Pergamon

European Journal of Cancer Vol. 32A, No. 2, pp. 195–200, 1996

Printed in Great Britain.
0959-8049/96 $15.00+0.00

International Cancer News

From Europe

EUROCARE Study Detects Substantial International Variations in Cancer Survival

A study published in 1995 by the International Agency for Research on Cancer (IARC) in Lyon, France is the most ambitious international comparison of cancer survival undertaken to date, according to the authors, and the first to examine survival variations in a wide range of populations across Europe. A collaborative effort of investigators at 30 cancer registries in 11 countries, the EUROCARE study summarises the survival of about 800 000 patients diagnosed from 1978 to 1985 and followed up through 1990 — almost 20% of the cancer patients diagnosed in Europe during that time. The study covers 27 different cancers in adults and eight in children. Registries contributing to EUROCARE cover the entire countries of Denmark, Estonia and Finland, and regions of France, Germany, Italy, The Netherlands, Poland, Spain, Switzerland and the United Kingdom (including the entire Scottish population and 46% of the English).

While concluding that survival rates are "broadly similar" for most cancer types in most countries, the EUROCARE study reveals substantial international differences in survival among patients with a variety of tumours including those of the breast, colon, rectum and stomach.

"Variation in cancer survival was smaller during this period in younger patients, those with good prognosis tumours, and those whose prognosis can be influenced by treatment, such as Hodgkin's disease and testicular cancer patients," said Dr Jan Willem Coebergh of the Eindhoven Cancer Registry in The Netherlands, a EUROCARE contributor and Associate Editor for the *European Journal of Cancer*. "Variations were larger in elderly patients, and patients whose tumours have a relatively bad prognosis, such as those of the lung and stomach". Coebergh discussed EUROCARE at a recent symposium to celebrate the 40th anniversary of the Eindhoven Registry, the only one in The Netherlands that was included in the study because it survived through a period in the 1970s and '80s when other Dutch registries closed down.

"There is substantial intercountry variation in cancer types for which stage is the overwhelming influence on survival", he added. "The more there is early detection, and the spectrum shifts to earlier disease, the better survival will be. I think this is one of the major elements which determines survival differences in Europe ".

"Part of the improved survival seen with early detection is an artefact of lead-time bias," he said. "We try to sort it out by looking at survival by stage, but even within stage there can be a shift. You can never do away with it completely ".

Across the spectrum of cancers, survival was highest in Finland, The Netherlands and Switzerland; lowest in Poland and Estonia. The United Kingdom ranked relatively low among Western European nations in survival of most cancers, except for those most successfully treated with chemotherapy.

Besides pronounced differences in breast cancer survival, (Figure 1) there was a 3-fold variation in survival of colon cancer patients. Switzerland again ranked at the top for both men (50%) and women (57%), while Poland ranked lowest (18% for men and 20% for women) (Figures 2 and 3). European differences were also evident in cancers with poorer overall survival. A 3-fold variation was found in 5-year survival among men with stomach cancer, from a high of 23% in Switzerland to a low of 7% in Scotland. For cancer of the pancreas in men, Germany had the highest 5-year survival with 6.2%, while Estonia was lowest at 1.7%.

One of the key tasks the EUROCARE investigators faced was ensuring that survival rates reported by the various registries were compared on an equal footing, said Professor Michel P. Coleman of the London School of Hygiene and Tropical Medicine, the British co-ordinator of the study. Date of diagnosis may be defined in different ways in different registries, for example, which could bias results.

At the Eindhoven meeting, Dr Hans Storm of the Danish Cancer Registry asked Dr Coebergh if the Dutch law prohibiting access to death records might have artificially inflated certain survival rates reported by the Eindhoven Registry, because some cases with very short survival times might have been missed by the registry and reported only at death. He noted that 8% of cancer incidence in Denmark is recorded from death records alone. While acknowledging that cancer registries should have access to death certificates for complete reporting, Coebergh said that because of his registry's close collaboration with the oncological care system, he does not believe many cases are missed in this way.

Another type of bias that may be introduced into survival comparisons is that diseases sometimes differ among populations in ways that affect survival. For example, Northern Europeans typically get larynx cancer on the vocal cords, causing early symptoms, while in Southern Europeans, this cancer usually arises in a different area of the larynx and causes symptoms at a more advanced stage. Survival differences thus may be a function of anatomic subsite, a detail that is not always recorded by registries.

The EUROCARE investigators believe they have surmounted most of these difficulties, however. "Many registries have published survival data in the past, but rarely so as to allow direct comparison, " they noted. "The key advantage of EUROCARE is that it has brought together data from 30 European cancer registries in a common format, using agreed definitions, for a systematic joint analysis, using standard techniques ".

Some major cancers were not included in the study because international variations in classification made it impossible to make direct comparisons. "We excluded what pathologists call

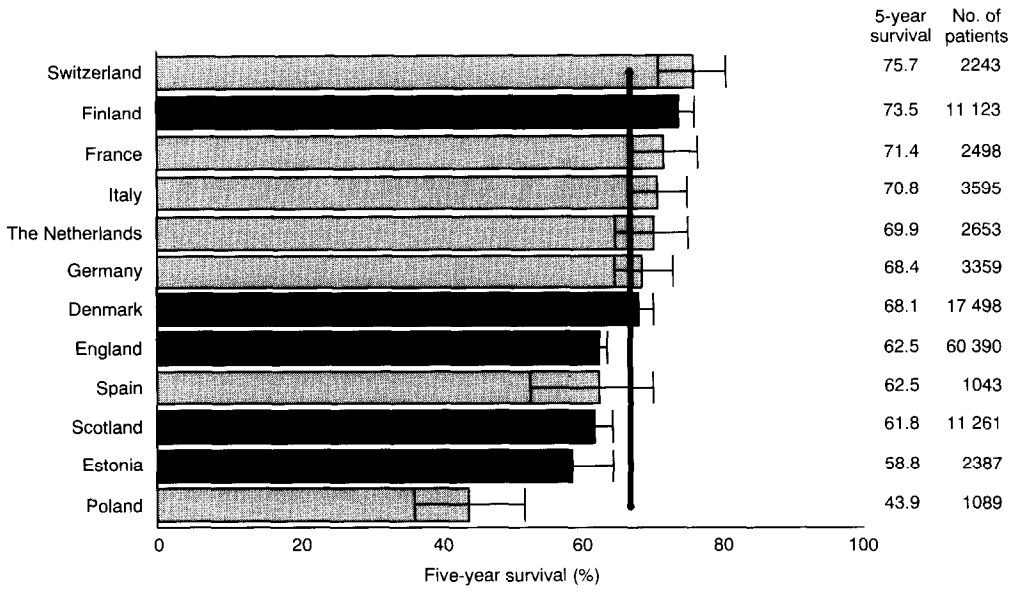


Figure 1. Breast cancer in Europe: 5-year survival (%) in women with 95% confidence interval and European average (vertical bar). Patients diagnosed 1978–1985 and followed up to 1990. Source: EUROCARE study (1995).

the "difficult " tumours: melanoma, prostate cancer, bladder cancer, non-Hodgkin's lymphoma" Coebergh said. "In the next version, an effort will be made to include them ". Prostate cancer was excluded because early detection with PSA and other techniques has spread more widely and more quickly in some countries than others. These intensive early detection practices have not been thoroughly documented and could create an artificial bias toward longer survival in the countries that adopted them earlier.

The EUROCARE investigators stress that the study does not permit direct conclusions about the relative efficacy of different national health care systems in diagnosis and treatment. Not enough information was available to make direct comparisons of stage distributions or treatment patterns. But Coebergh said that "although no hard explanations can be given, the study points to some indications of the quality of oncological care". Experts agreed that countries ranking consistently high on survival in EUROCARE are generally better supplied with oncologists, and have much more structured systems of cancer care, than most of those ranking lower.

Coleman said of the U.K. situation, "we're not the first to raise the issue that there's something wrong with the way we, as a nation, handle cancer. The fact that our results agree with others suggests that the problem is real". British health authoritities have recently adopted a plan to improve cancer services, creating a three-tiered system designed to provide

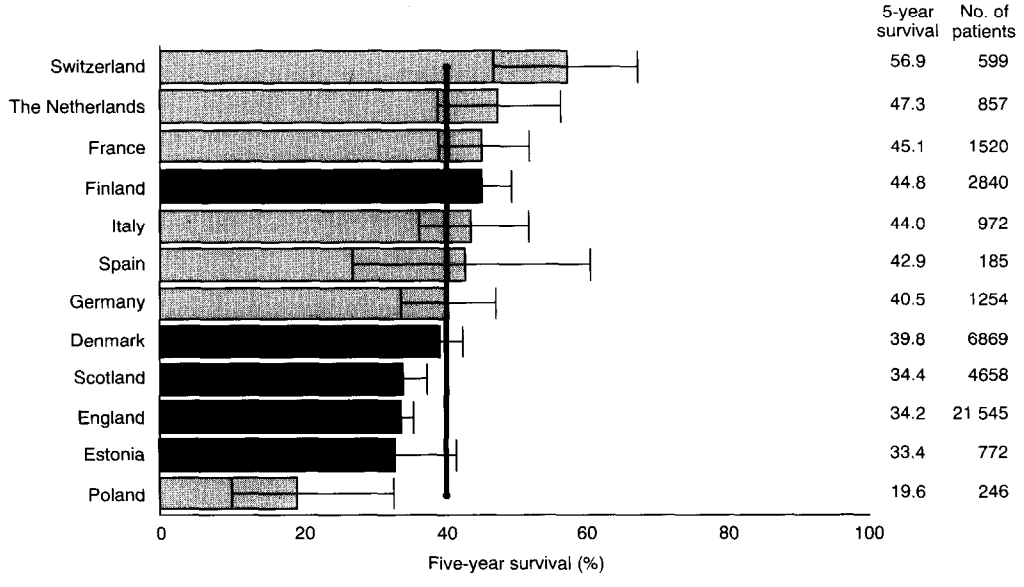


Figure 2. Colon cancer in Europe: 5-year survival (%) in women with 95% confidence interval and European average (vertical bar). Patients diagnosed 1978–1985 and followed up to 1990. Source: EUROCARE study (1995).

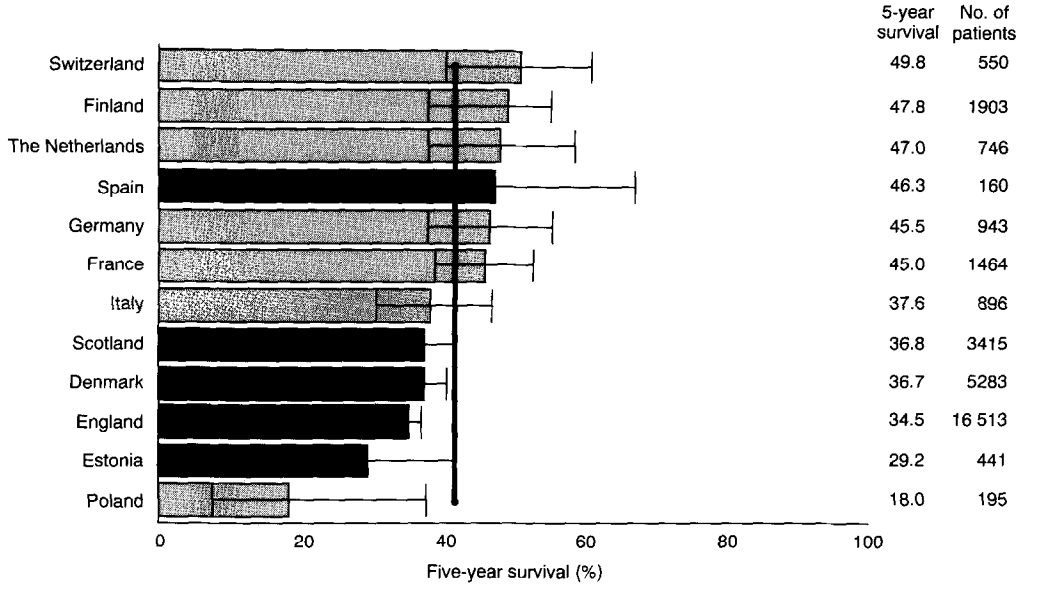


Figure 3. Colon cancer in Europe: 5-year survival (%) in men with 95% confidence interval and European average (vertical bar). Patients diagnosed 1978–1985 and followed up to 1990. Source: EUROCARE study (1995).

more equitable access to early detection and treatment. Coebergh, by contrast, said the results suggested no serious weaknesses in the system of cancer care in the Southeast Netherlands, the area covered by the Eindhoven Registry. As for The Netherlands as a whole, he reasoned that "it's unlikely survival would be worse in areas where there is a cancer centre", compared with the Eindhoven region which does not have a cancer centre (Figure 4).

Because coverage of most countries was far from complete — outside the United Kingdom and the three countries with national registries, coverage ranged from 2% to 14% of the national population — the areas included may not be thoroughly representative of the whole country, the authors caution.

In Switzerland, for example, only the registries in Geneva and Basel — representing 14% of the Swiss population — were included in EUROCARE. Dr Luc Raymond, consultant to the Geneva Cancer Registry, cautioned that "It's difficult to be precise about the degree of representativeness.... But my opinion is that survival is probably not so good in other areas of Switzerland". The reason, Raymond said, is that the Geneva and Basel populations include a higher proportion of the more affluent "service sector " than most other regions.

As for the 80% of Europe that was not included in the study, Coebergh reasoned that "If there are no registries and we don't know about survival, my opinion is that it's more likely to be worse than better ". The existence of a registry, he said, is one sign of "oncological civilisation ", suggesting that coun-

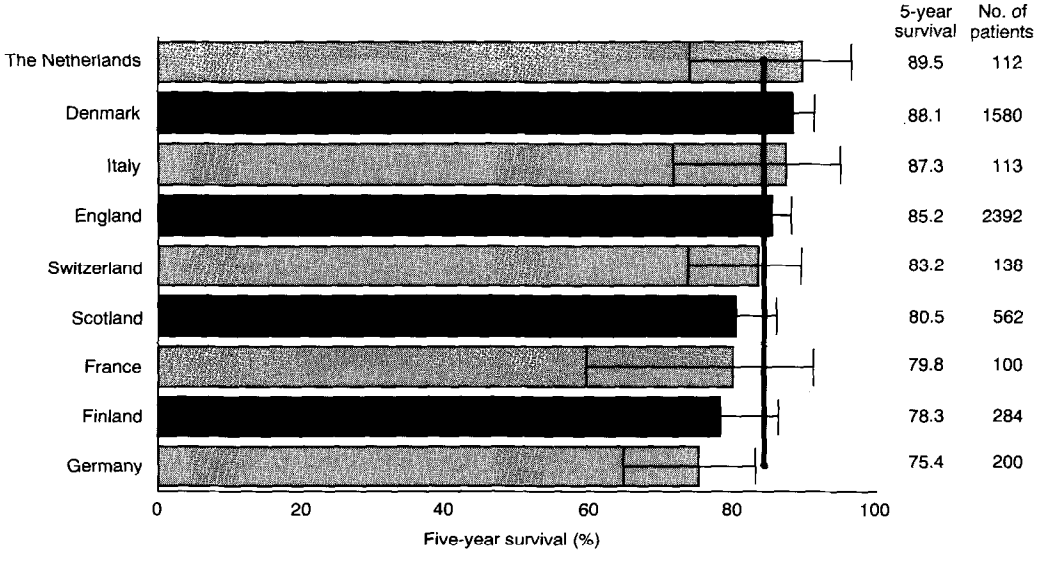


Figure 4. Testicular cancer in Europe: 5-year survival (%) 95% confidence interval and European average (vertical bar). Patients diagnosed 1978–1985 and followed up to 1990. Source: EUROCARE study (1995).

tries or regions with registries are also more likely to provide adequate early detection and treatment services.

How can treatment outcomes and survival be improved? asked Professor Dr Allen van Oosterom of the UZ (University Hospital of Antwerp, Belgium) Antwerp in a presentation at the Eindhoven meeting on the clinical implications of EUROCARE. Three factors are crucial he said: postgraduate education, both national and international; participation in clinical trials, again, on both the national, and particularly for rare tumours, international levels; and the use of treatment protocols produced by multidisciplinary teams. Van Oosterom emphasised the importance of timely adoption of treatment advances and strict adherence to quality control standards, and cited evidence from across Europe to drive home these points. Several studies showed enormous variability in surgical outcomes from one institution to another and from one surgeon to another. One study from Denmark demonstrated the importance, for treatment decisions and prognostic accuracy, of thorough lymph node biopsies in breast cancer patients. Another, from Sweden, found that a significant proportion of radiotherapy equipment was far from optimally calibrated, reducing therapeutic efficiency. Less quantifiable, but also an important influence on survival, said Coebergh, is the "culture of hopelessness " that prevails with regard to cancer in some countries, particularly the ones where early detection rates are low. "In certain countries and certain areas of Europe, patients still come very frequently with later-stage disease, " he said. "I think that's one of the reasons why in some of the Eastern European countries, and even in the U.K., there is more fatalism, the feeling that you can't do so much. It has to do in part with prosperity, with cultural attitudes, and whether the supply of specialised care is adequate ".

EUROCARE-2 will extend follow up through 1995 and add patients diagnosed through 1990 in most regions. This next phase, from which results are expected in 1997, will also include Lithuania, Slovakia and Slovenia, as well as more regions in Italy, Poland and Spain. In addition, special follow up studies are under way in a number of specific cancers to examine the relationships between stage distribution, diagnostic and treatment patterns, and survival rates.

Tom Reynolds
London, U.K., Bethesda, U.S.A.

Parts of this article first appeared in the News section of the *Journal of the National Cancer Institute*. Survival of Cancer Patients in Europe: The EUROCARE Study is available from IARC, 150 cours Albert Thomas, 69372 Cedex 08, Lyon, France.

ECL Conference in Cyprus

The 15th Annual Conference of the Association of European Cancer Leagues, Members of the UICC (ECL), was held 21–23 September 1995 in Nicosia. It was attended by delegates from 26 European leagues and associations and guests from Australia and New Zealand. Topics ranged from the tobacco problem in Europe, to professional education, clinical research, and electronic communication systems.

A presentation on tobacco and cancer by UICC President, Dr Nigel Gray, provided a unique opportunity to discuss a common strategy. It was unanimously agreed that the recommendations of the International Strategy for Tobacco Control should be a major priority of every ECL member over the next several years as a cancer prevention initiative. To meet another prime objective, that of achieving a majority in favour of restrictive legislation within the Health Council of the European Parliament, intensified collaboration with the ECL/UICC tobacco liaison office in Brussels was agreed.

Another outstanding contribution came from Professor John Smyth, representing FECS (Federation of European Cancer Societies), who addressed the delegates on the benefits and necessity of clinical research; all agreed that greater attention and support should be given to such research. Professor E. Robinson, UICC Executive Committee Member, made a presentation on undergraduate cancer education, after which the Leagues resolved to use their influence to improve medical education at both undergraduate and postgraduate levels.

Other discussions centred on new fundraising ideas, and on the subject of next year's European Week, "Sun Awareness ". The details provided by the delegates from Australia and New Zealand of their sun awareness campaigns were much appreciated and helped to make the exchange productive and useful.

Ms Sinéad Foran, ECL Coordinator
UICC News, December 1995

EORTC Activities in Healthcare Telematics

The technology of networking has advanced exponentially in the last years and terms like Internet and World Wide Web are in everyday use. EORTC too has evolved and in particular is now committed to facilitate dissemination of the results of its research very much more widely than before. The ultimate aim is to ensure that each cancer patient in Europe has access to state-of-the-art treatment, which in many instances could involve being in a research protocol.

The EORTC has joined forces with national cancer groups and a number of individual European cancer centres to set up a dedicated cancer communications network using multimedia. The name of the consortium is ACTION - Application Cluster: Telematics In Oncology.

From the clinician's viewpoint, the ACTION projects will provide:

- closer contact with developments in best practice though easier participation in clinical trials (MACRO);
- better availability of and access to best practice guidelines based on research evidence (ECOLE/GRIP);
- more effective, continuing education, based on up to data practice (MEDICO);
- active support and guidance during day-to-day clinical decision-making and patient management based on best practice (PROMPT);
- improved ability to compare against standards of best practice, and to contribute to development and maintenance of such standards (CONQUEST);
- more immediate access to third party remote specialist expertise and equipment (EUROPATH).

Other projects in the cluster address more specifically the data collection and management in bone marrow graft (MARGRITE), the medicinal product authorisation process (MANSEV), and consensus management between the application projects (HORIZON).

The nine projects of the ACTION cluster are funded by the DG XIII of the European Union. They started on 1 January 1996 and are expected to last 3 years.

EORTC is the co-ordinator of the MACRO project and is a partner in EUROPATH, CONQUEST and MEDICO.

The MACRO project develops a demonstrator of the telematics-based interaction between parties in clinical research:

- clinical trial offices which co-ordinate studies at regional, national and European level;
- clinicians in the hospitals, who treat the patients and provide clinical information to the clinical trials office.

The project aims at:

- the creation of a European network for Clinical Research for facilitating the international co-operation in clinical trials; and
- the demonstration on that network of an integrated system based on clinical databases, remote data entry, study monitoring, and patient randomisation software, in order to access the impact of telematics on data quality and on the speed of the clinical research process, as well as the administrative ease of participating in clinical research.

The approach is to integrate in a common telematics infrastructure commercial products and results achieved by previous research projects. The integration work will be performed by industrial partners following the requirements of healthcare professionals. The demonstrator will compare several solutions based on MS-Windows front-ends and World Wide Web technology.

The use of telematics techniques such as Remote Data Entry and Remote Study Monitoring will facilitate the participation in clinical trials and therefore increase the enrolment of patients and accelerate the introduction of more advanced treatment strategies. Once effectively demonstrated, the MACRO Application will be commercialised for use by any interested parties in the Medical Community at large, this will include other specialised agencies such as that for AIDS research as well as those individual physicians who have the facility of hooking into this application, and the Pharmaceutical Industry.

The EUROPATH project will foster telepathology in two directions:

- the integration of multimedia telecommunication between pathologists to improve quality assurance, diagnostic accuracy and cost efficiency of screening, diagnosis and prognosis of cancers in routine practice. In this respect the EUROPATH project will provide the inter-operable tools for:

1. remote consultation of peers or experts,
2. expertise through remotely driven microscopic observation, and
3. consensus diagnostic sessions through microscope teleconferencing

- The integration of multimedia working environment to set up European databases for evaluating the prognostic value (and then the therapeutic strategy) of the large amount of biological information now available on tumours provided by the rapidly increasing number of immunological markers and genetic probes which characterise malignant abnormalities. The co-operative multimedia working environment will be set up at the EORTC Data Centre.

The broad medical participation in the EUROPATH project will ensure the largest acceptability of the achievements by the community of pathologists. It will not only demonstrate the impact of telematics for pathology but also launch intensive tele-working for improved clinical routine, internal and external quality assurance, education, proficiency testing and clinical research since improved and consensus knowledge of malignant lesions is expected to provide the breakthrough for decreasing cancer mortality by 20% in the next decade.

The CONQUEST project develops generic, multimedia-based, quality assurance systems which can be rapidly disseminated by telematics to all relevant treatments sites and professionals so that variations in cancer treatment outcomes can be reduced or eliminated.

It is anticipated that improvement in the quality available cancer treatments will result in a 5 to 10 % improvement in survival rates. This means that within the EU, potentially 90 000 to 180 000 lives will be saved annually.

The MEDICO project will develop a range of telematics-based education and training materials incorporating best practice in oncology. EORTC will provide medical expertise. By conventional networking and satellite television, doctors will ask questions, comment on presentations and add their own experience.

To help in the management of its participation in the telematics projects, the EORTC has appointed a telematics consultant, named Mr Marc Peeters, who is Vice-President at the Janssen Research Foundation. An Information Systems consultant will be hired for the project management activities.

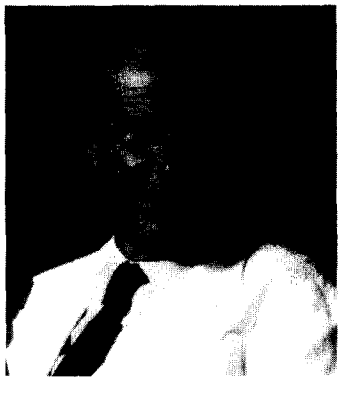
In conclusion, as the most represented partner, EORTC will provide the ACTION cluster with significant expertise for the improvement of the quality and consistency of cancer care across Europe, and for the improvement of the chances of survival of a patient with cancer.

Vincent Piedboeuf

From the Countries

Update of the Italian Tamoxifen Study

Three major studies of chemoprevention of breast cancer are presently going on: one in the U.S.A., one in the U.K. and one in Italy. While the first two studies are addressed to high risk subjects for breast cancer, the Italian trial has the distinction of being addressed to hysterectomised healthy women only. This decision was taken with the aim of avoiding the most important potential adverse effect of tamoxifen: the risk of an endometrial cancer is in fact the main argument against the use of tamoxifen in chemoprevention trials.



Professor U. Veronesi

The 46 centres participating in the trial (43 in Italy and 3 in South America) are co-ordinated by the European Institute of Oncology in Milan and they all have to meet the minimum requirements to join the study, in terms of clinical and radiological experience. A quality control system is operational for data, clinical and radiological management. Centres are regularly visited to check the quality and the validity of data. All centres must also follow the guidelines given to reach an homogeneously high standard of quality, both clinically and instrumentally.

The quality is periodically discussed and checked under the supervision of a team of experts in radiology and breast cancer clinics.

The Director of the Epidemiology and Statistic Department of the European Institute of Oncology, responsible for the data management, has established the "Data Monitoring Committee ", consisting of three statisticians (R. Brookmeyer, Baltimore; M. Hakama, Tampere; A. M. Walker, Boston) which holds periodical meetings to discuss the interim analysis of the data resulting from the study.

The Italian Chemoprevention Study started accrual in October 1992. As of 15 November 1995, 4229 subjects had been enrolled in the study, while the last descriptive analysis, to which the following data refer, was carried out in June, on a basis of 4033 women.

31.3% of the randomised subjects were aged between 50 and 54 years; 1.7% were less than 40 years old, while 11.6% were more than 60 years old.

46% of the women had bilateral oophorectomy during the hysterectomy, while 21% had monolateral oophorectomy only; in 26.5% of the cases both ovaries were spared during the post operation.

18% of women have at least one first degree relative suffering from breast cancer. 16% of the enrolled women are using hormonal replacement therapy which is not a criteria of ineligibility in our study, unless long-term usage is envisaged.

Follow-up data concerns 3220 women who carried out at least one follow-up visit with an overall median duration study of 11 months.

58% of subjects reported complaints, most of the symptoms being menopausal disturbances. Hot flushes were reported in 36% of the women (in 20% these symptoms were already present at the baseline), vaginal discharge in 11%, vaginal dryness in 11% (only 4.4% reported these two symptoms at the baseline).

Other symptoms noted are gastrointestinal disturbances (6%), urinary disturbances (6%), dermatological alterations (4%), anxiety (4%) and hypertension (2%). As far as new diseases during the treatment period, superficial phlebitis was reported in 18 subjects and deep thrombosis in 3 subjects. Moreover, there was 1 subject with pulmonary embolism after 26 weeks of use, who recovered after treatment.

The drop-out rate is presently 13%, 24.5% of which are due to referred symptoms and 14% to intercurrent events.

The accrual to the study has been quite constant over the past months and our aim, in the next two years, is to increase in a significant way the number of randomised women.

U. Veronesi, Milan, and the Italian Tamoxifen Trial Units

The Italian Tamoxifen Chemoprevention Study is made possible by The Italian League against Tumours (Milan), the Italian Association for Cancer Research (Milan), the American Italian Cancer Foundation (New York), the Italian Foundation for Cancer Research (Milan), the Foundation for the Training in Oncology (Milan), the National Research Council (Rome), the A.S.S.I.L.S. (Rome) and the Italian Diagnostic Centre (Milan).

NHL Trial in England Tests Antisense Drug

The Royal Marsden NHS Trust and Genta Inc. (NASDAQ:GNTA) have begun the first clinical trial to treat non-Hodgkin's lymphoma using an antisense drug.

The phase I/II trial is being conducted in England using the antisense drug Anticode G3139, designed to bind to the messenger RNA of BCL2. The gene product of BCL2 is present in higher concentrations than normal in many tumours including more than 80% of follicular lymphomas and 50% of intermediate/high-grade lymphomas.

The primary objective of the study is to determine the maximum tolerated dose. A secondary objective is to look for preliminary evidence of antitumour activity. BCL2 Anticode oligonucleotides are being administered as a subcutaneous infusion for 2 weeks. 30 patients are expected to be enrolled.

(Press Release, November 1995)