

EUROCARE-4

PROTOCOL FOR EUROPE-WIDE CANCER SURVIVAL STUDY

4 November 2004

INDEX

1. Introduction
 - 1.1 Aims of the project
 - 1.2 Resources
 - 1.3 Confidentiality and security
 - 1.4 Outcome and publication policy
2. Criteria for inclusion
3. Data to be collected
 - 3.1 Sex
 - 3.2 Date of birth
 - 3.3 Date of diagnosis
 - 3.4 Date of tumour registration
 - 3.5 Date of last known vital status
 - 3.6 Vital status
 - 3.7 Primary tumour site
 - 3.8 Microscopic confirmation of diagnosis
 - 3.9 Morphology
 - 3.10 Summary extent of disease at diagnosis
 - 3.11 Identification code
 - 3.12 Multiple tumours
 - 3.13 Stage at diagnosis
 - 3.13.1 TNM
 - 3.13.2 Condensed TNM
 - 3.14 Size of tumour in millimetres
 - 3.15 Number of examined nodes
 - 3.16 Number of metastatic nodes
 - 3.17 'C' factor
 - 3.18 Treatment
 - 3.18.1 Surgery with curative intent
 - 3.18.2 Chemotherapy with curative intent
 - 3.18.3 Radiotherapy with curative intent
 - 3.18.4 Other therapy
 - 3.18.5 Any symptomatic treatment
 - 3.19 Underlying cause of death
4. Updating the EUROCARE data
 - 4.1 Updating the EUROCARE data on survival
 - 4.2 Updating the life tables for general population mortality
5. References

1. INTRODUCTION

EUROCARE is a research collaboration established in 1989, and currently involving population-based cancer registries in 20 European countries, 17 of which are members of the European Union (enlarged to include 25 member states in May 2004). The EUROCARE project has provided regular monitoring of cancer patient survival in participating countries and, on a sample basis, evaluation of the care of cancer patients. EUROCARE-1 included patients diagnosed during the period 1978-85 and followed up to 1989. EUROCARE-2 and EUROCARE-3 were extended to include patients diagnosed during 1985-89 and 1990-94, respectively^{1,2}. This protocol refers to EUROCARE-4, which will include patients diagnosed between 1995 and 2002.

The EUROCARE Co-ordinating Centre is at the Istituto Nazionale per lo Studio e la Cura dei Tumori (INT) in Milan (Italy). Data checks and basic analyses are performed at the EUROCARE Data Analysis Centre at the Istituto Superiore di Sanità (ISS) in Rome (Italy), where the data are stored.

1.1 Aims of the project

This study protocol incorporates decisions taken by the EUROCARE Steering Committee at its meeting in Milan on 3 March 2004, and by the meeting of the EUROCARE working group in Ragusa, on 23rd September 2004.

Substantial changes in cancer patient survival are expected to have arisen in recent years. These will variously reflect changes in the health care systems in European countries, implementation of national cancer plans, implementation of screening programmes for new cancers or extension of screening to wider age ranges, and more generally, progress in diagnosis and therapeutics.

EUROCARE-4 will update and expand the existing EUROCARE survival data base in order to:

- To continue monitoring cancer survival in Europe, including additional countries if possible
- To shorten the time lag between data collection and publication;
- analyse whether the substantial differences in survival between countries which emerged from the previous surveys are still present;
- To proceed in the interpretation of survival differences, also using the available information on stage;
- To update prevalence estimates in Europe;
- To extend the follow-up of cancer patients included in previous analyses, in order to provide reliable estimates of temporal trend in cancer patient survival over long periods;
- To develop the application of mixture survival models to estimate the proportion of cancer patients who are 'cured';
- To improve the quality of survival statistics, e.g. by using available information on cause of death to compare relative with net survival;
- To quantify the effect on survival of possible incompleteness of incident cancer registration;
- To test the application of period survival analysis to European data; a specific study protocol has been prepared for this part (see the attached study protocol)
- To continue studying the outcome from rare tumours, by using the large data base now available;
- To make data sets available to participating EUROCARE centres for further analyses. As before, the Co-ordinating Centre (INT) and the Data Analysis Group (ISS) will give assistance to researchers interested in such studies.

1.2 Resources

Specific resources (personnel, computers, facilities) have been allocated by INT (Milan) and ISS (Rome) for the co-ordination and data analysis activities of the EURO CARE project. Six senior researchers (three in Milan and three in Rome) and two secretaries (one in Milan and one in Rome) will devote about 50% of their activity to the project. Two junior researchers (20% each) in Milan and two data analysts (80% and 20%) in Rome are also ready to spend part of their time for the project. A dedicated server is available at ISS for data storage and analysis. Limited funds for meetings and travels are in general available at the two Institutes, even though a specific budget cannot be stated in advance. Coverage for specific initiatives will be asked on a time to time basis.

1.3 Confidentiality, security and ethical approval

As in the previous EURO CARE studies, tumour data will be stored individually, but anonymously. Data will be stored in a dedicated computer that is not connected to the web, and according to the standard requirements for data security at ISS (Rome). Data handling conforms with the guidelines published by the International Association of Cancer Registries. (www.iarc.fr) The EURO CARE protocol received institutional approval as part of the CONCORD project from the Scientific Ethical Committee of the Istituto Superiore di Sanità in 2002.

1.4 Outcome and publication policy

The basic outcome of EURO CARE-4 will be the analysis and publication of survival of cases diagnosed in 1995-1999. Within May 2005, most registries will be able to provide survival on cases incident up to the year 1999 with follow-up to 31/12/2003. During 2005 these data will be checked and analysed by the methods developed in EURO CARE 1-3. By the end of 2006, the results will be published in a monograph presenting survival by country, and time trend analysis. Then, scientific articles will be planned on specific cancer sites, including analyses on prevalence, long-term survival, and proportion cured by stage.

A electronic publication (the EURO CARE-4 CD-ROM), similar to the EURO CARE-3 one, is also envisaged, including all the CR according to their available data.

The EURO CARE publication policy incorporates guidelines that have been approved by all participants, and last updated in September 2004. It is available on the EURO CARE web-site (www.eurocare.it).

2. CRITERIA FOR INCLUSION

All primary malignant cancers are eligible for inclusion in the database, except non-melanoma skin cancer. Data for all tumours will be collected, including death-certificate-only (DCO) cases, those discovered at autopsy and those lost to follow-up. The anatomic location of tumours will be coded according to the International Classification of Diseases (ICD), either 9th or 10th revision^[3,4]. Morphology will be coded according to ICD Oncology (ICD-O) (preferably 2nd revision, but the 1st and 3rd editions will also be accepted^[5,6]). Both microscopically verified and non-verified cases must be included.

In situ and benign neoplasms (as identified by the ICD-O behaviour code) will also be included in the database, but not in survival analyses. The relative frequency of such neoplasms will help in the interpretation of survival differences, because it may be an indicator of the intensity of early diagnostic activity.

A special procedure will be applied for **multiple primary malignant tumours**. As in previous EURO CARE studies, in the case of multiple malignant tumours, only the first malignant tumour in a given person will be included in basic survival analyses (non-melanoma skin cancer and benign and *in situ* tumours, however, will be ignored as the first cancer in a multiple primary sequence). Registries will also be requested to provide a separate file of tumours that were eliminated as second (third, etc.) malignant tumours in a given person. When possible, the same identification code should be given to all tumours that occurred in the same person. The structure of the records in files containing data for second or subsequent tumours should be the same as that of the main survival data file.

There are two main reasons for systematically collecting data on subsequent primary tumours:

1. A large data set such as EURO CARE may provide useful information on survival from a given first primary cancer, conditional on the development of a specific second primary malignancy. Such information is rarely available from either clinical or population-based case series.
2. Taking account of the occurrence of second cancers, especially for first tumours of relatively good prognosis, is essential for obtaining unbiased estimates of site-specific prevalence.

3. DATA TO BE COLLECTED

The structure of the data files requested for EUROCARE-4 will be the same as that used for EUROCARE-3, both to simplify data preparation for participating registries and to facilitate the integration of new data files with the existing EUROCARE data.

Codes for country and cancer registry, assigned to every participating centre, will be automatically inserted at the beginning of each individual tumour record in the survival file by the Data Analysis Centre. Standard UN codes will be used for the country, and the codes used for *Cancer Incidence in Five Continents* will be used for the cancer registries, in order to facilitate the integration of EUROCARE data with other data bases.

Other data are to be recorded on an individual basis. For each patient the following variables are required:

3.0 IARC check flag Compulsory

|1| = record checked according to the IARC CHECK program

|2| = record not checked

This field will be used to avoid useless requests for controlling again records already checked and verified by the registry.

3.1 Sex (one-digit variable) Compulsory

|1| = male

|2| = female

|9| = ambiguous or unknown sex

3.2 Date of birth Compulsory (two-digit variable for the month, four-digit variable for the year)

| | | | | | | |

month year

3.3 Date of diagnosis Compulsory (two-digit variable for the month, four-digit variable for the year)

The date of tumour occurrence should be consistent with that used for computing incidence in the study period. Every participating registry should describe how the index date was defined for the purpose of computing incidence.

| | | | | | | |

month year

Month of diagnosis is essential for the analysis of survival. If, in a few cases, the month is not available, the field must be left blank.

3.4 Date of case registration

Optional

(a two digit variable for the month and a four digit variable for the year)

This information is optional, and is expected to be provided only by the registries where it is routinely available. It will be used to study the frequency and the survival characteristics of late registrations, in order to estimate any bias due to incompleteness of recent incident data.

By default, this date is the one of first notification (requested here). However, some registries input the date when the case file is complete, at the end of the registration process. So, to be sure of the meaning of the date provided below, every centre will be requested to define which date is given in the accompanying letter.

In all situations, we should be able to deal with the date provided.

 |_|_| |_|_|_|_|
month year

3.5 Date of death or of last known vital status

Compulsory

(two-digit variable for the month, four-digit variable for the year)

Participating centres will follow patients up with their usual procedures. This field must be completed with the date of death or of last known vital status. For those who were lost to follow-up, the last date on which they were known to be alive must be reported.

 |_|_| |_|_|_|_|
month year

Registries are also requested to specify in the accompanying letter the date of the end of follow-up for the study as a whole, i.e. the most recent date at which follow-up of the entire patient cohort is considered to be acceptably complete.

3.6 Vital status (one-digit variable)

Compulsory

|1| = alive at the date of last known vital status

|2| = dead. Give the date of death in the variable (3.5) for last known vital status

 |3| = lost to follow-up. For these cases, the last date at which they were known to be alive should be given in variable 3.5 above. If no date is known, report the date of diagnosis

|4| = death-certificate-only (DCO) case. For these cases, the date of diagnosis is the same as that of death

|5| = autopsy-only case (detected only at autopsy). For these cases, the date of diagnosis is also the same as that of death

3.7 Primary tumour site (four-character variable, the last of which indicates subsite) Compulsory

ICD-O, ICD-9, or ICD-10 are allowed.

Registries are requested to specify in the accompanying letter which ICD classification is used.

|_|_|_|_|

Primary tumour site code

3.8 Microscopic confirmation of diagnosis (one-digit variable) Compulsory

|1| = histologically confirmed

|2| = cytologically confirmed

|3| = microscopically confirmed, but not known whether by histology or cytology

|4| = no microscopic confirmation

|9| = unknown

3.9 Morphology (five-digit variable) Compulsory

Tumour morphology should be coded to the International Classification of Diseases for Oncology (ICD-O), preferably the 2nd edition, but the 1st edition is also acceptable.

Registries are requested to specify in the accompanying letter which classification is used. Registries that do not record morphology according to the ICD-O criteria should state this and use their own code. They will be contacted individually.

Registries are also requested to state clearly the meaning of behaviour codes /6 and /9 when sending their data.

|_|_|_|_|

ICD-O morphology (4) and behaviour (1) codes

3.10 Summary extent of disease at diagnosis (one-digit variable) Compulsory

|1| = tumour is confined to the site of origin

|2| = tumour has spread to immediately adjacent tissues and/or regional lymph-nodes

|3| = tumour has spread to distant organs

|4| = tumour is not confined to the site of origin but not specified whether code 2 or 3 applies

|5| = no distant metastasis but not specified whether code 1 or 2 applies

If no stage information is available, or if the case cannot be classified, this field will be left blank.

3.11 Identification code (ten-digit field)

Compulsory

The anonymous identification code used by the registry will be used to retrieve those cases which present any problem when the data are checked. In order to avoid repeatedly being asked to check the same records, registries should if possible use the same identification codes used for EURO CARE-3 for those cases already analysed in EURO CARE-3.

|_|_|_|_|_|_|_|_|_|
Identification code

3.12 Multiple tumour code (one-digit variable)

Compulsory

Two separate files are requested. First primaries will be sent in one file; subsequent primaries will be sent in a second file. This field is not to be used for non-melanoma skin cancers, *in situ* tumours, and non-bladder benign tumours. The multiple tumour field has to be coded as follows:

|_| = non-melanoma skin cancer, *in situ* tumour or non-bladder benign tumour
|0| = single tumour (the only primary malignancy recorded for this person)
|1| = first primary malignancy of two or more primary malignancies
|2| = second or subsequent primary malignancy

Note: In the file of first primaries sent for analysis, only values 0, 1 or blank are allowed. In the file of second or subsequent primaries, only value 2 is allowed.

3.13 Stage at diagnosis

Optional

When stage data coded to the TNM classification are available, they should be reported. When TNM data are not fully available, it is proposed to record this information according to the recommendations of the IARC Working Group on the extent of disease (www.iarc.fr). If neither TNM nor the condensed TNM is available, the only information on stage will be that given in section 3.10. The pathological stage (pT and pN) should be reported, if available. Clinical stage should be reported only when pathological stage data are not available.

3.13.1 TNM^[7] (up to seven characters)

Optional

Pathological codes for tumour size (pT) and nodal involvement (pN) should be used if available. Clinical or pathological codes for metastases are both acceptable (M).

T |_| |_|
number letter(s)

N |_| |_|
number letter(s)

M |_|
number

3.13.2 Condensed TNM (three-digit variable) Optional

T |1| = Localised. This category includes T1-2 tumours. Exceptions: T3 tumours of the **thyroid, breast, and melanoma** (see below) are to be considered as *localised*
|2| = Advanced. This category includes T3-4 tumours. Exception: T2 tumours of **ovary** are to be considered as *advanced*

*Skin melanoma: code as T|1| (localised) those melanomas in TNM categories T1-3 (corresponding to Breslow thickness less than or equal to 4.00mm and Clark levels II-IV)
Code as T|2| (advanced) those melanomas in TNM category T4 (corresponding to Breslow thickness >4.00mm and Clark level V)*

N |0| = no regional lymph-node metastases
|1| = metastasis in the regional lymph-nodes

M |0| = no distant metastasis
|1| = distant metastasis

3.14 Size of tumour in millimetres (three-digit variable) Optional

This should be based on histological examination, if available.

|_|_|
millimetres

3.15 Number of examined nodes (three-digit variable) Optional

Report the exact number, as recorded in the pathological records.
If no information is available, or if pathological examination was not performed, code 999.

|_|_|
number of nodes examined

3.16 Number of metastatic nodes (three-digit variable) Optional

Report the exact number, as recorded in the pathological records.
If no information is available, or if pathological examination was not performed, code 999.

|_|_|
number of metastatic nodes

3.17 ‘C’ (certainty) factor (one-digit variable) Optional

This variable reflects the likely validity of the stage of disease data for a given tumour according to the diagnostic methods used to determine it. It refers to diagnostic examinations carried out to detect or exclude local extension or distant metastases. A simplified classification will be used, according to that proposed by the IARC Working Group on extent of disease [www.IARC.fr].

|1| = C1 - evidence from standard diagnostic methods only
|2| = C2 - evidence from special diagnostic methods

Use code 2 (C2) when computerised [axial] tomography (CT or CAT) scan, ultrasonography, nuclear magnetic resonance (NMR) imaging (MRI), or surgery have been used to explore the anatomic region where the tumour is located for cancers at the following sites:

- head and neck (ICD-9 140-149 and 160-161)
- thorax and mediastinum (ICD-9 150,162-164): examinations may also include mediastinoscopy
- pelvis (ICD-9 179-188): examinations may also include laparoscopy

Exceptions:

- digestive tract (ICD-9 151-157): use of code C2 requires evidence of liver imaging
- breast (ICD-9 174) and prostate (ICD-9 185): use of code C2 requires evidence of bone imaging (scintigraphy or multiple X-ray investigation)

*Note: The C code should be used to indicate whether the relevant examination has been performed, **regardless** of the result of the examination (positive or negative).*

3.18 Treatment

Optional

First course of therapy after diagnosis:

3.18.1 Surgery with curative intent (one-digit variable)

- |1| = yes
- |2| = no
- |9| = no information

3.18.2 Chemotherapy with curative intent, including adjuvant (one-digit variable)

- |1| = yes
- |2| = no
- |9| = no information

3.18.3 Radiotherapy with curative intent, including adjuvant (one-digit variable)

- |1| = yes
- |2| = no
- |9| = no information

3.18.4 Other therapy with curative intent (one-digit variable)

For example, hormonal treatments such as tamoxifen, etc.

- |1| = yes
- |2| = no
- |9| = no information

3.18.5 Symptomatic treatment (one-digit variable)

For example, radiotherapy given to bone metastases, or intestinal deviation.

- |1| = yes
- |2| = no

|9| = no information

3.19 Underlying cause of death

Optional

ICD-9 or ICD-10 are allowed.

Surely you must specify that you are referring to the underlying cause of death, i.e. the cause selected as the one to be coded for the purpose of mortality statistics, usually by the national or regional vital statistics office concerned. Also who determined the underlying cause of death. There may be inconsistencies between registries (some of which code the underlying cause of death themselves for net survival analysis) and the vital statistics office, and in a comparison of net and relative survival this is important.

Registries should specify in the accompanying letter the source of the code for underlying cause of death (e.g. the cancer registry, or the regional or national vital statistics office. If coding was done by the vital statistics office, please specify whether this was done manually by nosologists or with automated cause coding software).

|_|_|_|_|

ICD code for underlying cause of death

4. UPDATING THE EURO CARE DATA

4.1 Updating the EURO CARE survival data

Data for all cases collected by participating cancer registries and diagnosed from 1978 to 1999 inclusive should be sent to the Data Analysis Centre in Rome, using the record structure indicated in Section 3. A fixed format record is requested for each tumour. Data files will be submitted to the same checks and procedures that have been developed and tested in the framework of previous EURO CARE studies and published on the EURO CARE website www.eurocare.it.

All data files should be received in Rome by 31 May 2005, in order for preparation of the data base for analysis to be completed before the end of 2005.

4.2 Updating the life tables of general population mortality

These will be provided by the registries using the same modalities as for EURO CARE-3. In principle, it would be preferable to obtain from each registry life tables for the population of the territory they cover for single calendar years from 2000 up to the most recent year for which data are available.

Life tables may be sent either on magnetic media or as copies of official publications of the demographic and mortality data for the country or region covered by the registry. If life table files are sent electronically or on magnetic media (tape, disk, CDROM) the files must be sent separately from the cancer registry tumour data.

Survival probabilities, or general population mortality rates, should be provided to 5 or 6 decimal places or an equivalent number of significant figures (e.g. 0.012345 for a rate of 1,234.5 per 100,000) by sex, age and year, up to the most recent year available. The time periods must be indicated in the file. General population mortality is highly dependent on age. Whenever possible, data for one-year age classes should be provided, and in any case, the width of age classes must not exceed five years.

Availability of accurate mortality data for the oldest ages is also of the greatest importance for the correct calculation of relative survival rates. The upper age class provided for population mortality rates will preferably be for persons aged 85 or more, and should not be less than for persons aged 65 or more.

Full bibliographic citations to official literature or web-sites should be provided for the source of demographic data. Participating centres should also provide the name of a reference person able to provide more detailed information regarding general population demographic data if that should be required.

Data in any standard storage device should be sent by surface mail, along with an accompanying letter describing the content.

The life table data will be stored and submitted to centralized data checks and analysis at the Istituto Superiore di Sanità in Rome, Italy.

All data should be sent to:

Dr Riccardo Capocaccia
Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute
(*National Centre for Epidemiology, Surveillance and Health Promotion*)

Istituto Superiore di Sanità
Viale Regina Elena, 299
I-00161 Roma, Italy

References

1. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Esteve J (Eds). Survival of Cancer Patients in Europe. The EUROCORE Study. IARC Scientific Publications N.132. International Agency for Research on Cancer, Lyon 1995
2. Berrino F, Capocaccia R, Estève J, Gatta G, Hakulinen T, Micheli A, Sant M, Verdecchia A (Eds.). Survival of cancer patients in Europe 1985-89: The EUROCORE II Study. IARC Scient. Publ. No. 151:525-542, 1999.
3. Berrino F, Capocaccia R, Coleman MP, Estève J, Gatta G, Hakulinen T, Micheli A, Sant M, Verdecchia (Eds). Survival of Cancer Patients in Europe: the EUROCORE-3 Study. *Ann Oncol.* 2003;14 Suppl 5
4. Manual of the International statistical classification of diseases, injuries, and causes of death. Ninth revision (ICD-9). World Health Organisation Geneva, 1977
5. International statistical classification of diseases, injuries, and Related Health problems. Tenth Revision (ICD-10). World Health Organisation Geneva, 1991
6. International Classification of diseases for Oncology. First edition, World Health Organisation Geneva, 1976
7. Percy C, Van Holten V, Muir C (editors). International Classification of diseases for Oncology. Second edition, World Health Organisation Geneva, 1990
8. Spiessl B, Beahrs OH, Hermanek P, Hutter RVP, Scheibe O, Sobin LH *et al.* (eds.) *TNM Atlas: illustrated guide to the TNM/pTNM classification of malignant tumours* (3rd edition). Berlin: Springer Verlag, 1992.