate (30%), testis (44%), bladder (25%) and kidney (18%) and haematological malignancies (15 to 20%). In addition to improved treatment and supportive care the observed differences are in part due to a more favourable stage distribution as a result of earlier diagnosis - a process that has also become more sensitive and has led to shifts in pathological classification, e.g. for early gastric cancer, 'borderline' tumours of the ovary and papillomas of the bladder. On the other hand, more patients with tumours in an advanced stage may also have been registered as a result of better access to specialized care. After 1965 most hospitals in this area were renovated and/or expanded and the number of specialists involved in the management of patients with cancer increased during the seventies by about 25%, after correction for population growth and ageing. Despite the absence of a regional specialized centre some active tumour study groups were founded, e.g. for haemato-oncological, breast and gynaecological cancer.

Comparisons with registries in Finland,[14] Switzerland (canton de Vaud)[15] and the USA (Surveillance Epidemiology End Results Program, whites only)[16] revealed more similarities than differences. Relative survival rates for prostate (73%) and bladder (77%) cancer were clearly higher in the USA (see also appendix D) . Comparison of tumour-specific population-based survival rates should be stratified according to age and histological type, but can still be hampered by differences in the detection process, selective access to specialized care and as a result from varying registration procedures.[17] The determination of the moment of diagnosis and the numbers of cases with death certificates only may also be important. For instance in our study only 0.4% of patients

were excluded, versus 5% in the Swiss study, 7.5% in the Finnish[18] and an unknown percentage in the American study. In a recent study in Sweden 13% of registered cases were excluded from analysis which may largely explain the relatively high 5-year relative survival rates of 47% for men and 57% for women.[19] However, lung cancer in males is also 3 times less common in Sweden. When, for comparative reasons the relative survival rates were also computed after exclusion of those (5.6%) who died in the first month after diagnosis (table 2), the 5-year survival rate for males became 35% and for females 53%. For a more specific evaluation of (the lack of) changes in survival that takes potentially present artificial changes in incidence into account, several approaches to standardization have been considered. Feinstein suggested refinement of prognostic factors by supplementing staging information according to the TNM with a clinical taxonomy of - the duration and severity of - symptoms and of prognostic co-morbidity.[20] Bailar stressed the necessity of using age-adjusted cancer mortality rates as the bottom-line indicator of disease severity.[21] However, changes in cancer mortality can be caused by both changes in incidence and treatment and changes in cause of death due to other competing diseases. Among the middle-aged 40-50% of the total mortality is due to cancer and this decreases to less than 15% for the elderly. Analogous to an analysis by the Dutch scenario-committee[22] Doll analysed trends in age-specific cancer mortality in some European countries and concluded that better treatment results had most likely been obtained for younger patients, whereas underlying changes in incidence were more likely to affect cancer mortality for the middle-aged and elderly.[23] In southeastern Netherlands two opposite trends in cancer mortality were seen: falling rates for the young and rising rates for the elderly. Cancer mortality rose for adult men until 1981 and has declined since then, while for women it decreased until 1981 and then stabilized. For the elderly of both sexes an increase was observed. Trends in incidence and mortality rates for tobacco-related tumours, showing a decline for men and an increase for women,[3] certainly affected these cancer mortality rates. An indication of the possible influence of competing diseases is the marked decrease of the characteristically high (male) mortality due to cardiovascular diseases[24] in this region in the period 1970-86, whereas the overall cancer mortality rates did not change all that much (see appendix C).

## *Conclusion*

The survival of cancer patients in southeastern Netherlands does not differ much from that in other industrialized countries; it appears to be improving gradually for patients under 45 years of age and more or less stable in patients over this age, which would be in agreement with trends in cancer mortality and incidence.

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Chapter 4.3

# EPIDEMIOLOGICAL ASPECTS OF CANCER IN THE ELDERLY*


## SUMMARY

The incidence of cancer, especially the epithelial non-sex-related forms, increases exponentially with age. It appears that exposure to exogenous factors is the primary cause, especially for men. The percentage deaths due to cancer of the total number of deaths first increases and then decreases with increasing age. Also, it increases with time in each age group over 60 years of age, which may also be related to the decreasing mortality due to cardiovascular, cerebrovascular and pulmonary diseases. The prognosis of cancer decreases with increasing age, although this difference is less if death due to other causes is taken into account. The poorer prognosis for the elderly is generally explained by a more unfavourable stage distribution which in turn is partly attributable to "patient delay" and doctor's delay; the latter may be a result of the insufficient specificity of complaints and symptoms at older age. Whether the prognosis for the elderly is truly worse and whether they are over- or undertreated can only be evaluated with a more precise prognostic index which should include not only histological type and TNM stage at diagnosis but also co-morbidity and duration of the complaints as an indicator of tumour growth. The number of elderly patients with cancer may increase in the future by more than 2% per year and the percentage requiring home care by about 5% per year.


## INTRODUCTION

This paper on the incidence and prognosis of cancer among the elderly focusses on several basic questions: does ageing as a process play a role in the risk for cancer, is the prognosis worse for the elderly - also after correction for death due to other causes, and how will cancer in the elderly affect the demand for care in the near future?

For practical purposes only the more common tumours are considered in detail. Each general practitioner has in his practice on average 35 patients with cancer, about 25 or 70% of whom are older than 60 years and 9 or 25% are


* Coebergh JWW. Epidemiological aspects of cancer in the elderly. *The Practitioner* 1990;10:753-57 (in Dutch)

over 75 years. Every year a GP sees on average 8 new patients with cancer, 5 of whom are older than 60 years while 2 are over 75 years. These data are derived from the cause-of-death statistics of the Netherlands Central Bureau of Statistics (CBS) and the regional Eindhoven Cancer Registry, which has collected information from patient records in all hospitals in southeastern North Brabant and northern Limburg since 1975.[1] Some underestimation of the figures is possible, especially for the elderly, since not all of these patients are referred to a hospital and underdiagnosis due to concomitant diseases is possible. Based on (higher) mortality statistics this appears to apply especially for patients with lung, oesophagus, pancreas and brain cancer, which is largely confirmed by a survey of cancer incidence in general practice in 1983-85.[2] To permit a comparison with clinical studies the percentage of patients whose tumour was primarily not treated is also given.

## FREQUENCY

There are large differences in the incidence and mortality of cancer in the Netherlands between men and women (table 1). Despite a clearly higher incidence for men, the prevalence for women is higher because they have relatively more tumours with a favourable prognosis (table 2). Although the incidence of cancer among elderly women is much lower than that for men, the number of female patients with cancer is significantly higher because of the larger number (50% more) of elderly women at risk (not shown in table 2). The differences in incidence and mortality (not shown) between men and women are 5 to 15-fold for cancer of the lung, the head & neck region and the bladder and are smaller (1.1 to 1.5-fold) for cancer of the gastrointestinal tract and leukaemia and lymphoma. Excessive and prolonged use of tobacco and alcohol (of high percentage) and occupational exposure to certain chemicals appear to be responsible for these large differences.[3] Little is known with certainty about the role of diet as a separate cause of cancer. The marked decrease in the incidence and mortality of stomach cancer throughout the

TABLE 1 Basic epidemiological data on cancer in the Netherlands in 1985, according to sex

| Ratio | | Males | Females | ♂/♀ |
|---|---|---|---|---|
| Mortality | per $10^5$/year* | 305 | 165 | 1.85 |
| | no. of patients | 19,000 | 14,000 | 1.35 |
| Incidence | per $10^5$/year* | 405 | 290 | 1.40 |
| | no. of patients | 25,400 | 22,400 | 1.15 |
| Prevalence | per $10^5$/year* | 1595 | 1635 | 0.95 |
| | no. of patients | 88,000 | 129,000 | 0.68 |
| Survival# | 5-year | 32% | 50% | 0.64 |
| | 10-year | 25% | 42% | 0.49 |

source: Eindhoven Cancer Registry and CBS
* European standard population; # cumulative relative rate

**TABLE 2 Age-specific incidence of cancer in the elderly per 100,000 person-years, according to sex (in order of male frequency)**

| | Incidence by age group (years) | | | |
|---|---|---|---|---|
| | 60-74 | | ≥75 | |
| Site | ♂ | ♀ | ♂ | ♀ |
| Lung | 589 | 33 | 811 | 24 |
| Breast | | 261 | | 310 |
| Skin (only first tumour) | 322 | 174 | 700 | 410 |
| Prostate | 183 | | 544 | |
| Colon | 138 | 98 | 300 | 198 |
| Stomach | 115 | 49 | 220 | 141 |
| Bladder | 158 | 19 | 254 | 40 |
| Rectum | 97 | 49 | 178 | 94 |
| Leukaemia & lymphoma | 92 | 49 | 205 | 114 |
| Head-neck region | 83 | 12 | 93 | 21 |
| Endometrial | | 56 | | 55 |
| Ovary | | 52 | | 36 |
| Pancreas/gallbladder | 59 | 46 | 89 | 103 |
| All forms of cancer except skin | 1719 | 899 | 3035 | 1435 |

source: Eindhoven Cancer Registry, 1983-87

western world has not for example been explained satisfactorily. Only slight changes in the incidence of cancer will be observed in the near future: tobacco-related tumours will probably decrease among men and increase among women. Table 3 shows an estimate of the number of cancer patients per general practitioner in the Netherlands in 1990, irrespective of age; two-thirds is usually over 60 years of age and 25% over 75. In view of the

**TABLE 3 Estimation* of the average number of patients with cancer per general practice in 1990**

| Site | New per year | Present at given time |
|---|---|---|
| Lung | 1.3 | 1.8 |
| Breast | 1.1 | 8 |
| Skin (only first) | 1 | ? |
| Large bowel | 1 | 5 |
| Gallbladder/pancreas | 1/4 | 1/4 |
| Stomach | 2/5 | 1 |
| Prostate | 2/5 | 1.5 |
| Bladder | 1/3 | 1.5 |
| Leukaemia & lymphoma | 1/3 | 2 |
| Endometrium | 1/6 | 1 |
| Ovary | 1/6 | 1/2 |
| Cervix (invasive) | 1/10 | 1 |
| All forms of cancer except skin | 8 | 35 |

* based on Eindhoven Cancer Registry 1983-87 and 7000 practices of 2200 patients

expected demographic changes, the total number of (new) elderly cancer patients will increase by more than 1.5% per year.[3] This increase will be greater if the age-specific incidence would also be rising. This may indeed be the case in view of the currently decreasing mortality from cardio-, cerebrovascular and pulmonary diseases. According to national cause-of-death statistics the proportion of all deaths that is attributed to cancer has been increasing for men and women over 60 years of age for many years. For men, this was an obvious development because at the same time age-specific cancer mortality also increased; however for women the age-specific cancer mortality decreased, so that mortality due to other causes decreased even more rapidly. Despite a markedly increasing incidence and mortality of cancer with age, the relative mortality decreases from 40% for a 65-year-old to about 15% for an 85-year-old. This relative change is about the same for men and women whereas the incidence of cancer among the elderly differs markedly per sex (table 2). For the older age groups, death due to cancer and therefore the incidence may thus partly influenced by death due to other causes. In view of the decreasing mortality for competing causes of death and the demographic predictions for the Dutch population, expected increases in the number of new patients with cancer over 70 years will be even greater, possibly as much as 15-20% in the next 5 years. General practitioners in larger cities may observe a greater increase among migrants from southern countries, because the number of elderly among this group will increase markedly.[4] A pronounced increase in the need for palliative care for cancer patients, largely in the home care circuit, can thus be expected, leading to an increasing demand for medical and nursing care.[5]

## DOES AGEING PROMOTE THE DEVELOPMENT OF CANCER?

This popular belief has been supported by the exponential increase in the incidence of most of the common forms of cancer. Possible explanations are a decreased immunological resistance and diminished DNA-repair capacity. The decrease in the incidence after 80 years of age would then be explained predominantly by selection of the "strongest", i.e. those with better physiological functions, whereby less intensive diagnostics for the elderly may of course lead to underdiagnosis. However, for epithelial tumours, which are responsible for approximately two-thirds of the deaths due to cancer, a strong relation between ageing and the development of cancer would seem less likely because the role of exogenous risk factors is fairly well known.[6] This has also been confirmed by means of animal experiments and fits in well with the theories developed in the 'fifties on the development of cancer as a multistep process, usually 4 to 6 steps.[7] To give this process a chance a sufficiently long life is required. Acceleration of the steps may occur due to intensive exposure to exogenous factors, such as tobacco, liquor and harmful occupational substances such as asbestos, which applies predominantly for men.[8] The occurrence of tumours of the sexual organs, the incidence of which is relatively high for

middle-aged women, appears to be attributed chiefly to age-dependent hormones related to childbearing activities and exposure to viruses, in part connected to sexual activities. It is also feasible that ageing plays a role in the development of cancer of the prostate since the incidence continues to increase with age, also among the elderly. For non-epithelial tumours, for instance of the bones, soft tissues, skin (melanoma), brain and eye, as well as leukaemia and lymphoma, incidence does not rise as markedly with age.

The foregoing implies that primary prevention of cancer in the elderly, if at all possible, must take place at a considerably younger age and mainly among men. If an elderly individual were to stop or cut down on excessive alcohol or tobacco use, the preventive effect on cancer would presumably be small.

## DOES AGEING OR OLD AGE INFLUENCE THE PROGNOSIS FOR CANCER?

Do cancer survival rates decrease with increasing age, also when corrected for mortality due to other diseases - which gives the so-called relative survival rates? As is to be expected, the difference between the observed uncorrected and the relative survival rates increases with increasing age (table 4). The difference seems larger for patients with cancer of the breast, prostate and large bowel, who may rather die of other diseases, but smaller for patients with lung and stomach carcinoma. Other factors which can influence survival rates for patients with cancer are listed in table 5. The distribution according to histological type and other tissue characteristics can vary with age for the different types of cancer; for example, small cell lung cancer becomes relatively less frequent in the elderly. Stage at diagnosis is an important prognostic factor, although lead time and length time bias, which could be corrected for severity and duration of symptoms, are often ignored. In registry-based studies, the

TABLE 4 **Five-year cumulative observed (obs) and relative (rel) survival rates for elderly patients with common cancer in the period 1975-85**

| Site | | 5-year survival rate (%) by age (yrs) 45-59 | 60-74 | ≥75 |
|---|---|---|---|---|
| Lung | obs | 17 | 9 | 2 |
| | rel | 18 | 12 | 4 |
| Breast | obs | 71 | 59 | 38 |
| | rel | 72 | 66 | 60 |
| Prostate | obs | 56 | 44 | 25 |
| | rel | 60 | 57 | 49 |
| Colon | obs | 49 | 42 | 23 |
| | rel | 51 | 50 | 40 |
| Stomach | obs | 26 | 15 | 10 |
| | rel | 27 | 18 | 18 |

source: Eindhoven Cancer Registry, 1990

TABLE 5 Prognostic factors for cancer survival

| |
|---|
| Histological type and grade of differentiation |
| Stage at diagnosis |
| Prognostic co-morbidity |
| Choice of therapy |

distribution of patients according to stage, based on the TNM (tumoursize, node, metastasis) system, becomes much less favourable with increasing age, except for lung cancer. This may be the result of delay, as seen retrospectively, by patient and doctor rather than specific characteristics of the tumour. In view of the unspecific nature of complaints and symptoms in the early phase of the disease, also due to the possible presence of a variety of other diseases in the elderly, this does not come as a surprise. Nylenna demonstrated convincingly that the predictive value of most complaints and symptoms encountered in the practice of a general practitioner is not more than 5%.[9] In addition to treatment, concomitant disease also has considerable influence on the prognosis: consider, for example, diabetes mellitus, pulmonary diseases and (predictors of) cardiovascular diseases.[10] The nature of the co-morbidity may also depend on common risk factors such as smoking habits and obesity. After extensive studies of co-morbidity and duration of complaints (for correction of eventual lead time) among patients with lung, breast and endometrial carcinoma, Feinstein questioned the validity of the strict oncological view of a clinical reality based only on classification of stage and histological type.[11] He suggests that co-morbidity and duration and severity of complaints should also be taken into account as prognostic factors. The discussion on presumed overtreatment or undertreatment of elderly patients would then appear instead to deal with exceptions to rules that are not well-defined. Directly related in this respect is the question of whether and to what extent treatment is meant to be curative or palliative. We therefore also considered data on the percentage patients who received no treatment for their tumour in the period 1984-87 (table 6). It may not come as a surprise that this percentage increases with age. The survival rates listed in table 4 must be evaluated with this in mind. These figures may still be an underestimation of reality since only patients who were referred to a hospital were included.

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**TABLE 6 Patients with untreated cancer in the period 1984-87, according to age**

| Site | Untreated tumour (%) by age (yrs) 45-59 % | 60-74 % | ≥75 % |
|---|---|---|---|
| Stomach | 9 | 18 | 37 |
| Colon | 3 | 5 | 7 |
| Rectum | 2 | 3 | 10 |
| Lung | 11 | 17 | 39 |
| Prostate | 3 | 3 | 6 |
| Breast | 1 | 1 | 2 |
| Ovary | 1 | 8 | 19 |
| Bladder | 3 | 2 | 8 |
| Non-Hodgkin's lymphoma | 11 | 15 | 38 |
| All | 8 | 13 | 23 |

source: Eindhoven Cancer Registry

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CHAPTER 5

# INCIDENCE, SURVIVAL AND MORTALITY FROM SPECIFIC MALIGNANT TUMOURS

Chapter 5.1.1

# HAEMATOLOGICAL MALIGNANCIES IN COMMUNITY HOSPITALS IN SOUTHEASTERN NETHERLANDS:

## A registry-based study of incidence and survival in the period 1975-1987*


ABSTRACT

A population-based study was carried out to assess the frequency and prognosis of haematological malignancies (HM) in southeastern Netherlands. Data on 2016 patients diagnosed in the period 1975-87 in 11 community hospitals were collected directly from medical records by the Eindhoven Cancer Registry, that also traced referrals to specialized centres. HM were relatively common among young cancer patients, but more than 50% of our patients were over 60 years of age. The European standardized incidence rates were relatively high for males and about average for females, being 29.5 per 105 and 17.6 per 105 person-years, respectively. They resembled the incidence rates recently found in Britain. As in Norway and Denmark, an increase in acute non-lymphocytic leukaemia and non-Hodgkin's lymphoma (NHL), mainly among the elderly, was observed; despite better and earlier detection a decrease was observed in the incidence of CLL, especially for women, in part because of a shift in classification from CLL to NHL (immunocytoma). This would largely explain the improved 5-year relative survival of CLL patients from 52% in the period 1975-79 to 72% in 1980-85. Relative survival rates for patients with every type of HM, only determined for 1608 patients diagnosed from 1975-85, were similar to those of the SEER program for 1977-84. Survival improved mainly for the elderly, while rates for younger patients remained largely unaltered; a temporary decrease in mortality suggested short term treatment effects. As of 1986 the age-adjusted point-prevalence of HM was 97 and 74 per $10^5$ persons for males and females, suggesting an average duration of disease of 3.3 and 4.2 years, respectively.


* Coebergh JWW, Bosch LJ, Breed WPM, Crommelin MA, van der Heijden LH, Keuning JJ, Vrints LH, Verhagen-Teulings MT. Haematological Malignancies in community hospitals: a registry-based study of incidence and survival in southeastern Netherlands in the period 1975-87. (submitted)

## INTRODUCTION

Albeit rare with respect to other cancers, especially when viewed by (sub)type, haematological malignancies (HM) are of major clinical and epidemiological interest for two reasons: first, incidence among the young and middle-aged individuals is relatively high and second, marked improvements in the prognosis have occurred since the sixties due to more refined diagnosis, systemic treatment and better supportive care, that was initially offered mainly to younger patients in specialized centres.[1 2 3] In the seventies the arrival of newly trained haematologists in community hospitals may have resulted in more effective treatment for all patients with HM, also in southeastern Netherlands. Therefore, we carried out a study of survival of all patients with HM in southeastern Netherlands during the period 1975-87 by means of the Eindhoven Cancer Registry.[4] Since 1978, a regional study group for haemato-oncology regularly discussed patient management, reviewed diagnoses and examined in-depth prognostic factors for Hodgkin's disease, especially nodular sclerosing.[5]

Since changes in the diagnostic process may exert an influence on incidence and thus survival, we also considered trends in regional mortality as a bottom-line indicator of severity.

This study aims to give an overview of incidence and survival and compare morbidity figures (including prevalence) with data from Great Britain and the U.S.A. as well as with previously made estimations used for long-term planning of specialized health care in the Netherlands.[6]

## PATIENTS AND METHODS

### *Registry*

The Eindhoven Cancer Registry, started in 1955, operates in an area in southeastern North Brabant and northern Limburg, which is also served by the Department of Radiotherapy in Eindhoven. The area comprises almost one million inhabitants, 7% of the Dutch population, with a population density of 400 per $km^2$; 12% live in rural communities.

All 2016 registered patients with HM were diagnosed between January 1, 1975, and December 31, 1987. Data were collected by trained registry personnel in 12 - now 8 as a result of mergers - community hospitals directly from medical records, after routine notification of newly diagnosed cancers by 3 regional pathology laboratories, as well as by hospital medical archives, the radiotherapy department and clinical data from the secretariats of consultants. Referrals to clinics outside the region since 1973 were traced, especially in the Departments of Haematology and Children's Oncology of the Nijmegen University Hospital, and the two specialized cancer hospitals in Rotterdam and Amsterdam. Data for children were also cross-checked with the laboratory-based registry of the Dutch Childhood Leukaemia Study Group. There was no

notification via death certificates. Data on primary treatment were recorded; only the percentage of patients with untreated disease in the period 1984-87 is presented.

*Classification*

The diagnoses were all coded according to the International Classification of Disease (ICD), the 8th version until 1978 and then the 9th version, which was adopted for topography in that year.[7] The histological diagnosis *non-Hodgkin's lymphoma (NHL),* ICD 200 and 202, was coded according to the Kiel classification and these codes were 'translated' (only since 1978) into the major prognostic groups of the Working Formulation for Clinical Usage:[8] low, intermediate and high grade, except for 25% or 116 patients not otherwise specified (NOS) and 5% or 21 patients with other conditions such as mycosis fungoides, Sezary's disease, histiocytosis and hairy cell leukaemia. The Rye histological classification of *Hodgkin's disease (HD),* ICD 201, was used for subdivision into nodular sclerosing (NS), mixed cellularity (MC), lymphocyte predominant (LP) and lymphocyte depletion (LD). These diagnoses were reviewed and subdivision of NS occurred into NSI and II.[9] The Ann Arbor classification was used for staging.[10]

The diagnosis of *multiple myeloma (MM),* ICD 203, was based on criteria, such as presence of paraproteins, ≥10% plasma cells and atypical plasma cell morphology and osteolytic lesions. For *leukaemia* the following subtypes were distinguished: acute lymphocytic (ALL; ICD 204.0/2), chronic lymphocytic (CLL; ICD 204.1), acute non-lymphocytic (ANLL; ICD 205.0/2, 206.0/2, 207.0/2 and 208.0/2) and chronic myelocytic (CML; ICD 205.1). Primary and secondary ANLL were distinguished. N.O.S. were patients with the following codes: ICD 206.1, 207.1 and 208.1/8/9. Slides of leukaemia patients were partly reviewed by the National Dutch Bone Marrow Slides Committee. Because myelodysplasia and myeloproliferative conditions such as myelofibrosis, polycythaemia vera and thrombocytosis were incompletely registered, they were excluded from the analysis.

*Incidence, prevalence and mortality*

Age-specific (5- and 15-year age groups) incidence was derived from the registry and regional mortality from the Dutch Central Bureau for Statistics (CBS). Annual rates were computed per 100,000 person-years and as 3-year moving means for time trends. Point-prevalence rates were computed per January 1, 1986, using data on patients diagnosed in the period 1975-85.

*Survival*

Survival was determined for all 1610 patients with HM, diagnosed between January 1, 1975, and December 31, 1985. Information about the vital status of these patients up to December 31, 1987, was obtained from municipal population records. Fifteen patients (1%) were excluded due to administrative

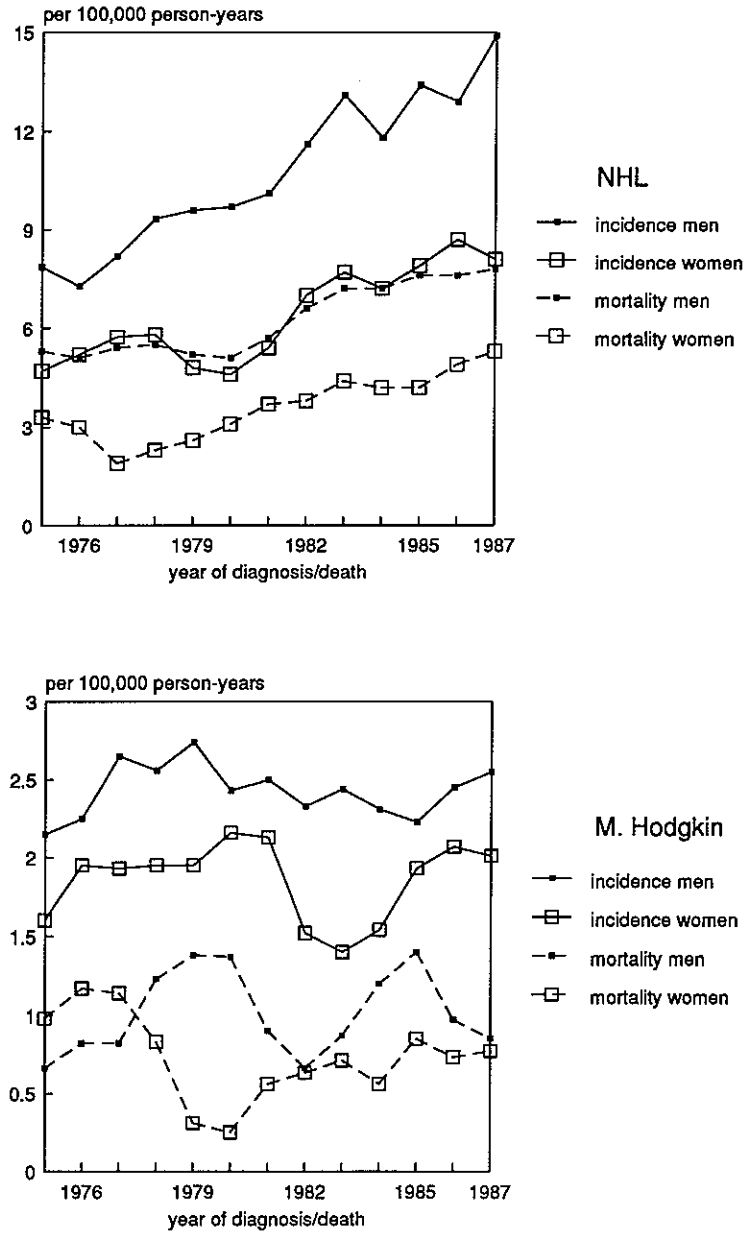
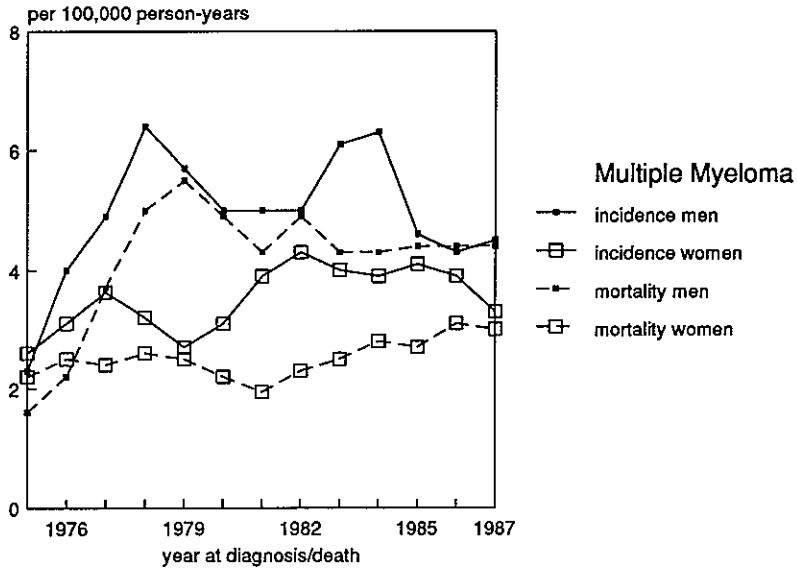



FIGURE 1 Trends in age-adjusted incidence of and mortality due to haematological malignancies in the period 1975-87



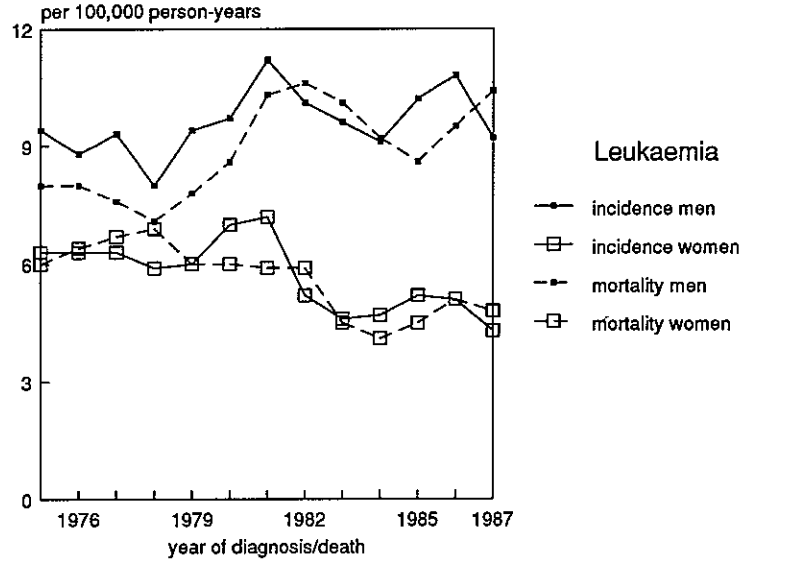




FIGURE 1 *(continued)*

errors and death before diagnosis, while 8 patients (0.5%) were lost to follow-up. Actuarial survival rates were computed for all disease categories mentioned above. The relative survival rate (RSR) was calculated by taking other causes of death into account; it is defined as the ratio of the observed survival (OSR) of patients, regardless of cause of death, and the expected rate due to other causes of death;[11] the latter is computed from regional death tables of the CBS for persons of the same age and sex. For the calculation of cumulative relative rates heterogeneity of patient withdrawal was taken into account.[12] RSR's were stratified according to 15- and 30-year age-groups and sex, but the outcome is only presented in the event of substantial differences. The RSR's were also compared for the periods 1975-79 and 1980-85. Survival analyses were carried out with a special computer program.[13]

## RESULTS

### *Incidence and prevalence*

The incidence of HM was 29.5 and 17.6 per $10^5$ person-years for males and females, respectively, in the period 1978-87. More than 50% of new patients with HM were older than 60 years, except for those with HD and ALL. The percentage patients with untreated disease varied from 1% in the ALL group to 64% in the CLL group (table 1). The average duration of disease, as indicated by the prevalence to incidence ratio, was about 3.5 years, ranging from 1.5 years for ANLL to almost 7 for HD. The incidence of HM was 60% higher for males

TABLE 1 **Incidence (in the period 1975-87) and prevalence (at 1/1/1986) of haematological malignancies, according to type: percentage patients over 60 years of age and with untreated tumours (in the period 1984-87)**

| | | New patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | total | | ≥60 yrs | untreated | Incidence | Prevalence# |
| Type | | no. | % | % | % | per $10^{5}$* | |
| All | | 2016 | 100 | 55 | | 22.8 | 85.0 |
| NHL | | 752 | 37 | 57 | 18 | 8.5 | 32.5 |
| HD | | 227 | 11 | 16 | 5 | 2.2 | 14.5 |
| MM | | 357 | 18 | 76 | 16 | 4.3 | 12.7 |
| LEU | | 680 | 34 | 58 | 14 | 7.8 | 26.3 |
| | ALL | 99 | 14@ | 15 | 1 | 1.0 | 5.7 |
| | CLL | 207 | 31@ | 77 | 64 | 2.6 | 12.6 |
| | ANLL | 228 | 34@ | 47 | 57 | 2.5 | 3.7 |
| | CML | 116 | 17@ | 60 | 49 | 1.5 | 2.5 |
| | NOS** | 30 | 4@ | 67 | 80 | 0.4 | 1.8 |

* European standard population
\# excluding patients diagnosed before January 1st 1975
@ percentage of all leukaemias
** not otherwise specified

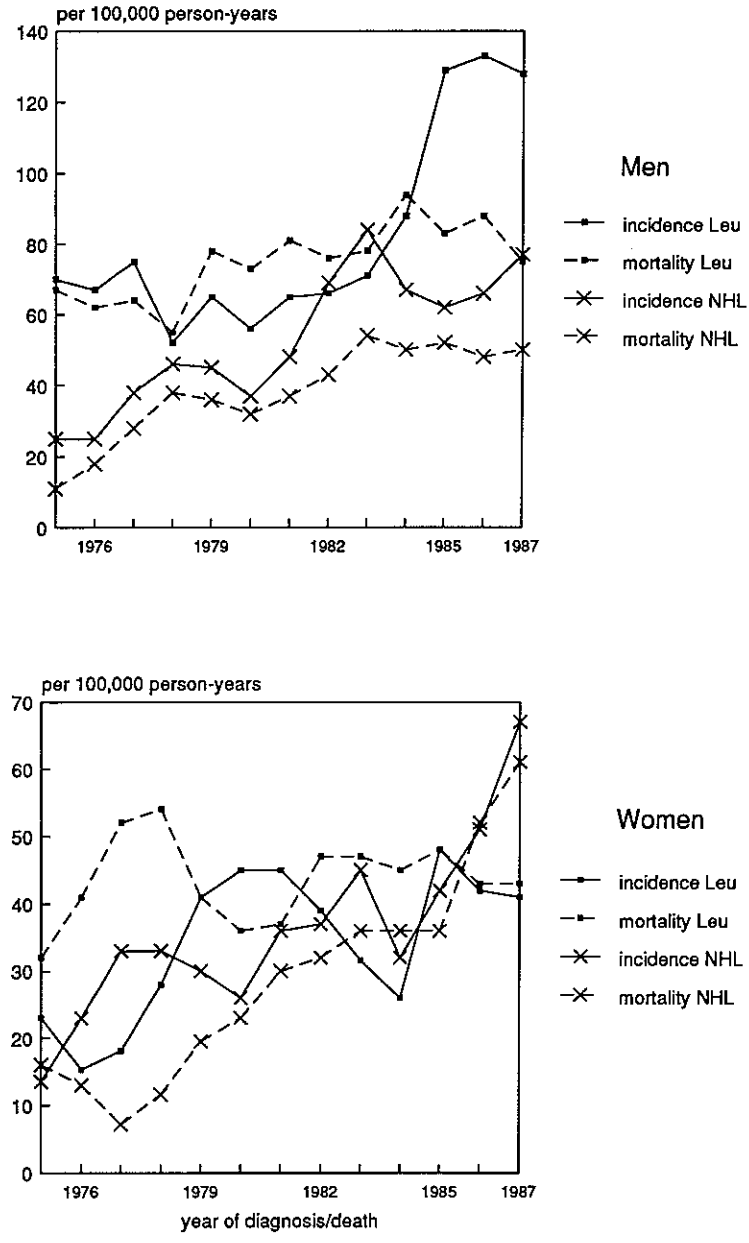



FIGURE 2 Trends in age-adjusted incidence of and mortality due to leukaemia and NHL in the elderly in the period 1975-87

than for females and it varied from 30% for HD to 70% for NHL and leukaemia (table 2). The male/female incidence ratios rose with increasing age, in particular for leukaemia. Tumour-specific data are presented below.

**TABLE 2 Age-specific (15-year age-groups) and adjusted* incidence of haematological malignancies, 1978-87: per 100,000 person-years and sex**

| Age (yrs) | Sex | No. of patients | NHL | HD | MM | Leukaemia | All |
|---|---|---|---|---|---|---|---|
| 0-14 | ♂ | 51 | 1.3 | 0.2 | | 3.8 | 5.3 |
| | ♀ | 41 | 0.8 | 0.5 | | 3.2 | 4.5 |
| 15-29 | ♂ | 64 | 1.6 | 2.4 | | 1.1 | 5.1 |
| | ♀ | 50 | 0.9 | 2.6 | | 1.0 | 4.5 |
| 30-44 | ♂ | 109 | 3.4 | 3.6 | 0.4 | 3.3 | 10.7 |
| | ♀ | 81 | 2.7 | 2.7 | 0.2 | 2.8 | 8.4 |
| 45-59 | ♂ | 210 | 14.3 | 3.3 | 4.8 | 8.1 | 30.5 |
| | ♀ | 128 | 8.3 | 1.0 | 4.2 | 5.5 | 19.0 |
| 60-74 | ♂ | 349 | 35.5 | 1.8 | 20.1 | 31.5 | 88.9 |
| | ♀ | 216 | 19.7 | 2.1 | 13.4 | 13.2 | 48.4 |
| ≥75 | ♂ | 191 | 53.0 | 5.2 | 34.7 | 73.4 | 166.3 |
| | ♀ | 188 | 35.1 | 4.0 | 25.4 | 49.6 | 114.7 |
| Total | ♂ | 974 | 10.6 | 2.4 | 4.9 | 9.9 | 27.8 |
| | ♀ | 704 | 6.3 | 1.9 | 3.6 | 5.7 | 17.5 |
| Ratio | ♂/♀ | 1.4 | 1.7 | 1.3 | 1.3 | 1.7 | 1.6 |

* European standard population

*Non-Hodgkin's lymphoma*

Survival: the observed survival rate (OSR) was clearly worse than the relative survival rate (RSR). The RSR decreased with increasing age, especially after age 60, and was distinctly best for low grade disease (table 3). The RSR appeared to be lower for patients over 60 in the period 1980-85 compared to 1975-79 and remained unaltered for patients under 60 (table 7). Incidence and mortality increased markedly and continuously (figure 1a). The increase in incidence and mortality was observed chiefly among those over 60, in particular over 75 (figure 2), for men in the 30-44 year-old group and for women in the 45-59 year-old group (not shown). The incidence for each type according to the Working Formulation was higher for males than females at every age; the largest difference (1.1 versus 0.1 per $10^5$ person-years) existed for 'other tumours'. This was only determined for the period 1984-87 when the percentage of unclassified patients dropped below 5% (figure 3) from about 40% in the 70's and 25% until 1983. Increases were found predominantly for the intermediate and high grade types.

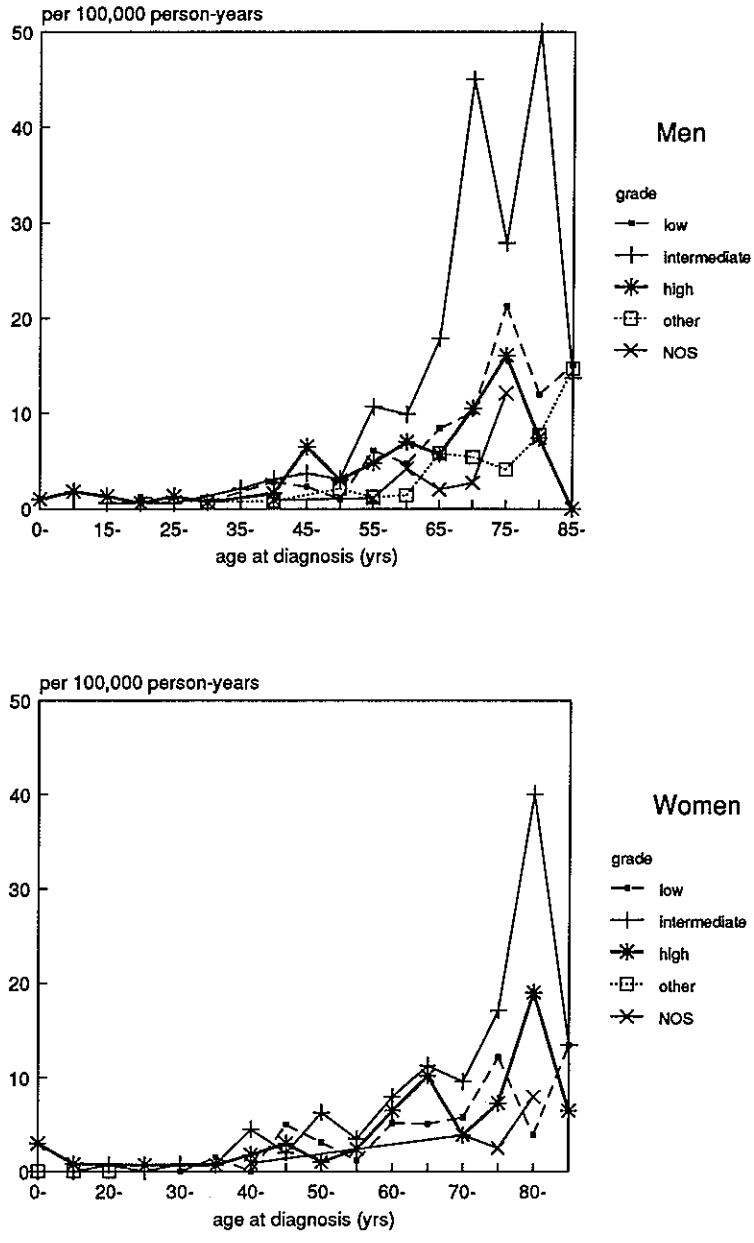



FIGURE 3 Age-specific incidence of non-Hodgkin's disease according to the Working Formulation in the period 1984-87

**TABLE 3 Cumulative relative survival (observed in parentheses) for non-Hodgkin's lymphoma in 1975-85: according to age and histological type***

| Type | | Age# yrs | Patients no. | % | Survival (%) after year: 1 | 3 | 5 | 8 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| All | | 59 | 567 | 100 | 69 | 52 | 43 | 36 | 31 |
| | *observed* | " | " | " | *(67* | *48* | *36* | *28* | *22)* |
| | age | <15 | 19 | 4 | 84 | 74 | 68 | 68 | 68 |
| | | 15-44 | 78 | 14 | 72 | 58 | 49 | 47 | 47 |
| | | 45-59 | 145 | 26 | 77 | 60 | 45 | 38 | 29 |
| | | ≥60 | 308 | 56 | 65 | 43 | 35 | 29 | 32 |
| WF*: | low | 62 | 80 | 18 | 90 | 74 | 49 | 43 | 47 |
| | intermediate | 60 | 162 | 36 | 72 | 53 | 41 | 30 | 28 |
| | high | 58 | 74 | 16 | 43 | 30 | 25 | 29 | 31 |
| | unspecified | 58 | 116 | 26 | 68 | 51 | 45 | 39 | 42 |
| Other | | 50 | 21 | 5 | 88 | 72 | 62 | 66 | 70 |

# mean age or group; * Working Formulation,7 only in period 1978-85

## *Hodgkin's disease*

Among adults the peak of the incidence, mainly for NS, occurred at an earlier age for women than for men. Middle-aged men exhibited higher rates, especially for MC. The age-specific incidence of LD was similar for the two sexes (figure 4). The RSR was better for NS especially for the group with NSI,

**TABLE 4 Cumulative relative survival (observed in parentheses) for Hodgkin's disease in 1975-85: according to age, histological type* and stage@**

| | | Age# yrs | Patients no. | % | Survival (%) after year: 1 | 3 | 5 | 8 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| All | | 39 | 184 | 100 | 88 | 81 | 77 | 69 | 66 |
| | *observed* | " | " | " | *(87* | *78* | *73* | *63* | *59)* |
| | | <15 | 6 | 3 | 100 | 83 | 65 | 65 | 65 |
| | | 15-59 | 147 | 80 | 95 | 87 | 82 | 74 | 70 |
| | | ≥60 | 31 | 17 | 51 | 42 | 47 | 28 | 32 |
| Type* | NS | 35 | 88 | 48 | 92 | 87 | 84 | 80 | 72 |
| | NS1 | 35 | 65 | *74@* | 93 | 87 | 88 | 83 | 79 |
| | NS2 | 39 | 12 | *14@* | 84 | 86 | 55 | 57 | – |
| | MC | 41 | 53 | 29 | 84 | 71 | 64 | 50 | 50 |
| | LP | 44 | 19 | 10 | 100 | 96 | 91 | 71 | 72 |
| | LD | 55 | 11 | 6 | 57 | 31 | 34 | 39 | 45 |
| Stage** | I | 44 | 34 | 18 | 94 | 94 | 97 | 94 | 96 |
| | II | 35 | 57 | 31 | 97 | 87 | 86 | 80 | 73 |
| | III | 35 | 49 | 27 | 92 | 83 | 74 | 66 | 61 |
| | IV | 48 | 37 | 20 | 61 | 52 | 43 | 31 | 32 |
| | unknown | 35 | 7 | 4 | 100 | 101 | 103 | | |

# mean age or group @ subdivision of NS (3 cases unknown) * Rye classification (only reviewed cases)
** Ann Arbor classification

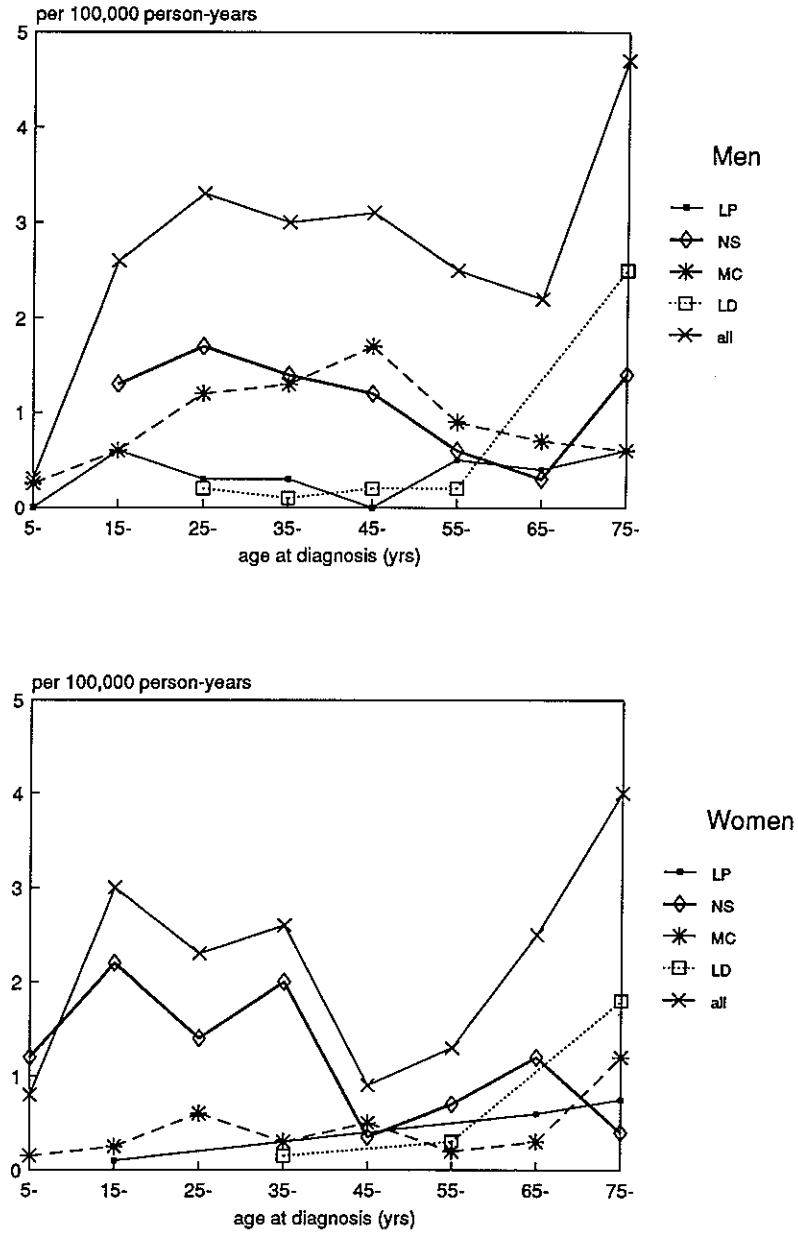



FIGURE 4 Age-specific incidence of Hodgkin's disease according to Rye subtype in the period 1975-87

decreased with higher stage and after age 60 (table 4) and was clearly worse for patients with LD or stage IV, despite a higher mean age. Improved survival over time was observed mainly for the (small) group of those over 60 years of age, whose 5-year survival rate rose from 38% to 60% (table 7). Age-adjusted incidence and mortality rates showed minor temporary variations (figure 1b). Below age 45 a temporary decrease in mortality was observed in the period 1977-84, while an increase was found for the elderly (not shown).

### *Multiple myeloma*

The difference between observed and relative survival rates was small (table 5). Despite a higher mean age, the RSR for women was clearly better than for men. Five year survival was worst for the 60-74 year-old group. Over time, the prognosis for the elderly appeared to improve in the first 3 years after diagnosis, while a decrease was observed for younger patients. Incidence and mortality remained unchanged after an initial increase in the period 1975-78 (figure 1c), except for a slight increase for the elderly (not shown).

**TABLE 5 Cumulative relative survival (observed in parentheses) for multiple myeloma in 1975-85: according to sex and age**

| | | Age# | Patients | | Survival (%) after year: | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | yrs | no. | % | 1 | 3 | 5 | 8 | 10 |
| All | | 67 | 285 | 100 | 67 | 40 | 26 | 14 | 8 |
| | *observed* | " | " | " | *(64* | *35* | *21* | *9* | *5)* |
| | ♂ | 66 | 146 | 51 | 57 | 35 | 25 | 13 | 8 |
| | ♀ | 68 | 139 | 49 | 77 | 45 | 27 | 14 | 7 |
| | | 30-59 | 72 | 25 | 75 | 44 | 30 | 17 | 10 |
| | | 60-74 | 134 | 47 | 68 | 37 | 20 | 13 | 5 |
| | | ≥75 | 79 | 28 | 55 | 41 | 35 | 11 | 15 |

# mean age or group

### *Leukaemia*

The incidence rates for CLL, ANLL and CML rose markedly with age, i.e. after age 45 for men and 55 for women. ALL was most common among children and young adults, ANLL in the middle-aged group and CLL in the elderly (figure 5). Over time a decrease was observed in CLL, mainly for women, and an increase in ANLL for men, in part due to an increase in secondary ANLL (11 cases in 1980-85 versus 1 in 1975-79) (figure 6). Both incidence and mortality rose markedly for older men (figure 2). A decrease in incidence and mortality was observed for women of the 45-59 year-old group, from about 8 to 3 per $10^5$, and in mortality for young adults (until 1985) from about 1.5 to 0.5 per $10^5$. The RSR for patients with ALL and CLL was clearly better than that for ANLL and CML (table 6). The RSR decreased with age for all types of leukaemia. Compared to the period 1975-79 the 5-year RSR for patients

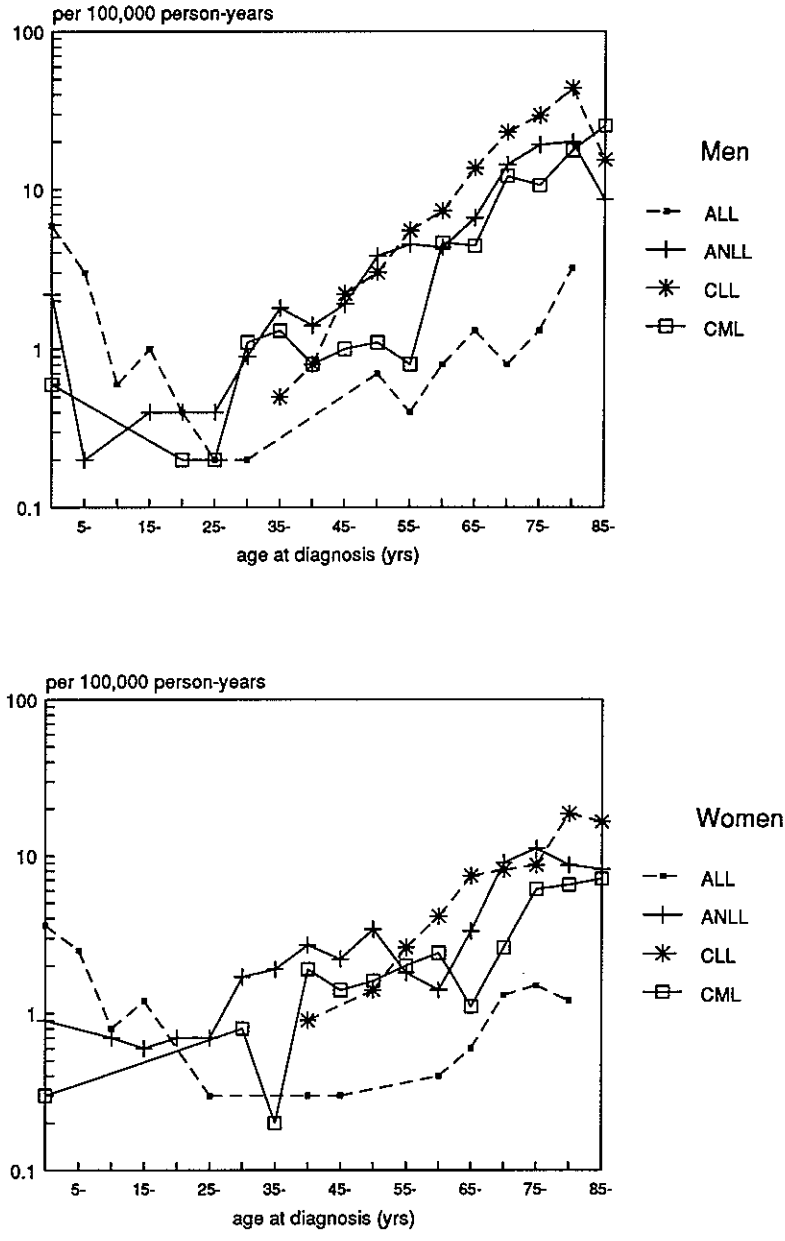



FIGURE 5 Age-specific incidence of leukaemia according to subtype and sex in the period 1975-87

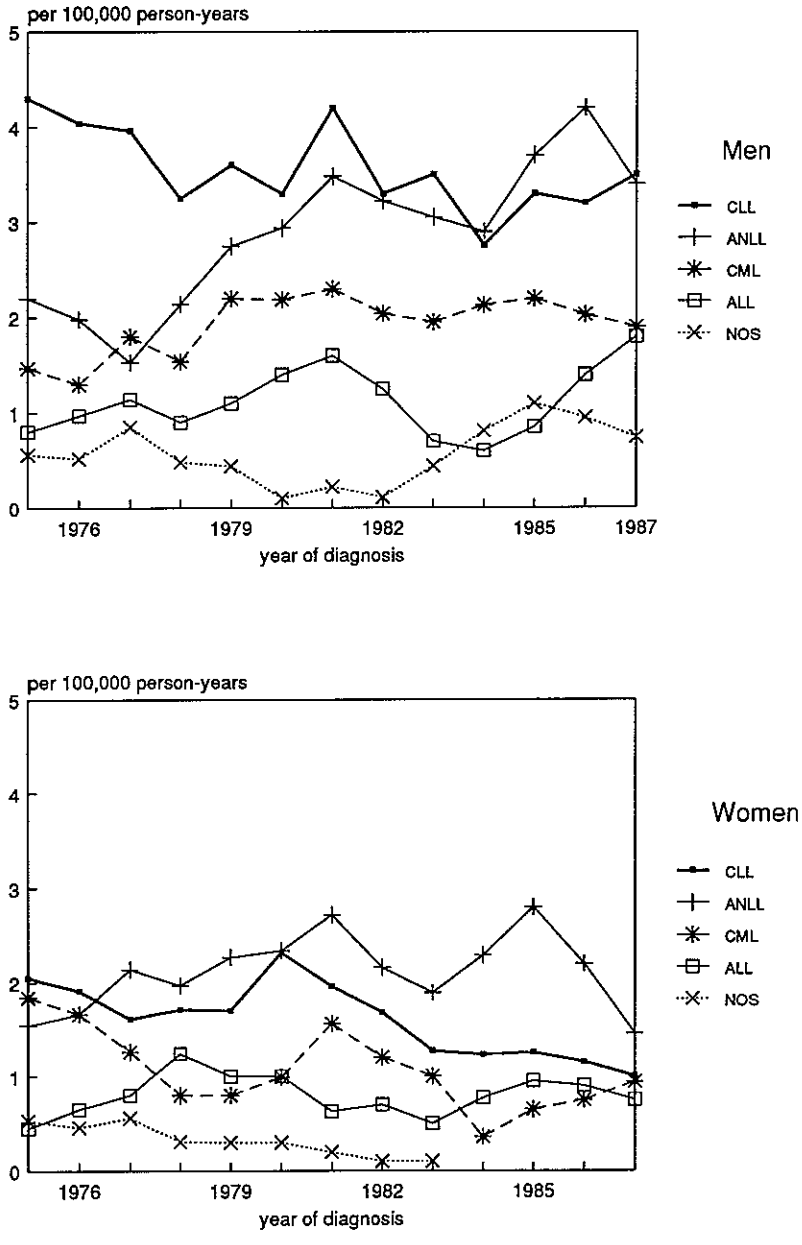



FIGURE 6 Trends in age-adjusted* incidence of leukaemia according to type and sex in the period 1975-87
* European Standard Population

TABLE 6 Cumulative relative survival (observed between parentheses) for leukaemia in 1975-85: according to type and age

| Type | | Age# yrs | Patients no. | % | Survival (%) after year: 1 | 3 | 5 | 8 | 10 |
|---|---|---|---|---|---|---|---|---|---|
| All | | 55 | 559 | 100 | 60 | 43 | 35 | 29 | 26 |
| | children | <15 | 67 | 12 | 82 | 64 | 59 | 55 | 55 |
| | adults | 61 | 492 | 88 | 57 | 40 | 31 | 24 | 20 |
| ALL | | 18 | 77 | 14 | 84 | 65 | 61 | 57 | 58 |
| | *observed* | " | " | " | *(83* | *63* | *59* | *55* | *55)* |
| | | <15 | 51 | | 92 | 75 | 70 | 65 | 65 |
| | | 15-44 | 14 | | 93 | 56 | 56 | 57 | 57 |
| | | ≥45 | 8 | | 51 | 40 | 28 | 30 | |
| CLL | | 68 | 174 | 31 | 86 | 76 | 61 | 48 | 41 |
| | *observed* | " | " | " | *(82* | *65* | *47* | *31* | *23)* |
| | | 30-59 | 41 | | 88 | 77 | 64 | 59 | 44 |
| | | ≥60 | 133 | | 86 | 76 | 60 | 42 | 39 |
| ANLL | | 53 | 186 | 33 | 31 | 14 | 10 | 9 | 8 |
| | *observed* | " | " | " | *(30* | *13* | *8* | *7* | *7)* |
| | | 15-44 | 45 | | 60 | 33 | 24 | 20 | 20 |
| | | 45-59 | 44 | | 30 | 9 | 3 | 3 | 3 |
| | | ≥60 | 83 | | 11 | 1 | 0 | | |
| CML | | 60 | 97 | 17 | 54 | 29 | 18 | 8 | 0 |
| | *observed* | " | " | " | *(52* | *26* | *15* | *6* | *0)* |
| | | 15-59 | 40 | | 75 | 28 | 19 | 5 | 0 |
| | | ≥60 | 55 | | 39 | 28 | 16 | 14 | 0 |
| NOS | | 67 | 25 | 4 | 42 | 37 | 35 | 33 | 28 |

# mean age or group

with CLL improved markedly in the period 1980-85; the same applies for 1-year survival for ANLL patients over 60. In younger patients with ALL and ANLL the 5-year RSR was unchanged; for CML this applied only for the first 3 years of follow-up.

## DISCUSSION

Age-specific incidence rates found for the various HM, also according to subtype, are fairly consistent with the findings of a recent population-based study in England & Wales[14] as well as results published in other industrialized countries.[15] Our figures for children are also similar to the results of national studies which in turn are comparable to international data.[16 17] Our relative survival rates are closely similar to those of the SEER-program in the USA[18] and, for children the recent study in Britain.[19] Although about 50% of patients were over 50 years of age, the relatively high incidence of HM out of all cancers in younger age groups is clear: whereas HM represent only 6-7% of the total cancer incidence and 8% of the prevalence, our study shows that these ratios

**TABLE 7 Cumulative relative survival for haematological malignancies in two periods: 1975-79 and 1980-85**

| Type | | Period | Age# yrs | no. | Survival (%) after year 1 | 3 | 5 |
|---|---|---|---|---|---|---|---|
| NHL | | 75-79 | 15-59 | 88 | 74 | 67 | 50 |
| | | 80-85 | 15-59 | 140 | 78 | 55 | 46 |
| | | 75-79 | ≥60 | 114 | 63 | 46 | 40 |
| | | 80-85 | ≥60 | 204 | 63 | 43 | 34 |
| HD | | 75-79 | 15-59 | 75 | 96 | 90 | 82 |
| | | 80-85 | 15-59 | 72 | 93 | 85 | 83 |
| | | 75-79 | ≥60 | 19 | 50 | 35 | 38 |
| | | 80-85 | ≥60 | 12 | 54 | 54 | 60 |
| MM | | 75-79 | 30-59 | 34 | 86 | 54 | 37 |
| | | 80-85 | 30-59 | 38 | 66 | 34 | 24 |
| | | 75-79 | ≥60 | 74 | 56 | 37 | 24 |
| | | 80-85 | ≥60 | 139 | 68 | 40 | 24 |
| LEU | ALL | 75-79 | 15 | 36 | 95 | 70 | 68 |
| | | 80-85 | 21 | 41 | 74 | 59 | 53 |
| | CLL | 75-79 | 69 | 76 | 84 | 71 | 52 |
| | | 80-85 | 68 | 98 | 88 | 80 | 69 |
| | ANLL | 75-79* | 15-59 | 35 | 50 | 24 | 13 |
| | | 80-85* | 15-59 | 51 | 43 | 19 | 16 |
| | | 75-79* | ≥60 | 21 | 0 | | |
| | | 80-85* | ≥60 | 52 | 16 | 1 | 0 |
| | CML | 75-79 | 55 | 36 | 57 | 36 | 19 |
| | | 80-85 | 62 | 61 | 53 | 24 | 19 |

# group or mean age
* excluding second cancers

are 45% and 50% for children, 33% and 40% for young adults and 16% and 25% for the middle-aged group.[20]

The major changes in this population were the rising incidence of and mortality due to NHL, the improved survival for CLL together with a lower incidence (for women), the rising incidence of ANLL (among elderly men), the improved survival of patients over 60 with HD, MM and leukaemia and, in contrast the decreased survival of younger patients with NHL and MM. A mixture of factors might be responsible, such as differential risks, better detection and classification, more effective treatment (including supportive care but also more side-effects of intensive treatment), a different natural history and, of course, random variations in rare conditions. The decentralized registration procedures remained largely unaltered. Incompleteness may have occurred since a (few?) out-patients with a cytological diagnosis established by a non-pathological laboratory may have died before being admitted. Access to specialized care has definitely improved since the mid-70's, since about 40 new internists (20 extra) have settled in the area, a fair number with special training

in haemato-oncology. Despite the absence of a regional cancer centre contacts with neighbouring centres have been good and the tumour study group, functioning since 1978 and comprising physicians from all hospitals, may well have contributed to more extensive diagnosis and uniform treatment of (adult) patients, especially patients with HD. Although these developments have also led to a higher detection rate for NHL, MM and leukaemia, especially for the more slowly growing forms and particularly among the elderly, the observed changes may still reflect real changes in risk: first, because they are often different for the sexes; second, because they often coincided with mortality trends. Other results will be discussed per tumour type.

*Non-Hodgkin's lymphoma*

Reclassification of diagnostic codes according to the Kiel classification to the composite groups of the Working Formulation (WF), only feasible (without review) for the period 1978-87, may have been sufficient,[21] although the percentage of unclassified cases only dropped below 5% after 1983. Moreover reviews of slides within laboratories and within the tumour study group have become more common. The type-specific survival rates show marked similarities to the (also unreviewed) population-based survival rates found by the SEER-program for the period 1977-84: the 5-year relative survival rates were 57% (49%) for low, 39% (41%) for intermediate and 31% (25%) for high grade, our rates being given in parentheses. Also similar results were reported by a population-based project in western Netherlands performed in the period 1981-86:[22] 3-year disease-free survival was 52% which is similar to our relative survival. This cooperative group was very careful to establish the diagnosis precisely. The proportion of WF-unclassified patients was 27%; our figure was similar until 1984.

The decrease in relative survival for patients over 60 in the period 1980-85 compared to 1975-79 can largely be attributed to a higher proportional incidence of intermediate and high grade tumours in the latter period. The increase in incidence among the elderly has been observed in most industrialized countries; although there is no clear explanation, changes in the diagnostic process (e.g. for CLL and Waldenström's disease) and decreasing competing causes of death could play a role. The increase in the incidence for men in the 30-44 year-old group (from 2 to 7 per $10^5$ person-years) started in 1982; it consists largely of low and intermediate types and, since Kaposi sarcoma was very rare, an association with the human immunodeficiency virus would seem unlikely.

*Hodgkin's disease*

The incidence and age distribution, also according to Rye subtype, are very similar to those found in the recent British study;[23] the UK age-adjusted rates for 1984-86 were (our rates in parentheses) 0.23 (0.19) per $10^5$ person-years for HDLP, 0.56 (0.6) for HDMC, 1.2 (1.05) for HDNS and 0.11 (0.17) for

HDLD. The RSR's are similar to those reported by the tumour study group for all 182 patients diagnosed from 1972 to 1983.[24] In addition an improvement over time can be seen for the elderly. The 5-year relative survival rate for the older age group (52%) appears to be better than that for a group of unselected patients from Sweden[25] (30%). Data on type-specific and stage-related incidence are fairly similar to SEER-data,[18] while the reported survival rates more closely reflect the outcome obtained in cancer centres.[26] The temporary decrease in mortality (figure 1b) may also be due to late death.

*Multiple myeloma*

Our mortality rates do not differ from nationwide rates, which were relatively high compared to other industrialized countries.[27 28] The increasing incidence observed in the 70's may in part be the result of improved case detection; however this may seem unlikely because of a simultaneous and identical increase in mortality. The contradictory changes in survival for young and older patients demand further investigation of the criteria for diagnosis and possible side effects of intensified therapy despite better supportive care. Our survival results are similar to those obtained in Finland for a group of patients undergoing non-protocol treatment in the period 1979-85[29] as well as for patients registered in the SEER-program after 1973.[18]

*Leukaemia*

The different trend in incidence for males (rising) and females (decreasing) is the result of contrasting developments in ANLL and CLL. When compared to the recent study in the UK[14] of the period 1984-86, our data must be considered less accurate because of the lack of systematic review procedures; nevertheless, agreement with their age-specific incidence of ALL and AML is remarkable.[30 31] Our incidence rate for ANLL may be lower (2.4 versus 3.4 per $10^5$) partly because we observe more unspecified leukaemias (0.55 per $10^5$). An increase in ANLL was observed, mainly among the elderly, and a decrease in chronic leukaemias. Similar developments in the age and type-specific distributions were observed in Norway[32] and Denmark.[33 34] Despite a similar proportion of untreated patients, our survival rates for acute leukaemia appear to be higher than those in the Stockholm area for the period 1978-81.[35] However, ANLL may also be detected earlier as appears from the increase in secondary ANLL; another factor could be the arbitrary definition of the onset of the disease. Effects of more intensive treatment have been described in a large series of CLL patients.[36] However, the markedly improved survival of CLL in this study could also be attributed to earlier diagnosis due to better detection; the decreasing incidence may be caused by a shift in classification to intermediate grade NHL (immunocytoma).

## *Conclusion*

The changes in the frequency and survival of HM observed in southeastern Netherlands warrant further study, especially those in NHL, CLL, ANLL and MM. Precise estimations of trends in survival are difficult. Review of diagnoses, especially for borderline conditions, and information on staging, therapy, and co-morbidity, especially in the elderly, are needed in order to explain trends. Such studies, if prospective, should also cover larger populations.

The incidence and prevalence of HM observed in this population generally agree with previously made estimates, largely derived from this registry, used for a national plan for specialized haemato-oncological services for the period 1985-95 in which it was foreseen that application of half-way technology would remain the predominant mode of treatment.[6]

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Chapter 5.1.2

# CHILDHOOD LEUKAEMIA IN THE NETHERLANDS, 1973-86

## Temporary variation of the incidence of acute lymphocytic leukaemia in young children*


SUMMARY

The incidence of childhood leukaemia in the Netherlands in the period 1973-86 was studied by means of the DCLSG nationwide register, which lists all patients according to bone marrow slides classified in the DCLSG central laboratory. ALL accounted for 81% of cases, ANLL 13%, CML 2.5% and AUL 3%. The peak incidence of ALL was at age 3, common-ALL and pre B-ALL comprising about 95% of the immunophenotypes at this age.

Incidence rates for ALL remained stable between 1973 and 1978 at 2.85 cases per $10^5$ children per year, exhibited a temporary increase between 1979 and 1984 to 3.60 and dropped back to the lower, previous level in 1985 and 1986. This rise was seen mainly among children in the 1-4 year age group, especially at age 3, and those with common-ALL and an initial WBC <5.0 x $10^9$/l. Cumulative incidence rates per year of birth were fairly homogeneous up to age 6, except for the 1978 birth cohort which exhibited higher rates. Incidence rates for ANLL, CML and AUL remained stable over time. Changes in ascertainment, declining birth rates, a 50% decrease in childhood mortality, e.g. from infectious diseases could not explain this temporary variation. Moreover incidence rates in this survey appeared to be similar to those reported in various developed countries for the same period. As far as the aetiology of childhood common-ALL is concerned, therefore, the Dutch data appear to support the hypothesis of 'random mutation' as well as that of a limited role of environmental factors.



* Coebergh JWW, van der Does-van den Berg A, van Wering ER, van Steensel-Moll HA, Valkenburg HA, van 't Veer MB, Schmitz PIM, van Zanen GE. Childhood leukaemia in the Netherlands, 1973-86: temporary variation of the incidence of acute lymphocytic leukaemia in young children. *Br J Cancer* 1989;59:100-5.

## INTRODUCTION

Since 1973 the occurrence of childhood leukaemia in the Netherlands has been documented accurately through the nationwide morbidity register of the Dutch Childhood Leukaemia Study Group (DCLSG). In a previous epidemiological study the DCLSG register proved to be almost complete. The incidence of childhood leukaemia appeared to be constant in the period 1973-79.[1] The present study covers the period 1973-86. For acute lymphocytic leukaemia (ALL) the distributions of the white blood cell counts at diagnosis (WBC) as well as that of the immunophenotypes have also been analysed, the latter since 1979. The aetiology of childhood leukaemia is still unknown, although several risk factors have been identified in case-control studies performed in the Netherlands[2 3 4] and elsewhere. Most of the aetiological studies have focused on ALL, since it accounts for more than 80% of the cases in developed countries and is characterized by a peak incidence for common-ALL between ages 2 and 5. With regard to the aetiology of childhood ALL, in particular concerning common-ALL in young children, two major hypotheses have recently been suggested: a major role for host-environment interactions[5] or spontaneous mutation of the rapidly proliferating lymphocyte progenitors in bone marrow.[6]

To assess the possible role of environmental factors in the aetiology of childhood ALL in the Netherlands, changes in demography as well as (competing?) mortality risks for children in the same period were evaluated.

## PATIENTS AND METHODS

### *Patients*

Patient and disease characteristics of children with (suspected) leukaemia were collected at the DCLSG through registration forms, completed by the attending paediatricians or by specially trained registration assistants in the various centres for childhood leukaemia. This study comprised 1596 children, 0-14 years of age, with leukaemia newly diagnosed between January 1st 1973 and January 1st 1987. Since the children had to be inhabitants of the Netherlands at the time of diagnosis, 30 patients were subsequently excluded. In 1980 the completeness of the register was verified by means of questionnaires sent to all Dutch paediatricians as well as compared with the Eindhoven regional cancer registry in the southeastern part of the country. Since then completeness has been checked incidentally by questioning of individual paediatricians, practising either in border areas of the country or in centres for childhood leukaemia. Only minor discrepancies were revealed by annual comparisons between the aggregate number of deceased patients registered at the DCLSG since 1980 by age and sex and those registered according to cause of death with the Department of Health Statistics of the Central Bureau of Statistics (CBS). Patients were grouped by sex and age at diagnosis: 0, 1-4, 5-9 and 10-14 years.

*Diagnosis*

The diagnosis was primarily made by morphological and cytochemical examination of blood and bone marrow smears in the hospital laboratory and had to be confirmed in the central laboratory of the DCLSG. Classification was performed according to FAB criteria, resulting in the following subtypes:[7] acute lymphocytic leukaemia (ALL), acute non-lymphocytic leukaemia (ANLL), chronic myelocytic leukaemia (CML) and acute unclassifiable leukaemia (AUL) whenever FAB-criteria did not fit. In the latter cases electron-microscopy studies have also been performed since 1982. Myelodysplastic syndromes (MDS) have also been registered since 1979. For patients with lymphoblastic malignancies the presence in the bone marrow of more than 25% lymphoblasts at diagnosis was considered characteristic of ALL. Patients with ALL were grouped according to white blood cell count at diagnosis (WBC): 0-4.9, 5-19.9, 20-49.9, 50-99.9 and ≥100.0 X $10^9$/l. The WBC's were determined in the hospitals concerned; data were not available in less than 1% of cases. Since 1979 immunophenotyping of bone marrow, obtained at diagnosis from 534 patients, has been carried out in the Central Laboratory of the Dutch Red Cross Blood Transfusion Service in Amsterdam. Thirty samples were typed in the Biochemical Laboratory of the Department of Paediatrics in the Radboud Hospital in Nijmegen. The proportion of typed ALL samples has increased gradually from 60% in 1979 to more than 90% in 1985. With regard to the variation in the incidence of ALL in young children the presence of a correlation between low initial WBC's and specific immunophenotypes, e.g. common-ALL, can therefore only be evaluated accurately from 1984 onwards. Marker studies included the use of polyclonal antibodies up till 1983[8] and monoclonal antibodies since then.

Five subgroups were thus distinguished: T-ALL (aT+), B-ALL (sIg+), common-ALL (c-ALL+, cIgM-), pre B-ALL (cALL+, cIgM+) and unclassifiable ALL ("Ia" + or -, other markers absent).

*Data analysis*

Data analysis was performed in the Department of Epidemiology of the Erasmus University. Annual mid-year population data per year of age, sex, region and degree of urbanization were provided by the Department of Population Statistics of the CBS. With regard to urbanization the official classification of municipalities was applied, leading to a division into rural areas and small and large cities, the corresponding distribution of the childhood population being 13.5, 40 and 46.5%, respectively. The changing age distributions for children in the Netherlands since 1973 are shown in table 1.

**TABLE 1 Age distribution of the childhood population in the Netherlands, 1973-86**

| | Number of children (N x 1000): age group and percentage of childhood population | | | | | |
|---|---|---|---|---|---|---|
| | 1973 | | 1979 | | 1986 | |
| Age (yrs) | No. | % | No. | % | No. | % |
| 0 | 195 | 5.5 | 175 | 5.5 | 184 | 6.5 |
| 1-4 | 932 | 26.5 | 712 | 22 | 695 | 25 |
| 5-9 | 1206 | 34 | 1108 | 34.5 | 890 | 32 |
| 10-14 | 1202 | 34 | 1221 | 38 | 1025 | 36.5 |
| 0-14 | 3535 | 100 | 3216 | 100 | 2794 | 100 |
| % | 100% | | 91% | | 79% | |

source: Central Bureau for Statistics

Annual incidence rates were calculated per 100,000 children according to type of leukaemia and sex and age of the patient. Age adjustment was performed on the basis of the world standard population, the weights for the above-mentioned age categories being 7.75, 31, 32.25 and 29%, respectively.* Incidence rates are presented both per year and as moving means per three-year periods of diagnosis. The observed variation in the annual ALL rates for the age group 1-4 years was tested for randomness by means of the One Sample Run Test.[9] Calculation of the cumulative rates per year of birth also included the cohorts of 1971 and 1972, whereby missing incidence data for the years prior to 1973 were assumed to be similar to those in 1973-75.

*International comparison*

Incidence data as well as ALL/ANLL ratios were obtained from the following countries and registers: Denmark in 1980-84 (JH Olsen, personal communication), Finland in 1971-82,[10] West Germany in 1980-86,[11] Manchester and West Midlands in 1971-83,[12] the Leukaemia Research Fund Data Collection Survey in 1984-86 (R.Cartwright, personal communication), the Paediatric Cancer Registry of Australia in 1977-82[13] and the SEER program in the USA in 1973-82[14] (in the latter register white and black children are listed separately). The data of most of these registers have been incorporated in an international collaborative study.[15]

*Mortality data*

Data on causes of death for children in the Netherlands since 1970 were obtained from the Department of Health Statistics of the CBS. Infectious diseases were grouped according to the ninth revision of the International

* In the previous study of the period 1973-79 the Dutch childhood population of 1979 (table 1) was used as a standard with markedly different weights for the various age categories, thus resulting in a 25% lower age-adjusted figure for ALL.

Classification of Diseases: infectious and parasitic diseases (code 001-136), meningitis and encephalitis (code 320-24) and bronchitis and pneumonia (code 480-87).

## RESULTS

### *Incidence of childhood leukaemia in 1973-1986*

The number of cases and the incidence according to morphological type and sex are shown in table 2. The proportional distributions of the various types for boys and girls are identical, ALL accounting for 81% of cases and ANLL for 13%. Age-adjusted sex ratios (boys/girls) were 1.16 for ALL and 1.11 for

**TABLE 2 Age adjusted incidence and number of cases (N) of childhood leukaemia in the Netherlands, 1973-86: according to type and sex**

| | Both sexes | | | Boys | | Girls | | |
|---|---|---|---|---|---|---|---|---|
| Type | No. | % | rate per $10^5$/yrs | No. | rate per $10^5$/yrs | No. | rate per $10^5$/yrs | Sex ratio |
| Total | 1566 | 100 | 3.93 | 867 | 4.21 | 699 | 3.59 | 1.16 |
| ALL | 1264 | 80.8 | 3.17 | 699 | 3.39 | 565 | 2.93 | 1.16 |
| ANLL | 200 | 12.8 | 0.47 | 108 | 0.49 | 92 | 0.44 | 1.11 |
| CML | 40 | 2.6 | 0.10 | 24 | 0.12 | 16 | 0.07 | 1.70 |
| AUL | 48 | 3.0 | 0.13 | 27 | 0.14 | 21 | 0.12 | 1.16 |
| MDS* | 14 | 0.8 | 0.06 | 9 | 0.07 | 5 | 0.04 | 1.80 |

* included since 1979

**TABLE 3 Age-specific incidence of childhood leukaemia in the Netherlands, 1973-86: according to type and sex**

| | | Cases/100,000/year per age group (yrs) | | | |
|---|---|---|---|---|---|
| Type | Sex | 0 | 1-4 | 5-9 | 10-14 |
| Total | boys | 3.21 | 7.19 | 3.46 | 2.03 |
| | girls | 3.37 | 6.36 | 2.67 | 1.68 |
| ALL | boys | 1.80 | 6.14 | 2.86 | 1.49 |
| | girls | 2.22 | 5.52 | 2.19 | 1.16 |
| ANLL | boys | 0.86 | 0.55 | 0.41 | 0.43 |
| | girls | 0.74 | 0.50 | 0.37 | 0.37 |
| CML | boys | 0.16 | 0.26 | 0.05 | 0.05 |
| | girls | 0.00 | 0.10 | 0.07 | 0.07 |
| AUL | boys | 0.31 | 0.20 | 0.11 | 0.05 |
| | girls | 0.25 | 0.23 | 0.04 | 0.04 |
| MDS* | boys | 0.00 | 0.07 | 0.03 | 0.06 |
| | girls | 0.39 | 0.00 | 0.00 | 0.09 |
| Total number | boys | (41) | (390) | (263) | (172) |
| | girls | (41) | (328) | (194) | (136) |

* included since 1979

ANLL. The age adjusted ALL/ANLL ratios were 8.5 for boys and 8.2 for girls. The age and sex-specific incidence figures for the various types of leukaemia are presented in table 3. ALL occurred more frequently in the 1-4 year age group, while ANLL was more common in infants. Analysis of the age-adjusted incidence of ALL according to degree of urbanization did not reveal any differences for girls; for boys rates for rural areas, smaller cities and larger cities were 2.9, 3.2 and 3.3 per 100,000 children per year, respectively.

*Time trend*

Annual age adjusted incidence rates for childhood ALL, ANLL and for all types are presented in figure 1. Incidence rates for ALL remained stable between 1973 and 1978 at 2.85 per $10^5$ children per year, increased between 1979 and 1984 to 3.60 and dropped back to the previous level after 1984. This pattern was similar for boys and girls. Incidence rates for ANLL, CML and AUL were more or less constant over time. Age-specific incidence rates for ALL are shown in figure 2 as three-year moving averages. Temporary variations in these rates occurred only among infants and children 1-4 years of age. In the latter group this variation in the annual rates could still be a random phenomenon, as tested by the One Sample Run Test (no. of runs = 5 for a median value of 5.8 X $10^5$ person-years).

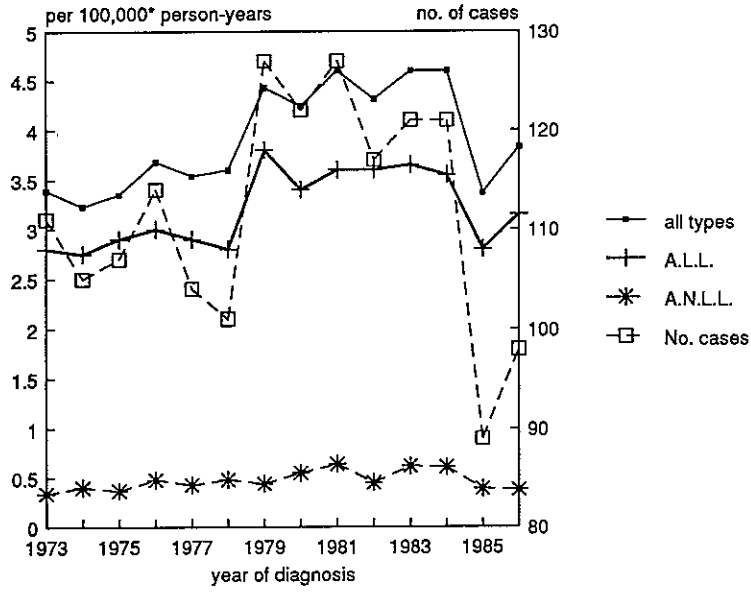


FIGURE 1 Childhood leukaemia in the Netherlands, 1973-86: annual age- adjusted* incidence rates for ALL, ANLL and all types per 100,000 children per year
* world standard population

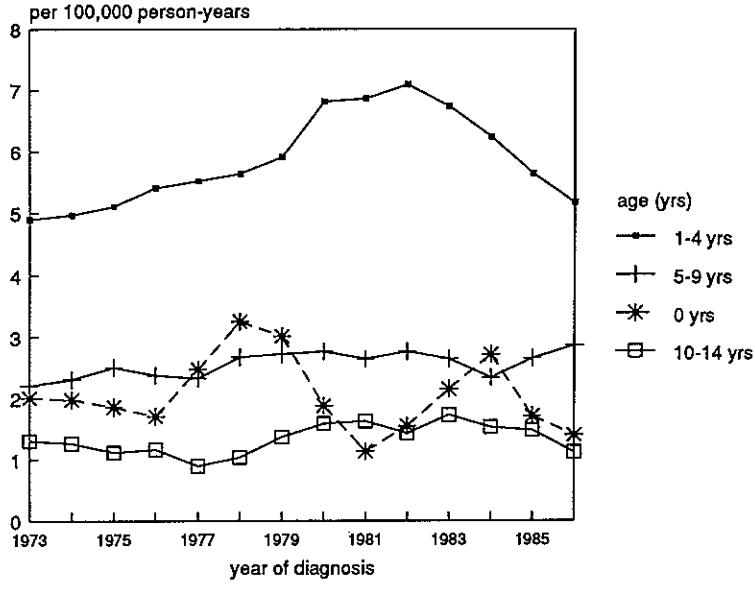


FIGURE 2 Age-specific incidence of acute lymphocytic leukaemia in children in the Netherlands, 1973-86: three year moving means per 100,000 children per year

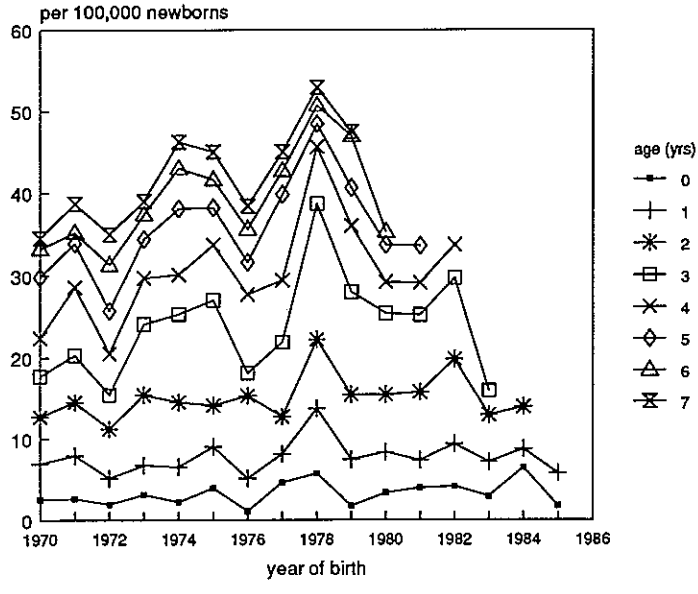


FIGURE 3 Annual incidence of acute lymphocytic leukaemia in young children in the Netherlands: age (1-4 and 2,3 and 4 years) and WBC at diagnosis per 100,000 children per year

The peak incidence of ALL appears to have occurred at age 3 since 1977, except in 1980 and 1985 (figure 3). The largest fluctuation also proved to be at this age, whereby rates for two-year-old patients show a reversed pattern. A cohort analysis by year of birth demonstrated similar cumulative incidence rates in the first 5 years of life, except that the rate for the birth cohort of 1978 was more than 30% higher than the average for the other years of birth (figure 4).

*Childhood ALL: WBC and immunophenotype*

The age-specific distribution of ALL according to WBC at diagnosis is presented in table 4. More than 75% of ALL cases (43% of infants) presented with an initial WBC $<50 \times 10^9$/l. An association appeared to exist between the initial WBC (table 4) and the sex ratio (boys/girls): an increase in the WBC corresponded with an increase in the sex ratio, the values being 1.04, 1.12, 1.23, 1.26 and 1.28, respectively. Incidence rates for ALL according to WBC at diagnosis varied mostly over time for values $<20 \times 10^9$/l, in particular $<5 \times 10^9$/l (figure 5). This occurred mainly in the 1-4 year old age group, in particular at age 3 in 1981, 1982 and 1983 (figure 3). The distribution of immunophenotypes according to age is presented in figure 6 and according to WBC at diagnosis in table 5. The most frequent phenotype was common-ALL since, together with pre B-ALL, it accounted for 74% of all cases, 90% of those in the age group 1-4 and 95% of those diagnosed at age 3. (The latter findings are based on 1985 and 1986 data) Patients with these phenotypes usually presented with a low WBC at diagnosis. T-cell ALL did not exhibit a definite age preference; these patients usually presented with a WBC $\geq 100.0 \times 10^9$/l. T-cell ALL occurred twice as often in boys as in girls, thus partly explaining the rise in the sex ratio for children with a higher initial WBC.

*International comparison*

Childhood leukaemia rates in the Netherlands appeared to be more or less similar to those in countries of identical socio-economic development (table 6). ALL/ANLL ratios were between 5 and 6 in most registers. The rates for

TABLE 4 Age-specific incidence of childhood ALL in the Netherlands, 1973-86: according to WBC at diagnosis

| WBC: no. of leukocytes $\times 10^9$/l | Cases/100,000/year per age group (yrs) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1-4 | 5-9 | 10-14 | 0-14 | No. of cases |
| -4.9 | 0.04 | 1.64 | 0.87 | 0.41 | 0.91 | (372) |
| 5.0-19.9 | 0.24 | 2.17 | 0.77 | 0.37 | 1.09 | (423) |
| 20.0-49.9 | 0.56 | 0.88 | 0.25 | 0.17 | 0.45 | (172) |
| 50.0-99.9 | 0.24 | 0.43 | 0.24 | 0.11 | 0.26 | (106) |
| ≥100 | 0.88 | 0.62 | 0.35 | 0.24 | 0.45 | (180) |
| Unknown | | | | | | ( 11) |

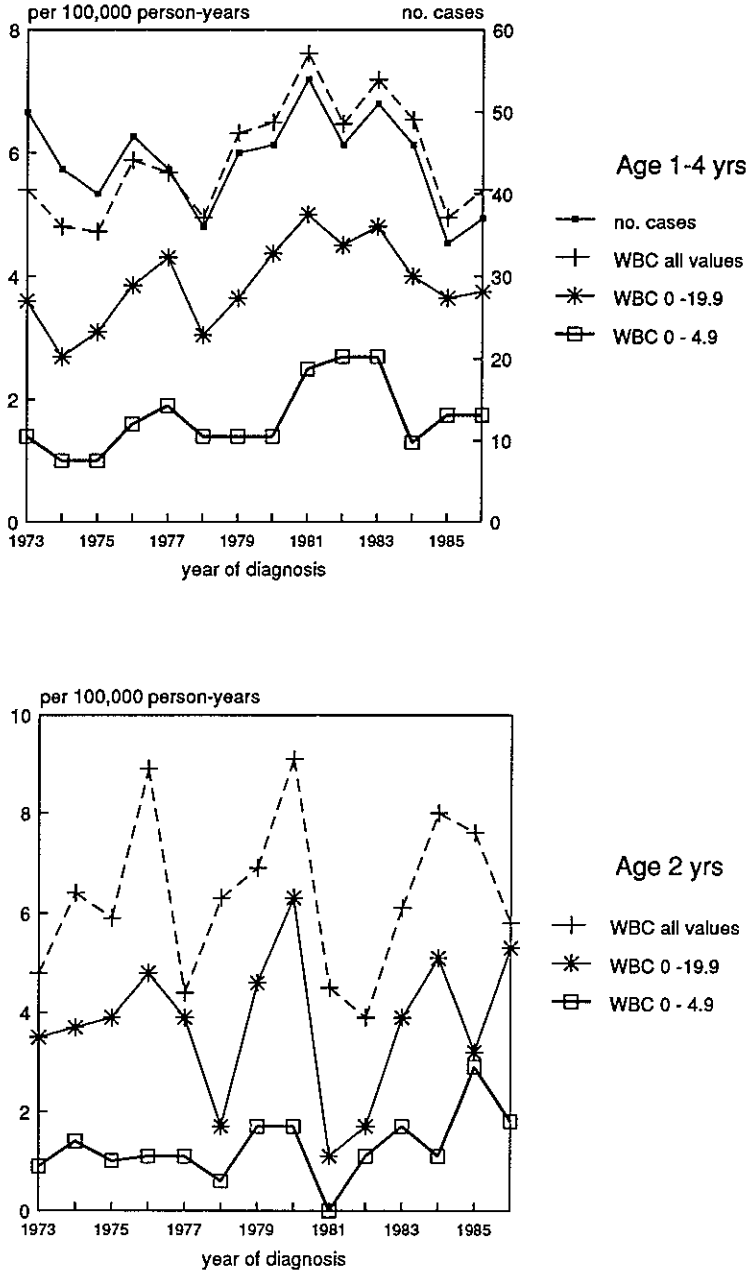


FIGURE 4 Cumulative incidence of childhood leukaemia (all types) in the Netherlands since 1971, per 100,000 newborns per year of birth

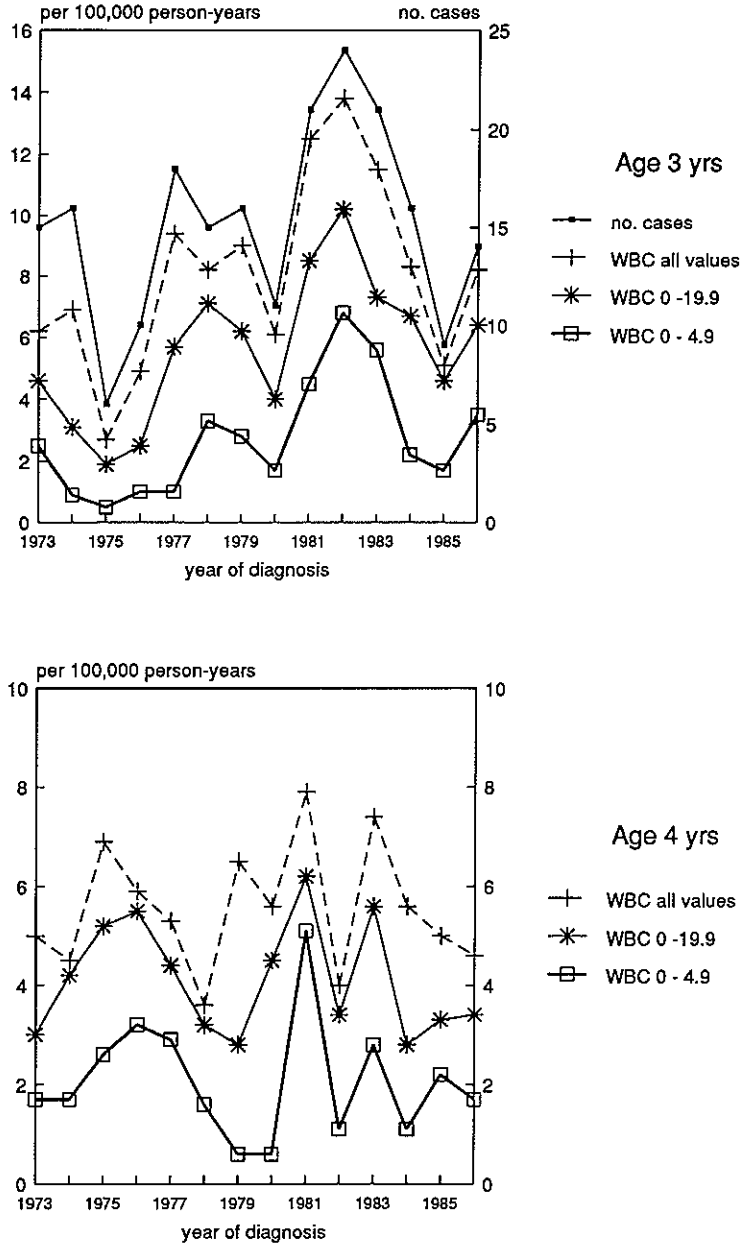


FIGURE 4 *(continued)*

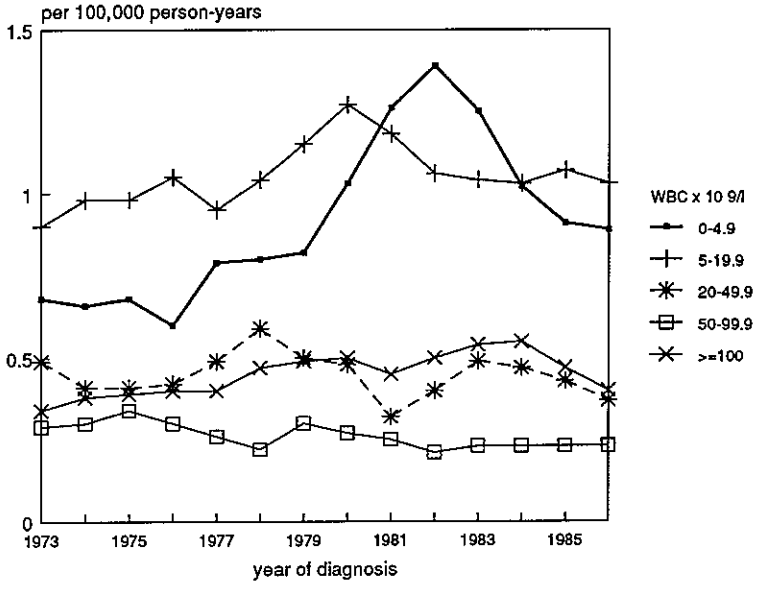


FIGURE 5 Age-adjusted* incidence of acute lymphocytic leukaemia in children in the Netherlands according to WBC** at diagnosis, 1973-86: 3 year moving means per 100,000 children per year
* world standard population

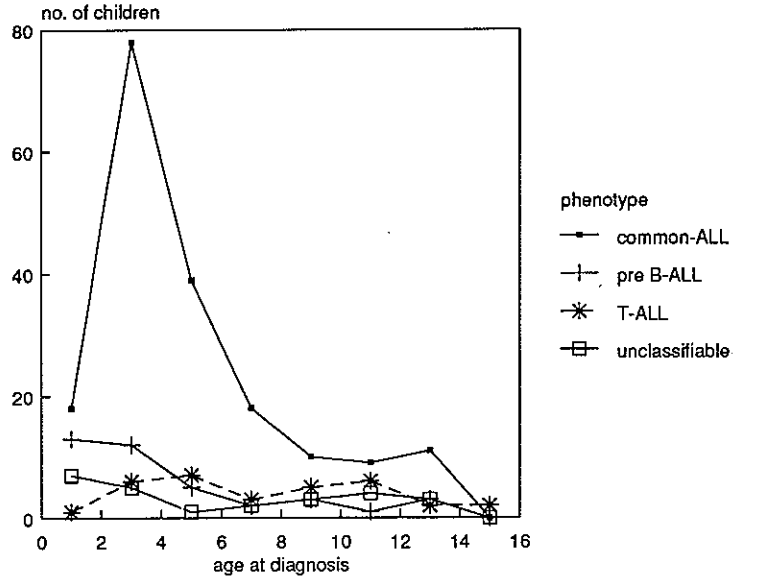


FIGURE 6 Acute lymphocytic leukaemia in children in the Netherlands: immunophenotype according to age in 1979-86

TABLE 5 Distribution of immunological phenotype of childhood ALL in the Netherlands, according to WBC at diagnosis: 1979-86

| No. of leucocytes X $10^9$/l (WBC) | T-cell | Common ALL | Pre-B | B-cell | Unclassifiable* | No test result** | Total | No test done |
|---|---|---|---|---|---|---|---|---|
| 0-4.9 | 3 | 132 | 14 | 0 | 7 | 26 | 182 | 51 |
| 5-19.9 | 6 | 130 | 23 | 2 | 11 | 6 | 182 | 66 |
| 20-49.9 | 6 | 41 | 18 | 1 | 4 | 3 | 73 | 20 |
| 50-99.9 | 7 | 20 | 9 | 2 | 1 | 1 | 40 | 13 |
| ≥100 | 47 | 20 | 6 | 0 | 14 | 1 | 88 | 18 |
| Unknown | 1 | 2 | 0 | 0 | 0 | 0 | 3 | 2 |
| Total | 70 | 345 | 70 | 5 | 37 | 37 | 564 | 170 |
| (%) | 12.4 | 61.2 | 12.4 | 0.9 | 6.6 | 6.6 | 100% | |

* immunologically; ** due to lack of sufficient material

ALL and the ALL/ANLL ratio among black children in America, as measured in the SEER-program, were definitely lower.

## DISCUSSION

The DCLSG registration rates most likely reflect the true incidence of childhood leukaemia in the Netherlands in the period 1973-86. These rates appear to be equivalent to those in countries with similar social-economic development (table 6), when expressed as the distribution of patients by age and sex as well as by morphological type of leukaemia. For ALL this also pertains to the distribution of initial WBC's and immunophenotypes.[16 17 18] Between 1979

TABLE 6 Incidence* of childhood leukaemia in Northern and Western Europe, the United States and Australia: from 1970

| Population/country | Period | Cases/100,000/year per age group (yrs) 0-4 | 5-9 | 10-14 | 0-14# | Ratio ALL/ANLL |
|---|---|---|---|---|---|---|
| USA/SEER whites | 73-82 | 6.8 | 3.5 | 2.3 | 4.4 | 5.4 |
| USA/SEER blacks | " | 3.4 | 2.0 | 2.0 | 2.5 | 2.9 |
| Australia | 77-82 | 7.4 | 3.6 | 2.2 | 4.6 | 5.3 |
| Finland | 71-82 | 5.4 | 3.0 | 2.7 | 3.9 | 5.0 |
| West Germany | 80-86 | 6.5 | 3.5 | 2.2 | 4.4 | 6.6 |
| Denmark | 80-84 | 5.7 | 2.7 | 2.8 | 3.9 | 5.3 |
| UK: Manchester | 71-83 | 5.7 | 3.2 | 2.2 | 3.8 | 5.7 |
| UK: LRF-survey* | 84-86 | 6.4 | 3.0 | 1.7 | 3.9 | 5.1 |
| The Netherlands | 73-86 | 6.1 | 3.1 | 1.9 | 3.9 | 8.3 |

* SW Scotland, Cumbria, Yorkshire, Trent, SW England, S Wales and E Suffolk
# world standard population

and 1984 an increase in the incidence of ALL was observed in young children in the Netherlands and consequently a larger ALL/ANLL ratio. This temporary increase is partly attributed to an almost 50% higher cumulative leukaemia rate for the 1978 birth cohort up to age 6. It was also found for 3-year old children with presumed common-ALL and a low WBC at diagnosis. In contrast incidence rates for patients with an initial WBC $\geq 50 \times 10^9$/l, 42% of whom had T-cell leukaemia (table 6), were constant over time. On the other hand incidence rates for ALL among infants with 60% of these WBC values showed some fluctuations (figure 2); the annual number of such cases was however small. In the Manchester region an increase was observed in the incidence of 1-4 year old children with ALL and an initial WBC $< 50 \times 10^9$/l in the period 1970-77.[12] In a larger study an increased rate was found in England for the 1974-78 period, but only in boys with an initial WBC $\geq 10 \times 10^9$/l.[18] In the Scandinavian countries age-adjusted rates for childhood leukaemia were about similar and remained more or less constant from 1965 until 1980.[19] In Denmark incidence rates for ALL in children of age 3 also showed a temporary increase, thus causing a definite peak in the period 1980-84.

The two hypotheses concerning the origin of common-ALL in childhood[5 6] also exhibit a certain degree of agreement: the random mutation theory does not exclude the possibility of an influence of exogeneous risk factors. Furthermore both hypotheses are based on the observation of similar patterns of incidence rates for childhood leukaemia in developed countries, as is confirmed by this study and descriptive studies from cancer registers in the period 1968-84.[15 20] In this respect the temporary variation in the incidence of childhood ALL, as observed in this study, invites consideration of the following points of interest.

*1* Changes in ascertainment might have occurred over time, especially for young children with common-ALL and a low initial WBC, because of its protracted natural course. However it is unlikely that these changes would be temporary.

*2* The temporary variation in the incidence rates for children in the 1-4 year age group, especially at age 3, may be a random phenomenon. This could become clearer after a longer observation period under the same conditions of ascertainment.

*3* Temporary changes in host-environment interactions.

Impressive demographic changes in relation to the health of children have occurred in the Netherlands during and prior to the period of study. Lower fertility rates (table 1) have resulted in a decline of the birth rate, smaller families and relatively more first-born children. In this period the proportion of immigrant children from (former) Dutch colonies as well as mediterranean countries has risen from 5% to almost 15%. In general housing conditions have further improved. The control of infectious diseases has improved through the various vaccination programmes, that for measles being the last to be introduced in 1976, and the use of more effective antibiotics. All this has un-

doubtedly led to lower risk of infection and may thus have resulted in a lower mortality in the precancer phase.[21] Although the mortality rates for children in the Netherlands were already low in 1970, an impressive and steady decrease in these rates for the major causes of death, including infectious diseases, has since occurred (table 7).

According to the results of an extensive population-based case-control study of (the same) children with ALL, diagnosed in the 1973-79 period, a risk increasing influence of 20% appeared to exist for higher socio-economic classes and 100% for first-borns. A decreased risk of 30% was also established for exposure to serious infections in the first year of life.[4] Changes in host-environment interactions were therefore substantial and complex prior to and during the period of study. However according to the data of this study their impact on the incidence of childhood leukaemia could only have been small.

4 Temporary changes in risk factors should be taken into account, especially for the birth cohort of 1978. From the case-control study of ALL-patients[23] relative risks of about 2 were indeed found for mothers exposed to prenatal X-rays, certain chemicals and pregnancy-saving hormones. However the contribution of these factors to the risk of leukaemia could not exceed 10%. In the period 1973-79 space-time clustering proved to be virtually absent for young children with ALL.[22] It can be concluded that there are no concrete clues in this respect, particularly not for the three small nuclear power plants.

*Conclusion*

There are no satisfactory explanations for either the observed temporary increase in the incidence of common-ALL in young children in the Netherlands or the difference in ALL in boys according to degree of urbanization. In view of the suggested effects of demographic and socio-economic changes on the incidence of lymphoproliferative diseases[23] and common aetiological and

TABLE 7 **Relative change in childhood mortality in the Netherlands, 1970-85: all causes of death (A) and infectious diseases (B)**

| | Cases/100,000/year by age group (1970-72= 100) | | | | | |
|---|---|---|---|---|---|---|
| | 0 yr | | 1 - 4 yr | | 5 - 9 yr | |
| Period | A | B | A | B | A | B |
| *1970-72* | *1215* | *79.4* | *81.1* | *11.5* | *41.8* | *2.1* |
| 1970-72 | 100 | 100 | 100 | 100 | 100 | 100 |
| 1973-75 | 92 | 91 | 89 | 83 | 87 | 90 |
| 1976-78 | 81 | 93 | 74 | 52 | 81 | 71 |
| 1979-81 | 70 | 64 | 68 | 38 | 64 | 67 |
| 1982-84 | 69 | 74 | 62 | 35 | 45 | 52 |
| 1985-86 | 55 | 39 | 51 | 31 | 42 | 48 |

source: C.B.S., Dept of Health Statistics

diagnostic aspects, the DCLSG has now started a study of the incidence of malignant lymphoma in children in the Netherlands in the same period.

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Chapter 5.1.3

# MALIGNANT LYMPHOMAS IN CHILDREN IN THE NETHERLANDS IN THE PERIOD 1973-1985: INCIDENCE IN RELATION TO LEUKAEMIA

## Report from the Dutch Childhood Leukaemia Study Group* (DCLSG)**


SUMMARY

A retrospective study was done of the incidence of non-Hodgkin's lymphoma (NHL) in children in the Netherlands in the period 1973-85 in relation to that of acute lymphoblastic leukaemia (ALL). Complete ascertainment of cases was most likely achieved through the network of cooperating paediatricians of the Dutch Childhood Leukaemia Study Group (DCLSG). The incidence of NHL remained constant at 0.75 per $10^5$ children per year; the boy/girl ratio was 2.5. In ±25% of cases the disease was localized at diagnosis. Of children with NHL who were not listed in the DCLSG leukaemia register, 19% had ≥25% lymphoblasts in the bone marrow at diagnosis, representing an overlap with ALL of ±5%. In 1% of the children with NHL an immuno-deficiency disorder preceded the diagnosis.

The incidence of Hodgkin's disease (HD) was 0.3 per $10^5$ children per year, with some fluctuation over time, the peak being 0.7 in 1983. The boy/girl ratio was 2.7.

Age-specific incidence rates, clinical features of NHL and HD as well as the ALL to NHL ratio corresponded with those in other European countries and for white children in the U.S.A..


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## INTRODUCTION

Malignant lymphomas (ML) in children, both non-Hodgkin's lymphoma (NHL) and Hodgkin's disease (HD), account for almost 10% of all new paediatric cancer patients in industrialized countries. Incidence rates are generally higher in Mediterranean countries.[1] Increasing deprivation seems to correspond with a higher incidence of NHL and a lower incidence of acute lymphoblastic leukaemia (ALL), in particular common-ALL.[2] The leukemia to non-Hodgkin's lymphoma ratio (LLR) varies from 4 to 6 in developed countries to less than one in third world countries.[3] Although 25% lymphoblasts in the bone marrow is considered the cut-off point for the diagnosis of NHL (<25%) or ALL (≥25%), the clinical distinction between NHL and ALL in children is not unequivocal, especially if a mediastinal mass is present.[4] Furthermore the natural history of NHL in children is often characterised by 'progress' to a leukaemic form. Thus the occurrence of childhood NHL is related to ALL and vice versa. The incidence of childhood leukaemia in the Netherlands has been determined since 1972 within the framework of the Dutch Childhood Leukaemia Study Group (DCLSG), a nationwide cooperative group of paediatricians. Between 1979 and 1985 a temporary increase in the incidence of ALL of ±30% was observed in young children, most of them with common-ALL.[5] To exclude a simultaneous decrease in the incidence of NHL the DCLSG initiated a retrospective study of the incidence of childhood NHL as well as of HD from 1973. To enhance relevance and accuracy data on preceding disease, localization and stage at diagnosis and histological subtype were also collected.

## PATIENTS AND METHODS

### *Patients*

All children with NHL and HD, newly diagnosed between January 1st, 1973, and December 31st, 1985, between 0 and 14 years of age and living in the Netherlands at least two months prior to diagnosis were included in the study. Patient and disease characteristics were obtained from clinical records via questionnaires, completed by paediatricians in community hospitals and by DCLSG data managers in paediatric oncology centers: the former Emma's children's hospital in Amsterdam and paediatric departments of the university hospitals in Amsterdam, Groningen, Leiden, Nijmegen, Rotterdam and Utrecht. Cooperation was obtained from paediatricians in 80% of the hospitals, including all of the larger clinics and oncology centers, to which about 95% of patients had been referred. Among the unreferred children some with NHL had died soon after diagnosis and a few with HD had been treated solely in community hospitals and centres for radiotherapy. Enquiries were also made at centres for radiotherapy, neurosurgery, head and neck surgery and adult haemato-oncology. Data were cross-checked with the Eindhoven cancer regis-

try, which covered 8% of Dutch children at the time. Excluded from the analysis were 10 children who lived outside the Netherlands at diagnosis and 15 children recorded with leukaemia at the DCLSG central register. A total of 311 children with NHL and 133 with HD were analysed. They were grouped according to sex and age at diagnosis: 0, 1-4, 5-9 and 10-14 years.

*Diagnosis*

The diagnosis ML has always been confirmed by histological and/or cytological examination of tumour specimens, often by more than one pathologist. For *non-Hodgkin's lymphoma* the original histological diagnoses mentioned in pathology reports were: lymphosarcoma; Burkitt's or Burkitt-like lymphoma; histiocytic, immunoblastic or centroblastic lymphoma; reticulum cell sarcoma and B or T-cell lymphoma. Included in the analysis were 59 patients with NHL (19% of 311), who had ≥25% lymphoblasts in the bone marrow but were unknown at the DCLSG leukaemia registry. Immunophenotyping of leukaemic blast cells was performed with increasing frequency over time: in 43% of the cases after 1977, 52% after 1980 and 70% after 1982.

The histological type of *Hodgkin's disease* was determined according to the Rye classification: nodular sclerosis, lymphocyte depleted, lymphocyte predominant and mixed cellularity. The Ann Arbor classification was in use for staging at diagnosis.

Data were collected on the following *indicators* of risk for development of ML: geographic origin of the parents and children, preceding serious diseases, residence at diagnosis; these items were reported in 93%, 90% and 100% respectively.

*Data analysis*

Annual mid-year population figures, per age group, sex and level of urbanization, were provided by the Department of Population Statistics of the Central Bureau of Statistics. During the study period the number of children at-risk decreased from 3.5 to 2.8 million. An official classification of degree of urbanization was used of rural communities, urbanizing communities and large cities.

Annual incidence rates for NHL and HD were calculated per 100,000 personyears according to sex and age group. For age-adjustment the world standard population was used, with its proportional distribution of the age-groups 0, 1-4, 5-9 and 10-14 years of 7.75, 31, 32.25 and 29%.

*International comparison of incidence*

Age-adjusted incidence rates were obtained from cancer registries in Denmark, Norway, Sweden, Switzerland (3 Western cantons), the USA (SEER-registry) and the specific childhood cancer registries in England & Wales, the Federal Republic of Germany, France and Torino (Italy).[1]

*Mortality*

Aggregate data on cause of death were supplied by the Central Bureau of Statistics since 1969. ICD-code 201 was used for HD, 200 and 202 were pooled for NHL and 204-208 for leukaemia.

## RESULTS

*Incidence*

The age-adjusted incidence rate for childhood malignant lymphoma in the Netherlands in the 1973-85 period was 1.0 per $10^5$ personyears, 1.4 for boys and 0.6 for girls (table 1). NHL occurred 2.6 times more often than HD in both boys and girls. The boy/girl ratio was 2.5 for NHL and 2.7 for HD; it increased with age in NHL and decreased in HD. The incidence of NHL reached a peak in boys of 5-9 years. HD was rare below age 5, especially among girls. After age 5-9 the incidence of HD rose with age in girls, but not in boys. The annual incidence rates for NHL were between 0.65 and 0.80 per $10^5$ personyears (figure 1). When related to the raised incidence of childhood ALL in the period 1979-84, rates of NHL were also slightly elevated in that period, as appears from the virtually unchanged LLR of 5. Variation in the age-specific rates over time was small. The annual incidence of HD showed a peak in 1983. Incidence rates, sex ratios and LLR's in the Netherlands were within the range of those in other European and the U.S.A. (table 2).

*Indicators of risk for development of ML*

No indications for case clustering were found upon analysis of the data according to residence of the patient. Incidence rates according to degree of urbanization or month of diagnosis did not differ. However slightly more children, whose parents had emigrated from Turkey and Marocco, were

TABLE 1 Incidence of malignant lymphoma among children in the Netherlands in 1973-85: according to age and sex

| | Age | Both sexes | | Boys | | Girls | | Ratio |
|---|---|---|---|---|---|---|---|---|
| Type | yrs | no. | per $10^5$ | no. | per $10^5$ | no. | per $10^5$ | ♂/♀ |
| NHL | 0-14* | 308 | 0.74 | 219 | 1.02 | 89 | 0.44 | 2.5 |
| | <1 | 7 | 0.30 | 4 | 0.34 | 3 | 0.27 | 1.3 |
| | 1-4 | 73 | 0.74 | 48 | 0.95 | 25 | 0.52 | 1.8 |
| | 5-9 | 131 | 0.94 | 97 | 1.36 | 35 | 0.50 | 2.6 |
| | 10-14 | 97 | 0.62 | 70 | 0.88 | 28 | 0.35 | 2.6 |
| HD | 0-14* | 133 | 0.29 | 96 | 0.41 | 37 | 0.15 | 2.7 |
| | <1 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | – |
| | 1-4 | 12 | 0.12 | 11 | 0.22 | 1 | 0.02 | 11 |
| | 5-9 | 52 | 0.37 | 40 | 0.56 | 12 | 0.18 | 3.1 |
| | 10-14 | 69 | 0.45 | 45 | 0.57 | 24 | 0.32 | 1.8 |

* world standard population

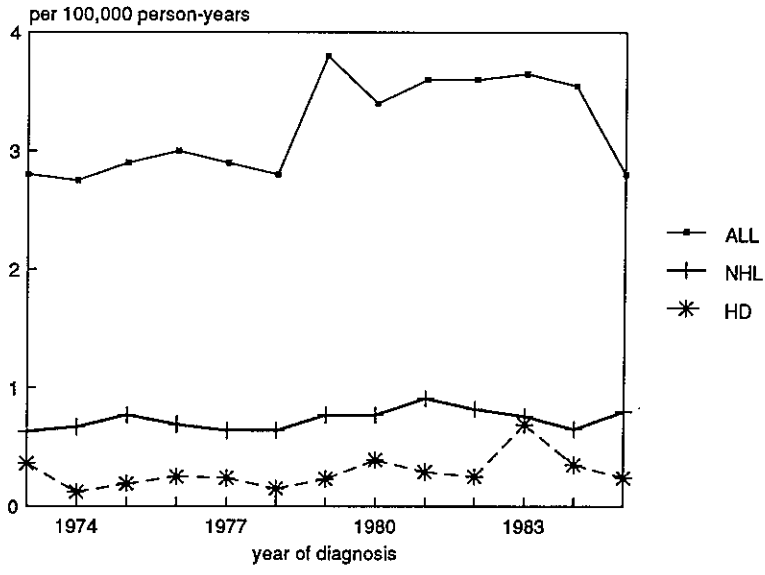


FIGURE 1 Annual age-adjusted* incidence of non-Hodgkin's lymphoma, Hodgkin's disease and acute lymphoblastic leukaemia in children in the Netherlands, 1973-85
* world standard population

TABLE 2 Age-adjusted incidence* of and sex ratio for malignant lymphoma, incidence of leukaemia and ALL/NHL ratio (LLR) for children in Europe and the USA

| Area/ country | Period | NHL per $10^5$ | NHL ratio ♂/♀ | HD per $10^5$ | HD ratio ♂/♀ | Leukaemia per $10^5$ | LLR |
|---|---|---|---|---|---|---|---|
| Denmark | 1978-82 | 0.8 | 3.4 | 0.4 | 1.2 | 3.9 | 4.9 |
| West Germany | 1982-84 | 0.5 | 2.8 | 0.5 | 2.1 | 4.4 | 8.8 |
| Finland | 1970-79 | 1.0 | 2.1 | 0.25 | 1.9 | 3.9 | 3.9 |
| France | 1983-85 | 0.7 | 3.3 | 0.4 | 1.5 | 4.0 | 5.7 |
| England & Wales | 1971-80 | 0.6 | 2.3 | 0.4 | 2.2 | 3.8 | 6.3 |
| Torino (Italy) | 1967-81 | 0.8 | 2.9 | 0.7 | 1.6 | 4.9 | 6.1 |
| Norway | 1970-79 | 0.55 | 3.0 | 0.25 | 1.7 | 4.5 | 8.2 |
| Sweden | 1970-82 | 0.9 | 2.0 | 0.35 | 4.0 | 4.4 | 4.9 |
| Switzerland | 1974-83 | 0.65 | 2.5 | 0.4 | 0.3 | 4.4 | 6.8 |
| USA-whites | 1973-82 | 0.85 | 2.8 | 0.6 | 1.1 | 4.4 | 5.2 |
| USA-blacks | " | 0.45 | 1.9 | 0.5 | 3.9 | 2.5 | 5.6 |
| Netherlands | 1973-86 | 0.75 | 2.4 | 0.3 | 2.7 | 3.9 | 5.2 |

source: 3
* world standard population

observed than the expected 6%: 11% for NHL below age 5 and 16% for HD below age 8. In 27 children (8%) NHL was preceded by serious diseases, 4 times an immuno-deficiency disorder (1 after kidney transplantation), 4 a viral infection, 2 hypothyreoidy, 2 haemangiomatosis and 2 congenital heart disorder. With respect to HD 10 children (8%) had such serious diseases, 2 of them had a nephrotic syndrome.

*Clinical features*

*Non Hodgkin's Lymphoma:* about 25% of the patients had localized disease at diagnosis (table 3). T and B-cell NHL were equally distributed. T-cell NHL was localized mainly in the mediastinum (60%), in the head-and-neck region (14%) and at multiple sites; B-cell NHL was mainly found in the abdomen (62%) and head and neck region (30%). In patients with ≥25% lymphoblasts in the bone marrow 42% of the tumours were in the mediastinum, 15% in the head-and-neck region and 29% at multiple sites; the ratio of T to B-cell NHL was 7 in this group and the boy/girl ratio was 4.

*Hodgkin's Disease:* the lymphocyte-predominant and lymphocyte-depleted histological subtypes were more frequent in boys, whereas nodular sclerosis was more frequent in girls (table 4). Stage at diagnosis and histological subtype did not correlate.

*Mortality*

Age-adjusted mortality rates for NHL, HD and leukaemia decreased in the period 1969-86, starting in 1973-74 for leukaemia, in 1981-82 for boys with NHL and in 1977-78 for girls. The mortality rate for HD was very low (figure 2).

## DISCUSSION

In the Netherlands neither a decrease in the incidence of NHL in children nor a marked increase in the LLR was observed in the period 1979-84, i.e. when the incidence of childhood leukaemia, in particular ALL, was about 30% higher

**TABLE 3 Clinical features of non-Hodgkin's lymphoma in children in the Netherlands, 1973-85: primary site and extent of disease at diagnosis**

| Primary site | % | Extent of disease | % |
|---|---|---|---|
| Thorax/mediastinum | 28 | localised | 23 |
| Head & neck | 21 | multiple sites | 39 |
| Abdomen | 31 | lymph nodes | 15 |
| Multiple sites | 14 | bone marrow | 9 |
| Unknown | 6 | pleura | 3 |
| | | ascites | 1 |
| | | unknown | 10 |

TABLE 4 Distribution of Hodgkin's disease in children in the Netherlands

A According to histological type and sex

| Type | Boys (%) | Girls (%) |
|---|---|---|
| Lymphocyte predominant | 14 | 3 |
| Lymphocyte depleted | 33 | 19 |
| Nodular sclerosis | 41 | 60 |
| Mixed cellularity | 4 | 3 |
| Unknown | 8 | 15 |

B According to stage at diagnosis* and per stage according to absence (A) or presence (B) of symptoms

| | | Symptoms | | |
|---|---|---|---|---|
| Stage | % | A (%) | B (%) | Unknown (%) |
| Unknown | 9 | | | not available |
| I | 32 | 84 | 10 | 6 |
| II | 25 | 64 | 24 | 12 |
| III | 24 | 40 | 52 | 8 |
| IV | 10 | 15 | 62 | 23 |
| All stages | 100% | | | |

* Ann Arbor classification

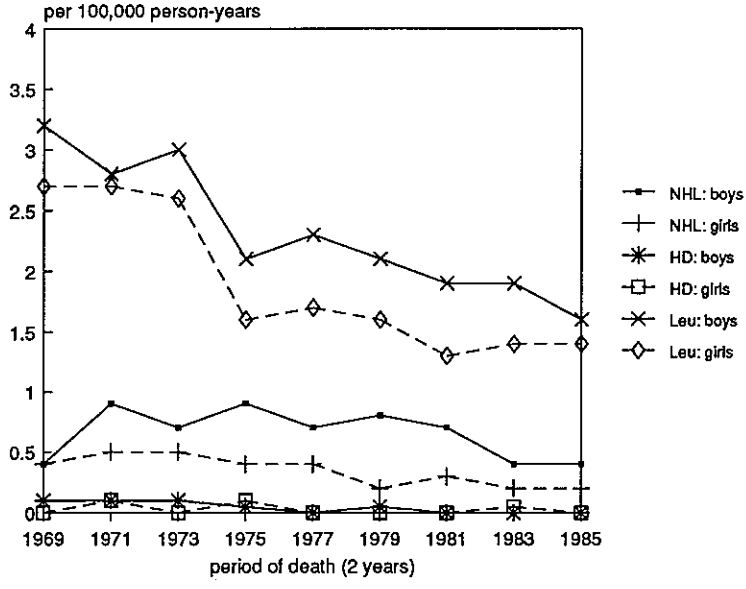


FIGURE 2 Age-adjusted* mortality rates for leukaemia and malignant lymphomas in children in the Netherlands, 1969-86
Source: Central Bureau of Statistics; * world standard population

than in the previous period.[5] The incidence rates and sex ratios for NHL and HD were consistent with the low incidence pattern in industrialized countries.[1]

Although underreporting and misclassification cannot be ruled out, especially in the early years of the study, this retrospective study appears to reflect the reality for the following reasons: 1. the response of the paediatricians in the larger hospitals was satisfactory, which is consistent with the existing cooperation within the DCLSG-network; 2. 95% of children with ML and with other solid tumours were referred to paediatric oncology centres, where mostly several pathologists were involved in the histological classification and diagnosis; 3. the proportion of cases reported by the Eindhoven regional cancer registry corresponded with its coverage of Dutch children at the time. Also, the mortality rate for NHL (figure 2) was clearly lower than the observed incidence, also in the early years of the study, when survival rates were still low.

As expected the distribution of clinical and pathological features at diagnosis was rather similar to that reported in other population-based series.[6 7] It appears that the 19% of cases with NHL and ≥25% lymphoblasts in the bone marrow at diagnosis resemble patients classified as lymphomatous leukaemia.[8] During the study period they were rather evenly distributed over time, which makes a shift in classification unlikely; if they had been classified as ALL its incidence would have been 5% higher, which would not explain the temporary rise in the incidence of ALL in the period 1979-84.5 Misclassification of NHL as leukaemia in this period seems unlikely due to the rather consistent classification of leukaemia in the DCLSG central laboratory, where many cases with NHL were also reviewed.

The most important risk indicator for the development of ML seems to be male gender. The similarity to the incidences reported in other European countries, the virtual absence of both space-time clustering and seasonal fluctuation do not provide strong clues for further aetiological study, neither does the weakly raised incidence among children whose parents came from Mediterranean countries.[1] The pronounced demographic changes in the Netherlands noted since 1970, characterized by a 40% lower birth rate, smaller families, fewer infections and lower mortality in children, do not seem to have affected the observed incidence rates. The mortality rate for NHL decreased, mainly after 1979 when the observed incidence rate remained stable or showed a small increase: this suggests improved treatment results, which would be in agreement with clinical data[9] and population-based findings in England and the U.S.A. both for NHL and HD.[10 11]

*In conclusion* this retrospective study of the incidence of malignant lymphoma in the Netherlands in the period 1973-85 shows more or less constant rates. It does not provide for an explanation for the increased incidence of childhood ALL in the period 1979-84. The apparent overlap between NHL and ALL necessitates a combined approach in clinical and epidemiological studies of

these diseases, also under the clearly defined conditions for the diagnosis of childhood leukaemia in the Netherlands.

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Chapter 5.2.1

# IMPROVED PROGNOSIS OF OVARIAN CANCER IN THE NETHERLANDS DURING THE PERIOD 1975-1985:

## A registry-based study*


SUMMARY

Survival was studied of 568 patients with ovarian cancer, diagnosed in 1975-85, by means of a population-based registry in southeastern Netherlands. Patients diagnosed in the period 1981-85 had a significantly better prognosis than patients diagnosed in 1975-80. This improvement of survival declined with advancing age of the patients. In women younger than 60 years, mortality from ovarian cancer decreased, while incidence remained stable. Apart from the effect of new treatment methods, consisting of more extensive tumour reduction and cisplatin-based combination chemotherapy, advances in supportive care as well as a trend towards earlier diagnosis, possibly in combination with an increasing proportion of less malignant tumours, may explain the improvement in prognosis. Survival was strongly related to stage at diagnosis, and to age, the prognosis of younger patients being more favourable. Patients with tumours of either germ cell or stromal origin generally survived longer than patients with epithelial tumours, but this difference disappeared after adjustment for stage and age. Patients still alive after 6 years did not have a significantly different survival as compared to the general female population.


INTRODUCTION

Ovarian cancer is the most frequent malignancy of the female genital tract in the Netherlands, causing 6% of cancer deaths in females.[1 2] Based on clinical trials, carried out during the past 15 years, the use of aggressive therapy (extensive surgery and cisplatin containing chemotherapeutic regimens) was recommended also outside the study setting.[3] The improvement in prognosis due to these treatment methods, however, can be assumed to be smaller outside


* Balvert-Locht HR, Coebergh JWW, Hop WCJ, Brölmann HAM, Crommelin MA, van Wijck DJAM, Verhagen-Teulings MTh. Improved prognosis of ovarian cancer in the Netherlands during the period 1975-85: a registry-based study. *Gynecol Oncol* (in press)

this setting, since the general population is likely to comprise more elderly and untreated patients and more patients with a poor performance status. Using data from a cancer registry, we investigated whether the population-based survival of ovarian cancer patients diagnosed from 1975 to 1980 differed from that of patients diagnosed from 1981 to 1986, when more advanced methods of staging and treatment were used. We also compared incidence and mortality rates over time in order to confirm changes in survival.

## MATERIAL AND METHODS

The Eindhoven Cancer Registry started in 1955 and covers an area in the Southeast of the Netherlands with about 1,000,000 inhabitants, 7% of the Dutch population.[1] Incidence-rates could be estimated from 1975 onwards in this population.[4] Data were collected directly from medical records in all 11 community hospitals which served the region. The registry was routinely informed of newly diagnosed cancers by pathology laboratories, the regional radiotherapy department and hospital medical archives. Referrals to specialised clinics outside the region were traced. In the period 1975-85 data on 610 new ovarian cancer patients were collected by the registry. Information about the vital status up to December 31, 1987, was obtained from municipal population-administrations. One woman was lost to follow-up after 3 years, while 7 patients could not be traced, leaving 603 patients for survival analysis. Survival of 35 patients with "borderline" malignant tumours, of whom only 4 were diagnosed before 1981, was analysed separately, leaving 568 patients for the main analyses. Histological classification was carried out by 8 pathologists in 3 laboratories. Retrospectively the following histological groups were distinguished: epithelial, stromal, germ cell origin, other histology or unknown histology. The stages, in 99% surgical (T.N.M.), were converted to F.I.G.O.-stages.[5] In 21 patients stage was not known. Primary treatment modalities were documented. Actuarial and Kaplan-Meier survival curves were computed, according to period of diagnosis (1975-80, 1981-85), age category (14-44, 45-59, 60-74 and 75 years and older), stage and histological group. The log-rank test was used to assess significance of differences in survival, also after adjustment (by stratification) for other variables. The prognostic value of several factors together was assessed using the Cox proportional hazards model,[6] applied in various follow-up intervals. Standard errors of relative death rates reported for this analysis are derived from first order Taylor expansions.[7] In order to take other causes of death into account, and for the purpose of comparing our results with others, relative survival was computed, using a computer-program from the Finnish cancer registry.[8] Relative survival is defined as the ratio of the observed survival rate of patients (all causes of death) and the expected survival rate.[9] The expected survival rates were computed from regional death tables (supplied by the Netherlands Central Bureau of Statistics) concerning females of the same age and time period as the patients.

Other statistical methods are indicated in the text. P-values reported are two-sided, with 0.05 taken as the limit of statistical significance. Age-specific incidence was derived from the registry, excluding borderline malignant tumors. Mortality from cancer of the adnexa (mainly ovarian cancer) in this region, as derived from death-certificates, was supplied by the Netherlands Central Bureau of Statistics. Incidence and mortality rates were computed per 100,000 womanyears as 3 year moving averages.

## RESULTS

Thirty-five patients had borderline malignant tumours. The mean age at diagnosis of these patients was 50 years (range: 20-74 years). None of these patients had died at the closing date. The following refers to the remaining group (n=568). The numbers of patients according to age, stage, and histological group are given in table 1. The age-distribution of patients diagnosed in 1981-85 (mean: 59 years, range: 14-89 years) did not differ significantly (Mann-Whitney's test) from those diagnosed in 1975-80 (mean: 57 years, range: 14-89 years). Neither did the stage-distribution and the distribution of histology differ significantly (chi-square test) between both periods. The distribution of applied treatment differed between the periods (table 2). In the second period more patients were treated by surgery only and less by radiotherapy than in the first period. Whereas single alkylating chemotherapy was the most common drug therapy in the first period, cisplatin containing combination chemotherapy was administered almost exclusively in the second period. There was a strong correlation between the age of the patients and stage within

TABLE 1 Number of patients with ovarian cancer according to age, stage and histology

| | | 1975-80 | 1981-85 | Total | (%) |
|---|---|---|---|---|---|
| Age (yrs) | 14-44 | 42 | 35 | 77 | (14) |
| | 45-59 | 104 | 111 | 215 | (38) |
| | 60-74 | 112 | 100 | 212 | (37) |
| | 75+ | 25 | 39 | 64 | (11) |
| Stage | I | 71 | 77 | 148 | (26) |
| | II | 26 | 31 | 57 | (10) |
| | III | 110 | 112 | 222 | (39) |
| | IV | 68 | 52 | 120 | (21) |
| | unknown | 8 | 13 | 21 | (4) |
| Histology | epithelial | 234 | 250 | 484 | (85) |
| | stromal | 19 | 14 | 33 | (6) |
| | germ-cell | 7 | 5 | 12 | (2) |
| | other | 9 | 7 | 16 | (3) |
| | unknown | 14 | 9 | 23 | (4) |
| Total | | 283 | 285 | 568 | (100) |

TABLE 2 Primary treatment methods of patients with ovarian cancer

| | 1975-80 | 1981-85 |
|---|---|---|
| Surgery + Single alkylating agents | 76 | 25 |
| Surgery + Cisplatin-based chemotherapy | 8 | 70 |
| Surgery + Other combination chemotherapy | 10 | 0 |
| Surgery + Other/unknown chemotherapy | 11 | 16 |
| Subtotal Surgery + Chemotherapy | 105 | 111 |
| Surgery only | 63 | 95 |
| Chemotherapy only | 37 | 24 |
| Surgery + Radiotherapy | 29 | 17 |
| Radiotherapy only | 4 | 2 |
| Chemotherapy + Radiotherapy | 5 | 0 |
| No cancer therapy | 40 | 36 |
| Total | 283 | 285 |

either period. The proportion of cases with stage I decreased with age from 46% in the age-category <45 years to 13% in the age category ≥75 years (chi-square test: $p<0.005$). Correspondingly, the percentage of cases with advanced stages increased with age. Survival of patients diagnosed in 1981-85 was significantly better than survival of patients diagnosed in 1975-80 ($p<0.001$) (figure 1). The difference remained significant after adjustment for age and stage ($p<0.001$). This improvement of prognosis was apparent in all age categories except for patients of 75 years or over, in all stage categories and

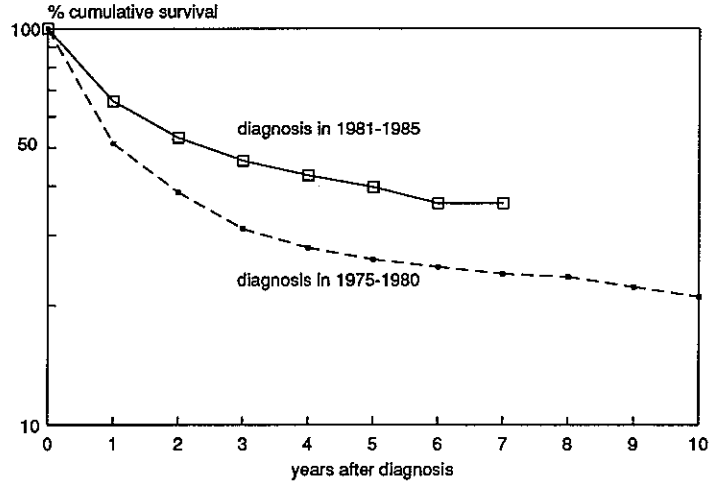


FIGURE 1 Cumulative survival (all causes of death) of ovarian cancer patients diagnosed in 1975-80 and in 1981-85 in southeastern Netherlands

in all histological categories except for patients with germ-cell tumours. Both age and stage were important prognostic factors, also after adjustment for each other (test for trend between age-groups: $p<0.0001$, also after adjustment for stage; test for trend between stage-groups: $p<0.0001$, also after adjustment for age). The decreasing survival with rising age could only partly be explained by lower expected survival rates: relative survival figures were also lower for older patients (table 3). Although patients with stromal tumours or germ-cell tumors had a significantly better survival as compared to patients with epithelial tumours, (5-year survival from all causes of death: 65%, 63% and 32%, respectively), there were no statistically significant differences after adjustment for stage and age. This could be explained by a more favourable stage distribution for patients with stromal tumours (52% stage I) as compared to patients with epithelial tumours (26% stage I) (chi-square test: $p<0.005$) and to a more favourable age distribution of patients with germ-cell tumours (mean age 35.9) as compared to those with epithelial tumours (mean age 58.3) (Mann-Whitney: $p<0.005$). Multivariate analysis by Cox-regression of the factors age, stage and period of diagnosis showed that the improvement of survival for patients diagnosed in 1981-85 as compared to patients diagnosed in 1975-80 only occurred during the first three years of follow up and was related to the age of the patients (table 4). The improvement of survival was greatest in younger patients and was no longer present for patients with advanced age at diagnosis. This implies also that the gradient of survival according to age at diagnosis was greater when diagnosis was made in 1981-85 as compared to 1975-80. During the 4th to 6th follow-up year, only stage was significantly related to survival: patients with stage I had a significantly better prognosis than those with a higher stage, whereas there were no significant differences between stages II, III and IV. After more than 6 years of follow-up (n=86) only age remained a significant prognostic factor. These patients, mainly diagnosed before 1981, did not have

**TABLE 3 Cumulative 3-, 5-, and 10-year relative survival of patients with ovarian cancer according to period of diagnosis, age and stage**

| | | 3-yr (%) | 5-yr (%) | 10-yr (%) |
|---|---|---|---|---|
| All patients | | 40 | 35 | 30 |
| | 1975-80 | 32 | 28 | 25 |
| | 1981-85 | 48 | 42 | |
| Age | 14-44 yrs | 69 | 66 | 62 |
| | 45-59 | 45 | 39 | 30 |
| | 60-74 | 29 | 24 | 22 |
| | 75+ | 23 | 20 | 17 |
| Stage | I | 80 | 76 | 64 |
| | II | 47 | 35 | 32 |
| | III | 29 | 22 | 20 |
| | IV | 6 | 6 | 03 |
| | unknown | 55 | 59 | 47 |

TABLE 4 **Death rate ratios (and standard errors) from Cox-regression for the first and second 3 years of follow-up, according to period of diagnosis, age and stage**

| Prognostic factor | | Years 0-3 (n=547) | Years 3-6 (n=191) |
|---|---|---|---|
| Period of diagnosis | 1981-85 | 1 | 1 |
| | 1975-80 | depending on age* | 0.9 (0.3) |
| | | 50 yrs: 2.1 (0.3) | |
| | | 65 yrs: 1.4 (0.2) | |
| | | 80 yrs: 1.0 (0.2) | |
| Age (as compared to 10 years younger) | | depending on period of diagnosis | 1.1 (0.2) |
| | | 1981-85: 1.6 (0.1) | |
| | | 1975-80: 1.3 (0.1) | |
| Stage I | | 1 | 1 |
| II | | 2.3 (0.6) | 4.5 (2.5) |
| III | | 4.5 (0.9) | 4.6 (2.1) |
| IV | | 8.6 (1.7) | 2.6 (2.9) |

* ages arbitrarily chosen

a significantly different survival as compared to women in the general regional population. Over the period 1975-85, mortality from cancer of the adnexa declined for patients under 60 years, while incidence remained stable (fig 2). For patients older than 60 years, the difference between mortality and incidence did not increase.

## DISCUSSION

Relative survival rates in this population-based study do not seem to differ much from survival in hospital-based studies in which deaths from intercurrent disease are excluded. For all stages combined, 3- and 5-year survival rates of 45.6% and 35.6% were published in the recent report of the International Federation of Gynecology and Obstetrics, concerning 7752 and 5102 patients with obvious malignant epithelial ovarian cancer, diagnosed in various countries between 1979 and 1981.[10] Similar results have also been obtained in population-based studies. In 770 ovarian cancer patients in the Stockholm-region, diagnosed in 1974-79, the uncorrected cumulative 5-year survival was 77% for early cases (stages I and IIA) and 28% for advanced cases; for women younger than 45 years these rates were 97% and 54%, respectively.[11] An unfavourable prognosis in elderly patients, also after correction for stage and for death from other causes, is often reported and attributed to different patient-, or tumour-characteristics, comorbidity and less aggressive treatment in the elderly.[12 13] Population-based survival of ovarian cancer in the fifties was in general lower than today: 5-year relative survival rates between 25 and 30% were found for patients diagnosed in the period 1945-56 in England & Wales, Finland, Norway and the USA.[14] For patients diagnosed in the Netherlands

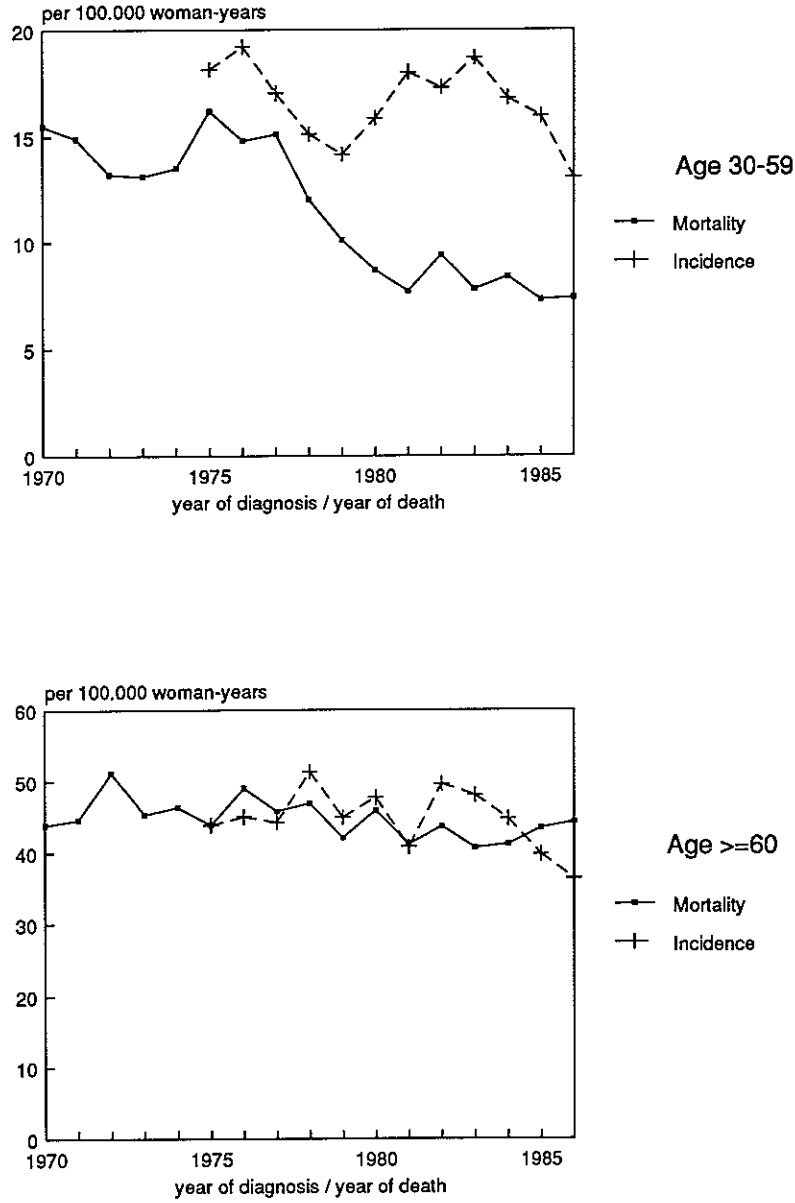


FIGURE 2 Age-specific incidence and mortality rates of ovarian cancer in southeastern the Netherlands (per 100,000 woman-years, 3-year moving averages)

in the periods 1953-55 and 1956-58, registry-based 5-year relative survival rates of 23 and 18%, respectively, were calculated.[15] [16] Several population-based studies have reported improvement of survival in ovarian cancer in the sixties and seventies. Five year relative survival rates in Finland increased from 25% in 1953-59 to 33% in 1960-66 but remained at this level since.[17] [18] An improved relative survival in the period 1970-79 compared to 1960-69 was observed for 754 patients from Cambridge and was suggested to result from better treatment methods.[19] An improvement of survival in 759 women with epithelial cancer of the ovary in Alberta, diagnosed from 1960 to 1979, was also attributed to better therapy.[20] Mainly based on data from hospital-registries, 5-year relative survival rates of 32 and 36% were found in the U.S.A. for the periods 1960-63 and 1970-73.[21] For the periods 1974-76, 1977-78 and 1979-84, rather stable population-based 5-year relative survival rates of 36, 37 and 37% were reported. For the marked improvement of survival found in this study, the following changes may have been responsible: earlier diagnosis, more benign tumour behaviour and improvement of therapy. Although ovarian cancer is known for its late onset of symptoms, a trend towards earlier diagnosis seems possible since access to gynaecology practices in this region changed along with the increasing number of gynaecologists (from 21 in 1975 to 31 in 1985). Moreover, ultrasonography was introduced in the hospitals in this period. Increased application of this technique in clinical practice, also by internists and surgeons, may have led to earlier detection. Furthermore, the introduction of promising new treatment methods in the late seventies may well have stimulated gynaecologists to put more effort in diagnostic activities. Although the proportion of patients with stage I did not increase markedly, this does not exclude improvements of early detection, since during the same period more patients were probably allocated to higher stages due to more extensive staging. There might have been an increasing amount of tumours of a lower degree of malignancy, even after the exclusion of "borderline"-tumors. This theoretically possible explanation is not yet supported by literature. "Borderline"-tumours were diagnosed mostly after 1980, but these cannot account for the improvement in survival since they were excluded from this analysis. On the contrary, we may have underestimated the improvement of survival if in the first years of the study some "borderlines" were not identified as such and therefore have not been excluded. Since the mid-seventies various claims have been forwarded regarding more efficacious therapy, consisting of chemotherapy mostly with alkylating agents, preceded by more extensive debulking operative therapy.[22] At the end of the seventies several clinical trials reported higher response rates as well as improvements in survival applying cisplatin containing combination chemotherapy together with aggressive tumour reduction.[23] [3] In a meta-analysis of recent clinical trials, cisplatin had a clear effect on survival for patients with stage II and III and a good condition.[24] In the Eindhoven area, treatment was not given in specialized centres. However, in hospitals with and without oncology services, the same

quality and outcome of care was found in Italy in 1978-79.[25] During this study, several changes occurred regarding therapy, which was increasingly given by a group of gynaecologists interested in oncology. Extensive debulking was attempted as well as better staging, which may also have contributed to the removal of tumourload. Cisplatin containing combination chemotherapy was used merely after 1980. The finding that prognosis improved especially in younger women is compatible with an effect of these newly introduced intensive treatment methods. Supportive care such as nutrition, prevention of complications, and treatment of comorbidity, may also have become better, thereby not only contributing to the improvement of the prognosis of intensively treated patients, but also of elderly and untreated patients and patients with a poor performance status. Apart from the introduction of more extensive tumour reduction and cisplatin-based combination chemotherapy, advances in supportive care as well as a trend towards earlier diagnosis, possibly in combination with an increasing frequency of less malignant tumours, may have resulted in the significant improvement of the prognosis of ovarian cancer patients diagnosed after 1980 in this population.

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Chapter 5.2.2

# BREAST CANCER IN SOUTHEASTERN NORTH BRABANT AND NORTHERN LIMBURG:

## Trends in incidence and earlier diagnosis in an unscreened female population, 1975-86*


SUMMARY

Between 1975 and 1986 the age-adjusted incidence of breast cancer in south-eastern North Brabant and northern Limburg increased by approximately 1% per year, mainly among females under 50 years. Mortality appeared to decrease for women in the 45-59-year-old group. There was a clear tendency towards earlier diagnosis: the percentage of all tumours that were >5 cm or had invaded the skin decreased from more than 40% to 15% while the percentage measuring 2.1-5 cm increased slightly from 30% to 35% and the percentage measuring ≤2 cm rose from more than 20% to almost 45%, especially in the younger age groups. The observed decrease in tumour size cannot be attributed to distortion due to screening or a systematic change in measurement techniques. A more likely explanation is the influence of the steadily increasing use of mammography, later in combination with cytological examination, for women with minor complaints and small lumps. There were also changes in the treatment of these women: at present breast-saving procedures are used in 40% of all cases. These changes have important implications for the organization and expected results of a proposed population screening programme, in which less than 35% of women with invasive breast cancer would actually be exposed to screening.


INTRODUCTION

Breast cancer is the most common type of cancer among women in southeastern North Brabant and northern Limburg. In this region approximately one-half of all tumours in females between 35 and 65 years of age were attributable to


* Coebergh JWW, Crommelin MA, Kluck HM, van Beek M, van der Horst F, Verhagen-Teulings MTh. Breast cancer in southeastern North Brabant and northern Limburg: trends in incidence and earlier diagnosis in an unscreened female population, 1975-86. *Ned Tijdschr Geneeskd* 1990;134:760-65.

breast cancer in the period 1978-82. The incidence in this region was one of the highest in western Europe.[1] Earlier diagnosis is considered at present to be the best way to improve the prognosis. As a result of the introduction of modern mammography 15 years ago and the supplementary application of echography and cytology, more asymptomatic tumours can be detected. In the past 10 years, the use of breast-saving procedures has proven to be another important development, particularly with respect to the quality-of-life.[2] This approach consists of a limited surgical procedure followed by extensive radiotherapy. On the basis of several population-based screening research programmes carried out between 1974 and 1982 in Sweden and the Netherlands, the Health Council advised that all Dutch women between 50 and 70 years of age should be offered the opportunity to undergo mammography every two years in the near future.[3] The question is how the incidence, stage at diagnosis and mortality due to breast cancer in an as yet unscreened female population will be influenced by the above-mentioned changes in diagnostics and treatment. Data on cases recorded since 1975 were obtained from the Eindhoven Cancer Registry and cause-of-death statistics, data on medical management from a Documentation Project of the regional Breast Cancer Study Group started in 1983.

## PATIENTS AND METHODS

### *Registration: region and population*

In 1955 registration of cancer patients in southeastern North Brabant was started as part of a project to establish a national cancer registry; the area covered was served by the Department of Radiotherapy in Eindhoven. Since 1970 medical staffs and hospitals in a combined region, which also includes northern and (temporarily) the middle part of Limburg and comprises about 1 million people, have participated in the project. For breast tumours the registration was considered to be complete as of 1975 for the nucleus of the region with 850,000 inhabitants.[4]

### *Patients: diagnosis and registration*

This analysis covers all women living in the nucleus area for whom the diagnosis breast cancer was established between January 1, 1975, and January 1, 1987. A woman with a second tumour in the contralateral breast was considered a new patient if the second tumour was diagnosed at least two months after the first. In the period 1978-82 the diagnosis was based on histology in 97.5% of cases, cytology alone in 0.5% and clinical evaluation in 2% of cases. Tissue examination was carried out by 9 pathologists in laboratories in Venlo, Helmond and Eindhoven. Registration of new patients was based on reports from these laboratories, the Departments of Radiotherapy and medical records offices of participating hospitals. Specialized clinics in other parts of the country also provided information upon request. Codification of the histological type

and the preoperative and postoperative stages of the tumour was based on data obtained directly from the clinical record, using the TNM classification system.[5] For this analysis, the postoperative tumour size was classified as follows: ≤2 cm: pT1, 2.1-5 cm: pT2, >5 cm: pT3 and invasion of the skin: pT4; since 1982 a more precise classification system for tumours ≤2 cm has been used. The presence or absence of involved lymph nodes was also recorded. Data on women treated in the St. Joseph Hospital in Eindhoven[6] were considered separately because of the precision of this information which was collected and analysed independently of the registry.

*Diagnosis and treatment*

Radiologists in the various hospitals provided information on the year of installation of the mammograph. Since 1984 the application of mammography was derived from the Documentation Project. The pathologists provided information on introduction of routine cytological examination in various hospitals. The use of breast-saving procedures was apparent from data provided by the Department of Radiotherapy and the Documentation Project which aimed to evaluate this therapeutic modality.

*Mortality*

The Central Bureau of Statistics (CBS) provided annual regional mortality figures for breast cancer as of 1970.

*Statistical analysis*

The age and sex distributions of the population were obtained each year from the CBS, Population Statistics Section. Age-specific incidence and mortality rates for breast cancer were calculated per 100,000 women per year. For calculation of the total figures, the European standard population was used. For tumour size and axillary lymph node involvement an age-specific proportional distribution was determined for year of diagnosis. Three-year moving means were computed for the analysis of trends.

## RESULTS

*Incidence*

Of the women with breast cancer, 45% were between 50 and 70 years old. The number of new patients per year, also when classified in 10-year age groups, and the age-adjusted incidence has exhibited an increase since 1975. There was some variation, specifically for the years 1979, 1980, 1981 and 1983 (table 1). The age-adjusted mortality also showed fluctuations but appeared to fall behind the incidence. The age-specific incidence was higher for young women in every consecutive period (figure 1). For women between 30 and 39 years of age there was an increase in incidence in the period 1975-78 and then stabilization; incidence in the 40-49-year-old age group increased during the

**TABLE 1 Number of new patients with breast cancer per 10-year age groups and age-adjusted incidence and mortality in southeastern Netherlands, 1975-86**

| | Number of patients by age group (yrs) | | | | | | | | Total Incidence | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|
| Year | 20-9 | 30-9 | 40-9 | 50-9 | 60-9 | 70-9 | 80+ | all | per $10^5$* | |
| 1975# | 4 | 20 | 45 | 65 | 55 | 43 | 17 | 249 | 86.4 | 48.7 |
| 1976# | 2 | 10 | 66 | 64 | 66 | 52 | 13 | 273 | 93.7 | 42.7 |
| 1977# | 2 | 31 | 60 | 70 | 77 | 38 | 17 | 295 | 97.7 | 42.0 |
| 1978 | 2 | 35 | 66 | 68 | 73 | 46 | 23 | 313 | 94.3 | 27.7 |
| 1979 | 2 | 33 | 72 | 85 | 83 | 58 | 20 | 353 | 103.4 | 37.5 |
| 1980 | 5 | 24 | 65 | 74 | 72 | 55 | 19 | 314 | 89.6 | 38.1 |
| 1981 | 1 | 20 | 80 | 85 | 81 | 78 | 26 | 371 | 102.9 | 40.9 |
| 1982 | 2 | 37 | 79 | 68 | 66 | 86 | 23 | 361 | 96.7 | 41.3 |
| 1983 | 1 | 28 | 67 | 66 | 69 | 58 | 26 | 315 | 83.5 | 38.0 |
| 1984 | 3 | 35 | 81 | 90 | 77 | 59 | 35 | 380 | 98.7 | 34.5 |
| 1985 | 4 | 30 | 83 | 83 | 98 | 85 | 30 | 413 | 104.5 | 38.9 |
| 1986 | 1 | 34 | 98 | 104 | 81 | 72 | 28 | 418 | 106.7 | 38.9 |
| All | 29 | 337 | 862 | 922 | 898 | 730 | 277 | 4055 | | |
| % | 0.7 | 8.3 | 21 | 23 | 22 | 18 | 7 | 100 | | |

source: Eindhoven Cancer Registry
* European standard population; # a smaller registration area was used

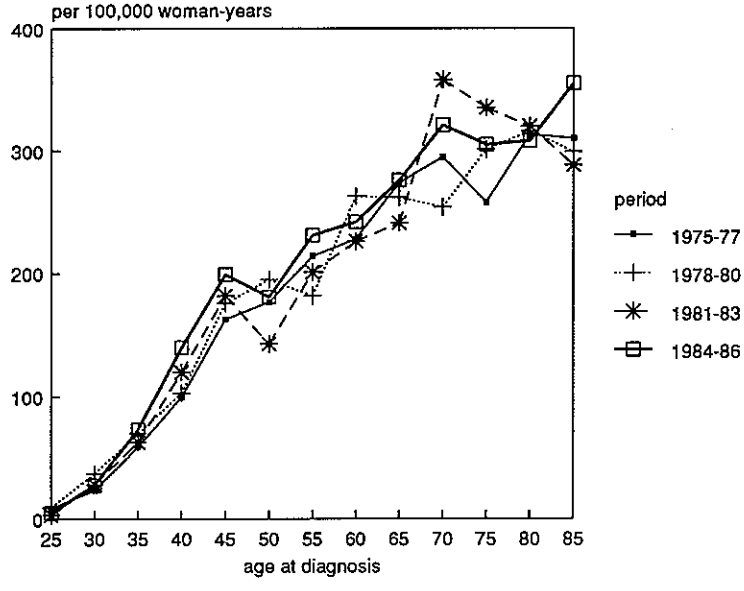


**FIGURE 1 Breast cancer among women in southeastern North Brabant and northern Limburg, 1975-86: age-specific incidence in 1975-80 and 1981-86 per 100,000 person-years**
source: Eindhoven Cancer Registry

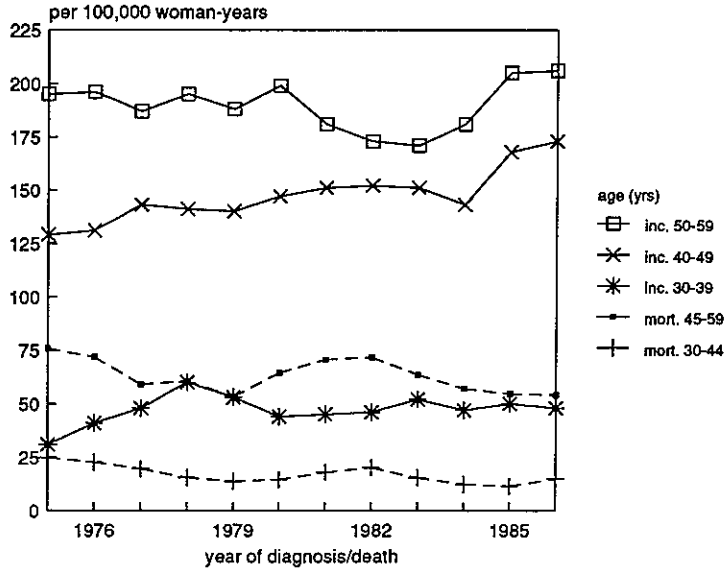


**FIGURE 2 Trend of the incidence of and mortality from breast cancer among 30-60-year-old females per 100,000 person-years as 3-year moving means**
source: Eindhoven Cancer Registry and Central Bureau of Statistics

entire period and fluctuated for women between 50 and 59 years old with a possible increase in recent years (figure 2). The mortality in these age groups tended to fluctuate and is decreasing since 1982.

### *Histological type, tumour size and axillary lymph nodes*

As far as histological type is concerned, the majority were of the ductal type (table 2). This distribution was not markedly influenced by separation into age

**TABLE 2 Breast cancer among women in southeastern North Brabant and northern Limburg, according to histological type, 1975-86**

| Histological type | | No. of patients | % |
|---|---|---|---|
| Invasive | ductal | 3365 | 83 |
| | lobular; mixed lobular/ductal | 303 | 7.5 |
| | mucinous | 44 | 1 |
| | tubular | 20 | 0.5 |
| | medullary | 44 | 1 |
| | other | 42 | 1 |
| Non-invasive | intraductal | 77 | 1.9 |
| Sarcoma | | 12 | 0.3 |
| Unclassified | | 118 | 3.0 |
| Total | | 4055 | 100 |

source: Eindhoven Cancer Registry

groups. The percentage women with a tumour >5 cm clearly decreased in all age groups. The group with a skin invasive tumour increased in the early years of the study, incidentally together with a decrease in the percentage of patients with unknown (in the registry) tumour size (figure 3). In the 40-49-year-old age group the percentage tumours ≤2 cm increased - especially after 1980 - from 30 to 50% and in the 50-69-year-old group from 20 to 40% while in the 70-79-year-old group the percentage of tumours between 2.1 and 5 cm increased. The data from the St Joseph Hospital pointed in the same direction (table 3). Smaller tumours were found relatively more often in younger women (figure 4). In the period 1984-86, the percentage tumours ≤1 cm decreased with rising age while the percentage tumours ≤3 cm remained more or less constant. When the tumour was ≤2 cm, lymph nodes were negative in 75% of the cases, irrespective of age. Among women with a tumour 2.1-5 cm in diameter, this percentage increased from 42% in 30-39-year-old women to 48% in 50-59-year-old and 54% among women over 60. For women with a tumour ≤2 cm, the percentage with positive lymph nodes increased gradually over time from 20% in 1975-78 to 30% in 1985-86.

### *Diagnosis and treatment*

Midway through the seventies modern mammography was introduced in all (9) hospitals (figure 5); in 1984-86 mammography had been carried out in more than 90% of cases. The introduction of the cytological examination lasted from 1978 to 1986. Since 1981 breast-saving procedures were used with increasing frequency: in 1984-86 for about 40% of women with tumours ≤2 cm and 15% with tumours 2-3 cm in diameter.

## DISCUSSION

### *Incidence*

Since 1975 the age-adjusted incidence of breast cancer in this part of the Netherlands increased on the average by 1% per year without a clear-cut explanation. Such an increase in the registered incidence can be real but also

**TABLE 3 Breast cancer among women treated in the St. Joseph Hospital: distribution of tumour size (pT) at the time of diagnosis in 1970-80 and 1984-86**

| | Percentage patients in | |
|---|---|---|
| Tumour size | 1970-80 | 1984-86 |
| In situ | – | 1.5 |
| ≤2 cm | 28 | 42 |
| 2,1-5 cm | 52 | 41 |
| >5 cm | 10 | 2.5 |
| Extension | 10 | 13 |

source: Rutgers 1983, and Documentation project of the Breast Cancer Study Group

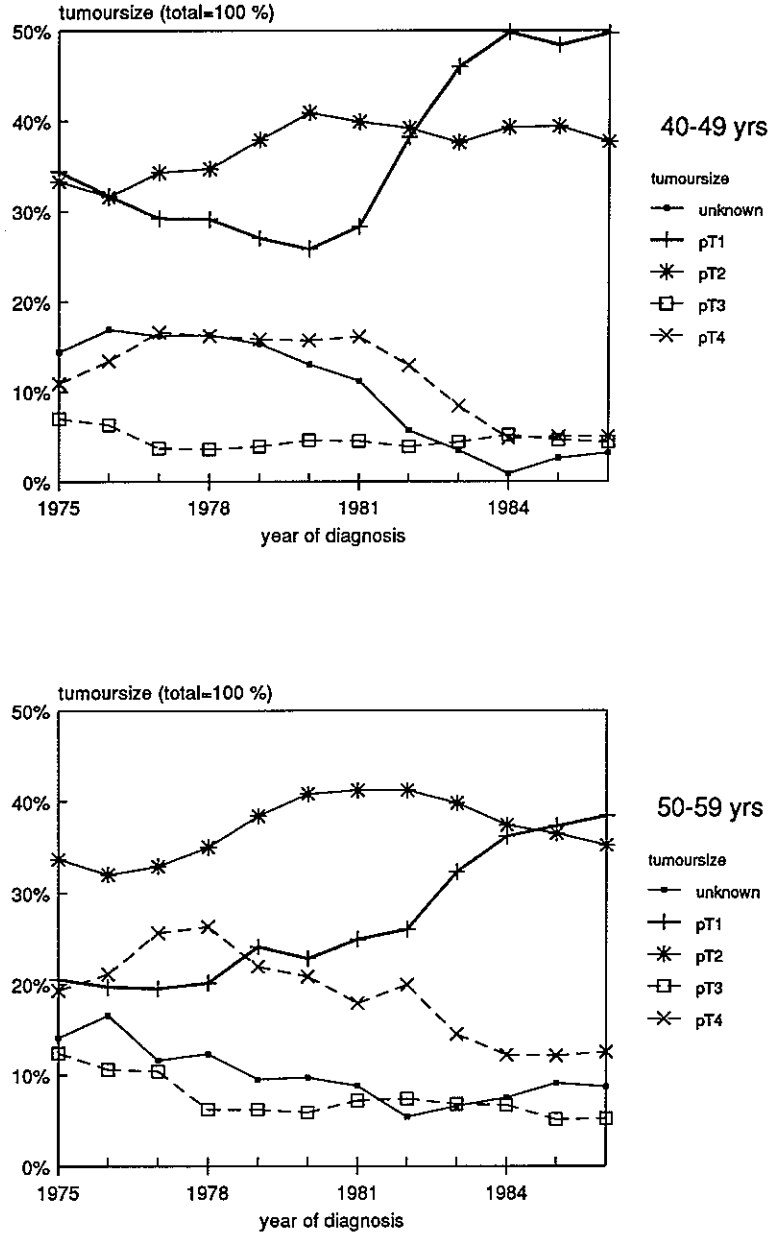


FIGURE 3 Trend in distribution of postoperatively established tumour size of breast cancer in southeastern North Brabant and northern Limburg, 1975-86, per 10-year age groups as 3-year moving means
source: Eindhoven Cancer Registry

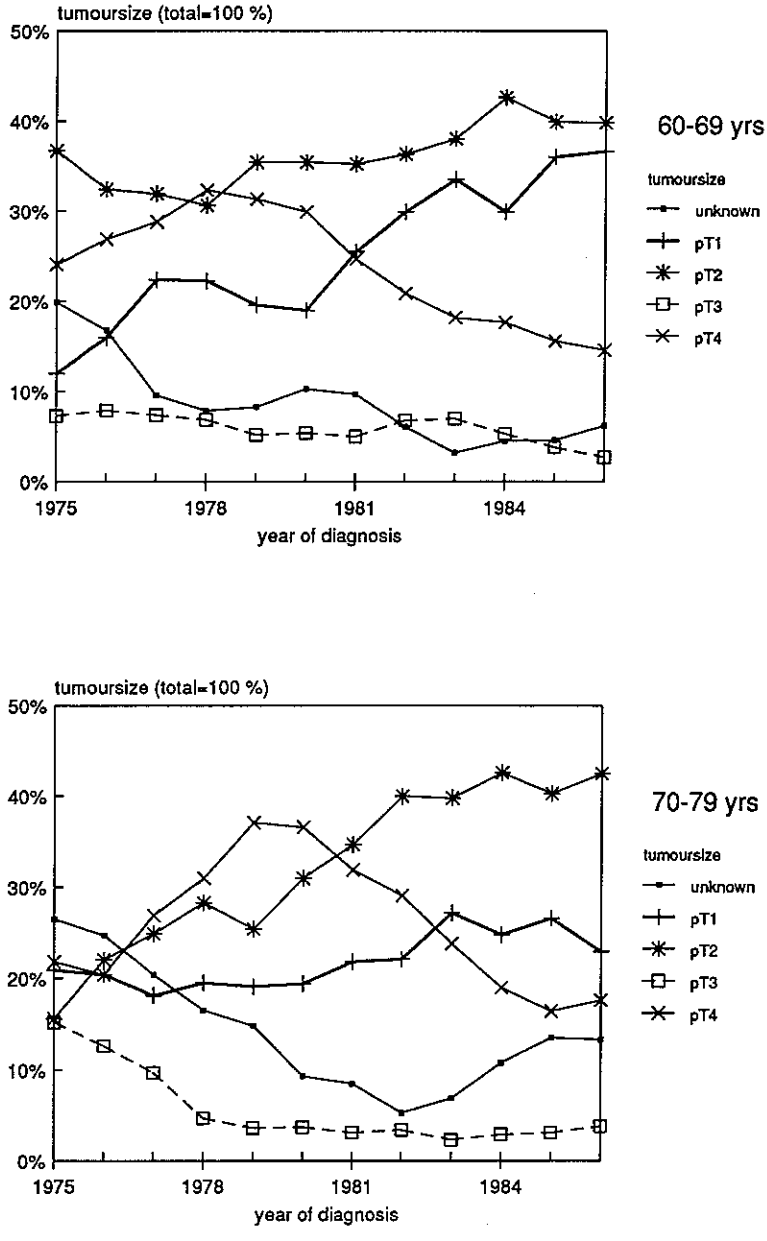


FIGURE 3 *(continued)*

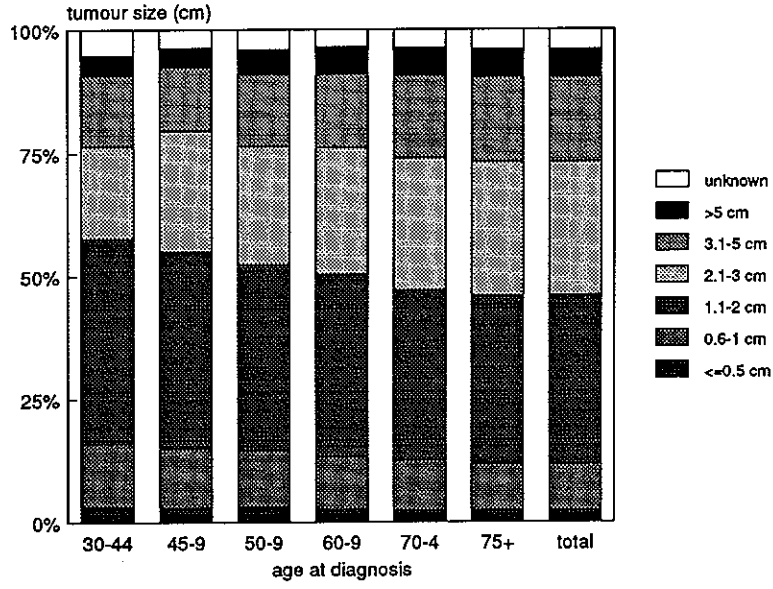


FIGURE 4 **Breast cancer among women in southeastern North Brabant and northern Limburg, 1984-86; distribution of postoperatively established tumour size per age group**
source: Documentation Project of the Breast Cancer Study Group

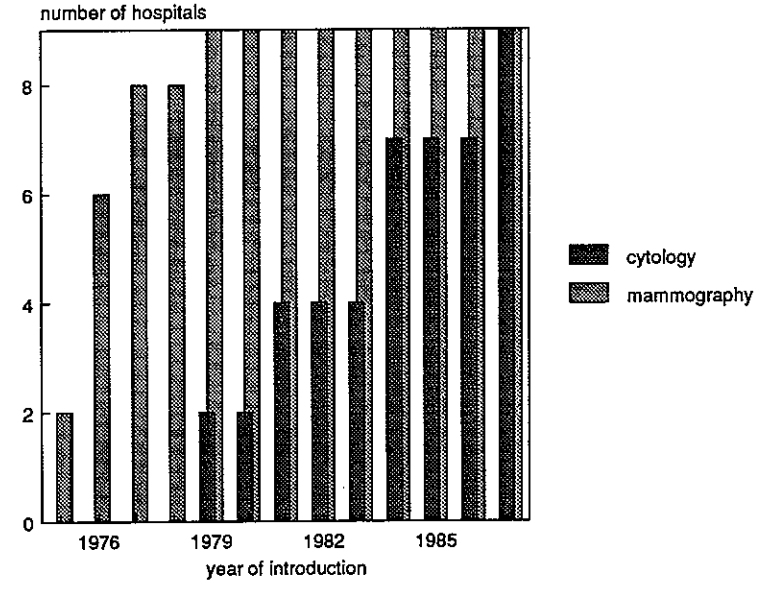


FIGURE 5 **Introduction of modern mammography and cytology for early diagnosis of breast cancer in the hospitals of the SOOZ region, 1975-86**
source: Breast Cancer Study Group

virtual since it could for example be associated with earlier diagnosis and/or more precise diagnostics. This seems to be the case here, although to a limited extent since a population screening programme was not carried out. An (unchanged) low percentage of patients had carcinoma in-situ. Extensive changes in the registration methods are considered unlikely and would in any case have the same effect in all age groups. An increase in the true incidence for women in the 40-49-year-old group appears therefore to have occurred. This might be related to a different (more rapid) natural history of the disease in some of the women and/or a higher prevalence of risk factors. In this respect the (higher) age at the time of birth of the first child and the 50% decrease in the - formerly high - fertility rates for this region since 1967 may be considered (written communication JP Mackenbach, 1989).

The combination of an increasing incidence of and the slightly decreasing mortality for breast cancer in the younger age groups (see figure 2) indicates improvement in the survival rates. The earlier diagnosis would seem to have more influence in this respect than new therapeutic modalities. For instance fewer than 20% of the women with involved lymph nodes received adjuvant chemotherapy. A similar pattern of rising incidence and constant mortality has been observed in Denmark since 1960, especially among women below 55 years of age, as well as in the United States, especially during the 1970's.[7 8]

*Earlier diagnosis*

We observed a 50% decrease in the percentage women with a pT3 and/or pT4 and a two-fold increase in patients with a pT1, these changes being more marked at younger age (figure 3). It may be assumed that they correspond with experience of many hospitals in the Netherlands. The group pTx, varying widely per hospital in the earlier years of the study, presumably consisted mainly of patients with pT4 (more in the elderly) and pT1. We have no indications that distortion of the observations occurred as a result from systematic changes in measurements by the pathologists. The fact that the degree of change varies with age supports this assumption. We tend to explain the earlier diagnosis by the increase in self-examination, the tendency to visit the physician sooner in the event of symptoms of the breast, more health education and increased media coverage of early diagnostics as a consequence from the population screening programmes. The diagnosis of smaller tumours by the radiologist appears to have been more prominant in this area, whereas learning effects usually take several years.[9] This also applies for the supplementary cytological examination by the pathologist.[10] The increased percentage patients with a pT1 and positive lymph nodes appears to be due to "stage migration" resulting from more precise diagnostics[11] and increased interest in lymph node excision by both the surgeon and the pathologist.[12] In general the care for women with breast cancer has become increasingly more precise, as indicated by a more intensive cooperation between radiologist, pathologist and surgeon and in the field of therapy between surgeon, radiotherapist and internist.

Will the process of earlier diagnosis, described above, continue and what could this mean for the proposed breast cancer screening programme? On the basis of figure 3 the increase in the percentage tumours ≤2 cm, especially among women between 50 and 70 years of age, has not yet come to an end. It remains to be seen whether the percentage tumours ≤1 cm (about 12% in 1984-86) will increase. The differences in the process of diagnosis and treatment of breast cancer between areas with and without population screening programmes will most likely become smaller as well as the yield of the screening programmes, calculated on the basis of historical data.[13] More earlier diagnosis in the control group is after all one of the explanations for the lack of a favourable effect of the population screening programme in Malmö.[14] The observed changes in our population also show another phenomenon. If a screening programme is offered for females between 50 and 70 years of age, then an attendance of 70% will lead to a maximum coverage of 0.7 x 45% = 32% of all patients with invasive breast cancer. Is it then not worthwhile to consider the possibility of offering earlier diagnosis for females of all ages before starting - or even instead of - a screening programme for a limited group of women, especially when the current "spontaneous trend" continues? Considering also the problems of the follow-up this has become a complicated multidisciplinary field of medicine, for which protocols would be useful.[15] Cancer registries now in operation throughout the country would be able to monitor these changes and their effects.

ACKNOWLEDGMENT

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Chapter 5.3

# EPIDEMIOLOGY OF LUNG CANCER IN THE NETHERLANDS:

## Trends in incidence, patterns of care and survival in southeastern Netherlands in the period 1975-87*

## I. EPIDEMIOLOGICAL FEATURES IN THE NETHERLANDS

### MORTALITY

As of 1990 lung cancer will presumably be diagnosed in about 9500 patients, 8200 men and 1300 women, in the Netherlands each year; almost 8500 persons died of lung cancer in 1987, about 7500 men and 1000 women, and according to the Netherlands Central Bureau for Statistics (CBS) another 261 had lung cancer as secondary cause of death. Cancer of the pleura, that accounted for an additional 232 deaths, remains outside the scope of this survey. The proportional mortality for lung cancer with respect to all deaths was 11.5% for men and 1.8% for women in 1987; it caused 15% of the deaths among men in the 40 to 80 year-old group and 40% of all cancer deaths in this age group. For women lung cancer occupied the third place after breast and colorectal cancer; for women between 40 and 80 years of age the proportional mortality was 5% of all deaths and 10% of cancer deaths. Age-specific lung cancer mortality in 1987 (figure 1) showed a marked increase in the male/female ratio from 3 for the middle-aged group to about 15 at old age. More than 30% of all new male cancer patients in southeastern Netherlands in the period 1983-86 had lung cancer versus 3.5% of female patients.[1]

Starting in the 20's, the age-adjusted lung cancer mortality for males in the Netherlands increased steadily to its highest value in 1980; since then it has decreased (figure 2),[2] first for the middle-aged group in the 70's, later also for older men and most recently in the 70-74 year-old group. However mortality

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* Revised overview prepared for a Consensus Development Meeting on the Diagnostic Approach to Lung Cancer.
Coebergh JWW, Schipper RM, Wagenaar SjSc. Epidemiology of lung cancer in the Netherlands: trends in incidence, patterns of care and survival in southeastern Netherlands in the period 1975-87. in: *Diagnostiek Longkanker.* Utrecht: CBO, 1990: pp 3-13. (in Dutch)

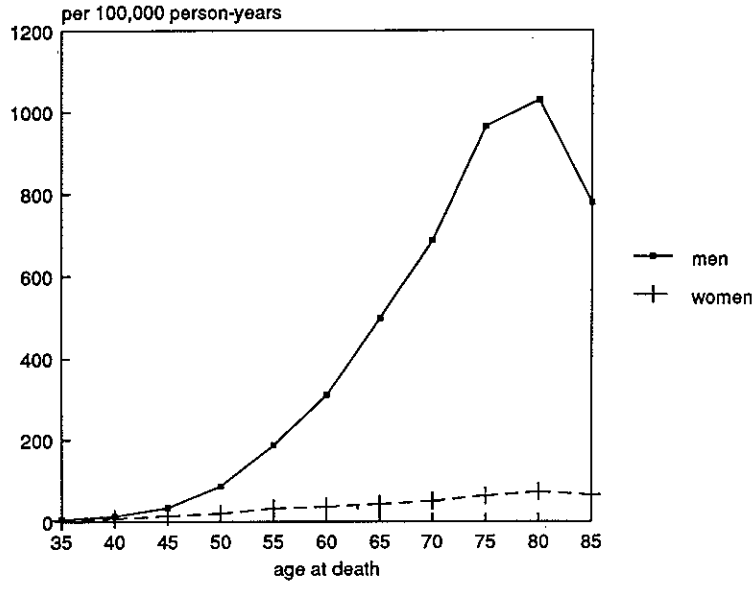


FIGURE 1 **Age-specific mortality due to lung cancer in the Netherlands in 1987, according to sex**
source: Central Bureau for Statistics

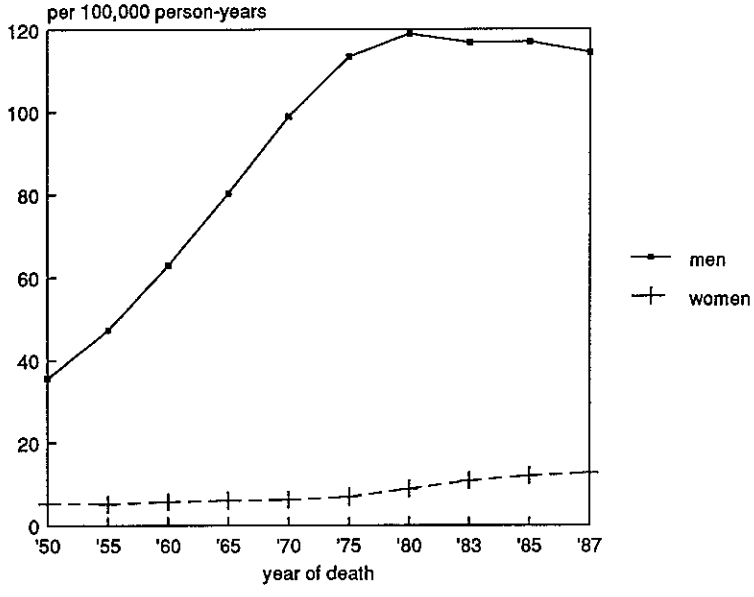


FIGURE 2 **Trend in age-adjusted mortality due to lung cancer in the Netherlands since 1950, according to sex**

is still increasing for men over 75. In 1987, for the first time in more than half a century, the number of male lung cancer deaths was lower than in the previous year. The annual increase in the number of female lung cancer deaths has been about 50 for the past 10 years; and the age-standardized (European standard) rate doubled from 6 to 12 per 100,000 woman-years and rose in all age groups. Trends in lung cancer mortality are rather accurately reflected by the incidence in southeastern Netherlands (figure 3).

## ETIOLOGY

In a recent epidemiological overview of lung cancer in the Netherlands smoking is considered the major cause together with occupational exposures as well as certain deficiencies in the diet, e.g. vitamins, regular exposure to caged birds kept in the home and a history of chronic aspecific respiratory conditions.[3] The role of endogenous factors is unknown. Smoking appears to exhibit a closer association with squamous and small cell carcinoma than adenocarcinoma, that is relatively more frequent among women.[4]

## EXPECTED NUMBER OF PATIENTS

Despite the decline in the number and the proportion of tobacco smokers in the last 20 years, especially among men, a marked decrease in the number of new patients cannot be expected at the present time.[5] It takes 5 to 15 years for the risk of lung cancer for a former smoker to decrease, depending on the duration and intensity of smoking and the age when smoking started. While the percentage of male smokers and the tar content of cigarettes have decreased, the number of cigarettes per smoker has increased. This also indicates that selection mechanisms play a role in the decision to stop or continue smoking: voluntary stoppers are more likely to have smoked less and had a 'healthier' life style and thus may have had a lower risk. Moreover, a delaying effect can be expected from the shift of smoking habits from 'higher' social classes where they were most intense to 'lower' social classes who are exposed more to other risk factors.

The current smoking discouragement policy, which seems to be aimed primarily toward the reduction of involuntary smoking, will have only a small impact on the lung cancer problem. For example, if the lung cancer risk for passive non-smokers were to increase by 30%,[6] the incidence in this group would rise from 3 to only 4 per 100,000 woman-years.

Moreover, the incidence of and mortality due to lung cancer among older males may decrease less or may even increase as a result from the declining mortality due to competing cardiovascular and cerebrovascular diseases. The number of patients in this group would then increase even more, because of the rising number of older men. (In the period 1983-86 more than 30% of new

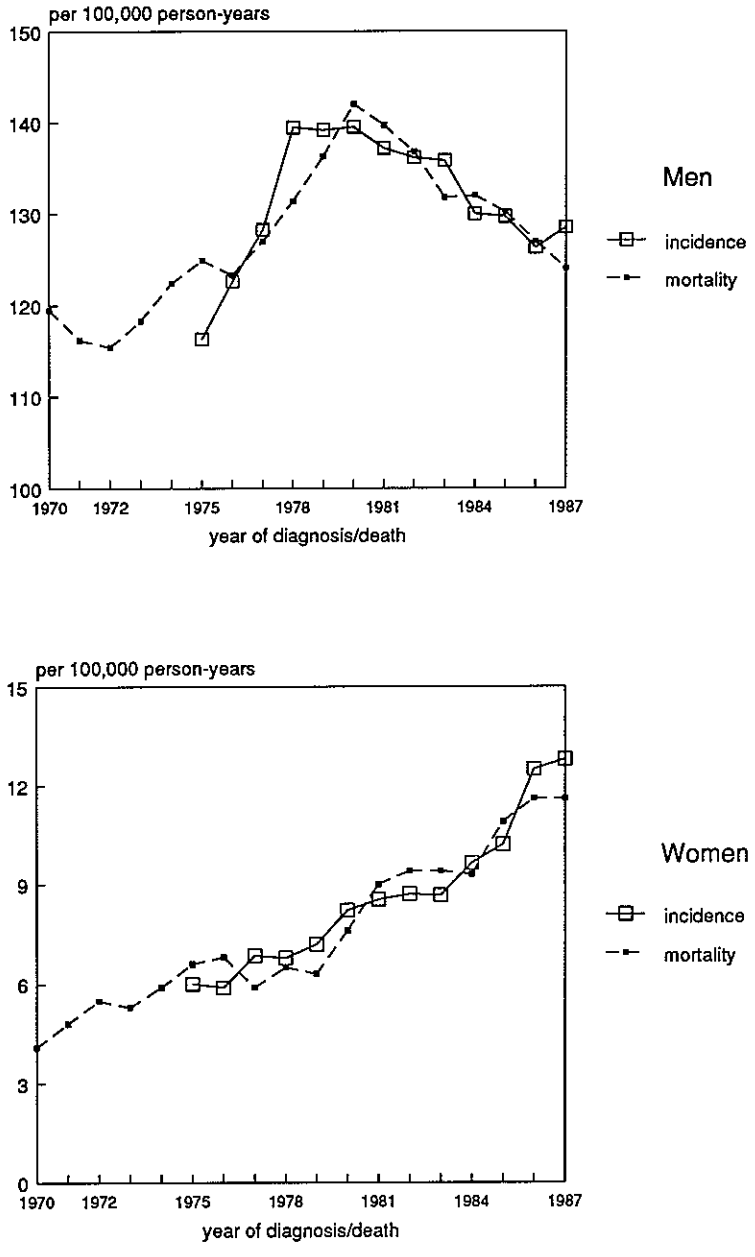


FIGURE 3 **Trends in incidence of and mortality due to lung cancer in southeastern Netherlands in the period 1970-87**
sources: Eindhoven Cancer Registry and C.B.S.

patients were over 75 years old and 20% were younger than 60.) For women a similar development, but at a lower level can be expected.

For the time being, an increase in the number of older patients with lung cancer and a decreasing number of middle-aged patients with a lower male/female ratio are considered likely. The optimistic scenario[5] seems to lie closest to current realities. Regional differences in the start of the lung cancer epidemic (first in the west and south and then in the north and east) will probably also be manifest in the decline. All together a period of 100 to 150 years may be involved in the rise and decline of this epidemic.[7]

## DIAGNOSIS AND PROGNOSIS

For the informed layman lung cancer appears to be a uniform disease with a fatal prognosis, known cause(s) and predictable localization, symptoms and natural history; to others it is characterized by a multitude of complex clinical situations in both the preclinical and clinical phases. Depending on the histological type, large variations may exist in the pattern of symptoms related to the disease as well as to co-morbidity. The picture becomes even more diffuse when the signs and symptoms of other diseases become manifest. Lung cancer generally leads to specific complaints or symptoms late in the disease and the patients, quite a few of whom are used to coughing and bronchitis, hesitate to visit their doctors, who generally are aware of the low predictive value of coughing.[8] On the average each general practitioner sees one new lung cancer patient per 9 months. Nevertheless signs and symptoms are important prognostic indicators. A clinical taxonomy of symptoms and co-morbidity (determined retrospectively in a group of patients diagnosed in the period 1953-77) had a better predictive value for 6-month survival than stage, classified according to TNM (Tumour, Node, Metastasis[9]). Stage migration had also occurred as a result of more refined diagnostics during this period;[10] the consequence is 'downstaging' and better survival for each stage, but the outcome for the total group remained about the same. More refined diagnostics result instead in better selection of - fewer - patients for curative, radical treatment and thus in better quality-of-life for those not (or no longer) eligible for such treatment. The clinical taxonomy*, developed by Feinstein, would seem to be an indispensable part of every decision analysis for the diagnostic approach to patients with (suspected) lung cancer. Because risk factors for lung cancer are also risk factors for vascular diseases, co-morbidity is an important prognostic factor.

The 5-year cumulative survival is usually about 10%. However the prognosis is clearly better for those in certain subgroups, namely patients with small, often peripherally located, tumours. The percentage surgical patients, usually 20 to 25%, is also determined by the staging policy; inter-hospital variation may exist,

* Feinstein distinguishes 4 categories of patients on the basis of symptoms: asymptomatic, primary, systemic and metastatic.

depending on the presence of chest surgery and the age distribution of the referral population. The percentage surgical patients may have been higher in the past because of the lower mean age of the patients and the screening programmes for tuberculosis in the Netherlands that were stopped at the end of the 70's. However, screening for lung cancer by means of chest X-rays and sputum cytology has not proved to be effective if measured by its impact on mortality.[11] Improved survival as a result of earlier detection of more slowly growing tumours and even false-positive results was in fact confounded by lead, length time and classification bias. On the other hand, marked effects due to screening in the American studies of high-risk individuals could hardly be expected because there was only little difference between medical care for the screened and unscreened groups.[12] If present, a strong effect of screening would nevertheless have become visible. In view of the current state of diagnostics, screening is unlikely to have an effect on mortality. This may change when more sensitive and simpler diagnostic techniques become available. For lung cancer another aspect is important: when, relatively speaking, much is known about the cause of a disease - in other words when the disease is preventable - one may argue that primary prevention should be given priority over early detection, even though it will only be effective in the long term. Such either/or discussions usually have a rather paralyzing effect because of their 'all or nothing' nature. For practical purposes a combined approach of primary prevention and early detection could be considered for those exposed involuntarily (in industry) and patients with obstructive lung diseases or head & neck[13] and lung cancer who have stopped smoking.[14] Although the effects of such a pragmatic approach are of course uncertain, it has the advantage of being able to do something about a serious problem by improving the existing situation a bit. A large-scale prospective randomized trial to evaluate the effect of early detection on mortality, such as advocated by the Health Council in 1982, will presumably not be able to take into account sufficiently the variations in risk groups. Moreover, the possibilities for translating this type of demonstration project to actual practice are rather limited.

# II. INCIDENCE, PATTERNS OF CARE AND SURVIVAL OF LUNG CANCER IN SOUTHEASTERN NETHERLANDS IN THE PERIOD 1975-87

These data, presented as background information for the consensus development process and derived from the Eindhoven Cancer Registry are presented to answer the following questions: what were the most important changes in incidence, specific disease characteristics, prognosis, patterns of diagnosis and therapeutic modalities?

## PATIENTS AND METHODS

Included are all new patients diagnosed with lung cancer in the period 1975-87 in 12, now 8 as a result of several mergers, community hospitals in southeastern North Brabant and northern Limburg, with a population of almost one million inhabitants. Notified by the pathological laboratories in Venlo and Eindhoven (lately also Helmond), the regional Department of Radiotherapy and most Departments of Medical Records, trained personnel were sent to collect data on patients, diseases and methods of detection and treatment directly from clinical records. The data were coded according to site and morphological features, according to the International Classification of Disease (ICD-8 until 1978 and ICD-9 since that year); they were classified in groups according to the second edition of the World Health Organization histological classification of lung tumours,[15] as follows (the ICD codes are given in parentheses): squamous cell (807 and 808), small cell (804), adenocarcinoma (814, 826, 831, 848), undifferentiated (801 and 802), alveolar (825), carcinoid (824) and other and undefined.

### *Medical care*

During the study period the number of internists and pulmonologists increased by almost 50%, about 30% after standardization for age and size of the population; limited screening programmes for lung cancer (originating from tuberculosis surveillance) were discontinued, also in the Eindhoven area,[16] and in 1980 a specialized department of thoracic surgery was established in one of the larger hospitals.

Regional mortality rates for lung cancer, obtained from the Central Bureau for Statistics (CBS) for the same area, were used for comparison purposes; for the elderly higher mortality rates were found, which may suggest incompleteness of ascertainment and thus registration. The diagnosis lung cancer is sometimes only made by means of X-ray without morphological confirmation; moreover a cytological diagnosis made by individual pulmonologists may not always have been reported to the registry. This would pertain especially to elder patients with advanced disease who were not hospitalized and did not receive radiotherapy.

Incidence and mortality rates were computed per 100,000 person-years and standardized for age, using the European standard population. Data on the detection and therapeutic processes were computed proportionally in periods of three years.

Relative survival was determined as the ratio of observed survival, regardless of the cause of death, and expected survival based on regional mortality rates derived from the CBS. A special computer program was obtained from the Finnish Cancer Registry.[17] All patients not known to have died were traced via municipal population registries as of December 31, 1987. Less than 1% of the patients were diagnosed after death, could not be traced or lost to follow-up.

## RESULTS AND DISCUSSION

*Localization:* 1% of the tumours were found in the trachea, 10% in the main bronchus, 50% in the upper lobes, 5% in the mid lobe, 25% in the lower lobes and the other 9% at other or overlapping sites.

*Histological type* (table 1, figure 4): the age-adjusted incidence and the proportional distribution show a striking increase in adenocarcinoma for males and females, while a decline is observed in squamous cell and small cell carcinoma for males; for females the incidence of all types, including undifferentiated cancer, increased.

**TABLE 1 Proportional distribution of lung cancer according to histological type in southeastern Netherlands in 1975-86**

| Histological type | 1975-77@ % | 1978-80 % | 1981-83 % | 1984-86 % |
|---|---|---|---|---|
| **Males** | | | | |
| Adeno | 5 | 5 | 10 | 13 |
| Squamous | 56 | 62 | 56 | 55 |
| Small cell | 18 | 18 | 18 | 17 |
| Undifferentiated | 8 | 5 | 8 | 6 |
| Other* | 12 | 12 | 8 | 8 |
| All types | 100 | 100 | 100 | 100 |
| No. of patients | 918@ | 1170 | 1227 | 1198 |
| **Females** | | | | |
| Adeno | 22 | 20 | 19 | 30 |
| Squamous | 28 | 28 | 26 | 30 |
| Small cell | 18 | 28 | 17 | 23 |
| Undifferentiated | 7 | 10 | 12 | 7 |
| Other* | 26 | 16 | 27 | 10 |
| All types | 100 | 100 | 100 | 100 |
| No. of patients | 52@ | 73 | 95 | 120 |

source: Eindhoven Cancer Registry
* NOS, carcinoid, alveolar; @ smaller registration area

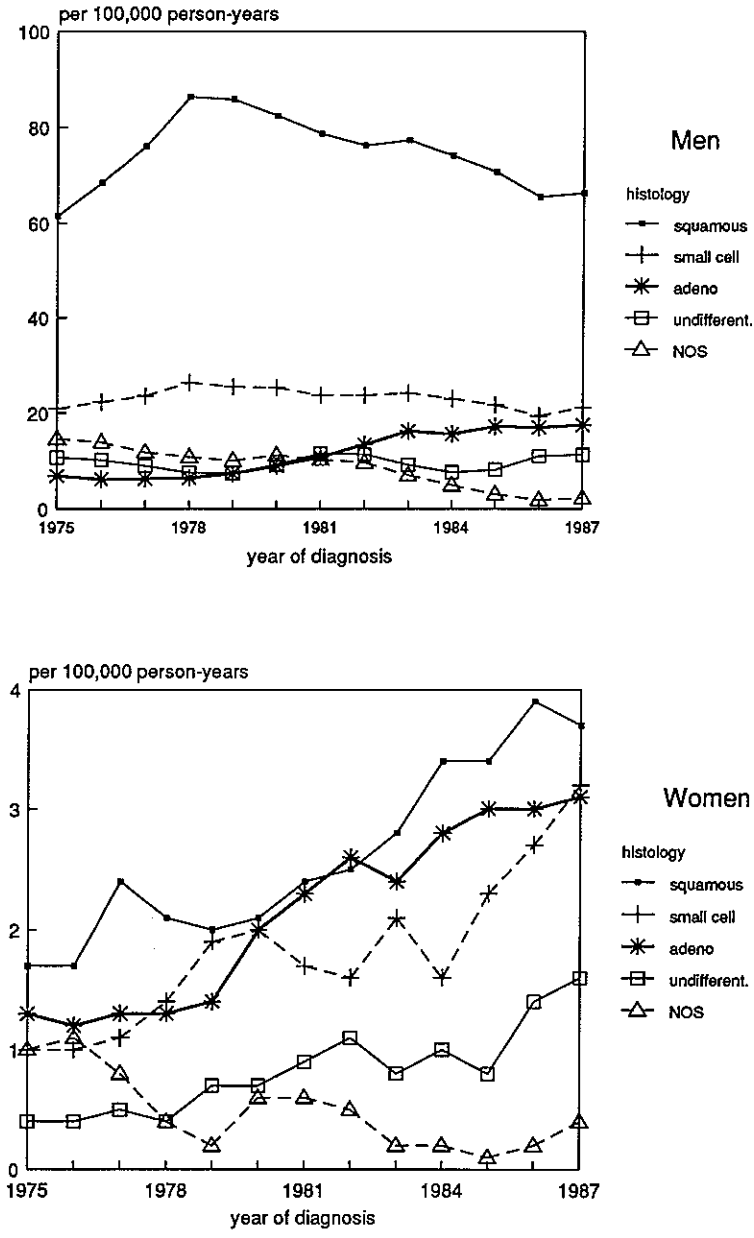


FIGURE 4 Trend in age-adjusted incidence of lung cancer in southeastern Netherlands in the period 1975-87, according to histological type
source: Eindhoven Cancer Registry

*Diagnosis:* cytological verification clearly increased over time and age, in part due to more complete registration (table 2). The percentage patients with a clinical diagnosis remained constant over time but increased markedly with age. The percentage unstaged or 'stage not reported' patients decreased, particularly for surgical patients (from 47% in 1975-77 to 0.5% in 1987). The percentage with unknown lymph node status decreased from 67% to 3%.

TABLE 2 Patterns of diagnosis for patients with lung cancer in southeastern Netherlands according to period and age

| According to period | | | | |
|---|---|---|---|---|
| | 1975-77 | 1978-80 | 1981-83 | 1984-86 |
| Method | % | % | % | % |
| Clinical | 6 | 4 | 4 | 4 |
| Histological | 90 | 91 | 85 | 74 |
| Cytological | 2 | 2 | 7 | 21 |
| Autopsy | 3 | 4 | 5 | 2 |
| Total | 100 | 100 | 100 | 100 |
| **According to age (yrs)** | | | | |
| | 30-44 | 45-59 | 60-74 | >74 |
| Method | % | % | % | % |
| Clinical | 1 | 3 | 4 | 11 |
| Histological | 95 | 91 | 87 | 71 |
| Cytological | 2 | 5 | 7 | 12 |
| Autopsy | 3 | 2 | 3 | 6 |
| Total | 100 | 100 | 100 | 100 |

source: Eindhoven Cancer Registry

*Therapy* (table 3): in the group of patients with small cell lung cancer, chemotherapy replaced radiotherapy as primary treatment, whereas radiotherapy was used more often to treat patients with adenocarcinoma; in this latter group the application of surgical therapy decreased. The use of chemotherapy markedly declined with increasing age among patients with squamous cell as well as small cell lung cancer.

*Survival:* relative survival clearly declined with age and was better for females at any age (table 4). Survival improved for females between 40 and 60 years of age. Relative survival remained remarkably constant over time, except for patients with small cell lung cancer: one-year survival appeared to increase by 50% in the second period; on the other hand the 5-year relative survival found for older patients with adenocarcinoma declined markedly. Relative survival was fairly similar to that found in the SEER program (table 5).[18] Corresponding to clinical findings, the increased use of chemotherapy may be responsible for the improved survival of patients with small cell lung cancer. The decreased

TABLE 3A **Trend in primary therapy for lung cancer according to histological type in southeastern Netherlands in 1975-86**

| Therapy | 1975-77 % | 1978-80 % | 1981-83 % | 1984-86 % |
|---|---|---|---|---|
| **All types** | | | | |
| Radiotherapy | 28 | 42 | 37 | 36 |
| Chemotherapy | 10 | 9 | 14 | 15 |
| Surgical | 25 | 21 | 27 | 23 |
| Other+none | 37 | 29 | 22 | 26 |
| **Squamous** | | | | |
| Radiotherapy | 40 | 45 | 48 | 48 |
| Chemotherapy | 9 | 5 | 3 | 2 |
| Surgical | 27 | 22 | 27 | 29 |
| Other+none | 25 | 27 | 22 | 21 |
| **Small cell** | | | | |
| Radiotherapy | 51 | 37 | 11 | 7 |
| Chemotherapy | 14 | 24 | 57 | 74 |
| Surgical | 10 | 8 | 2 | 4 |
| Other+none | 25 | 33 | 32 | 15 |
| **Adeno** | | | | |
| Radiotherapy | 10 | 22 | 32 | 40 |
| Chemotherapy | 2 | 4 | 5 | 3 |
| Surgical | 62 | 42 | 38 | 34 |
| Other+none | 27 | 29 | 27 | 23 |

TABLE 3B **Primary therapy for squamous and small cell lung cancer in men in 1984-86: according to age (yrs)**

| Therapy | 30-44 % | 45-59 % | 60-74 % | >74 % |
|---|---|---|---|---|
| **Squamous** | | | | |
| Radiotherapy | 53 | 42 | 46 | 53 |
| Chemotherapy | 16 | 4 | 4 | 1.5 |
| Surgical | 31 | 42 | 35 | 7 |
| None* | – | 12 | 15 | 39 |
| **Small cell** | | | | |
| Radiotherapy | 0 | 2 | 5 | 17 |
| Chemotherapy | 100 | 87 | 77 | 52 |
| Surgical | 0 | 2 | 5 | 5 |
| None* | 0 | 9 | 14 | 26 |

source: Eindhoven Cancer Registry

TABLE 4 One-, 3-, 5- and 8-year cumulative relative survival rates for patients with lung cancer in southeastern Netherlands in two periods: 1975-79 (I) and 1980-85 (II)

| Period | Age (yrs) group | Age (yrs) mean | No. of patients | Year of follow-up 1 % | 3 % | 5 % | 8 % |
|---|---|---|---|---|---|---|---|
| **A All histological types** | | | | | | | |
| **Males** | | | | | | | |
| I | 0-99 | 66 | 1706 | 37 | 17 | 13 | 10 |
| II | " | 66 | 2423 | 39 | 16 | 13 | 11 |
| I | 0-39 | 3 | 18 | 43 | 25 | 25 | 25 |
| II | " | 36 | 20 | 40 | 35 | 35 | 35 |
| I | 40-59 | 54 | 405 | 43 | 21 | 18 | 15 |
| II | " | 54 | 557 | 46 | 21 | 18 | 14 |
| I | 60-99 | 70 | 1283 | 33 | 15 | 11 | 8 |
| II | " | 70 | 1846 | 37 | 15 | 10 | 8 |
| **Females** | | | | | | | |
| I | 0-99 | 60 | 100 | 33 | 17 | 15 | 15 |
| II | " | 60 | 198 | 42 | 22 | 20 | 19 |
| I | 0-39 | 35 | 4 | 75 | 50 | 50 | 50 |
| II | " | 34 | 13 | 69 | 54 | 54 | 54 |
| I | 40-59 | 50 | 40 | 28 | 15 | 8 | 8 |
| II | " | 52 | 82 | 44 | 23 | 22 | 22 |
| I | 60-99 | 70 | 56 | 33 | 16 | 17 | 17 |
| II | " | 70 | 103 | 36 | 17 | 13 | 8 |
| **B According to histological type and age** | | | | | | | |
| **Squamous** | | | | | | | |
| I | 40-59 | | 210 | 50 | 23 | 19 | 16 |
| II | " | | 257 | 52 | 24 | 19 | 13 |
| I | 60-99 | | 459 | 43 | 18 | 13 | 9 |
| II | " | | 1110 | 43 | 18 | 13 | 9 |
| **Small cell** | | | | | | | |
| I | 40-59 | | 97 | 20 | 6 | 5 | 4 |
| II | " | | 122 | 31 | 3 | 2 | – |
| I | 60-99 | | 225 | 11 | 5 | 4 | 3 |
| II | " | | 304 | 18 | 3 | 2 | 2 |
| **Adeno** | | | | | | | |
| I | 40-59 | | 31 | 62 | 37 | 34 | 32 |
| II | " | | 90 | 56 | 35 | 30 | 32 |
| I | 60-99 | | 56 | 54 | 39 | 28 | 17 |
| II | " | | 157 | 34 | 18 | 17 | 15 |

TABLE 5 **Five-year cumulative relative survival of patients with squamous cell and small cell lung cancer: comparison between Eindhoven Cancer Registry and SEER[19] program in the USA (whites only)**

| | Squamous (%) | Small cell (%) |
|---|---|---|
| ECR 1980-85 | 12.6 | 3 |
| SEER 1979-84 | 13 | 4 |

survival of those with adenocarcinoma must be related to the rise in incidence, which suggests a different biological behaviour and/or a shift in classification from one of the other types or the group NOS. Elsewhere shifts mainly occurred from large or undifferentiated cell carcinoma to adenocarcinoma.[19]

*In conclusion:* the incidence of lung cancer among males in southeastern Netherlands has clearly started to decline despite an increase in the incidence of adenocarcinoma; for females a marked increase has been observed for all histological types. Despite quite a few changes in the diagnosis and treatment of patients with lung cancer, improvement in survival has only been found for patients with small cell lung cancer in the first year after diagnosis; there was a decrease in the survival rates for adenocarcinoma. Except for patients with small cell cancer and some operable patients treatment of patients with lung cancer seems to consist largely of observing the natural history and trying to influence the quality-of-life.

ACKNOWLEDGEMENT

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Chapter 5.4

# TRENDS IN THE INCIDENCE OF NON-MELANOMA SKIN CANCER IN SOUTHEASTERN NETHERLANDS IN 1975-1988:

## A registry based study *


SUMMARY

Trends in the incidence and site-specific distribution of primary basal cell (BCC) and squamous cell carcinoma (SCC) of the skin, diagnosed in a defined population of 650,000 persons in southeastern Netherlands during the period 1975-88 were examined. Guided by routine reports from pathological laboratories, patient data was obtained via the population-based Eindhoven Cancer Registry from dermatological and surgical clinics in 12 community hospitals. The world standardized incidence rates for primary BCC rose from about 42 to 53 per $10^5$ person-years for males and from about 24 to 38 for females. Incidence rates for SCC varied between 9 and 14 per $10^5$ person-years for males and between 2 and 5 for females; a temporary decrease was observed for SCC in 1976-82, followed by an increase - mainly among males. As in other countries, BCC and SCC occurred in about 80% of the cases on the head and neck region. Even with some detection bias we observed a rise in the true incidence of BCC and SCC, the latter only since 1982, mostly for the head and neck region and the upper limbs (especially among males) and the trunk (females). The incidence of SCC of the lips in males declined markedly. Taking into account geographical location and altitude as well as the distribution of skin types, both the magnitude of our rates and the trends fit the pattern of incidence figures observed elsewhere in Europe.


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## INTRODUCTION

Despite disquieting news of increased, skin damaging, exposure to sunlight and a presumably rising incidence of basal cell (BCC) and squamous cell carcinoma (SCC) of the skin among whites in southern countries, such as Australia, and the U.S.A. [1 2] little is known of its incidence in Western Europe[3 4] and even less of changes in these rates.[5] Regular exposure to ultraviolet radiation, fair skin and reduced immunity, possibly related to ageing, appear to be the major risk factors for the most common types of non-melanoma skin cancer and for SCC also chronic skin damage.[6] Current figures from most cancer registries[7] only partially reflect the true incidence, which in turn hampers appraisal of time trends. This applies especially for skin cancer occurring at multiple sites. Unless extensive surveys are carried out,[8] complete assessment of a population is primarily dependent on adequate histological verification. In addition to extensive reporting by pathologists to a cancer registry direct access to patient data on site and stage is essential in various dermatological and surgical clinics. These conditions were met in a well defined area, in southeastern Netherlands by the cancer registry in Eindhoven.[9] As a result, trends in the site-specific incidence of BCC and SCC from 1975 onwards could be investigated, together with patterns of diagnosis. For reasons of accuracy and comparability we restricted the analysis to primary tumours only, either BCC or SCC or both.

## PATIENTS AND METHODS

### *Population, medical care and registry*

The study population lived in 45 municipalities in southeastern North-Brabant, adjacent to Belgium, and northern Limburg, adjacent to West Germany. The area is located 5° east, 51.5° north and lies 20 to 50 metres above sea level. The population density is about 400 per $km^2$; 12% of the population lived in rural communities. Specialized care, usually after referral by a general practitioner, was available originally in 12 community hospitals, now 9 as a result of mergers, which were supported by 10 pathologists working in 3 laboratories and one regional Department of Radiotherapy. From 1975 to 1984 the number of practising dermatologists increased from 8 to 12. The regional cancer registry, which has collected patient data since 1955, became population-based for almost 850,000 people in 1974. This study was restricted to 650,000 people living in 35 municipalities, served by 2 of the 3 pathological laboratories and 10 of the 12 dermatologists. The pathologists routinely supplied data to the registry on all tissue specimens with a diagnosis of (suspected) cancer. The medical records of these patients, identified by address at diagnosis, were tracked by the registry staff during periodic visits to the hospitals.

*Patients*

Included in this study were data on all patients with histologically verified BCC and SCC of the skin and of the lip, who were first diagnosed between January 1st, 1975 and December 31st, 1988. All other types of skin cancer were excluded. Based on the International Classification of Diseases (ICD) the histological codes for BCC were 809 in the 8th version and 8090-8095 in the 9th; for SCC they were 807 and 8070-8076, respectively. The anatomical site was recorded to the 4th digit of the topography code, i.e. 140 for the lip, only external lips (140.0/1) and commissure (140.6), and 173 for the skin, subdivided as follows: lips (173.0), eyelids (173.1), external ears (173.2), face (173.3), scalp & neck (173.4), trunk (173.5), upper limbs (173.6), lower limbs (173.7), multiple sites (173.8) and site unknown (173.9). Anatomical sites of cases diagnosed in the period 1975-78 and classified according to ICD-8 were recoded to ICD-9; this resulted in exclusion of BCC and SCC of the genital organs and a shift from lip to skin for BCC and from skin to lip for SCC.

*Data analysis*

Annual figures on the population at risk were obtained for the diverse communities from the Netherlands Central Bureau of Statistics (CBS). Annual age-specific and age-adjusted (World and European standard population, the first because of international comparability, the second corresponds to reality) rates were computed per 100,000 person-years and sex, and as 3-year moving means for trend analysis. Age-specific figures are also presented for the periods 1975-81 and 1982-88 for BCC and 1978-82 and 1983-88 for SCC (due to presumably biased high rates in the early years as a result from possible misclassification with keratoacanthoma). BCC to SCC ratios were computed per anatomical site and age.

Annual regional cancer mortality figures were derived from the cause of death register of the CBS.

## RESULTS

All together, 4,714 primary invasive epidermal tumours in 4,607 patients, i.e. 107 patients (2.3%) had both BCC and SCC, were registered. BCC was observed in 81% of male and 89% of female patients (table 1). Incidence rates for BCC started to rise after age 35, were equal for the two sexes until age 45 and then became significantly higher for males; after age 75 the male/female difference became smaller again (table 2). The incidence of SCC started to rise after age 45 for males and after age 65 for females, and the male/female ratio gradually decreased from about 4 to 2. The BCC to SCC ratios gradually declined with rising age; they were more than 5 for males up to age 60 and for females up to age 80. In 1978-88 the age-adjusted (European standard) incidence rates for primary BCC and SCC of the skin and lips together were 84.6 per $10^5$ person-years for males and 51.7 for females, i.e. 67.5 for BCC

TABLE 1 **Annual age-adjusted* incidence (per 100,000 person-years) and number of patients with BCC and SCC of the skin and lips in the period 1975-88: according to sex**

| | BCC | | | | SCC | | | |
|---|---|---|---|---|---|---|---|---|
| | males | | females | | males | | females | |
| Year | no. | inc* | no. | inc* | no. | inc* | no. | inc* |
| 1975# | 119 | 44.2 | 61 | 19.6 | 31 | 11.2 | 12 | 3.9 |
| 1976# | 115 | 40.8 | 86 | 26.4 | 38 | 13.4 | 13 | 3.6 |
| 1977# | 134 | 47.3 | 96 | 28.5 | 25 | 8.7 | 11 | 3.0 |
| 1978 | 118 | 36.0 | 95 | 25.8 | 38 | 11.2 | 15 | 3.7 |
| 1979 | 148 | 44.0 | 128 | 33.2 | 29 | 9.3 | 19 | 4.2 |
| 1980 | 134 | 41.3 | 85 | 20.9 | 40 | 12.2 | 8 | 1.6 |
| 1981 | 151 | 43.9 | 135 | 31.1 | 24 | 7.4 | 15 | 3.3 |
| 1982 | 155 | 44.4 | 138 | 32.4 | 31 | 9.1 | 11 | 2.2 |
| 1983 | 159 | 44.8 | 148 | 32.9 | 32 | 9.3 | 13 | 2.6 |
| 1984 | 139 | 39.0 | 135 | 29.0 | 32 | 8.8 | 17 | 3.3 |
| 1985 | 209 | 56.8 | 139 | 29.0 | 49 | 13.7 | 30 | 5.4 |
| 1986 | 195 | 51.9 | 173 | 38.4 | 44 | 11.9 | 28 | 4.8 |
| 1987 | 188 | 47.8 | 176 | 36.6 | 41 | 10.9 | 12 | 1.9 |
| 1988 | 219 | 56.3 | 194 | 40.3 | 58 | 14.7 | 20 | 3.4 |
| total | 2183 | 45.6 | 1789 | 30.3 | 512 | 10.9 | 224 | 3.4 |
| 100% | 81% | | 89% | | 19% | | 11% | |

source: Eindhoven Cancer Registry
* world standard population; # smaller source population

and 17.1 for SCC for males and 46.3 and 5.4 for females, respectively. The corresponding BCC/SCC ratios were 3.9 for males and 8.5 for females; the male/female ratios for BCC and SCC were 1.4 and 3.2. BCC/SCC ratios were highest for the eyelids and trunk and lowest for the lips, external ears and limbs, the latter especially in males (table 3). The mean age of patients with BCC was generally lower than that of patients with SCC, except for SCC of the trunk; patients with a tumour of the external ears were the oldest.

### *Time trend*

Age-adjusted incidence rates for BCC increased gradually over time, for males only after 1984 (figure 1), and showed little annual variation (table 1). However SCC exhibited some annual variation: low rates for males in 1977, 1979 and 1981-84 and for females in 1980, 1982-83 and 1987. Compared to the period 1975-81 age-specific rates for BCC in 1982-88 were higher for those over age 50, although this was less distinct for women under 75 (figure 2). For SCC an increase was observed for men between 60 and 75 years of age and a decrease in older age groups; age-specific rates for women with SCC were slightly higher in the second period, especially in those over 85.

Age-adjusted mortality rates for BCC and SCC varied between 0.4 and 0.6 per 100,000 person-years for males and between 0.1 and 0.4 for females.

TABLE 2 Age-specific incidence (per $10^5$ person-years) of BCC and SCC of skin and lips and BCC/SCC ratio in southeastern Netherlands, 1978-88

| Age (yrs) | BCC males $10^5$py | BCC males no. | BCC females $10^5$py | BCC females no. | SCC males $10^5$py | SCC males no. | SCC females $10^5$py | SCC females no. | BCC/SCC ratio ♂ | BCC/SCC ratio ♀ |
|---|---|---|---|---|---|---|---|---|---|---|
| 0-14 | 0.5 | 1 | – | – | – | – | | | ∞ | – |
| 15-19 | 0.3 | 1 | 0.3 | 1 | – | – | | | ∞ | ∞ |
| 20-24 | – | – | 1.6 | 5 | 0.3 | 1 | | | – | ∞ |
| 25-29 | 4.5 | 14 | 5.0 | 14 | – | | 0.4 | 1 | ∞ | 14 |
| 30-34 | 6.4 | 19 | 5.9 | 16 | 0.7 | 2 | – | | 9.5 | ∞ |
| 35-39 | 15.7 | 42 | 16.8 | 43 | 0.4 | 1 | 0.9 | 2 | 42 | 22 |
| 40-44 | 27.9 | 69 | 29.9 | 68 | 3.8 | 9 | 1.3 | 3 | 7.7 | 23 |
| 45-49 | 56.0 | 123 | 42.8 | 90 | 7.4 | 16 | 2.8 | 6 | 7.8 | 15 |
| 50-54 | 87.5 | 171 | 61.9 | 121 | 7.8 | 15 | 3.0 | 6 | 11.4 | 20 |
| 55-59 | 136.0 | 230 | 86.1 | 150 | 18.0 | 30 | 4.1 | 7 | 7.7 | 21 |
| 60-64 | 179.3 | 245 | 125.0 | 186 | 39.4 | 54 | 6.5 | 9 | 4.5 | 21 |
| 65-69 | 246.7 | 257 | 133.8 | 168 | 57.2 | 59 | 14.4 | 18 | 4.4 | 9.3 |
| 70-74 | 304.2 | 239 | 187.1 | 202 | 90.6 | 72 | 28.7 | 31 | 3.3 | 6.5 |
| 75-79 | 392.7 | 205 | 254.0 | 205 | 126.2 | 74 | 44.4 | 36 | 2.8 | 5.7 |
| 80-84 | 462.9 | 127 | 343.9 | 169 | 352.1 | 84 | 76.5 | 36 | 1.5 | 4.7 |
| 85+ | 495.6 | 72 | 384.4 | 108 | 352.1 | 51 | 113.6 | 33 | 1.4 | 3.2 |
| world | 46.0 | | 31.8 | | 10.8 | | 3.3 | | 4.3 | 9.6 |
| europe | 67.5 | | 46.3 | | 17.1 | | 5.4 | | 3.9 | 8.6 |

source: Eindhoven Cancer Registry

TABLE 3 Site-specific distribution and mean age of patients with BCC and SCC of the skin and lips in the period 1975-88: according to sex

| site | BCC ♂ % | BCC ♀ % | BCC age ♂/♀ (yrs) | SCC ♂ % | SCC ♀ % | SCC age ♂/♀ (yrs) | BCC/SCC ratio ♂ | BCC/SCC ratio ♀ |
|---|---|---|---|---|---|---|---|---|
| Lips | 2 | 4 | (64/69) | 18 | 4 | (66/67) | <1 | 7 |
| Eyelids | 11 | 9 | (63/63) | 1 | 4 | (73/72) | 41 | 16 |
| External ears | 7 | 3 | (67/74) | 24 | 5 | (74/77) | 1 | 3 |
| Face | 57 | 59 | (64/67) | 34 | 51 | (71/76) | 7 | 9 |
| Scalp & neck | 7 | 6 | (63/64) | 7 | 7 | (73/71) | 5 | 8 |
| *Total Head & neck* | *84* | *81* | | *84* | *71* | | *4* | *9* |
| Trunk | 9 | 10 | (59/62) | 2 | 4 | (58/64) | 25 | 22 |
| Upper limbs | 3 | 3 | (64/63) | 11 | 13 | (67/72) | 1 | 2 |
| Lower limbs | 1 | 3 | (66/67) | 3 | 10 | (60/75) | 2 | 3 |
| Other/NOS | 2 | 3 | | <1 | 1 | | | |
| All sites | | 100% | | | 100% | | | |

source: Eindhoven Cancer Registry

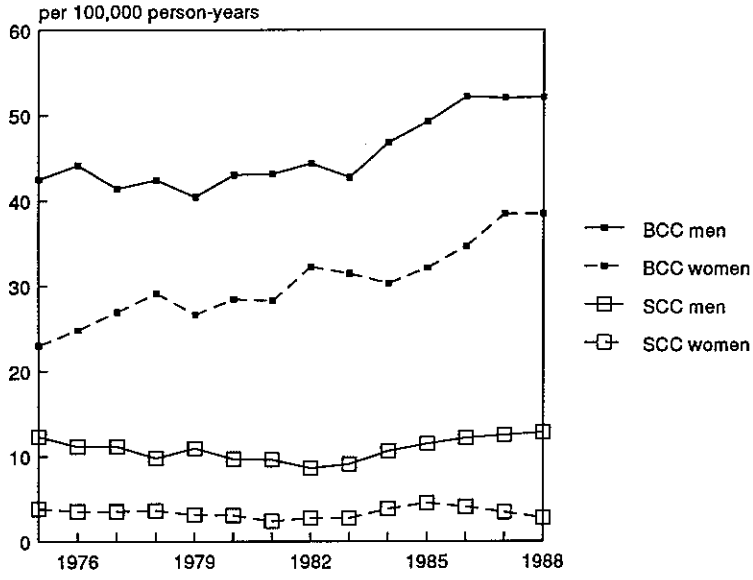


FIGURE 1 Trends# in age-adjusted* incidence of BCC and SCC of skin and lips, 1975-1988
source: Eindhoven Cancer Registry
# 3-year moving means; * world standard

Age-adjusted site-specific incidence rates for BCC and SCC showed a diversity of trends (figure 3). Among males there was an increase in BCC of the face and eyelids (both after 1984), scalp and neck (between 1978 and 1982) and, with some fluctuation the trunk (until 1985) and upper limbs; SCC of the upper limbs and scalp and neck area increased (after 1984); SCC of the lips decreased after 1979. Both the magnitude and the fluctuating pattern (falling until 1981 and rising from 1983) of the incidence of BCC and SCC of the external ears in males were similar. Among females a fluctuating pattern was seen for BCC of the lips, eyelids and lower limbs and an increase in BCC of the face, scalp and neck, trunk and upper limbs; for SCC a very low incidence ($<0.5$ per $10^5$) with few changes was found for women at most sites, except for the upper limbs and scalp and neck area where an increase was observed since 1983.

## DISCUSSION

This registry-based study from southeastern Netherlands may have been hampered by the usual weaknesses of descriptive epidemiological studies of the true incidence of BCC and SCC: underdiagnosis, deficient histological verification, lack of review - mainly desirable for SCC - and underregistration only based on histological verification. Moreover, trend analyses of the incidence of

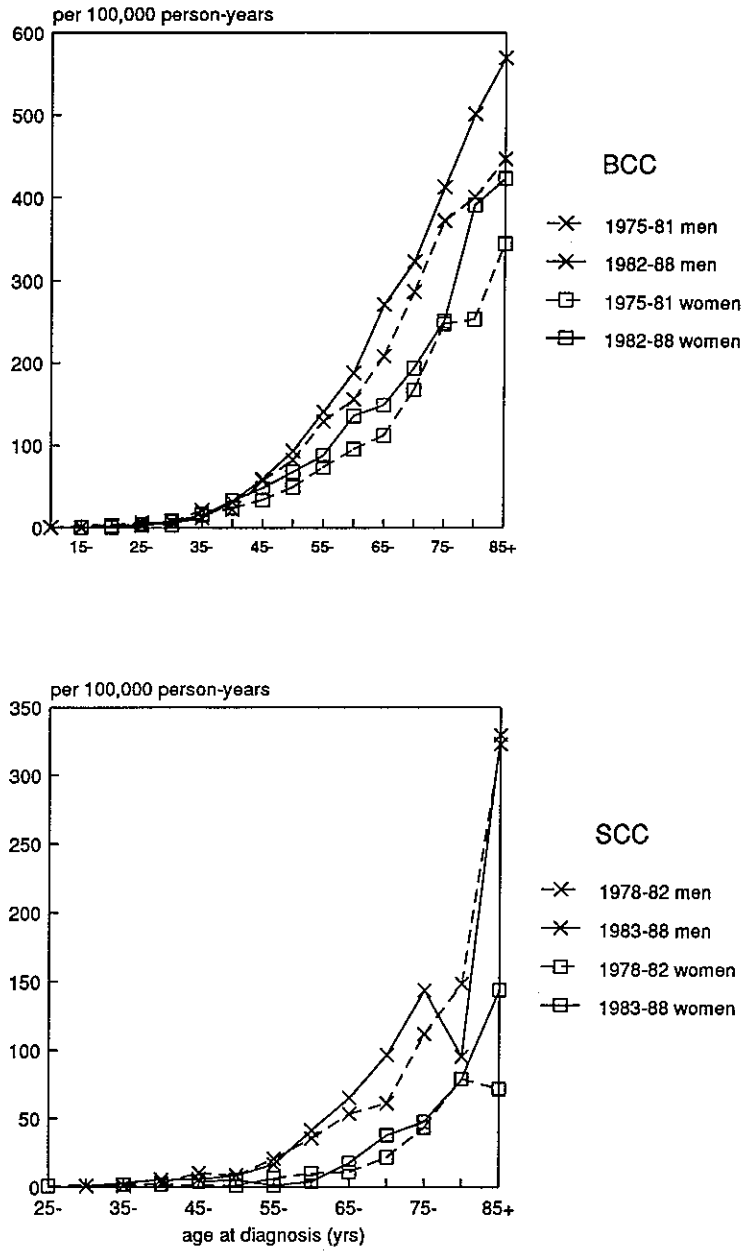


FIGURE 2 Age-specific incidence of BCC and SCC of skin and lips in two periods: by sex
source: Eindhoven Cancer Registry

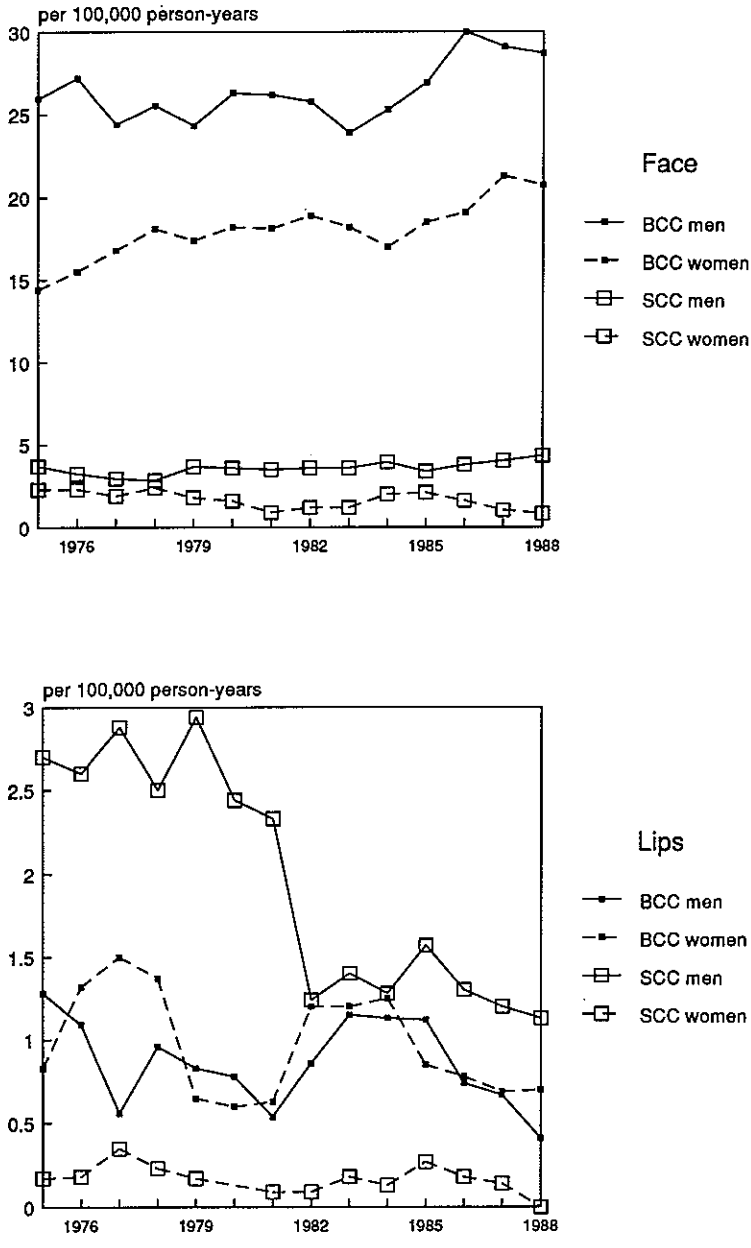


FIGURE 3 Trends# in age-adjusted* site-specific incidence of BCC and SCC in 1975-1988
source: Eindhoven Cancer Registry
# 3-year moving means
* world standard population

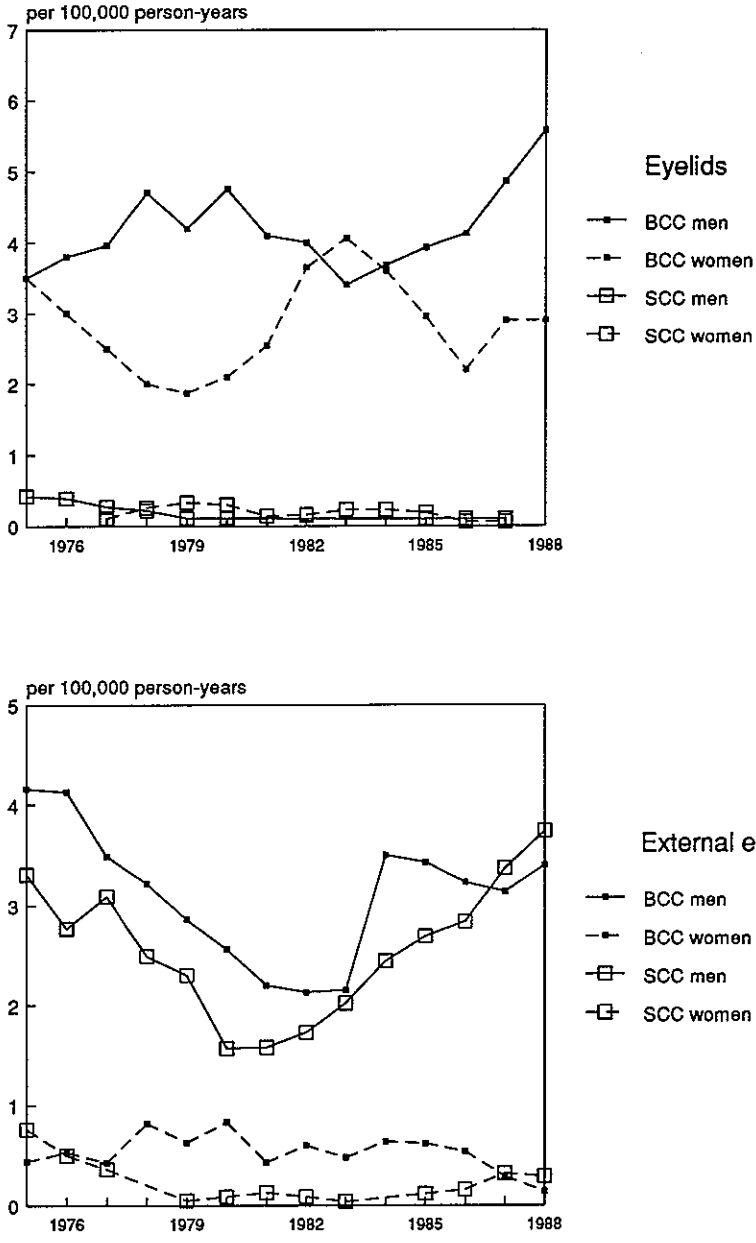


FIGURE 3 *(continued)*

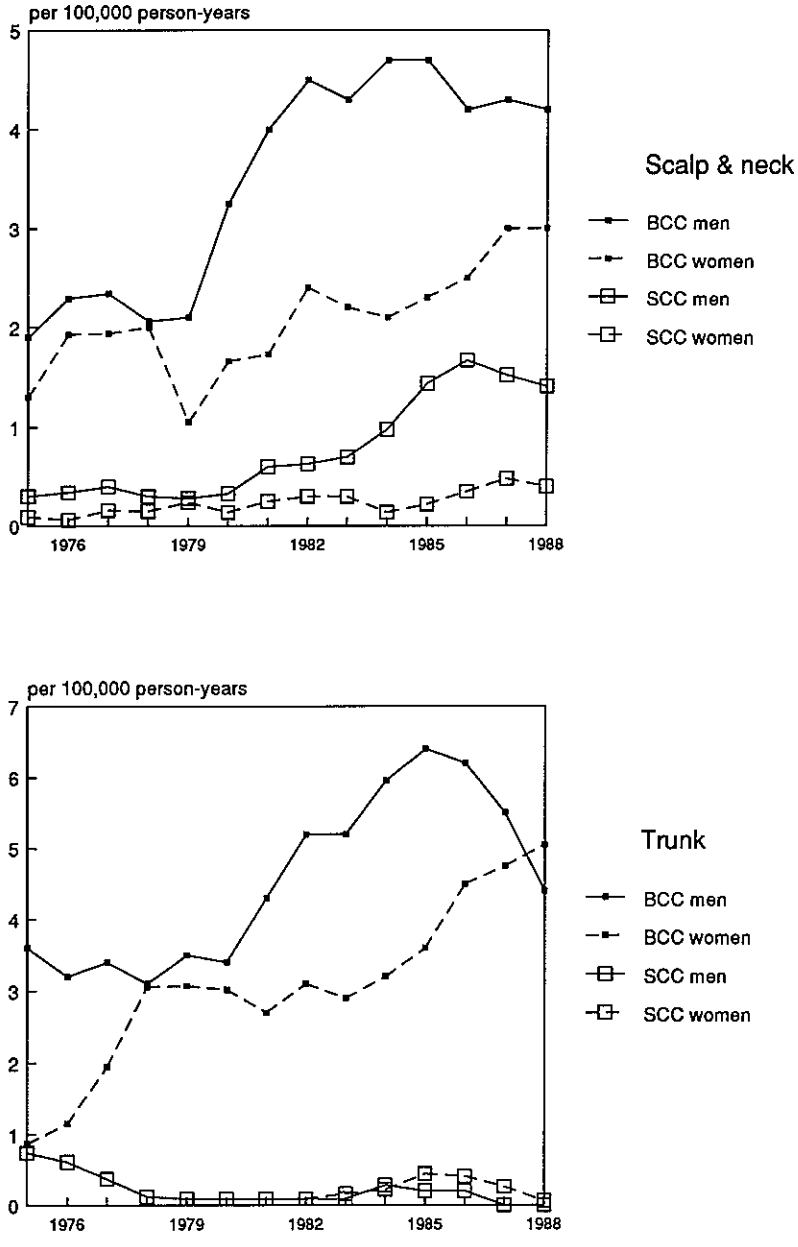


FIGURE 3 *(continued)*

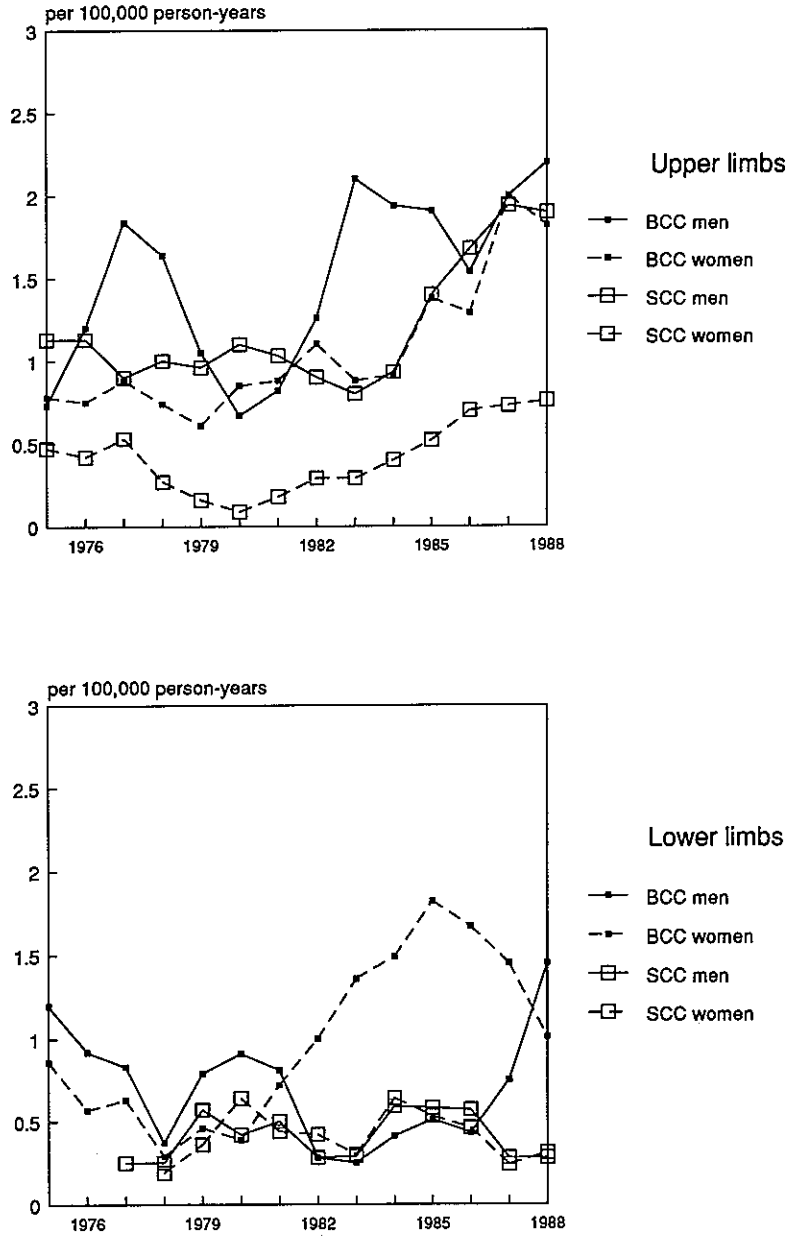


FIGURE 3 *(continued)*

slowly growing tumours at apparent locations are generally sensitive to changes in the care-seeking behaviour of patients and medical diagnostics; intensification of both aspects would rather lead to higher registration rates than to higher - true - incidence rates. This is not unlikely, especially because of the rising number of practising dermatologists, also freshly trained, during the study period. The percentage of tumours detected by dermatologists increased from 62% in 1975-78 to about 78% in 1987-88, while the share reported by (plastic) surgeons diminished from 32% to 16%. General practitioners may have referred more patients with suspected cancer and also earlier. General practitioners do not often treat these patients in the Netherlands, where distances to hospitals are generally less than 30 km. A recent survey among general practitioners in the Utrecht region (in the middle of the Netherlands) showed that almost all patients suspected of skin cancer are diagnosed histologically and/or referred to specialists.[10]

The decline of SCC found for many sites in the period 1977-82 may be partly explained by a shift in the histological classification of SCC with regard to keratoacanthoma, which may have been diagnosed more often in recent years. However, a plausible explanation for the marked and continuous decrease in the incidence of SCC of the lips in men would also be reduced exposure to (pipe)smoking, as the incidence of other tobacco-related cancer has also decreased in our area since 1978-80.[11] If the incidence rates for BCC and SCC are exclusively affected by intensification of the detection process, the pattern of site-specific changes should have been more homogeneous. Moreover, we have reduced the problem of underascertainment by restricting the analysis to patients with a primary BCC and/or SCC and to the area where the registration procedure was most adequate and remained virtually unaltered. For insight in the incidence of multiple skin tumours, special follow-up studies would be necessary. In 2 such studies within the USA 5-year cumulative incidence rates for multiple BCC and SCC after diagnosis of the primary tumour were found to vary from 35% in the north to 59% in the south.[12 13]

Compared to other regions in Western Europe incidence rates for BCC in southeastern Netherlands were 25 to 50% higher than in Denmark,[4] 15 to 30% lower than in the canton Vaud[5] (Switzerland) and almost 60% lower than in southern Wales;[3] for SCC all of these differences were larger. The geographical latitudes, the higher average altitude of the canton Vaud and the high proportion of individuals with skin types I and II in Wales may explain these differences to a large extent. However, in all of these studies the BCC/SCC ratios were roughly similar, about 4 for males and 9 for females, as were the sex ratios, about 1.5 for BCC and 3 for SCC, and the proportion of tumours located in the head and neck area, about 80%, and 60 to 70% for SCC in women. The site-specific distribution also corresponded closely with the results of the studies summarized by Pearl and Scott,[14] the population-based, albeit incomplete, study from Finland[15] and the laboratory-based study from Belgium.[16] Changes in the incidence of BCC correspond to those observed in

the San Francisco area in the USA.[2] The real increase in the incidence of SCC in our area since 1983, applying for all sites of SCC in men and for the upper limbs and scalp and neck area in women, also corresponds to the recently observed increases of the incidence of SCC in the canton Vaud and the USA.[17]

Do the observed changes in incidence in our area reflect changing patterns of exposure to relevant risk factors? Small but consistent increases were found for of old, regularly sun-exposed sites such as the face, scalp and neck and upper limbs. The increase for the trunk may reflect more intensive sun-bathing of the past 25 years. Although the, originally rural, Eindhoven area has urbanized as a result of population growth and industrialization and increasing air pollution has been registered by the National Institute for Public Health and Environmental Hygiene, (mainly from neighbouring areas and even as far away as from Eastern Europe), our rates would unlikely have been substantially affected. Neither will this already apply for the ozone depletion of a more recent date.

We conclude carefully that the incidence of primary BCC in southeastern Netherlands has indeed been increasing for sun-exposed sites; for SCC this would pertain mainly after 1983 and except for the lips, where a decrease was observed.

A regional cancer registry may be able to handle registration of BCC and SCC of the skin, provided regular communication exists between registry staff and pathological laboratories as well as ample access to medical records, especially those of the dermatology departments. The risk for multiple primary BCC and SCC should be studied in specific cohort studies in clinics with adequate dermatological surveillance and good collaboration with (plastic) surgeons.

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CHAPTER 6

# GENERAL DISCUSSION

## Chapter 6

# GENERAL DISCUSSION

The studies on the morbidity and mortality of cancer in the Netherlands reported in this thesis represent the primary function of cancer registries, i.e. to monitor cancer frequency and prognosis. Because precise data were lacking in the Netherlands these studies now serve as reference information for education,[1 2] research (see list of publications in appendix E), international comparison,[3 4 5] and, particularly fot those of the Eindhoven Cancer Registry (ECR), health care policy at regional[6] and even national levels.[7 8 9] Two general remarks will be made about the merits of cancer registry for health policy and medical care in the Netherlands. With respect to cancer the health policy and health care planning 'scene' has become much more transparent in recent years thanks to the quantitative contributions from cancer registries. Around the registries groups of physicians now reap the fruits of being better informed and thus have a wider perspective on oncological care. Elsewhere, good examples exist in southern Sweden[10] and West Scotland, and with regard to childhood cancer in Great Britain showing the value of a long history[11] and since 1981, West Germany.

The implications of the findings of the studies in this thesis are discussed below, in particular with respect to opportunities for further registry-based or supported research, separately for **incidence** as a measure of risk and **survival** as a measure of prognosis.

### I INCIDENCE

The various opportunities for interpretation of the incidence data as an indicator of risk will be discussed, mainly with respect to the Eindhoven Cancer Registry, as it was already done rather specific for childhood leukaemia and malignant lymphomas in 5.1.2 and 5.1.3. Subsequently the role of a registry in aetiological research will be considered.

#### *1.1 Indicator of risk*

When the Dutch figures from the period 1978-82 are compared with other cancer registries in the European Community (EC), a distinct pattern emerges from our studies: highly similar incidence rates for children[3] and until about the age of 45;[12] above this age 'unfavourable' rates are found for Dutch males, especially those aged 65 and over. Within the EC the Dutch rates were relatively

high for carcinoma of the lung, colon, gallbladder, pancreas and kidney and non-Hodgkin's lymphoma and multiple myeloma (table 1). According to appendix B male mortality due to these tumours was also relatively high in the ECR area compared to the Netherlands. The pattern for females within the Netherlands and in Europe showed less variation: on the one hand high rates for cancer of the breast, colorectum, gallbladder, pancreas, kidney and of non-Hodgkin's lymphoma and multiple myeloma; on the other hand low incidence rates were found for cancer of the respiratory and upper digestive tract and cervical cancer, all of which were however increasing (4.1). The unfavourable pattern of male mortality in southeastern Netherlands[13] was confirmed and appeared to correspond with cancer incidence and mortality rates in nearby Belgium and Germany.[14]

TABLE 1 The incidence of cancer in the Netherlands with respect to other countries of the European Community in the period 1978-82

| Site | Males | Females |
|---|---|---|
| All sites | high | average |
| Head & neck | low | low |
| Oesophagus | low | low |
| Larynx | low | very low |
| Lung | very high | low |
| Stomach | average | low |
| Colon | high | high |
| Rectum | average | average |
| Liver | very low | very low |
| Gallbladder | high | high |
| Pancreas | high | high |
| Melanoma | high | high |
| Breast | | high |
| Cervix uteri | | low |
| Corpus uteri | | average |
| Ovary | | average |
| Prostate | average | |
| Testis | average | |
| Bladder | average | average |
| Kidney | high | high |
| Brain | average | average |
| Non Hodgkin's | high | high |
| Hodgkin's disease | average | average |
| Multiple myeloma | high | high |
| Leukaemia | average | average |

source: Jensen et al [12]

To interpret changes in incidence with a cancer registry three approaches can be followed:

**(a) analysis according to histological type, stage and subsite**
The studies in chapter 5 on haematological malignancies, breast, ovarian, lung and non-melanoma skin cancer demonstrate sufficiently that monitoring changes in the distribution of these features may provide clues about potential causes and changes in exposure to risk factors. Proper registration and coding of these features while maintaining constant quality requires trained registration officers with access to clinical records; it is also essential for a reliable analysis of trends in survival.

**(b) consideration of changes in detection and classification**
In each of the studies described in chapter 5, a number of clinicians and diagnostic experts assisted closely in the process of analysis. Within the ECR, members of regional tumour study groups for breast, gynaecological, haematological and skin cancer and especially pathologists and, mostly, radiotherapists provided support; they thus supplemented the medical officer who provided continuity by being responsible for data collection and coding since 1967. It was particularly important for recognising changes in classification (and detection?) of papillomas of the bladder and borderline tumours of the ovary; there was also the shift from chronic lymphatic leukaemia to non-Hodgkin's lymphoma, which may also be detected more frequently at the cost of undifferentiated tumours; the improved distinction between keratoacanthoma and squamous cell cancer of the skin is also of interest. For the studies on childhood leukaemia and lymphoma - also showing some overlap - the DCLSG board of paediatricians represented by the subcommittee on epidemiology provided continuity and support while the laboratory of the DCLSG served as a reference for the diagnosis of leukaemia from the start.

**(c) consideration of trends in cancer mortality**
Analogous to the analyses of Bailar[15] and Doll and Peto,[16] trends in cancer mortality served as an indicator of severity of morbidity in order to identify detection and classification bias, that may affect both incidence and survival, with regard to less severe forms. Trends in age-adjusted and age-specific mortality rates ran remarkably parallel to trends in incidence, except for tumours with markedly changing survival rates (e.g. testicular or ovarian cancer) (5.2.1). In the course of time mortality rates for the young declined not only relatively with respect to incidence but also absolutely, while differences between incidence and mortality remained unaltered for the elderly. Increased differences may reflect growing effectiveness of treatment for the young (10-15% of patients). On the other hand for the elderly changes in cancer mortality, mostly increases, seem instead to be influenced by changes in incidence. However we have to take into account the less accurate specification of the

cause of death for the elderly. Moreover, the increases in cancer mortality may be related to the decreasing mortality due to other causes of death, especially diseases such as vascular and lung diseases characterised by similar risk factors. The overview of such changes in the major causes of death in the Eindhoven area since 1970 (appendix C) shows that mortality rates for almost all other causes of death have declined. For children the situation seems different: childhood mortality rates for the whole country declined declined sharply after 1970 and this also happened for leukaemia and non-Hodgkin's lymphoma (5.1.3).

*1.2 studies of cancer aetiology*

Another function of a registry is to generate hypotheses on changes in incidence and to enable subsequent analyses or studies. This was effectuated extensively for childhood leukaemia.[17] In the ECR with its wider spectrum of tumours different strategies can be followed, in part depending on the level of the incidence rate. We distinguish low and high frequency tumours and multiple primary cancers that provide opportunities for research of side-effects of treatment. Finally, the role of the registry in record-linkage will be discussed.

(a) low frequency

Increases in incidence of rare tumours may be an indicator of an increased level of exposure to known agents or the existence of new 'dangers', that could have been introduced many years ago. The low but rising incidence rates for neoplasms in the upper digestive and respiratory tracts illustrate the former, while the latter could apply for unusual neoplasms such as cancer of the liver, bone, vagina and mesothelioma. (upon close view such changes were hardly visible in the latter group in the period 1975-87) It could also apply for common tumours at young age, such as cancer of the breast and colon. As far as the findings of the ECR are concerned the causes for the rise of the incidence of melanoma, adenocarcinoma of the lung and non-Hodgkin's lymphoma remain largely unknown. Are we dealing with beginning epidemics or is there just a temporary variation, such as that found for childhood leukaemia? In a study of possible carcinogenic side-effects of the Chernobyl accident in 1986 an anticipatory approach for all of Europe is now being followed by the International Agency for the Research on Cancer (IARC): the incidence of childhood leukaemia and lymphoma is currently being monitored in most of the exposed and some unexposed parts of Europe throughout the period 1980-2000.[18] Recently the IARC has started an extensive case-control study of causes of childhood leukaemia, again. However, the discovery of such epidemics as diethylstilboestrol (DES)-related carcinoma of the vagina[19] and asbestos-related mesothelioma[20] can in fact rather be attributed to attentive physicians who conducted case series and case-control studies which gave very high relative risks. Minimally needed is - the largest possible - registry that enables estimation of incidence and serves as sampling frame for case-control

or follow-up studies. If the carcinogenic effects involved are not strong, 'negative' or inconclusive results are likely. Only a high prevalence of exposure would still be a reason to study the effects. Moreover, a reassuring effect can also be desirable from the public health point of view, as experience with childhood leukaemia in the Netherlands showed. With this respect a paradoxical relationship may actually exist between the extremely low childhood mortality and morbidity due to severe diseases and worries about child health in industrialized countries. We can learn to be cautious from the extensive studies of childhood cancer and low-dose radiation in Great Britain, which continue to yield inconclusive results despite evidence of carcinogenic exposures. Neutra stresses that in case of rare tumours relative risks in the order of 8 should only warrant further investigation.[21] This cannot be stressed enough, because an increasing number of time-consuming ecological cluster analyses is currently being carried out by the various regional public health departments (Basisgezondheidsdiensten) in the Netherlands. A final word: the studies on epidemics of meningitis repeatedly show that the elucidation of clusters is more complex than the search for causes, because also host factors are involved.

(b) high frequency tumours

Tumours become more common as incidence increases exponentially with rising age. We already emphasized the value of studying differential trends according to histological type (e.g. for lung and ovarian cancer and leukaemia), subsite (e.g. for stomach, colon and skin cancer) or stage (e.g. breast and ovarian cancer). One may first think of changes in past exposure to risk factors with a substantial attributive risk, such as tobacco and alcohol, while small effects of weaker or less well defined exposures of e.g. dietary and environmental origin will hardly be detected. Although regional differences give some clues, the underlying causes remain highly speculative.[13] Major risk factors for cancer have been and will be determined in case-control studies. Although these studies do not need to be based on registries, such studies are definitely facilitated by registries by providing a sampling frame and appropriate selection of controls from the same source population. Even if the effects of certain risk factors, such as smoking, are known, it may be desirable to study a local situation showing very high values because of the possibility of interaction with other factors. A good example is the study on smoking and lung cancer in West Scotland, an area with a very high incidence of lung cancer.[22] Thus, it could be worthwhile to study the combined influence of cage birds and smoking and (high frequency) male lung cancer in southeastern Netherlands, because the habit of having cage-birds in the house is rather wide-spread.[23] If one wants to study the rate of changes in incidence over time in specific populations, surveys of relevant dietary and smoking habits and occupational and environmental exposures can be carried out among well-defined groups of new cases and healthy controls. Although awareness bias may occur aetiological studies will be easier to carry out, to the degree that the attending physicians have become

more aware of the problem, possibly because 'their' registry shows peculiar rates. The on-going case-control study of breast cancer in young women as related to life-style by the Netherlands Cancer Institute (NKI) recruits newly detected cases in 4 regional cancer registries;[24] it attained a (high) response rate of more than 90% in the ECR-area, due to the - registry initiated - close cooperation between investigators and attending specialists, especially radiotherapists. A tumour study group that meets regularly is more likely to become curious about unsolved mysteries which is of major importance for enabling research projects conducted by 'others'.

**(c) multiple primary cancer**

Multiple primary cancers may develop in paired organs, e.g. the breasts, kidneys and ovaries, or in extensive organ systems, e.g. respiratory, digestive or urinary tracts or skin. They may be aetiologically related to the first tumour or an unwanted side-effect of therapy, or just a random event. From the large studies carried by the cancer registries of Denmark and Connecticut the risk for a second tumour may be increased by as much as 30%.[25] With regard to research design, nested case-control studies are feasible within cohorts of registered patients, thus rendering unnecessary the retrieval of large amounts of patient data. Until now, only a preliminary study of the incidence of leukaemia in patients with Hodgkin's disease has been carried out by means of the ECR.[26] Because treatment related events are rare, international collaborative studies seem the best approach.[27] [28] Quite a few studies can be expected to follow, when the data registered in the period 1955 to 1975 have been processed. Information on primary treatment has been recorded rather accurately in the registry for surgery and radiotherapy and can be traced in more detail in the records of the regional radiotherapy department. Such projects are currently in progress for testicular cancer (another study of the NKI), breast (own study) and gynaecological cancers and Hodgkin's disease (on behalf of regional tumour study groups). Another registry-based case-control study of the causes of contralateral breast cancer, using patients with unilateral breast cancer as controls, has been proposed by the NKI; a retrospective analysis of the frequency of the second tumour and the duration after the first in patients diagnosed since 1955, is being planned. Because the ECR is one of the few European registries adequate surveillance of non-melanoma skin cancer, the occurrence of multiple primary skin cancer can be studied in cohorts of patients with a primary diagnosis; effects of preventive and therapeutical interventions can also be examined. The DCLSG is studying the long term prognosis and occurrence of serious diseases such as secondary cancer.[29]

**(d) all tumours: record linkage**

For cohort studies, e.g. on occupational risks, registries are more or less indispensable, but have a passive role in just providing record-linkage.[30] Currently the ECR is involved in record linkage for a major on-going cohort

study of diet and cancer. The option also exists of a follow-up study of healthy donors of blood to a regional blood bank in an attempt to trace early pathogenic or preventive factors in frozen serum. Use of the archives of the regional microbiological laboratory could be made to study the association between previous infections (e.g. herpes viruses[31], urinary infections[32]) and the incidence of cancer after a latent period. Actually, related to the methods of data collection, innumerable opportunities exist to study the cancer risk in patients with of a variety of syndromes determined in clinical practice, e.g. trombosis,[33] irritable bowel syndrome, more general all possible symptoms of early cancers. Such studies have regularly been carried out in the Scandinavian countries, facilitated by a unique personal identification number and various national registration systems for e.g. occupations (supported by employers and labour). Moreover, Scandinavian privacy regulations better account for research by established investigators. At this point the future is rather uncertain in the Netherlands: well-intended rules to protect the individual patient have created a psychological climate in many hospitals that hampers current and future studies, the latter because they are no longer even considered.

## 2 SURVIVAL

In this section the value of and conditions for survival studies with a cancer registry will be discussed. Survival is not only considered as a descriptive indicator of prognosis, but also as an indicator of effectiveness of specific treatment strategies, including early detection. In combination with the monitoring of diffusion of new treatments a reliable impression can be obtained of the real changes in prognosis in oncological practice.

### *2.1 Indicator of prognosis*

Reports on survival, primarily aim to monitor changes in the prognosis for unselected patients and may thus also signal changes in incidence. While the pattern of population-based relative survival reported by registries (appendix D) is remarkably similar, these rates may be confounded due to selection, detection and classification bias, a consequence of differences in medical care, both in terms of access to care and diagnostic management. The following diagnostic biases are most important: lead time bias and length time bias, which are related to earlier diagnosis, and stage migration bias, which is related to more sensitive diagnostic procedures. Lead time bias can in part be dealt with by analysis according to stage, length time bias by refined histological information on features of growth and invasiveness; the latter can be determined for example by DNA flow cytometry, which provides valuable information on disease severity for a number of cancers, such as of the breast, (non-small cell) lung, colon, kidney, bladder, prostate, ovaries and corpus uteri as well as melanoma stage I.[34] A consequence from the application of increasingly sensitive diagnostic methods, e.g. CT-scanning or more extensive lymph node

sampling by surgeons and pathologists is that the stage distribution of the patients becomes more unfavourable; this is called downstaging or stage-migration; survival of all the stages increases, but for the total group there is no improvement, unless the therapy had become more effective.[35] Based on experience with lung cancer, Feinstein proposed to circumvent this bias by applying a clinical taxonomy based on (duration and severity of) symptoms and co-morbidity supplementary to staging according to TNM.[36] Hakulinen drew attention to bias caused by different distributions of traditional prognostic factors such as age, histology and stage.[37] Furthermore, registration procedures may play a role: decentralized registries can obtain better data from clinical records and trace more patients with a clinical diagnosis or with a second cancer than centralized registries. As already discussed in chapter 4.2, appraisal of time trends as well as mutual comparisons of survival between registries (appendix D) must thus be conducted carefully. If the above-mentioned diagnostic biases cannot be dealt with, these comparisons must be supported by mortality figures. Cancer of the bladder, prostate, corpus uteri and breast showed artificial increases of survival but mortality didn't change very much. Of course, results from clinical studies and registry-based surveys of specific treatment patterns should support interpretation of changes in survival rates.

For example the increase in 5-year survival rates observed in chapters 4 and 5 among patients with Hodgkin's disease (only elderly) (5.1.1) childhood and testicular (4.2), ovarian (mostly in women younger than 60) (5.2.1) and small cell lung cancer (only in the first year of follow-up) (5.3) may be real. On the basis of clinical studies these improvements can probably be attributed to therapeutic effects, since simultaneous decreases were seen in mortality that cannot be attributed to similar changes in incidence. Although survival rates were not computed, a real improvement would be very likely for childhood leukaemia and non-Hodgkin's lymphoma (5.1.3). When comparing mortality with incidence of diseases with a good survival, 'carry-over' effects to an older age group may occur; quite a few children with cancer die as young adults.

### *2.2 Population-based evaluation of clinical interventions*

Population-based evaluation of new therapies, that may have proved efficacious in selected groups of patients in clinical trials, also consists of monitoring diffusion. Dutch registries collect data on given treatments routinely in the first four months after diagnosis. The ovarian (5.2.1) and lung cancer (5.3) survival studies indicate that indeed chemotherapy was given to a larger proportion, especially to younger patients. For ovarian cancer a recent report from West Scotland confirms our findings.[38] It would be difficult to explain the improved survival otherwise than by medical intervention. Such effects may now be studied using registry data - additional data are to be collected - prospectively for patients with Dukes B and C colon cancer receiving adjuvant chemotherapy. Questions may be answered on the diffusion of this treatment and possible changes in the stage distribution of colo-rectal cancer as a result of better

staging. The comparison of survival rates for multiple myeloma carried out in Finland between groups of patients undergoing protocollized and non-protocollized treatment is another example.[39] The marked changes, both positive and negative, in survival of male patients with melanoma, bladder and colon cancer and of patients with adenocarcinoma of the lung, chronic lymphocytic leukaemia and non-Hodgkin's lymphoma were only tentatively explained, and should lead to further study. Although the multivariate analysis of survival of ovarian cancer identified relevant prognostic factors, an altered biology of the disease cannot be excluded. Application of a clinical taxonomy of (duration and severity of) symptoms and/or review of the histological diagnosis by means of DNA flow cytometry may provide answers retrospectively.

One could argue that the more a group of patients in population-based studies of survival is restricted in the analysis, e.g. by exclusion of untreated and elderly patients, the smaller differences with clinical studies will become, enabling an impression of therapeutical effectiveness. This will be increasingly true when the effects of therapy are more pronounced and in particular when a certain protocol is followed by a tumour study group.

Thus, all-or-nothing situations can be avoided with regard to the best approach of clinical research. Currently, participation in clinical studies, either randomized trials or follow-up studies of prognostic factors, may be more than 80% for childhood leukaemia (one of the major 'raisons d'être' for the DCLSG) versus only a few percent of the patients in the ECR area. This represents a tremendous loss of clinical experience for research. In addition to its specific value registry-based studies certainly increase curiosity or doubts on the value of treatment strategies and thus also enlarge the number of patients enrolled in trials.*

Clinical studies of the prognostic value of a variety of diagnostic features may be conducted among unselected patients, whereby registries could be responsible for data management - in particular the follow-up. Moreover, the distribution of such features can be determined in the population as well as changes over time, which may be relevant for the interpretation of changes in either survival or incidence or both. A good example is the nationwide multi-pathology laboratory study of the value of morphometry in breast cancer, as a following step of a hospital-based study.[40] This would also apply for DNA flow cytometry when it is carried out more regularly. Notably the largest pathological laboratory in the ECR-area that covers about 60% of the population has paraffin-blocks of all histological specimens since 1972.

Another specific feature is that the patients, registered with the ECR, especially those with common cancers, have almost all been treated in community hospitals. Real improvements in survival among these patients may be more

* the strategy of collecting vast amounts of information per patient may prohibit good participation in trials even with good data management facilities.

illustrative for 'progress' in cancer treatment than the results of clinical studies carried out among selected (especially by age) groups of patients. This is an essential function of registries provided they interpret their own survival data properly, i.e. that have invested in staff and involvement of tumour study groups. Currently, a study on breast cancer in the elderly is carried out together with the Netherlands Cancer Institute. Another approach is shown in Italy, where the Interdisciplinary Group of Cancer Care Evaluation (GIVIO) has recently demonstrated interesting discrepancies between ideal care and real care in a variety of studies of the care and survival of patients managed in a nationwide group of community hospitals, assembled for this purpose.[41 42 43]

### *2.3 evaluation of the effect of earlier diagnosis*

Earlier diagnosis of cancer is increasing as well as screening for all kinds of risk groups. There is a growing need for research on the best diagnostic strategies for 'ordinary' clinical practice. The primary role of the registry is to describe changes in stage distribution and changes in survival and incidence. Mortality can always be considered. Data on early diagnostic strategy are generally not included in the clinical record. Randomized trials to evaluate screening are considered essential but do not help much, not only because these results come too late, and they are hard to translate to the 'ordinary' clinical practice, which is continuously changing. Therefore, there is a need to study the value of new diagnostic technologies in 'ordinary' clinical practice while taking into account learning effects. Can the diagnostic value of various methods not be assessed in defined groups of patients in cohort studies in clinical practice? It will be difficult to conduct randomized trials to assess situations with common diagnostic decisions whenever there is a trend toward examination of asymptomatic patients, also patients in follow-up after treatment of a first tumour.

## 3 CONCLUSION

Apart from the clinical and epidemiological value of the studies presented in this thesis, the proposed analyses of survival, prognostic factors and patterns of care have stimulated evaluation of medical practice. In this respect the value of the ECR is rather that it reflects changes in established medical practice, while the DCLSG also focusses on evaluation of new methods. Both are desirable in times of change brought about by the application of 'half-way technology', medicine that does not cure or cures with many side-effects. Moreover, when such studies are conducted they will generate more interest in aetiological studies, that are registry-based. In his last address to the annual (1990) meeting of the International Association of Cancer Registries in Hamburg the departing secretary, the famous Dr. C.S. Muir, made the following remarks in a lecture on "The future of cancer registration and epidemiological research":

> A cancer registry can be defined as an organization for the collection, storage, analysis and interpretation of data on persons with cancer. As such, it constitutes a major component in the rational programme of cancer control. Rarely in the forefront, the tasks are rather in the nature of intelligence gathering about the current cancer burden in a community, providing the data needed to uncover the causes of cancer and the evaluation of the effects of steps to control the disease. Cancer registries ultimately depend on the willingness of the medical profession to report directly or indirectly newly diagnosed cases. Collaboration being a two-way process the registry must provide a service in return, the information most appreciated is that useful to the physician in his daily work of patient care. Without this recognition of the utility of the registry it is not likely to succeed.

### *3.1 Implications for cancer registration in the Netherlands*

From the foregoing, it is clear that evaluation of the process and outcome of oncological care is an essential condition for continuation of any registry that wants to 'produce' realistic information about prognosis and incidence, which would have added value with respect to the Cause of Death Register of the Central Bureau of Statistics. For this reason nationwide hospital morbidity statistics and register of pathological diagnoses have a limited value for research. Also, the importance of regular communication with the specialists is stressed, preferrably through tumour study groups, both to improve the quality of the data and to stimulate use of the registry as a sampling frame for aetiological research. This may become more important in the future because stricter privacy regulations, meant to protect the patient, may rather lead to the refusal of physicians to expose 'their' patients (read: practice) to research than to refusals of patients. It is also sad that a research policy has not yet been established for the optimal use of registries and their environments or 'roots' on behalf of cancer research in the Netherlands. The replacement of the National Cancer Research Council by the Coordinating Council of Comprehensive Cancer Centres has certainly not worked well for research policy. The latter organization attaches rather importance to financial, organizational and privacy matters, most of which appear to be computer-derived. Such policies do not lead to synergy but rather to more of the same in 8 comprehensive cancer centres.

One could envisage the following change for optimal cancer registration in the Netherlands. The national registry need not record more than a minimal data set, consisting of diagnosis (anatomical site, morphology), date of diagnosis, age, residence and ascertaining hospital, pathological laboratory or registry. It must serve as a sampling frame for aetiological studies or for record linkage and thus only some sort of unique identification number is needed; it must enable the computation of incidence rates. The 'real' work, with added clinical and epidemiological value, would be the responsibility of specialized national registries for rare tumours and a limited number of regional registries for the more common tumours. One criterion for such a specialized national registry,

to be governed by scientific medical societies, is the existence of diagnostic complexity, e.g. resulting from the involvement of rapidly developing diagnostic disciplines other than morphology (such as immunology and cytogenetics) or special techniques (such as electronmicroscopy), and thus the need for a review of diagnosis. Another criterion could be therapeutic intensity and complexity in conjunction with uncertainty about the prognostic value of methods of diagnosis and treatment. In addition to the DCLSG being a good example one could think of national registries for solid childhood cancers, bone tumours, soft tissue sarcomas, melanoma, testicular cancer, mesothelioma, cancer of the nervous system, the eye, the thyroid and other endocrinological organs and the various haematological malignancies. There is no sharp cut-off point between rare and common as for the latter tumours regional projects have also proved to be viable, such as the study of Hodgkin's disease in southeastern Netherlands[44] and of non-Hodgkin's lymphoma in western Netherlands.[45] Corresponding to current realities, regional registries should concentrate primarily on clinical and epidemiological studies of the more common tumours e.g. of the skin and the gastro-intestinal, respiratory, female genital and urogenital tracts, most of which develop to a large extent later in life; these patients represent the majority of patients treated in community hospitals. In conjunction with national registries substudies are worthwhile of the rare tumours that frequently occur in the elderly. Special attention should be given to aspects of both diagnostic and prognostic co-morbidity, early diagnosis and the occurrence of multiple primary cancer, problems of increasing importance. The main criterion would be the existence of regional tumour study groups to generate ideas, that are properly supported by the registry for data collection and evaluation. The cancer registry should remain close to its roots. In view of current experience only a limited number of these regional registries appear to be viable and one can also think of certain areas within comprehensive cancer centres.

Increasing cooperation is developing at a European level, as indicated by recent initiatives of collaborative EC-supported projects of cancer registries. Collaboration with the European Organization for Research on Treatment of Cancer seems necessary, because the activities are not only complementary, they may give each other added value.

*Scientific coordination of the clinical research activities of these specialized and regional registries is needed.* For adequate staffing cancer registries (to be considered as research enterprise) need university departments of epidemiology, which in turn need registries for research purposes and access to representative information on an important group of diseases. It is evident that funding of the staff for quality-of-care and research oriented registries is the combined responsibility for health insurance societies and the Netherlands Cancer Society.

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CHAPTER 7

# SAMENVATTING

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Dit proefschrift illustreert de mogelijkheden om met behulp van een tweetal morbiditeitsregistraties de kennis van het risico op en de prognose van kanker in Nederland te vergroten tegen de achtergrond van het beloop van de kankersterfte; deze is afkomstig uit de registratie van doodsoorzaken van het Centraal Bureau voor de Statistiek (CBS). Het betreft de in 1955 gestarte regionale registratie van alle vormen van kanker in zuidoost Noord-Brabant en Noord-Limburg (tot eind 70er jaren ook Midden-Limburg) en een landelijke registratie van leukemie bij kinderen, die beiden in de 70er jaren tot bloei kwamen, terwijl kankerregistraties elders in Nederland teloor gingen. Overigens vond de eerste beschrijvende epidemiologische activiteit van kanker in Nederland, een punt-prevalentiemeting, reeds in het jaar 1900 plaats als 'concerted action' met Duitsland.

In dit proefschrift worden niet alleen getalsmatige uitkomsten van deze registraties, voorzien van interpretatie, gepresenteerd, maar ook komen de wijze van functioneren en de ingrediënten van 'succes' van kankerregistraties aan de orde: hoe blijft een kankerregistratie, als boom op te vatten, vruchten dragen en voedzame wortels behouden?

Als leidraad bij de studies in dit proefschrift golden vooral de diverse toekomstverkenningen in de vorm van scenario's, welke in hoge mate zijn ontwikkeld met gegevens van deze registraties, zowel ten behoeve van het landelijk plan voor Intensieve zorg voor patiënten met bloed- of lymfeklierkanker, als van de toekomstverkenningen voor de kankerbestrijding in verband van de Stuurgroep Toekomstscenario's Gezondheidszorg.

Behalve overzichtsstudies van de incidentie en prognose van kanker bij ouderen wordt een zestal diepergaande analyses gepresenteerd van 10 tumoren die ongeveer 45% van alle kanker betreffen, voorts een analyse van het weinig kwaadaardige kanker van de opperhuid, dat doorgaans apart wordt beschouwd.

Als hoopvolle ontwikkeling wordt aangegeven, dat het medisch-wetenschappelijk en beleidsmatig gebruik van kankerregistraties, mede dankzij automatisering, in de afgelopen jaren sterk is toegenomen, hetgeen op zich het bestaan van registraties lijkt te rechtvaardigen.

In **hoofdstuk 2** wordt **het fenomeen kankerregistratie** besproken als onderdeel van de medische praktijk en het medisch wetenschappelijk onderzoek en

in de historische context van de kankerbestrijding. Kankerregistraties voorzien in een tijdgebonden behoefte aan kennis over kanker. Niet helemaal duidelijk is waarom die behoefte soms groter is. Zeker is dat in de huidige tijd automatisering behalve vergemakkelijkend ook initiërend werkt en dat het alleszins de vraag is of dit een goede ontwikkeling is. In de oudere registraties bleek na een pioniersfase van professionele nieuwsgierigheid en veelal gedreven enthousiasme altijd een kwetsbare fase op te treden, waarin vragen worden gesteld als voor wie, door wie, van wie en wie betaalt. Hierin raakt altijd de Overheid betrokken; duidelijk is dat succesvolle registraties in het buitenland qua financiering op 2 benen lopen: een patiëntenzorg en een onderzoekspoot. Het ongrijpbare van een registratie is dat het doel of het bestaansrecht mee verandert met de gedaante van de ziekte, de stand van de geneeskunde en de hieruit voortvloeiende behoefte om het 'management' van de ziekte en de zieken te verbeteren of beter aan te passen aan de toegenomen mogelijkheden voor onderzoek en behandeling. Bij de vormgeving van registraties is in het buitenland reeds veel ervaring opgedaan, met name in de Angelsaksische en Scandinavische landen. Indirect heeft sturing plaats van de activiteiten via de communicatiestructuur van de International Association of Cancer Registries, welke in de jaren 60 ontstond en de Unit for Descriptive Epidemiology van de International Agency for Research on Cancer.

De beide in dit proefschrift nader bewerkte registraties hebben gemeen dat zij wortelen in en meegroeien met de medische praktijk; ze zijn dus als 'bottom-up' initiatieven te kenschetsen. De in 1984 nieuw opgerichte, tussen 1966 en 1974 ter ziele gegane, landelijke kankerregistratie heeft daarentegen meer een 'top-down' (overheids) karakter; dit betekent dat het middel registratie (codering, financiering, regulering, automatisering en privacy) veel aandacht krijgt, uitgaande van een vaststaand doel. De vervanging van de Nationale Commissie Kankeronderzoek door het Landelijk Overleg Integrale Kankercentra heeft niet geleid tot inhoudelijke sturing van een onderzoeksinspanning als een kankerregistratie.

In **hoofdstuk 3.1.** worden **de geschiedenis en de werkwijze van de regionale IKZ/SOOZ kankerregistratie** in Eindhoven beschreven als onderdeel van de specialistische zorg in zuidoost Noord-Brabant en Noord- en Midden Limburg. In deze regio is geen gespecialiseerd oncologisch centrum, maar heeft de radiotherapie een bindende en vooral dienende rol vervuld voor de regionale samenwerking. Ook de patholoog-anatomen werkten van meet af aan actief mee bij de signalering van patiënten en de gegevensverzameling. De verwevenheid van de registratie met de specialistische zorg heeft, tezamen met enige volharding van de - sinds kort met pensioen gegane en bijna 24 jaar werkzame - registratie-arts, de bestuurders weten te weerhouden de boom te kappen of te laten dood gaan. De gegevensverzameling in de ziekenhuizen, vaak met raadpleging van de status op de klinische afdelingen, direct uit de status zorgde voor vertrouwen en getrouwheid ten opzichte van het vigerende medisch handelen. Als zodanig is deze registratie als een verlengstuk op te vatten van het archief

van medische specialisten, die gezamenlijk de patiëntengegevens bijeen lieten brengen om behalve de kanker ook hun relatieve onwetendheid te bestrijden.

Voor de interpretatie van belang is voorts dat er behalve van een sterk gestegen welvaart in toenemende mate sprake is van bodemverontreiniging en grensoverschrijdende luchtverontreiniging. De traditioneel katholieke bevolking maakte een secularisatieproces door, waarin met name de positie van de vrouw sterk veranderd is: minder kinderen, meer buitenshuis werken en een toename van het gebruik van tabak en alcohol, overigens vanaf een laag uitgangsniveau. Bij de man vigeert een ongunstig patroon van de sterfte aan belangrijke doodsoorzaken als hart- en vaatziekten en longkanker. E.e.a. komt duidelijk naar voren in het patroon van en de veranderingen in de kankerincidentie in hoofdstuk 4.1. Via opname van de gegevens in Cancer Incidence in Five Continents ontstaat steeds meer internationale, met name Europese samenwerking.

Het gebied is gelegen tussen België en Duitsland, landen met een geringe staat qua kankerregistratie, hetgeen de gebruikswaarde een ruimer perspectief biedt.

De **registratie van kinderen met leukemie** door de Stichting Nederlandse Werkgroep Leukemie bij Kinderen (SNWLK) wordt besproken in **hoofdstuk 3.2.** De SNWLK was destijds een initiatief van een werkgroep binnen de Nederlandse Vereniging voor Kindergeneeskunde. De registratie is op te vatten als een bijprodukt van de organisatie van de vernieuwde medische diagnostiek en behandeling van deze patiënten in het begin van de jaren 70, waarbij de noodzaak van verfijnde en uniforme diagnostiek en evaluatie van steeds meer geprotocolleerde, intensieve, behandeling op korte en lange termijn centraal stond. Standaardisering van de diagnostiek is hierbij gerealiseerd in een centraal laboratorium. Met het Instituut Epidemiologie van de Erasmus universiteit werd sinds 1980 samengewerkt in verband van epidemiologisch onderzoek, dat zich dankzij het netwerk van kinderartsen en de aanwezige gegevens vlot kon ontwikkelen. In een korte tijd werden beschrijvende studies en een uitgebreid patiënt-controle onderzoek uitgevoerd, waarin de belangrijkste risicofactoren voor kinderleukemie bevestigd werden. Thans blijkt hiervan de waarde bij het kunnen onderbouwen van geruststellende adviezen bij de vele clusters die steeds meer 'ontdekt' worden. In internationaal verband heeft dit bestand een referentiefunktie gekregen.

In **hoofdstuk 4** staat een overzicht van de **belangrijkste ontwikkelingen in het risico en de prognose van kanker** op basis van de regionale IKZ/SOOZ-kankerregistratie in Eindhoven. De beoordeling van veranderingen in de incidentie en in de overleving wordt aangevuld met regionale kankersterftecijfers, afkomstig van het Centraal Bureau voor de Statistiek: aldus worden eventuele kunstmatige veranderingen (meestal verhogingen) als gevolg van verschuivingen (naar minder kwaadaardige vormen) in de veelal meer verfijnde diagnostiek en classificatie getoetst.

In **hoofdstuk 4.1** zijn trends in de incidentie bestudeerd in de periode 1975-86. Bij vrouwen is een toename te zien van borstkanker (zie verder 5.2.2), van melanoom en van de aanvankelijk zeer zeldzame tumoren in het hoofd-halsgebied, luchtwegen en blaas, terwijl de incidentie van maag- en galblaaskanker afnam. Bij mannen nam de incidentie van maag- en galblaaskanker ook af en er bleek bij hen een piek op te treden van de incidentie van kanker in het hoofd-halsgebied, de lagere luchtwegen, prostaat, nier, pancreas en hersenen tussen 1978 en 1983, terwijl de incidentie van dikke darmkanker permanent toenam. De in internationaal opzicht uitzonderlijk hoge man/vrouw verhouding van de incidentie van aan tabaksgebruik en beroep gerelateerde tumoren werd beduidend kleiner in deze periode, bijvoorbeeld van 20 naar 12 bij longkanker. De veranderingen in de kankerincidentie strookten in het algemeen met die in de regionale sterfte, met uitzondering van de situatie in de jongere leeftijdsgroepen en bij tumoren waar een daling in de sterftekansen door verbeterde behandeling aannemelijk was, zoals kanker van de zaadbal en eierstok.

In **hoofdstuk 4.2** wordt een overzicht gegeven van de **relatieve overleving van kanker**, dat is de kans om niet aan de bewuste kanker te overlijden. De 5- en 10-jaars relatieve overleving blijken 33% en 27% te zijn voor mannen en 51% en 44% voor vrouwen. De gegevens voor afzonderlijke tumoren weken niet erg af van gelijksoortige bevindingen in Finland, de Verenigde Staten en het kanton Vaud in Zwitserland (zie ook appendix D). In de periode 1975-85 verbeterde de 5-jaars relatieve overleving vooral bij patiënten onder de 45 jaar en bij vrouwen. Meer specifiek waren de verbeteringen bij vrouwen met kanker van de eierstok en borst en bij mannen met kanker van de zaadbal, alsook de blaas. Voor een nauwkeurig beeld van veranderingen, met name vooruitgang in de kankerbehandeling, dienen echter meer prognostische factoren te worden vastgelegd dan de morfologie en het stadium volgens TNM (classificatie van tumorgrootte, lymfeklierstatus en metastasering); duur en ernst van symptomen en de aanwezigheid van andere ziekten (co-morbiditeit), maar ook aan een verfijnde typering van de maligniteitsgraad zijn het meest voor de hand liggend. Daarnaast bleek ook in deze analyse het belang van kankersterftecijfers als ultieme maat voor ernst van de ziekte; zij daalden eveneens onder het 45ste jaar en bij vrouwen, alsmede bij kanker van de zaadbal en eierstok, doch niet bij kanker van borst en blaas. Dit laatste betekent dat er mogelijk sprake is van vroegere diagnostiek.

In **hoofdstuk 4.3** wordt een overzicht gegeven van **kanker bij ouderen**, waarbij onder andere de vraag wordt besproken of kanker een verouderingsziekte is. Bij epitheliale tumoren met een hoge incidentie bij mannen lijkt vooral sprake van de inwerking van schadelijke exogene factoren gedurende het leven. Op het ontstaan of de uitgroei van geslachtsgebonden tumoren zijn hormonale veranderingen en invloeden in verschillende fasen van het leven belangrijker. Voor de hoogte van de incidentie op oudere leeftijd wordt de dalende sterfte

aan hart- en vaatziekten steeds belangrijker, deels omdat dezelfde risicofactoren in het geding zijn, deels omdat - ondanks de sterk met de leeftijd stijgende kankerincidentie en -sterfte - het percentage van de totale aan kanker toe te schrijven sterfte, sterk afneemt met de leeftijd na het 65ste jaar. Bij ouderen met een stijgende levensverwachting wordt kanker in de toekomst verhoudingsgewijze een steeds belangrijker doodsoorzaak. Een meer verfijnde prognostische index met name bij ouderen, waarin ook co-morbiditeit en duur van de klachten is opgenomen lijkt nodig om de vraag te kunnen beantwoorden of de afname van de relatieve overlevingskansen met het stijgen van de leeftijd vooral aan een ongunstiger stadiumverdeling is toe te schrijven en/of aan een ander gedrag van de tumor, dan wel aan een afnemend vermogen van de patiënt om ingrijpende behandelingen te verdragen. Uit de kankerregistratie blijkt een duidelijk met de leeftijd stijgend percentage van de patiënten niet voor de tumor te wordt behandeld. In dit ten behoeve van huisartsen geschreven hoofdstuk, wordt ook aangegeven dat de incidentie van kanker bij ouderen, in totaal ongeveer twee derde deel van het totaal aantal patiënten, per jaar met ruim twee procent zal toenemen en het aantal voor thuiszorg in aanmerking komende patiënten met 3 tot 5% per jaar.

In **hoofdstuk 5** staat een aantal diepergaande studies van tumoren, waarvoor speciale belangstelling bestond. Aanleiding was meestal dat er iets veranderde in de ziektefrequentie dan wel in de stand van de geneeskunde. De aanwezigheid van een tumorwerkgroep, die iets aan waardering van vernieuwing wil doen, zoals de SNWLK op landelijke schaal te beschouwen is, heeft hier vermoedelijk iets mee te maken.

**Hoofdstuk 5.1** gaat over **bloed- en lymfeklierkanker**: in **5.1.1** zijn de uitkomsten van de regionale registratie beschreven over de periode 1975-1987, voornamelijk volwassenen betreffende. De belangrijkste bevindingen zijn dat de incidentie van het non-Hodgkin's lymfoom (NHL) bij mannen en vrouwen duidelijk steeg, evenals de incidentie van leukemie bij mannen, vooral op oudere leeftijd en met acute non-lymfocytaire leukemie. Bij vrouwen nam de incidentie van leukemie in de tijd af, vooral van de chronisch lymfocytaire leukemie (CLL); dit laatste was ook bij mannen in lichte mate het geval. De afname van CLL lijkt grotendeels het gevolg van de benoeming tot immunocytoom, hetgeen tot het NHL wordt gerekend en sinds 1980 in toenemende mate geregistreerd, hetgeen dus een deel van de toename van het NHL verklaart. In vergelijking met de recente studie van het Leukaemia Reseach Fund in Engeland, blijken opvallende overeenkomsten in de incidentie zowel qua leeftijdsverdeling als per subtype. De 5-jaars relatieve overlevingskansen waren 43% voor patiënten met een NHL, 77% met de ziekte van Hodgkin, 26% met de ziekte van Kahler en 59% voor leukemie bij kinderen en 31% bij volwassenen. Ze kwamen in hoge mate overeen met die in Amerika en andere landen (appendix D) en lijken, behalve een lichte verbetering bij ouderen, weinig veranderd in de periode van 1975 tot 1985.

In **hoofdstuk 5.1.2** zijn veranderingen beschreven in de **incidentie van leukemie bij kinderen** en in **hoofdstuk 5.1.3** de **incidentie van maligne lymfomen**, het non-Hodgkin lymfoom (NHL) en de ziekte van Hodgkin, beide op landelijke schaal. De tweede studie werd uitgelokt door de eerste, waarin een opvallende toename van de incidentie van acute lymfocytaire leukemie (ALL) beschreven was in de periode 1979 tot en met 1984. De incidentie van leukemie bij kinderen was bijna 4 per 100.000 per jaar, van het NHL 0,7 en van de ziekte van Hodgkin 0,3 per 100.000 per jaar. Opvallend aan deze tumoren was hun nagenoeg gelijke incidentie in de meeste geïndustrialiseerde landen, een vrijwel identieke verdeling naar subtype en geringe veranderingen in de tijd. Overeenkomstig de verwachting bleek tussen ALL en NHL een zekere overlap in de diagnose te bestaan van ongeveer 5% van de kinderen met ALL en bijna 20% met NHL. Dit lijkt onvermijdelijk en pleit onder andere voor bestudering van het risico op en de prognose van deze beide tumoren gezamenlijk. Terwijl de incidentie van leukemie bij kinderen ongeveer gelijk bleef daalde de sterfte aanzienlijk, zodat een toename van de overlevingskansen voor de hand ligt. Hetzelfde gold voor kinderen met NHL, maar in mindere mate. Overeenkomstig de frequenties in de landen van herkomst komen NHL en de ziekte van Hodgkin in licht verhoogde mate voor bij kinderen van migranten uit zuidelijke streken en voorts bij kinderen met stoornissen van het afweerapparaat.

In **hoofdstuk 5.2** worden vrouwen met kanker van de eierstok en borst bestudeerd. Bij vrouwen met **kanker van de eierstok (hoofdstuk 5.2.1)** blijkt in de periode 1981-85 ten opzichte van de periode 1975-80 een aanzienlijke verbetering van de relatieve 5-jaars overleving te zijn opgetreden en wel van ongeveer 30% tot bijna 45%. Tegelijkertijd werd ook de intensieve behandeling (met cis-platina) en uitgebreide stagering steeds meer toegepast, zodat een verband hiermee niet onaannemelijk lijkt. In een multivariate analyse bleek de verbetering van de prognose bovendien vooral opgetreden bij vrouwen jonger dan 70 jaar, in wier leeftijdsgroep ook de sterfte daalde. Toch is niet uitgesloten dat een verbetering van het natuurlijk beloop heeft plaatsgevonden als gevolg van een onbekende factor. Dit kan nader worden uitgezocht door met terugwerkende kracht bijvoorbeeld DNA-flowcytometrisch onderzoek te verrichten met de vraag of de verdeling naar maligniteitsgraad veranderd is.

**Borstkanker** komt naar verhouding frequent voor in zuidoost Noord-Brabant en Noord Limburg (**hoofdstuk 5.2.2**). Bij vrouwen met borstkanker werd een lichte toename van de incidentie en een aanzienlijke vervroeging van de diagnose vastgesteld met name bij jongere vrouwen. Waren in 1975 ongeveer 25% van de tumoren kleiner dan 2 cm, in 1986 was dit bijna 50%. Ondanks het feit dat geen bevolkingsonderzoek plaatsvond is deze verandering niet zo verwonderlijk: er is verbeterde apparatuur (mammografie) op de markt gekomen en ook de cytologische punctie wordt steeds meer toegepast op geleide van echografie. Het gevolg is dat de zorg voor vrouwen met borstkanker en met name van vrouwen verdacht van borstkanker steeds ingewikkelder is geworden

voor huisarts, chirurg, radioloog en patholoog; bovendien is de toepassing van borstsparende behandeling sterk toegenomen. Deze stadiumverschuiving noopt ook tot bezinning op het voorgenomen bevolkingsonderzoek, waaraan overigens niet veel meer dan 25% van alle vrouwen met borstkanker zullen deelnemen. Een lager 'rendement' ligt in de verwachting en de vraag ligt voor de hand om prioriteit te geven aan de organisatie van de - zo ingewikkelde - vroege diagnostiek gericht op alle en met name jongere vrouwen.

In **hoofdstuk 5.3** wordt een epidemiologisch overzicht van **longkanker** gegeven, dat voor een consensusbijeenkomst van het CBO over diagnostiek van longkanker geschreven werd. Longkanker bij mannen kwam naar verhouding zeer veel voor in Nederland en het omgekeerde is het geval bij vrouwen; hierin kwam echter langzaam verandering, zodat mede gezien de toename van het aantal ouderen, het aantal patiënten vooralsnog niet veel zal veranderen. Rond 1980 kwam de epidemie van longkanker bij mannen in Zuidoost Nederland op zijn hoogtepunt: incidentie en sterfte namen sindsdien af op middelbare leeftijd en bij de '3de generatie', stegen daarentegen nog bij ouderen; op hen zal in de nabije toekomst een steeds groter deel van de zorg gericht zijn. Er voltrokken zich de volgende belangrijke veranderingen in de aanpak van diagnostiek en behandeling: de diagnose werd beduidend meer met behulp van cytologisch onderzoek gesteld; bij patiënten met het kleincellig carcinoom is een verbetering van de 1-jaars overleving opgetreden. Verder nam de incidentie van het adenocarcinoom sterk toe, zowel bij mannen als bij vrouwen en dit histologisch type lijkt een andere ziekte geworden: vroeger meer ontdekt als perifere afwijking, die goed operabel was, tegenwoordig vaker centraal gelegen en uitgezaaid bij diagnose met een duidelijk slechtere prognose dan voorheen. De waarde van de door Feinstein ontwikkelde klinische taxonomie van symptomen of klachten en co-morbiditeit werd benadrukt in alle fasen van het diagnostisch proces.

**Huidkanker** (alles behalve het maligne melanoom) is een der meest frequente tumoren, zeker wanneer alle afzonderlijke tumoren worden meegeteld. In **hoofdstuk 5.4** werd een analyse gerapporteerd van de incidentie van alleen de eerste tumor, in dat deel (ongeveer 80%) van het registratiegebied, waarin de rapportage van patholoog-anatomen traditioneel goed was. De incidentie van het primaire basaalcelcarcinoom nam geleidelijk toe bij mannen van ruim 40 per 100.000 per jaar eind van de jaren zeventig tot ongeveer 55 in de periode 1986-88 en bij vrouwen van ongeveer 25 tot 40 per 100.000 per jaar. De toename vond vooral plaats op de traditioneel regelmatig aan zonlicht blootgestelde lichaamsdelen als de nek en het aangezicht, de armen (bij mannen), maar ook op de romp bij vrouwen. De incidentie van het plaveiselcarcinoom leek tot 1982 eerder te dalen dan te stijgen met name op de lip (bij mannen), hetgeen ook een gevolg kan zijn van minder pijprokers. Verder kan de afname van de incidentie van het plaveiselcarcinoom veroorzaakt zijn door verbeterde diagnostiek, waarbij vaker de diagnose keratoacanthoom wordt gesteld. Tot slot werd benadrukt dat kankerregistraties deze relatief moeilijke (door weinig

registraties goed uitgevoerde) registratieactiviteit kunnen volvoeren, mits ze over nauwe contacten met behandelende specialisten en pathologische laboratoria beschikken. Voor het bepalen van de frequentie van meervoudige tumoren zijn speciale cohort studies noodzakelijk.

In de bij dit proefschrift behorende bijlagen staan de volgende gegevens:

A: **de incidentie van kanker in zuidoost Noord-Brabant en Noord-Limburg** voor de periode 1983-87 en voor kinderen voor de periode 1973-1987 (deze laatste hoeveelheid komt bijna overeen met één jaar incidentie in geheel Nederland anno 1990)

B: **de sterfte aan de verschillende vormen van kanker in zuidoost Noord-Brabant en Noord-Limburg vergeleken met die in geheel Nederland** in de periode 1983-87. Hieruit blijkt de kankersterfte in dit gebied bij mannen ruim 5% hoger te zijn en bij vrouwen gelijk aan het landelijk gemiddelde. Dit betekent dat extrapolaties mogelijk zijn, waarbij een landelijk gemiddelde van de kankersterfte en dus ook van de incidentie meer als een gemiddelde dan een reëel cijfer moet worden opgevat.

C: **de veranderingen in de sterfte aan belangrijke doodsoorzaken in zuidoost Noord-Brabant en Noord-Limburg** in de periode 1985-86 ten opzichte van 1970-72. In deze periode blijkt de sterfte aan nagenoeg alle doodsoorzaken en de totale sterfte aanzienlijk te zijn gedaald, vooral bij vrouwen. De kankersterfte, die ongeveer gelijk bleef, steeg proportioneel van ruim 25% naar bijna 30% bij mannen en van 22% naar 28% bij vrouwen. Niet uitgesloten is dat er verschuivingen optraden in de zogenaamde concurrerende sterfte, dat wil zeggen dat mensen meer aan kanker overlijden dankzij uitstel of misschien zelfs afstel van sterfte aan andere ziekten.

D: **een vergelijking van 5-jaars relatieve overlevingskansen uit kankerregistraties** laat geringe verschillen zien voor de afzonderlijke vormen van kanker. Deze overeenkomsten wijzen op een gelijk natuurlijk beloop en/of gelijke doeltreffendheid van behandeling, die in min of meer gelijke mate wordt toegepast. Toch zijn er verschillen in de diagnostiek, behandeling en registratieprocedures en uiteraard ook in de aard van de ziekte. Dergelijke vergelijkingen hebben dus steeds een globale betekenis.

E: een **overzicht van publikaties** uit de beide registraties van de afgelopen 10 jaar; dit laat niet alleen een toename zien in het aantal publikaties per jaar, ook blijkt - met name in de IKZ/SOOZ-registratie - een grote verscheidenheid aan onderwerpen in de oncologie aan de orde te komen.

In de **algemene discussie (hoofdstuk 6)** wordt nader ingegaan op de mogelijkheden van kankerregistraties voor het leveren van adequate informatie over kanker, maar bovenal voor het mogelijk maken en aanleiding geven tot onderzoek, dit laatste kan bijvoorbeeld gebeuren door te rapporteren over opvallende frequentie veranderingen, bijvoorbeeld van nieuwe tumoren. Aangegeven wordt dat registraties niet zaligmakend zijn; oplettende dokters blijven

altijd noodzakelijk. Bij het rapporteren over trends is van belang dat behalve de ziekte (lees: de verschillende vormen van kanker), ook het immer onvolmaakte medisch handelen kan veranderen, bijvoorbeeld door verfijning en vervroeging van diagnostiek. Dit speelde onder andere bij kanker van de blaas, eierstok, borst en chronisch lymfatische leukemie. Hierdoor kan gemakkelijk een vertekend beeld, meestal in de vorm van pseudo-stijgingen, ontstaan bij analyse van trends in de incidentie en schijnbare verbeteringen van prognose. Als onderzoek van trends in de incidentie en evaluatie van medische zorg het eigenlijke doel van de registratie - op te vatten als boom - is en e.e.a. vooral waardevol wordt na langere tijd, dienen hiertoe voorwaarden geschapen te worden: deze strekken verder dan het strikt verzamelen van gegevens. Een absolute voorwaarde is te zorgen voor betrokkenheid van berichtgevende artsen (de wortels); aldus komen ze ook in een waarderende rol veelal via tumorwerkgroepen. Ter ondersteuning hiervan dient onderzoekscapaciteit beschikbaar te zijn voor gezamenlijke evaluatieprojecten. Voor een optimale aanpak hiervan komt men voor studies van meer frequente tumoren op regionale schaal uit en van meer zeldzame tumoren, als leukemie bij kinderen op landelijke schaal. Een landelijke aanpak is verder aangewezen voor tumoren waarbij vanwege de complexiteit van de diagnostiek review-procedures noodzakelijk zijn, als bij diverse soorten kanker bij kinderen, bloed- en lymfeklierkanker, endocrinologische tumoren, mesothelioom, bottumoren en weke delen sarcoom: ook lijkt dit aangewezen voor tumoren waarvan de behandeling complex en ingrijpend is, hetgeen voor een groot deel van de bovengenoemde het geval is. Gepleit wordt dus voor aanpassing van de huidige werkwijze in Nederland: een summiere landelijke registratie van alle tumoren, gespecialiseerde registraties van zeldzame tumoren en enkele regionale registraties van frequente tumoren, waarin het onderzoek van trends in de incidentie, overleving en 'patterns of care' plaats moet vinden. Landelijk blijft voorts de behoefte bestaan aan een 'sampling frame', een 'minimal data set', teneinde 'record linkage' op eenvoudige wijze mogelijk te maken. Betrokkenheid van behandelende artsen bij de evaluatie en dus bij de registratie vergroot niet alleen hun eigen relativerend vermogen, ook komt dit de mogelijkheden voor het doen van onderzoek door andere onderzoekers ten goede. Dit is met name belangrijk in een tijd met zoveel aandacht voor de privacy, die een prachtig alibi vormt voor artsen die niet 'onderzoek-minded' zijn om zich hieraan te onttrekken.

Gepleit wordt tot slot voor onderzoekbeleid waarbij de kankerregistraties optimaal worden benut voor het kankeronderzoek en het onderzoek van de oncologische zorg.

# APPENDICES

# Appendix A

# INCIDENCE OF CANCER IN SOUTHEASTERN NETHERLANDS

1. All patients during the period 1983-87

2. Children during the period 1973-87

**legends:**
ASR: average standardized rate per 100,000 person-years
(world: adjusted for world standard population)
(eur: adjusted for european standard population)
crude: unadjusted per 100,000 person-years
CR: cumulative risk at age 75 in %

**Average incidence per 100,000 person-years by age-group (yrs) in the period 1983-87**

## MALE

| ICD Site | All ages | 0- | 5- | 10- | 15- | 20- | 25- | 30- | 35- | 40- | 45- | 50- | 55- | 60- | 65- | 70- | 75- | 80- | 85+ | Crude Rate | CR 74 | ASR EUR | ASR World |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 140 Lip | 37 | - | - | - | - | - | - | - | - | 1.3 | 1.5 | 2.5 | 1.9 | 9.1 | 8.0 | 14.9 | 19.4 | 6.0 | 11.6 | 1.7 | 0.2 | 2.3 | 1.6 |
| 141 Tongue | 31 | - | - | - | - | - | - | 1.1 | - | 2.0 | 0.8 | - | - | 4.6 | 11.2 | 12.8 | 9.7 | 17.9 | 23.2 | 1.4 | 0.2 | 1.9 | 1.3 |
| 142 Salivary gland | 13 | - | - | - | - | - | - | - | - | 2.7 | - | 0.8 | - | 4.6 | 4.8 | 2.1 | - | - | - | 0.6 | 0.1 | 0.7 | 0.6 |
| 143-145 Mouth | 34 | - | - | - | - | - | 0.5 | - | 1.7 | 0.7 | 0.8 | 3.3 | 5.8 | 5.7 | 4.8 | 14.9 | 3.2 | 6.0 | 11.6 | 1.6 | 0.2 | 2.0 | 1.4 |
| 146-149 Pharynx | 54 | - | - | - | - | - | - | - | 1.1 | 0.7 | 2.3 | 1.6 | 8.7 | 10.3 | 11.2 | 17.0 | 29.1 | 17.9 | 11.6 | 2.5 | 0.3 | 3.3 | 2.2 |
| 150 Oesophagus | 76 | - | - | - | - | - | - | - | - | 2.0 | 3.0 | 4.9 | 11.7 | 12.5 | 17.7 | 36.2 | 25.9 | 11.9 | 23.2 | 3.6 | 0.4 | 4.7 | 3.2 |
| 151 Stomach | 477 | - | - | - | - | 0.5 | 0.5 | 1.1 | 3.4 | 10.0 | 15.1 | 29.5 | 42.7 | 79.9 | 127 | 166 | 210 | 238 | 232 | 22.3 | 2.4 | 29.7 | 19.8 |
| 152 Small intestine | 18 | - | - | - | - | - | - | - | - | - | 0.8 | - | 2.9 | 5.7 | 4.8 | 2.1 | 9.7 | - | 23.2 | 0.8 | 0.1 | 1.2 | 0.8 |
| 153 Colon | 586 | - | - | 0.6 | 0.5 | 1.0 | 2.6 | 4.5 | 6.8 | 11.3 | 9.1 | 35.2 | 44.7 | 97.0 | 161 | 174 | 301 | 286 | 360 | 27.4 | 2.7 | 36.7 | 24.3 |
| 154 Rectum | 389 | - | - | - | - | - | 0.5 | 3.9 | 5.6 | 8.6 | 8.3 | 20.5 | 35.0 | 73.0 | 94.7 | 140 | 162 | 208 | 139 | 18.2 | 2.0 | 23.8 | 16.0 |
| 155 Liver | 33 | 0.8 | - | - | - | - | - | - | 0.6 | 1.3 | - | 2.5 | 3.9 | 5.7 | 11.2 | 8.5 | 12.9 | 11.9 | - | 1.5 | 0.2 | 2.0 | 1.4 |
| 156.0 Gallbladder | 24 | - | - | - | - | - | - | - | - | - | - | 0.8 | 3.9 | 2.3 | 9.6 | 10.6 | 9.7 | - | 34.9 | 1.1 | 0.1 | 1.7 | 1.1 |
| 156.1-9 Gallducts etc. | 52 | - | - | - | - | - | - | - | 1.1 | 1.3 | - | 2.5 | 7.8 | 10.3 | 6.4 | 14.9 | 25.9 | 35.7 | 34.9 | 2.4 | 0.2 | 3.3 | 2.1 |
| 157 Pancreas | 152 | - | - | - | - | - | - | - | 1.7 | 1.3 | 5.3 | 8.2 | 17.5 | 28.5 | 46.5 | 65.9 | 55.0 | 35.7 | 46.5 | 7.1 | 0.9 | 9.4 | 6.4 |
| 158 Peritoneum | 8 | - | - | - | - | - | - | - | - | 0.7 | - | 2.5 | 1.9 | 2.3 | - | - | - | - | - | 0.4 | 0.0 | 0.4 | 0.3 |
| 160 Nose, sinuses etc. | 10 | - | - | - | - | - | - | - | - | - | - | - | 1.9 | 1.1 | 3.2 | 6.4 | 6.5 | - | - | 0.5 | 0.1 | 0.6 | 0.4 |
| 161 Larynx | 131 | - | - | - | - | - | - | - | 0.6 | 0.7 | 3.0 | 13.9 | 17.5 | 29.7 | 36.9 | 36.2 | 38.8 | 35.7 | 69.7 | 6.1 | 0.7 | 8.2 | 5.6 |
| 162 Lung | 2,092 | - | - | - | - | - | 1.1 | 1.1 | 4.5 | 18.0 | 36.3 | 129 | 222 | 395 | 634 | 891 | 965 | 720 | 465 | 97.7 | 11.7 | 129.6 | 87.2 |
| 163 Pleura | 14 | - | - | - | - | - | - | - | 0.6 | 0.7 | 1.5 | 2.5 | 1.0 | 3.4 | 1.6 | 4.3 | - | - | - | 0.7 | 0.1 | 0.8 | 0.6 |
| 164 Mediastinum | 10 | - | - | - | - | 0.5 | - | - | - | - | 0.8 | 1.6 | 1.0 | - | 1.6 | 4.3 | 3.2 | 6.0 | - | 0.5 | 0.0 | 0.6 | 0.4 |
| 170 Bone | 24 | - | 0.7 | 4.2 | 1.5 | 0.5 | 0.5 | 0.6 | 0.6 | 1.3 | 1.5 | 1.6 | - | 2.3 | - | - | - | - | 11.6 | 1.1 | 0.1 | 1.1 | 1.1 |
| 171 Connective tissue | 56 | - | - | 0.6 | - | 2.0 | 0.5 | 1.1 | 1.7 | 4.0 | 5.3 | 4.9 | 5.8 | 8.0 | 8.0 | 6.4 | 3.2 | 11.9 | 23.2 | 2.6 | 0.2 | 3.1 | 2.4 |
| 172 Melanoma of skin | 104 | - | - | 0.6 | - | - | 2.1 | 2.8 | 9.0 | 6.0 | 7.6 | 9.0 | 11.7 | 12.5 | 14.4 | 2.1 | 16.2 | 23.8 | 69.7 | 4.9 | 0.4 | 5.8 | 4.3 |
| 175 Breast | 9 | - | - | - | - | - | - | - | - | - | - | 0.8 | - | 4.6 | 3.2 | 2.1 | - | - | 11.6 | 0.4 | 0.1 | 0.6 | 0.4 |

| ICD Site | All ages | 0- | 5- | 10- | 15- | 20- | 25- | 30- | 35- | 40- | 45- | 50- | 55- | 60- | 65- | 70- | 75- | 80- | 85+ | Crude Rate | CR 74 | ASR EUR | ASR World |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 185 Prostate | 706 | - | - | - | - | - | - | - | 0.6 | 0.7 | - | 12.3 | 30.1 | 75.3 | 188 | 342 | 479 | 619 | 721 | 33.0 | 3.2 | 47.3 | 28.9 |
| 186 Testis | 77 | - | - | - | 1.5 | 8.9 | 5.3 | 7.9 | 5.1 | 2.0 | 4.5 | 2.5 | 5.8 | 2.3 | 1.6 | - | 6.5 | - | - | 3.6 | 0.2 | 3.3 | 3.0 |
| 187.1-4 Penis | 16 | - | - | - | - | - | - | 0.6 | - | - | 0.8 | 0.8 | 1.0 | - | - | 10.6 | 16.2 | - | 23.2 | 0.7 | 0.1 | 1.1 | 0.6 |
| 187.5-9 Other genital | 8 | - | - | - | - | - | - | - | - | 1.3 | - | 0.8 | - | - | - | 4.3 | 6.5 | - | 11.6 | 0.4 | 0.0 | 0.5 | 0.3 |
| 188 Bladder | 441 | - | - | - | - | - | 1.6 | 1.1 | 3.4 | 2.7 | 14.4 | 27.9 | 36.9 | 83.3 | 104 | 183 | 188 | 196 | 232 | 20.6 | 2.3 | 27.6 | 18.4 |
| 189.0 Kidney | 147 | 3.8 | 0.7 | - | - | - | 1.1 | 0.6 | 1.1 | 2.7 | 5.3 | 13.9 | 24.3 | 26.2 | 25.7 | 36.2 | 61.5 | 23.8 | 46.5 | 6.9 | 0.7 | 8.9 | 6.4 |
| 189.1-9 Urinary tract | 56 | - | - | - | - | - | - | - | - | - | 0.8 | 7.4 | 3.9 | 11.4 | 17.7 | 12.8 | 25.9 | 11.9 | 58.1 | 2.6 | 0.3 | 3.7 | 2.4 |
| 190 Eye | 6 | - | 0.7 | - | - | - | - | - | - | - | - | - | 1.0 | 1.1 | - | 2.1 | 6.5 | - | - | 0.3 | 0.0 | 0.4 | 0.3 |
| 191 Brain | 94 | 0.8 | 1.5 | 3.0 | 1.5 | 1.5 | 2.6 | 3.9 | 2.8 | 4.7 | 7.6 | 4.1 | 6.8 | 11.4 | 20.9 | 12.8 | 16.2 | - | - | 4.4 | 0.4 | 4.9 | 4.1 |
| 192 Nervous system | 8 | - | - | 0.6 | - | 0.5 | - | 1.1 | 0.6 | - | - | - | - | 2.3 | 1.6 | - | - | - | - | 0.4 | 0.0 | 0.4 | 0.3 |
| 193 Thyroid | 16 | - | - | - | - | - | 0.5 | - | 0.6 | 1.3 | 1.5 | 2.5 | 1.0 | 4.6 | - | 4.3 | - | - | - | 0.7 | 0.1 | 0.9 | 0.7 |
| 194 Other endocrine | 9 | 2.3 | - | - | - | - | - | - | - | - | 0.8 | 0.8 | - | - | - | 2.1 | 6.5 | 6.0 | - | 0.4 | 0.0 | 0.5 | 0.5 |
| 201 Hodgkin's disease | 52 | - | - | 0.6 | 2.5 | 4.0 | 1.6 | 3.4 | 2.3 | 5.3 | 3.8 | 1.6 | 2.9 | 1.1 | 3.2 | - | 9.7 | 6.0 | - | 2.4 | 0.2 | 2.4 | 2.1 |
| 200/2 Non-Hodgkin | 220 | 0.8 | 2.2 | - | 1.5 | 2.0 | 1.6 | 2.8 | 5.6 | 8.6 | 9.8 | 13.1 | 21.4 | 29.7 | 38.5 | 78.7 | 74.4 | 71.4 | 58.1 | 10.3 | 1.1 | 12.8 | 9.2 |
| 203 Multiple myeloma | 79 | - | - | - | - | - | - | 1.1 | - | 0.7 | 1.5 | 3.3 | 6.8 | 17.1 | 32.1 | 12.8 | 38.8 | 29.8 | 58.1 | 3.7 | 0.4 | 5.0 | 3.4 |
| 204.0 ALL | 21 | 5.3 | 2.2 | 0.6 | 1.5 | 0.5 | - | 0.6 | - | - | - | 0.8 | - | 2.3 | - | 2.1 | 3.2 | - | - | 1.0 | 0.1 | 1.1 | 1.3 |
| 204.1 CLL | 49 | - | - | - | - | - | - | - | 0.6 | 0.7 | 2.3 | 1.6 | 3.9 | 4.6 | 19.3 | 14.9 | 22.7 | 35.7 | 23.2 | 2.3 | 0.2 | 3.1 | 2.0 |
| 205/6.0 ANLL | 60 | 1.5 | - | - | 0.5 | 0.5 | 0.5 | 1.7 | 1.1 | 0.7 | 1.5 | 4.1 | 4.9 | 3.4 | 8.0 | 23.4 | 32.4 | 35.7 | 23.2 | 2.8 | 0.4 | 3.6 | 2.5 |
| 205.1 CML | 30 | - | - | - | - | - | - | 1.7 | 0.6 | 0.7 | - | 0.8 | - | 4.6 | 4.8 | 14.9 | 12.9 | 17.9 | 34.9 | 1.4 | 0.1 | 1.9 | 1.2 |
| Leukaemia NOS | 12 | - | - | - | - | - | - | - | - | - | 0.8 | 0.8 | - | - | 3.2 | 4.3 | 6.5 | 11.9 | 23.2 | 0.6 | 0.0 | 0.8 | 0.5 |
| Primary site uncertain | 320 | - | - | - | - | 1.0 | - | 1.1 | 1.7 | 6.0 | 11.3 | 18.8 | 44.7 | 55.9 | 73.8 | 119 | 126 | 131 | 93.0 | 15.0 | 1.3 | 19.6 | 13.2 |
| All sites but 173 | 6,861 | 15.2 | 8.0 | 10.9 | 11.0 | 23.3 | 23.3 | 44.0 | 64.7 | 112 | 169 | 396 | 645 | 1144 | 1764 | 2514 | 3046 | 2868 | 3010 | 321 | 34.7 | 423 | 286 |
| Rate for 1 case | | 0.76 | 0.73 | 0.61 | 0.50 | 0.50 | 0.53 | 0.56 | 0.56 | 0.66 | 0.76 | 0.82 | 0.97 | 1.14 | 1.61 | 2.13 | 3.24 | 5.95 | 11.6 | | | | |

Average incidence per 100,000 person-years by age-group (yrs) in the period 1983-87

FEMALE

| ICD | Site | All ages | 0- | 5- | 10- | 15- | 20- | 25- | 30- | 35- | 40- | 45- | 50- | 55- | 60- | 65- | 70- | 75- | 80- | 85+ | Crude Rate | CR 74 | ASR EUR | ASR World |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 140 | Lip | 5 | - | - | - | - | - | - | - | 0.6 | - | 0.8 | 0.8 | - | - | 1.3 | - | - | 3.3 | - | 0.2 | 0.0 | 0.2 | 0.2 |
| 141 | Tongue | 22 | - | - | - | - | - | - | 1.2 | 0.6 | - | 1.6 | 3.4 | 1.9 | 3.2 | 1.3 | 3.1 | 4.0 | 3.3 | 11.0 | 1.0 | 0.1 | 1.1 | 0.8 |
| 142 | Salivary gland | 8 | - | - | 0.6 | - | - | - | 0.6 | - | - | - | 0.8 | 1.9 | 1.1 | 1.3 | - | - | - | 5.5 | 0.4 | 0.0 | 0.4 | 0.3 |
| 143-145 | Mouth | 20 | - | - | 0.6 | 0.5 | - | - | - | 1.2 | 0.7 | 1.6 | 1.7 | - | 1.1 | 1.3 | 3.1 | 6.0 | 9.8 | 5.5 | 0.9 | 0.1 | 0.9 | 0.7 |
| 146-149 | Pharynx | 16 | - | - | - | - | - | - | 0.6 | - | 0.7 | 1.6 | 3.4 | 3.8 | 1.1 | 1.3 | 1.6 | - | - | 5.5 | 0.8 | 0.1 | 0.9 | 0.6 |
| 150 | Oesophagus | 30 | - | - | - | - | - | - | - | - | - | 3.2 | 0.8 | - | 4.3 | 6.7 | 6.2 | 16.0 | 13.0 | - | 1.4 | 0.1 | 1.4 | 1.0 |
| 151 | Stomach | 297 | - | - | - | - | - | 1.2 | 0.6 | 2.4 | 2.9 | 2.4 | 11.7 | 15.0 | 25.6 | 63.4 | 66.7 | 108 | 185 | 155 | 14.1 | 1.0 | 13.8 | 8.8 |
| 152 | Small intestine | 12 | - | - | - | - | - | - | - | - | 1.4 | - | 0.8 | 0.9 | 3.2 | 5.4 | - | 2.0 | - | - | 0.6 | 0.1 | 0.6 | 0.5 |
| 153 | Colon | 586 | - | - | 3.2 | 1.1 | 3.8 | - | 1.8 | 5.5 | 10.1 | 18.4 | 35.2 | 39.4 | 77.8 | 101 | 141 | 190 | 228 | 193 | 27.8 | 2.2 | 28.1 | 19.1 |
| 154 | Rectum | 288 | - | - | - | - | - | - | - | 1.8 | 5.8 | 8.8 | 18.5 | 45.0 | 29.8 | 45.8 | 68.3 | 74.2 | 107 | 110 | 13.7 | 1.1 | 14.2 | 9.5 |
| 155 | Liver | 11 | - | - | - | - | - | 0.6 | - | - | - | 0.8 | 1.7 | 0.9 | 1.1 | 1.3 | 3.1 | 2.0 | 3.3 | - | 0.5 | 0.0 | 0.5 | 0.4 |
| 156.0 | Gallbladder | 62 | - | - | - | - | - | - | - | - | - | - | - | 3.8 | 4.3 | 17.5 | 15.5 | 30.1 | 32.5 | 33.1 | 2.9 | 0.2 | 2.9 | 1.8 |
| 156.1-9 | Gallducts etc. | 42 | - | - | - | - | - | - | - | - | - | 0.8 | 2.5 | 1.9 | 5.3 | 10.8 | 4.7 | 16.0 | 22.8 | 27.6 | 2.0 | 0.1 | 2.0 | 1.3 |
| 157 | Pancreas | 142 | - | - | - | - | - | - | - | 0.6 | 2.9 | 4.0 | 3.4 | 14.1 | 18.1 | 25.6 | 38.8 | 50.1 | 65.0 | 38.6 | 6.7 | 0.5 | 6.7 | 4.5 |
| 158 | Peritoneum | 10 | - | - | - | 0.5 | - | - | - | - | 0.7 | 2.4 | - | 0.9 | - | 1.3 | 1.6 | 2.0 | 3.3 | - | 0.5 | 0.0 | 0.5 | 0.4 |
| 160 | Nose, sinuses etc. | 7 | - | - | - | - | - | - | - | - | 0.7 | - | 0.8 | - | 1.1 | 1.3 | 1.6 | 2.0 | 3.3 | - | 0.3 | 0.0 | 0.3 | 0.2 |
| 161 | Larynx | 17 | - | - | - | - | - | - | - | - | - | 1.6 | 2.5 | 5.6 | 4.3 | 1.3 | - | - | 3.3 | - | 0.8 | 0.1 | 0.9 | 0.7 |
| 162 | Lung | 217 | - | - | - | - | - | 0.6 | 1.8 | 4.9 | 7.2 | 14.4 | 17.6 | 35.6 | 35.2 | 29.7 | 43.5 | 40.1 | 42.3 | 11.0 | 10.3 | 1.0 | 11.0 | 7.9 |
| 163 | Pleura | 6 | - | - | - | - | - | - | - | - | 0.7 | 0.8 | - | 0.9 | - | 1.3 | - | 2.0 | 3.3 | - | 0.3 | 0.0 | 0.3 | 0.2 |
| 164 | Mediastinum | 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | 2.7 | - | - | - | - | 0.1 | 0.0 | 0.1 | 0.1 |
| 170 | Bone | 12 | - | - | 0.6 | 1.6 | 0.5 | 1.8 | - | - | - | - | - | 1.9 | 1.1 | - | - | 2.0 | - | - | 0.6 | 0.0 | 0.5 | 0.5 |
| 171 | Connective tissue | 30 | 0.8 | - | - | 0.5 | - | 2.9 | 0.6 | 1.2 | - | 4.0 | 0.8 | 3.8 | 1.1 | 1.3 | 4.7 | 4.0 | 6.5 | 5.5 | 1.4 | 0.1 | 1.4 | 1.2 |
| 172 | Melanoma of skin | 164 | - | - | - | 0.5 | 3.8 | 6.4 | 7.4 | 9.7 | 16.6 | 14.4 | 12.6 | 5.6 | 14.9 | 14.8 | 15.5 | 20.0 | 16.3 | 27.6 | 7.8 | 0.6 | 8.0 | 6.4 |
| 174 | Breast | 1,955 | - | - | - | 0.5 | - | 4.1 | 24.6 | 65.7 | 121 | 182 | 180 | 231 | 245 | 266 | 307 | 317 | 299 | 370 | 92.8 | 8.1 | 99.5 | 72.7 |

| ICD Site | All ages | 0- | 5- | 10- | 15- | 20- | 25- | 30- | 35- | 40- | 45- | 50- | 55- | 60- | 65- | 70- | 75- | 80- | 85+ | C F | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 180 Cervix uteri | 161 | - | - | - | - | - | 6.4 | 9.2 | 11.6 | 15.9 | 8.8 | 10.1 | 7.5 | 20.2 | 21.6 | 14.0 | 18.0 | 22.8 | 16.6 | 7.6 | 0.6 | 7.8 | 6.2 |
| 181 Placenta | 1 | - | - | - | - | - | 0.6 | - | - | - | - | - | - | - | - | - | - | - | - | 0.0 | 0.0 | 0.0 | 0.0 |
| 182 Corpus uteri | 310 | - | - | - | - | - | - | 0.6 | 0.6 | 5.8 | 18.4 | 36.1 | 46.0 | 57.5 | 58.0 | 48.1 | 52.1 | 55.3 | 77.3 | 14.7 | 1.4 | 16.1 | 11.4 |
| 183 Ovary etc. | 279 | - | - | 0.6 | 1.1 | 2.7 | 1.8 | 3.7 | 5.5 | 3.6 | 16.0 | 34.4 | 42.2 | 39.4 | 51.2 | 49.7 | 44.1 | 22.8 | 33.1 | 13.2 | 1.3 | 14.3 | 10.5 |
| 184.0 Vagina | 6 | - | - | - | - | - | - | - | - | - | - | - | - | 2.1 | - | - | 2.0 | 6.5 | 5.5 | 0.3 | 0.0 | 0.3 | 0.2 |
| 184.1-9 Vulva | 34 | - | - | - | - | 0.5 | - | - | 0.6 | - | - | 1.7 | 1.9 | 6.4 | 5.4 | 9.3 | 12.0 | 13.0 | 11.0 | 1.6 | 0.1 | 1.6 | 1.1 |
| 188 Bladder | 135 | - | - | - | 0.5 | - | - | 0.6 | 1.8 | 3.6 | 0.8 | 3.4 | 9.4 | 16.0 | 27.0 | 37.2 | 46.1 | 61.8 | 49.7 | 6.4 | 0.5 | 6.3 | 4.2 |
| 189.0 Kidney | 116 | 2.4 | - | - | - | - | 0.6 | - | 1.8 | 2.9 | 5.6 | 5.9 | 13.1 | 13.9 | 13.5 | 35.7 | 32.1 | 26.0 | 38.6 | 5.5 | 0.5 | 5.7 | 4.1 |
| 189.1-9 Urinary tract | 28 | - | - | - | - | - | - | - | - | - | 0.8 | 3.4 | 2.8 | 5.3 | 4.0 | 4.7 | 4.0 | 16.3 | 11.0 | 1.3 | 0.1 | 1.4 | 0.9 |
| 190 Eye | 6 | 0.8 | - | - | - | 0.5 | - | - | 0.6 | 0.7 | 0.8 | - | - | - | 1.3 | - | - | - | - | 0.3 | 0.0 | 0.3 | 0.3 |
| 191 Brain | 70 | - | 2.3 | 1.9 | 1.1 | 2.7 | 1.8 | 1.8 | 3.0 | 4.3 | 1.6 | 5.9 | 8.4 | 3.2 | 9.4 | 7.8 | 4.0 | 16.3 | - | 3.3 | 0.3 | 3.4 | 2.8 |
| 192 Nervous system | 4 | - | - | - | - | - | - | - | 0.6 | 0.7 | 0.8 | - | - | 1.1 | - | - | - | - | - | 0.2 | 0.0 | 0.2 | 0.2 |
| 193 Thyroid | 52 | - | - | - | 0.5 | 2.2 | 1.8 | 3.1 | 1.2 | 2.9 | 3.2 | 2.5 | 2.8 | 3.2 | 5.4 | 10.9 | 10.0 | 9.8 | 5.5 | 2.5 | 0.2 | 2.4 | 1.9 |
| 194 Other endocrine | 7 | - | - | - | - | - | 0.6 | - | - | - | 0.8 | - | - | 4.3 | 1.3 | - | - | - | - | 0.3 | 0.0 | 0.4 | 0.3 |
| 201 Hodgkin's disease | 40 | - | - | 1.9 | 2.1 | 4.3 | 1.2 | 3.1 | 3.0 | 2.2 | - | 0.8 | 0.9 | - | - | 1.6 | 6.0 | 3.3 | 16.6 | 1.9 | 0.1 | 1.7 | 1.6 |
| 200/2 Non-Hodgkin | 160 | 3.2 | - | 0.6 | 0.5 | 1.1 | 1.2 | 1.2 | 3.0 | 5.8 | 9.6 | 10.9 | 8.4 | 19.2 | 31.0 | 21.7 | 36.1 | 61.8 | 49.7 | 7.6 | 0.6 | 7.8 | 5.8 |
| 203 Multiple myeloma | 82 | - | - | - | - | - | - | - | - | 0.7 | 1.6 | 3.4 | 7.5 | 11.7 | 17.5 | 18.6 | 30.1 | 48.8 | 5.5 | 3.9 | 0.3 | 3.8 | 2.5 |
| 204.0 ALL | 17 | 2.4 | 3.0 | 0.6 | 1.6 | - | - | - | - | - | - | - | - | 1.1 | 1.3 | 1.6 | 4.0 | 3.3 | - | 0.8 | 0.1 | 0.8 | 1.0 |
| 204.1 CLL | 22 | - | - | - | - | - | - | - | - | 0.7 | - | 1.7 | 3.8 | 5.3 | - | 6.2 | 4.0 | 9.8 | 5.5 | 1.0 | 0.1 | 1.1 | 0.7 |
| 205/6.0 ANLL | 42 | 0.8 | - | 1.3 | 1.1 | - | - | 1.8 | 2.4 | 2.2 | 0.8 | 4.2 | 0.9 | 1.1 | 4.0 | 7.8 | 14.0 | 9.8 | 5.5 | 2.0 | 0.2 | 2.0 | 1.5 |
| 205.1 CML | 13 | 0.8 | - | - | - | - | - | - | 0.6 | 1.4 | - | - | - | 3.2 | - | 1.6 | 4.0 | 6.5 | 5.5 | 0.6 | 0.0 | 0.6 | 0.5 |
| Leukaemia NOS | 2 | - | - | - | - | - | - | - | - | - | - | - | - | - | 1.3 | - | 2.0 | - | - | 0.1 | 0.0 | 0.1 | 0.1 |
| Primary site uncertain | 297 | - | - | - | - | - | 0.6 | 1.2 | 3.7 | 5.1 | 10.4 | 9.2 | 21.6 | 32.0 | 58.0 | 68.3 | 118 | 124 | 110 | 14.1 | 0.8 | 14.1 | 9.3 |
| All sites but 173 | 5,845 | 11.1 | 5.3 | 12.0 | 13.8 | 22.3 | 33.8 | 65.7 | 134 | 231 | 344 | 433 | 591 | 725 | 916 | 1071 | 1331 | 1567 | 1446 | 277 | 23 | 289 | 207 |
| Rate for 1 case | | 0.79 | 0.76 | 0.63 | 0.53 | 0.54 | 0.58 | 0.61 | 0.61 | 0.72 | 0.80 | 0.84 | 0.94 | 1.07 | 1.35 | 1.55 | 2.00 | 3.25 | 5.52 | | | | |

**Average incidence for children by age-group (yrs) in the period 1973-87: number of patients**

| Site | All ages | 0- | 1- | 5- | 10- |
|---|---|---|---|---|---|
| Salivary gland | 1 | - | - | - | 1 |
| Mouth | 1 | - | - | - | 1 |
| Pharynx | 2 | - | - | - | 2 |
| Colon | 9 | - | - | - | 9 |
| Liver | 2 | - | 2 | - | - |
| Mediastinum | 1 | - | - | - | 1 |
| Bone | 24 | - | - | 5 | 19 |
| Connective tissue | 14 | 1 | 7 | 3 | 3 |
| Melanoma of skin | 4 | - | - | - | 4 |
| Basal cell skin | 9 | 2 | - | - | 7 |
| Ovary etc. | 3 | - | - | - | 3 |
| Testis | 4 | 1 | 3 | - | - |
| Bladder | 1 | - | 1 | - | - |
| Nephroblastoma | 16 | 2 | 11 | 3 | - |
| Eye | 10 | 7 | 1 | 2 | - |
| Brain | 46 | 5 | 6 | 16 | 19 |
| Nervous system | 2 | - | 1 | - | 1 |
| Thyroid | 1 | - | - | - | 1 |
| Other endocrine | 14 | 4 | 9 | 1 | - |
| Non-Hodgkin's lymphoma | 31 | 4 | 11 | 11 | 5 |
| Hodgkin's disease | 11 | - | 1 | 2 | 8 |
| Acute lymphocytic leukaemia | 76 | 2 | 38 | 25 | 11 |
| Acute non-lymphocytic leukaemia | 17 | 2 | 10 | 2 | 3 |
| Chronic myelocytic leukaemia | 3 | 1 | 2 | - | - |
| Unspecified leukaemia | 2 | 1 | - | - | 1 |
| Primary site uncertain | 3 | - | 1 | 1 | 1 |
| All sites | 307 | 32 | 104 | 71 | 100 |

Average incidence for children per million person-years by age-group (yrs) in the period 1973-87

| Site | All ages | 0- | 5- | 10- | ASR World |
|---|---|---|---|---|---|
| Salivary gland | 1 | - | - | 1.0 | 0.3 |
| Mouth | 1 | - | - | 1.0 | 0.3 |
| Pharynx | 2 | - | - | 1.8 | 0.5 |
| Colon | 9 | - | - | 8.7 | 2.5 |
| Liver | 2 | 2.4 | - | - | 0.9 |
| Mediastinum | 1 | - | - | 0.8 | 0.2 |
| Bone | 24 | - | 5.1 | 17.7 | 6.8 |
| Connective tissue | 14 | 9.3 | 3.1 | 2.7 | 5.4 |
| Melanoma of skin | 4 | - | - | 3.5 | 1.0 |
| Basal cell skin | 9 | 2.6 | - | 6.1 | 2.8 |
| Ovary etc.* | 3 | - | - | 5.9 | 1.7 |
| Testis* | 4 | 9.6 | - | - | 3.7 |
| Bladder | 1 | 1.2 | - | - | 0.5 |
| Nephroblastoma | 16 | 16.3 | 3.1 | - | 7.3 |
| Eye | 10 | 9.3 | 2.2 | - | 4.3 |
| Brain | 46 | 13.5 | 17.2 | 17.9 | 16.0 |
| Nervous system | 2 | 1.3 | - | 1.1 | 0.8 |
| Thyroid | 1 | - | - | 0.9 | 0.3 |
| Other endocrine | 14 | 15.7 | 0.9 | - | 6.4 |
| Non-Hodgkin's lymphoma | 31 | 18.5 | 11.7 | 4.6 | 12.2 |
| Hodgkin's disease | 11 | 1.2 | 2.3 | 7.9 | 3.5 |
| Acute lymphocytic leukaemia | 76 | 48.8 | 26.0 | 9.8 | 30.1 |
| Acute non-lymphocytic leukaemia | 17 | 14.8 | 2.0 | 2.8 | 7.2 |
| Chronic myelocytic leukaemia | 3 | 3.8 | - | - | 1.5 |
| Unspecified leukaemia | 2 | 1.0 | - | 0.9 | 0.7 |
| Primary site uncertain | 3 | 1.1 | 0.9 | 0.9 | 1.0 |
| All sites | 307 | 165.6 | 74.5 | 92.9 | 115.1 |

* per 500.000 person-years

# Appendix B

**Age-adjusted* cancer mortality in southeastern North Brabant and northern Limburg# compared to national (NL) average in the period 1983-87: sites with major differences only, according to sex**

| | Males | | Females | |
|---|---|---|---|---|
| Site | SOOZ | NL | SOOZ | NL |
| All sites | 327 | 308 | 166 | 163 |
| Head & neck@ | 3.5 | 3.0 | 1.0 | 1.1 |
| Oesophagus | 6.0 | 6.3 | 1.7 | 2.2 |
| Stomach | 26.0 | 23.8 | 12.7 | 9.8 |
| Colo-rectal | 36.8 | 30.1 | 25.3 | 22.3 |
| Gallbladder | 3.4 | 3.0 | 4.2 | 4.7 |
| Pancreas | 13.4 | 13.5 | 9.3 | 8.6 |
| Larynx | 3.2 | 2.6 | 0.5 | 0.3 |
| Lung | 130 | 116.2 | 10.2 | 11.8 |
| Breast | | | 38.4 | 37.9 |
| Cervix uteri | | | 3.6 | 3.9 |
| Ovary | | | 10.3 | 11.6 |
| Prostate | 27.4 | 29.6 | | |
| Bladder | 9.4 | 12.2 | 3.2 | 2.9 |
| Haematological | 22.6 | 20.6 | 12.5 | 13.0 |

source: Central Bureau for Statistics
* European Standard Population
#(COROP-areas 36 and 37, SOOZ-area)
@ cancer of tongue, mouth and pharynx combined

# Appendix C

**Trends in mortality from important causes of death in southeastern North Brabant and northern Limburg, in the period 1970-86: per 100,000* person-years**

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| Infections | 8 | → | 5 | 7.5 | → | 4 |
| Endocrinological | 15 | = | 15 | 25 | → | 15 |
| Rheuma | 7 | → | 2 | 7 | → | 2 |
| Hypertension | 10 | → | 3 | 13 | → | 4 |
| Cardiovascular | 360 | → | 320 | 140 | → | 115 |
| Cerebrovascular | 125 | → | 80 | 110 | → | 75 |
| Vascular | 40 | → | 35 | 35 | → | 13 |
| Lung diseases | 100 | → | 90 | 45 | → | 35 |
| Gastro-intestinal | 30 | = | 30 | 25 | → | 20 |
| Kidney/urinary tract | 22 | → | 13 | 15 | → | 8 |
| Accidents | 90 | → | 50 | 45 | → | 25 |
| Cancer | 300 | → | 320 | 168 | → | 168 |
| All causes of death | 1170 | → | 1030 | 765 | → | 600 |

source: Central Bureau for Statistics
* European standard population

# Appendix D

**Five year cumulative relative survival of patients with cancer in southeastern Netherlands (ECR, 1975-85), Finland (1974-81), the canton Vaud (Switzerland, 1974-85) and the USA (SEER-programme, 1979-81)**

| | Males | | | ♂+♀ | Females | | |
|---|---|---|---|---|---|---|---|
| | ECR | FIN | VAUD | USA | ECR | FINL | VAUD |
| Tumour-site | % | % | % | % | % | % | % |
| All sites | 33 | 30 | ? | 50 | 51 | 47 | ? |
| Oesophagus | 9 | 4 | 7 | 7 | 8 | 8 | 13 |
| Stomach | 22 | 16 | 24 | 16 | 20 | 14 | 24 |
| Colon | 53 | 41 | 48 | 54 | 48 | 43 | 53 |
| Rectum | 40 | 43 | 45 | 52 | 42 | 46 | 56 |
| Pancreas | 5 | 2 | 5 | 3 | 5 | 2 | 5 |
| Larynx | 72 | 59 | 65 | 66 | 62 | | |
| Lung | 12 | 10 | 9 | 13 | 18 | 13 | 10 |
| Melanoma | 65 | 60 | 63 | 80 | 84 | 76 | 77 |
| Breast | | | | 75 | 69 | 70 | 70 |
| Cervix uteri | | | | 67 | 63 | 61 | 66 |
| Corpus uteri | | | | 83 | 80 | 78 | 76 |
| Ovarium | | | | 37 | 39 | 39 | 32 |
| Prostate | 54 | 56 | 47 | 73 | | | |
| Testis | 84 | 65 | 78 | 91 | | | |
| Bladder | 66 | 59 | 29 | 77 | 46 | 58 | 32 |
| Kidney | 46 | 37 | 45 | 51 | 43 | 40 | 44 |
| Brain | 27 | 36 | 22 | 23 | 23 | 49 | 22 |
| Non-Hodgkin's | 41 | 32 | 48 | 49 | 46 | 37 | 52 |
| M. Hodgkin | 74 | 57 | 62 | 74 | 79 | 63 | 73 |
| M. Kahler | 25 | 30 | 36 | 24 | 28 | 28 | 46 |
| Leukaemia | 34 | 22 | 28 | 32 | 38 | 22 | 32 |

sources: Eindhoven Cancer Registry, Finnish Cancer Registry, canton Vaud, SEER-programme (see chapter 4.2 for references)

# Appendix E

# LIST OF PUBLICATIONS*

## I. Eindhoven Cancer Registry

### 1980

* Wolff AAC. De Stichting Samenwerkingsorgaan Oncologie Ziekenhuizen (SOOZ): Samenwerking Kankerbestrijding in Zuidoost Noord Brabant en Noord-Midden Limburg. (The Foundation of Cooperating Hospitals in Oncology in southeastern North Brabant and northern and middle Limburg) *Med Contact* 1980;35:730-2.

### 1982

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### 1983

Coebergh JWW, Bakker D, Crommelin MA, Verhagen-Teulings MTh. Kankerregistratie in Zuidoost Nederland; volledigheid in relatie tot de mogelijkheid tot schatting van de incidentie in de periode 1975-81. (Cancer registration in southeastern Netherlands; completeness in relation to the possible estimation of incidence in the period 1975-81) *T Soc Geneeskd* 1983;61:799-801.

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* Publications with an asterix * are only partly based on data of the registries.

## 1984

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* Coebergh JWW. Maligne aandoeningen van de tractus digestivus: enkele epidemiologische aspecten. (Epidemiological aspects of malignancies of the gastro-intestinal tract) *IKR-bulletin* 1984;8:14-7.

## 1985

* de Waard F, van Zonneveld RJ. Epidemiologie van kanker. In: Zwaveling A, van Zonneveld RJ, Schaberg A, (eds.) *Oncologie* (3rd edition). Alphen a/d Rijn: Samson-Stafleu, 1985: 36-48.

Coebergh JWW, Crommelin MA, Verhagen-Teulings MTh. Enkele opvallende uitkomsten van de IKZ/SOOZ kankerregistratie in de periode 1977-1981. (Remarkable results from the Eindhoven Cancer Registry in 1977-81) *T Soc Gez* 1985;63:239-40.

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## 1987

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Wijlhuizen ThJ, Breed WPM. (namens de Haemato-Oncologische werkgroep van het SOOZ, HOMAAN). Secundaire maligniteiten na behandeling van de ziekte van Hodgkin. (Second malignancies after treatment of Hodgkin's disease) *Ned Tijdschr Geneeskd* 1987;131:1342-6.

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Coebergh JWW, Verhagen-Teulings MTh, van der Heijden LH. Epidemiologie van hersentumoren in Zuidoost Noord-Brabant en Noord Limburg, 1975-1986. (Epidemiology of brain cancer in southeastern North Brabant and northern Limburg, 1975-86) *IKZ/Integraal* 1989;3:18-20.

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Coebergh JWW, Bosch LJ, Breed WPM, Crommelin MA, van der Heijden LH, Keuning JJ, Vrints LW, Verhagen-Teulings MTh. Haematological malignancies in community hospitals in southeastern Netherlands: a registry-based study of incidence and survival in 1975-1987. (submitted)

Balvert-Locht HR, Coebergh JWW, Hop WCJ, Brölmann HAM, Crommelin MA, van Wijck DJAM, Verhagen-Teulings MTh. Improved prognosis of ovarian cancer in the Netherlands during the period 1975-85: a registry-based study. *Gynecol Oncol* 1991 (in press)

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# II. Dutch Childhood Leukaemia Study Group

van Steensel-Moll HA, Valkenburg HA, van Zanen GE. De geografische verdeling van kinderen met leukemie in Nederland, 1973-79. (Geographical distribution of childhood leukaemia in the Netherlands, 1973-79) *Ned Tijdschr Geneeskd* 1983;127:1287-91.

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# List of abbreviations

| | |
|---|---|
| ALL | acute lymphocytic leukaemia |
| AML | acute myelocytic leukaemia |
| ANLL | acute non-lymphocytic leukaemia |
| AUL | acute unclassifiable leukaemia |
| BCC | basal cell cancer |
| CBS | Central Bureau for Statistics |
| CLL | chronic lymphocytic leukaemia |
| CML | chronic myelocytic leukaemia |
| DCLSG | Dutch Childhood Leukaemia Study Group |
| FAB | French-American-British classification |
| HD | Hodgkin's disease |
| HM | haematological malignancies |
| ICD | International Classification of Diseases |
| LD | lymphocyte depletion |
| LEU | leukaemia |
| LLR | leukaemia to lymphoma ratio |
| LP | lymphocyte predominant |
| MC | mixed cellularity |
| MDS | myelodysplastic syndrome |
| ML | malignant lymphoma |
| MM | multiple myeloma |
| NHL | non-Hodgkin's lymphoma |
| NOS | not otherwise specified |
| NS | nodular sclerosing |
| OSR | observed survival rate |
| RSR | relative survival rate |
| SCC | squamous cell cancer |
| SEER | Surveillance, Epidemiology, End Results Programme |
| WBC | white blood cell count |
| WF | Working Formulation for clinical usage (of NHL) |

# EPILOOG

Mijn belangstelling voor epidemiologie is ontstaan tijdens mijn werkzaamheden in de sfeer van planning en organisatie. Hieraan ontbrak een strategische dimensie, namelijk die van de ziektebestrijding, de ontwikkeling van vraag naar en het aanbod van zorg. Door mijn komst naar Rotterdam ben ik, wat dat betreft, in de laatste 10 jaar goed aan mijn trekken gekomen in een instituut waar vele belangrijke ziekten over de tafel en door de computer gingen. Daarnaast noopte het onderwijs bij de Studierichting Algemene Gezondheidszorg, later Beleid en Management geheten, een en ander beleidsmatig te vertalen.

Het onderzoeksproces is natuurlijk systematischer, maar ook beperkter, dan beleidsontwikkeling waarin veel meer ongelijksoortige variabelen en vooral waarden meespelen, hetgeen het voor velen tamelijk ongrijpbaar maakt.

Al diegenen in Rotterdam met wie ik, vooral in de laatste 7 jaar heb samengewerkt, dank ik voor de plezierige wijze waarop dit geschiedde en waarmee menig gesprek of discussie verliep zelfs wanneer onbegrip de uitkomst was. Na een fase van "deprofessionalisatie" werd mij duidelijk dat de buitenwereld, vaak vertegenwoordigd door andere disciplines, vooral baat heeft bij duidelijkheid over het medisch handelen, juist omdat het zo vaak een "handel in twijfel" is. De epidemiologie biedt hiervoor een uitstekend handvat.

In de Scenariocommissie Kanker kreeg een en ander vorm door middel van scenario's ten behoeve van toekomstverkenningen. De leden van deze commissie ben ik bijzonder erkentelijk voor hun bijdrage aan mijn leerproces. Eén persoon wil ik speciaal noemen: Symon Terpstra. Al bijna 20 jaar had hij als geen ander steeds door waar "het" heen gaat en herkende in een vroeg stadium het belang van epidemiologische kennis voor de beleidsontwikkeling. Dat nog vele studenten van jouw kennis en ervaring mogen profiteren.

Symon bracht mij ook in contact met de Stichting Nederlandse Werkgroep Leukemie bij Kinderen (SNWLK) en met Mariad Crommelin en Douwe Bakker, die in verband van het Samenwerkings Orgaan Oncologie Ziekenhuizen (SOOZ) de kankerregistratie uit het verzamelmoeras (in het Duits Datenfriedhof) trokken. Zonder jullie was dit nooit goed gekomen. Niet zozeer het belang van "domme" cijfers, maar bovenal de manier waarop gegevens over ziekten werden verzameld en geïnterpreteerd werd mij als wezenlijk voorgehouden in de COMBAT-groep die tijdelijk voor veel dynamiek zorgde. Genomens zijn minder waardevol dan gegevens.

Het opbouwwerk in Eindhoven heeft nu geleid tot een organisatie die informatie genereert over kanker, waarbij het Integraal Kankercentrum Zuid een nuttige ondersteuning vormde.

Bijzondere dank ben ik verschuldigd aan Marijke Verhagen, die mij na enige tijd van gezond wantrouwen, de ruimte schonk om nuttige dingen te doen met de gegevens van 'haar' patiënten: privacybewaking 'avant la lettre'. Met je gezonde medische verstand wist je een vermeend gebrek aan kennis van epidemiologie, statistiek en computers aardig te compenseren en je hebt laten zien wat karakter zoal vermag.

De SNWLK redde zichzelf beter, wellicht ook omdat het ging om één vorm van kanker en dan nog bij kinderen. De inzet van de bestuursleden is respectabel.

Ik dank al diegenen in deze organisaties voor het vertrouwen en soms geduld dat zij mij schonken om informatie te "produceren" met hun gegevens. Speciaal moet deze dank toevloeien aan alle 29 co-auteurs die min of meer actief hebben meegewerkt aan de publikaties in dit proefschrift. In leeftijd variëren ze van ruim 60 tot bijna 30 jaar en dit houdt in dat belangrijke leereffecten zijn opgetreden. Met name het contact met de jongeren met wie een onderzoeksgroep is ontstaan werkt aanstekelijk.

De combinatie van karakters van Bert Hofman en Hans Valkenburg heeft mij over de streep van dit proefschrift getrokken. Ik ben uiteraard dankbaar voor de ruimte die mij altijd geboden is in Rotterdam om mijn plannen en problemen te bespreken.

Speciale dank uit ik ook aan al diegenen die in de diverse organisaties computers en secretariaten bemanden. De eerste groep is voldoende bedankt bij de afzonderlijke hoofdstukken van dit proefschrift, de tweede groep wil ik hier speciaal bedanken voor al hun speurtochten naar deze vliegende dokter.

Over mijn gezin heb ik niets te klagen gehad, maar zij wel over mij. Dat laat ik graag aan hen over.

# CURRICULUM VITAE

Jan Willem Coebergh was born in 1946 in Bussum and attended Gymnasium β from 1958 to 1964. He then studied French, Spanish and philosophy for one year at the University of Fribourg in Switzerland. From 1965 to 1974 he studied medicine at the University of Leiden. During this time he spent almost 2 years as a member of the Board of NBBS, the Dutch student travel agency.

From 1974 to 1979 he was assistant to the Medical Director of the University Hospital in Leiden (A.Th. Schweizer). Initially he was involved in the planning of the new university hospital and conducted studies on regionalization of health services and education (under supervision of Prof. A. Querido); later he analysed medical developments, such as Intensive Care, related to problems of capacity and organization in various clinics and services. Between 1975 and 1979 he followed postgraduate training in Social Medicine (Public Health Administration) at the Netherlands Institute for Preventive Health Care in Leiden and obtained a degree in 1979. During 1979 he worked for one day per week at the Health Council as a secretary to the committee on Screening for Breast Cancer (chairman Prof. F. de Waard).

In 1980-81 he was a resident of Internal Medicine at the St Elisabeth hospital in Leiderdorp (Dr. W.J. van Amstel). Thanks to a 'stimulation arrangement' of the Ministry of Education he started training in Epidemiology at the Department of Epidemiology of the Erasmus University in Rotterdam (Prof. H.A. Valkenburg, since 1988 Prof. A. Hofman). In 1981-84 he was involved in a policy analysis of possible long term developments of - increasingly intensive - specialized care for patients with Haematological Malignancies (together with S. Terpstra). This work was extended to cover all cancers for the Scenario Committee on Cancer 1985-2000 (chairman Prof. F.J. Cleton), that produced a final report in 1987. Since 1982, he has been involved in the evaluation of the completeness and accuracy of the Eindhoven Cancer Registry (Mrs. M.Th. Verhagen-Teulings, M.A. Crommelin, D. Bakker). In 1984 he was appointed as an epidemiological consultant by the Comprehensive Cancer Centre South for 1 day per week and since 1987, when the follow-up project on cancer survival was started, for two days per week.

Since 1984 he has also served as ad-hoc epidemiological consultant for the Dutch Childhood Leukaemia Study Group (chairman Dr. G.E. van Zanen, since 1987 Dr. W.A. Kamps).

In 1984 he became assistant-professor in Social Medicine and Epidemiology at the Department of Health Policy and Management of the Erasmus University (Prof. J. Moll, since 1986 Prof. A.F. Casparie).

Since 1983 he has organized, together with Dr. G.A. de Jong (initially) and Dr. J.P. Mackenbach on behalf of the Dutch Society of Social Medicine, the

annual Health Services Research Day, until 1987 in Rotterdam and since 1988 in behalf of the Society for Public Health and Science in other university cities.

Since 1987 he is treasurer of the Netherlands Society for Epidemiology after having been involved in the organization of its annual meetings 1n 1983, 1984 and 1985. Currently he is a member of the scientific advisory board and the executive board of PALGA (the National Pathology Registry), a Health Council committee on centralization of patient management in oncology and an advisory committee on cancer research of the Council for Health Research.

He is married with Christiane Surie since 1971 and has two children, born in 1975 and 1978.

# STELLINGEN

## behorend bij het proefschrift van JWW Coebergh "Incidence and prognosis of cancer in the Netherlands: studies based on cancer registries" Rotterdam, 5 juni 1991

1. De kankerregistratie in Nederland dient te bestaan uit een landelijke "minimal-data set" van alle nieuwe patiënten als "sampling frame", enkele uitgebreide regionale registraties van vooral frequente tumoren en landelijke registers voor patiënten met zeldzame tumoren (dit proefschrift).

2. Evenals in klinisch onderzoek kan in onderzoek gebaseerd op kankerregistraties selectie-bias optreden als gevolg van de medische werkwijze en de registratie-procedures (dit proefschrift).

3. Uitspraken over trends in incidentie en prognose van kanker dienen vergezeld te gaan van een beschouwing van de kankersterfte en bij ouderen ook van de co-morbiditeit en sterfte aan concurrerende doodsoorzaken (dit proefschrift).

4. Voor het adequaat weergeven van ziektefrequenties is standaardisering van het gebruik van standaardbevolkingen gewenst (dit proefschrift).

5. Diepgaand epidemiologisch onderzoek van clusters van kanker is zelden noodzakelijk.

6. Ziekteregistraties dienen onder medisch toezicht te staan, vanwege het risico dat gegevens "genomens" worden.

7. Het feit dat het eerste formele patiënt-controle onderzoek naar het verband tussen roken en longkanker in Nederland is uitgevoerd (WF Wassink, Ned Tijdschr Geneeskd 1948;97:3732-47) heeft de preventie van longkanker in Nederland niet veel geholpen.

8. Voor het vaststellen van kwaliteit van leven van patiënten lijdend aan kanker in de algemene klinische praktijk is de QL-index van Spitzer et al. (J Chron Dis 1981;34:585-97) zeer geschikt.

9. Het optreden van decompressie van morbiditeit op oudere leeftijd, vooral bij mensen die gezond leefden, pleit tegen premiedifferentiëring voor de ziektekostenverzekering op grond van gedrag.

10. In kosten-effectiviteitsanalyses van potentieel levensverlengende technologieën dienen uitgaven aan ziekenzorg in de gewonnen levensjaren te worden 'meegenomen'.

11. De stelling "Het is in hooge mate te betreuren, dat in de groote dagbladen voorloopige mededelingen over nieuwe behandelingswijzen van chronische ziekten geplaatst worden, vóórdat over de waarde van die methoden eenige meerdere zekerheid is verkregen" (laatste stelling bij het proefschrift "Over de Oorzaken van Dwarsligging" van JWW Coebergh, Leiden 1909) is onverminderd van kracht.

12. Met één Nederlandse "School of Public Health" is de kans groot op verstarring van het beleid voor ziektebestrijding.

13. Academische ziekenhuizen moeten worden beschouwd als een stelsel van paviljoenen met een voortdurend wisselende combinatie van specialistische kennis.

14. Directeuren van ziekenzorginstellingen dienen kleine werkkamers te hebben, teneinde permanent geprikkeld te worden tot 'management by walking around'.

15. Voor de volksgezondheid is veilig rijen van beduidend groter belang dan veilig vrijen.