Hamburg University of Applied Sciences
Postgraduate Course ‘Master of Public Health’

Feasibility and use of registry-based cancer survival analysis, demonstrated for malignancies of the colon, breast, prostate and bladder in Hamburg

– Master Thesis –

submitted February 27th 2006
by

Dr. Alice Nennecke
Kirchentwiete 29b
22765 Hamburg

Ref.:
Prof. Dr. Ralf Reintjes
Dr. Stefan Hentschel

Contents

Abbreviations

95%CI	95% confidence interval
BCG	Bacille-Calmette-Guérin *(tuberculosis vaccine)*
BMG	Bundesministerium für Gesundheit
Cobs	Cumulative observed survival
Crel	Cumulative relative survival
DCO	Death Certificate Only
DIMDI	Deutsches Institut für Medizinische Information und Dokumentation
EDP	Electronic Data Processing
GEKID	Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.
HCR	Hamburg Cancer Registry
HmbKrebsRG	Hamburgisches Krebsregistergesetz
IARC	International Agency for Research on Cancer
ICD-O-3	International Classification of Diseases for Oncology, 3rd Revision
ICD10	International Classification of Diseases, 10th Revision
MARIE	Mammakarzinom-Risikofaktoren-Erhebung
PSA	Prostate Specific Antigen
RKI	Robert Koch-Institut
SE	Standard Error
SEER	Surveillance, Epidemiology and End Results
TNM classification	*cancer staging system*, *indicating* tumor size, lymph node metastases *and* distant metastases
UICC	Union Internationale Contre le Cancer

1. Introduction

Cancer is a global public health problem, and the world population growth and ageing imply a progressive increase in the cancer burden. Estimates concerning the year 2000 showed 10 million new cases and more than 6 million deaths tantamount to second leading cause worldwide (Parkin 2001, 533). Yet the frequencies and profiles vary greatly in different populations and over time, and their understanding helps to define causal hypotheses. Data on disease occurrence and outcome are essential to scientific research and health policy by quantifying the problems, identifying priorities and evaluating outcomes in relation to resource inputs. With regard to malignancies population-based cancer registries are the appropriate institutions for the continuous and systematic collection, storage, processing, analysis and interpretation of data on incidence and mortality of reportable neoplasms in defined regions, focusing on epidemiology and public health (GEKID 2006, 4; Sankila 2005).

The present study deals with the issue of registry-based cancer survival analysis. Patient survival is generally accepted as the principal criterion for measuring the effectiveness of prevention and treatment in cancer, and becomes even more important in the context of quality assurance. Its feasibility and explanatory power in relation to a particular population depends on the quality of the respective database. The Hamburg Cancer Registry exemplifies the subject in this investigation. Prior to the central investigation the institution is introduced by a brief chapter on its history, followed by the presentation of legislation and current performance. The preliminary part closes with a paragraph on basic concepts of survival analysis. According to the task of a self-contained second part minor recurrences, particularly in 3.1., were accepted.

2. The Hamburg Cancer Registry

2.1. History[1]

The Hamburg Cancer Registry (HCR) belongs to the oldest population-based cancer registries of the world (IARC 1993).The origins of systematic registration of malignancies in the Hanseatic city may be traced back more than 100 years. Already at the turn of the 19th century scientific papers dealing with statistical evaluation of cancer-related mortality in the city at that time were published: “Zur Statistik des Carcinoms” presented cancer related deaths in 1872-1898, classified according to sex and 18 sites, and was followed by “Sterbefälle an Krebs in Hamburg, 1900 bis 1929” (Reiche 1900; Schwanke 1930). First approaches

---

[1] The following text is based on the sources STATISTISCHES LANDESAMT 1973, VII-VIII; HOFFMEISTER 1981, 43-46 and BUCHHOFER 1987, 19-22, if not cited otherwise.

to invent a continuous notification system started in 1927. The Hamburg health authority induced general hospitals to regularly complete so-called tumor cards, which were to be collected and checked by the health authority at the end of the year. Having been passed on to the statistical state office for further processing deaths were separated, and cards to be continued were returned to the issuing institutions. When in 1929 a cancer welfare service of the public health office, called ‘Nachgehender Krankenhilfsdienst’, took up its work cancer statistics were attached to it right from the beginning. The HCR had been founded as a by-product, also dependent on the statistical state office as data processing facility. Up to World War II the medical district officer Sieveking advocated its improvement and completion.

In 1952 the central Hamburg cancer statistics were reconstructed by cooperation of health authority and statistical state office. During the following years systematic adjustments, conversions, the application of standardized tables and the combination with the official mortality statistics were realized. Until the late seventies the working methods hardly changed: On a voluntary basis hospitals, radiotherapy and pathology institutes sent tumor cards on cancer cases, cancer-related deaths and post-mortem findings to the health authority’s cancer welfare service. The respective nurses continued the forms by documenting results of follow-up examinations, and passed them on to the statistical state office to be integrated into the central cancer card-index. Multiple notifications were prevented by use of an alphabetical search register, information from death certificates served for the purpose of control and completion.

The participation in international projects like regular reports to the Union Internationale Contre le Cancer (UICC) and a pilot study on cancer morbidity supported by the European council during the sixties caused a revised design of tumor reporting cards and reformed processing directives. Machine-made calculations resp. automatic data keeping and processing by the central city's EDP were invented. In 1973 the first of several consecutive periodic publications was edited as “Hamburger Krebsdokumentation”, covering the years 1956-1971.

The second serious recess in the HCR´s history occurred in the early eighties including a period of stagnation and reconstruction lasting for years. It had been triggered by an altered legal assessment of traditional registration methods, criticizing the lack of a statutory basis for the electronical storage of personal data. Contemporaneously the Federal Government and its Laender began to engage in cancer epidemiology, in 1983 they agreed on 16 theses concerning the establishment of regional cancer registries (Schleswig-Holsteinischer Landtag 1996, 7). Based on these the Hamburg citizen's parliament passed its cancer registration law “Hamburgisches Krebsregistergesetz“ in 1984, see below.

In 1986 the HCR became a self-contained section of the newly founded department 'Health and Environment' within the health authority, now independent of cancer welfare service, statistical state office and central city's EDP. After a considerably declined notification yield in 1980-1986, the situation gradually improved by a systematic utilisation of statutory options. During the nineties further steps enhancing both quantity and quality of reported case were undertaken, including reimbursement of physicians and the systematic retracing of cases having been reported to the HCR by death certificates only (DCO-cases).

2. 2. Legislation and data protection

The cancer registration law, titled "Hamburgisches Krebsregistergesetz" (HmbKrebsRG) became effective on January 1st 1985, with amendments in 1990 and 2004 (A-3 - A10). The law defines the HCR to be run by the competent authority, presently the Hamburg Authority of Science and Health, the tasks and general conditions. Its main intention consists in the support of cancer research by means of collection, processing, analysis and distribution of data on origin, incidence and course of malignancies (§1). The essential elements are the principle of informed consent concerning the patient and voluntariness of cooperation on the part of the physician (§2). Contrary to frequently uttered scepticism, the majority of patients is reported to willingly provide their data for scientific purposes (Hamburgisches Krebsregister 2004, 8). On behalf of targeted completeness an exception of informed consent had been integrated into the law, specifying the patient's long-term inability to approve of notification and the risk of impending deterioration by enlightenment on diagnosis §2(2).

The contents of notifications, the evaluation of further documents and the data storage, esp. an obligatory separation of personal and anonymized data groups, are regulated by §§3-5, while §§6-9 refer to utilization of data. Particularly the use of individual-related information has to be allowed by the head of authority after having heard the data protection officer and the Hamburg medical association's ethical committee (§9). If patients or third parties ought to be interviewed the voluntariness of their cooperation has to be pointed out to them (§§10,11). The rights of persons concerned include informational issues as well as an option to claim cancellation of their particulars (§12).

Data protection is emphasized additionally by technical facilities: Data entry and keeping are executed by an in-house EDP-System including a PC network, exclusively serving registry tasks and not linked to any other computer system. The server is placed solely in a safeguarded room which may be entered by authorized persons only. All premises where sensitive data are being processed, as well as the server, are covered by an alarm system, and the computer access is password protected. The delivery of documents containing personal data is particularly secured, too.

A temporarily enacted federal law (1995-1999) directing the establishment of population-based cancer registries in all German states did not require any adjustments of the legal regulations in Hamburg (Gesetz über Krebsregister 1994). The constitution of neighbouring registries nevertheless resulted in the request of data transmission concerning patients resident beyond Hamburg and vice versa, which was enabled by an amendatory alteration of §2(5) HmbKrebsRG in 2004.

2. 3. Methods of registration and data processing

The HCR registers all malignant neoplasms including second primary cancers. Benign neoplasms and suspicions of malignancies are not documented, while neoplasms of uncertain or unknown behaviour as well as In situ stages are recorded without being included into incidence calculations.

The variables to be documented in the scope of notification comprise the items presented in table 1.

Table 1: Requested variables in notifications of malignancies to the HCR

Subject	**Variable**
Notification:	notifying institution* and physician/dentist*
	type of notification*, i.e. consent / exception / death
	date of notification*
Personal data:	fore-* and surname*, previous names
	address*
	date of birth*
	nationality
	sex*
	smoking habits
Medical data:	date of diagnosis*
	topography, i.e. primary site (ICD10)*
	laterality
	extent of disease (stage resp. T*N*M*-code)
	certain site-specific indices: Breslow index, Gleason-score
	morphology, i.e. histology*
	histopathological grading
	most valid basis of diagnosis
	if applicable: date of death*

* obligatory statement; concerning medical data the option ‘not specified’ is provided

The classification of topography, i.e. primary site, is based on the current German version of the International Classification of Diseases ICD10 (DIMDI 2003a). Morphological resp. histological characteristics are coded by means of the ICD for Oncology ICD-O-3 (DIMDI 2003b). The “TNM Classification of Malignant Tumours” (6th edition), and a table on transformation of TNM-classifications to stages of cancer spread by the GEKID are applied if the extent of disease is to be documented (Wittekind et al. 2002; GEKID 2005). It is assumed that notifying physicians use former editions of coding directions to some extent, and that despite transformation processes integrated into the registry’s software minor inaccuracies are inevitable.

Both the HCR and those notifying aim at the lowest possible effort to integrate the reporting procedure into the clinical work. Therefore several ways to notify cases of cancer have been developed:

The ‘classic’ notification sheet is completed by hand, and widely-used by medical practitioners, hospitals and sporadically nursing homes (A-11). Another paper way results from the cooperation with pathologists, where the attending physician receives along with the report on pathological findings a separate EDP-derived form containing relevant information on the malignancy. This has to be supplemented only by missing data like date of diagnosis etc. Electronical data transmission turns out to be an increasing potential, realised at present by servicing of cooperating practitioners with a purpose-developed software, which transfers data from the surgery's software into an electronic notification. Again this has to be completed on screen by the physician. A newly introduced option is the USB-stick eliminating the necessity to install additional software (Hamburgisches Krebsregister 2005). A rising number of hospitals is supplied with facilities to enable electronical notifications, too.

Transfer from further written documents like discharge letters and other clinical records may be utilized, though in fact this option has lost its relevance due to data protection. Finally all death certificates issued in Hamburg are temporarily placed at the HCR's disposal by local health authorities. Personal data are matched to the HCR's stock and relevant information like date of death, autopsy findings or further tumors are added where appropriate. If malignancies are mentioned on the death certificate without the person being known in the HCR, the case is documented as ‘DCO’.

The processing starts with feeding data into the computer by hand resp. with their electronic import. By means of the software data are checked at entry concerning declaration of obligatory facts, identification of double resp. second notifications and second primary tumors. In addition numerous tests for plausibility of information run at this stage, during electronical reorganisation and previous to data preparation for research tasks. The scrutinies comprise the plausibility and chronology of all data specifications, the combinations of several variables like age and site, site and histology, TNM and stage, etc. The decision about the classification of two tumours as one or two primary malignancies is integrated according to rules of the International Agency for Research on Cancer (IARC), supplemented by recommendations of the SEER[2]-program. The actual existence of each address in Hamburg is verified by an integrated complete directory of streets and addresses, and then is documented in addition by Gauß-Krüger coordinates.

Matching the data with information kept in residential registry offices as intended in §4(2) HmbKrebsRG, to get notice on changes of address, names, nationality and sex, had been accomplished sporadically in the past. A systematic transfer of data was started in 2004. It has been subdivided into a one-time check of 75,000 patients documented in the HCR without date of death, and a continuous update with the deceased, moves and further changes mentioned above.

Finally a 'Best-of tumour information' is generated by means of the available data concerning one case. In case of an already existent 'Best-of' it is checked in view of improvement by new information. The resp. table stored in the database aims at an optimisation of the data-stock by ranking the particular statements according to their accuracy.

2.4. Registry population and data quantities

A population-based cancer registry refers to a defined region, which in the context of the HCR is limited by the administrative borders of the 'Freie und Hansestadt Hamburg' to 755,32 km^2. The data-stock predominantly contains cases of patients residing within this area at date of diagnosis. Due to the large catchment area of the Hanseatic city a certain proportion of notified cancer patients lives in neighbouring federal states. Their data are not included into incidence and mortality calculation, but passed on with respect to the particular legal situation.

---

[2] Surveillance Epidemiology and End Results, a program of the National Cancer Institute in the United States

According to the statistical population projection the population of Hamburg increased between 1990 and 2003 from 1.65 million to 1.73 million by more than 80 000 inhabitants (Statistisches Amt für Hamburg und Schleswig-Holstein 2003). At the same time the ratio of male to female sex changed towards an increasing yet still smaller proportion of male residents, i.e. from 47,5% in 1990 to 48,6% in 2003. The age distribution at December 31st 2003 is shown in figure 1.

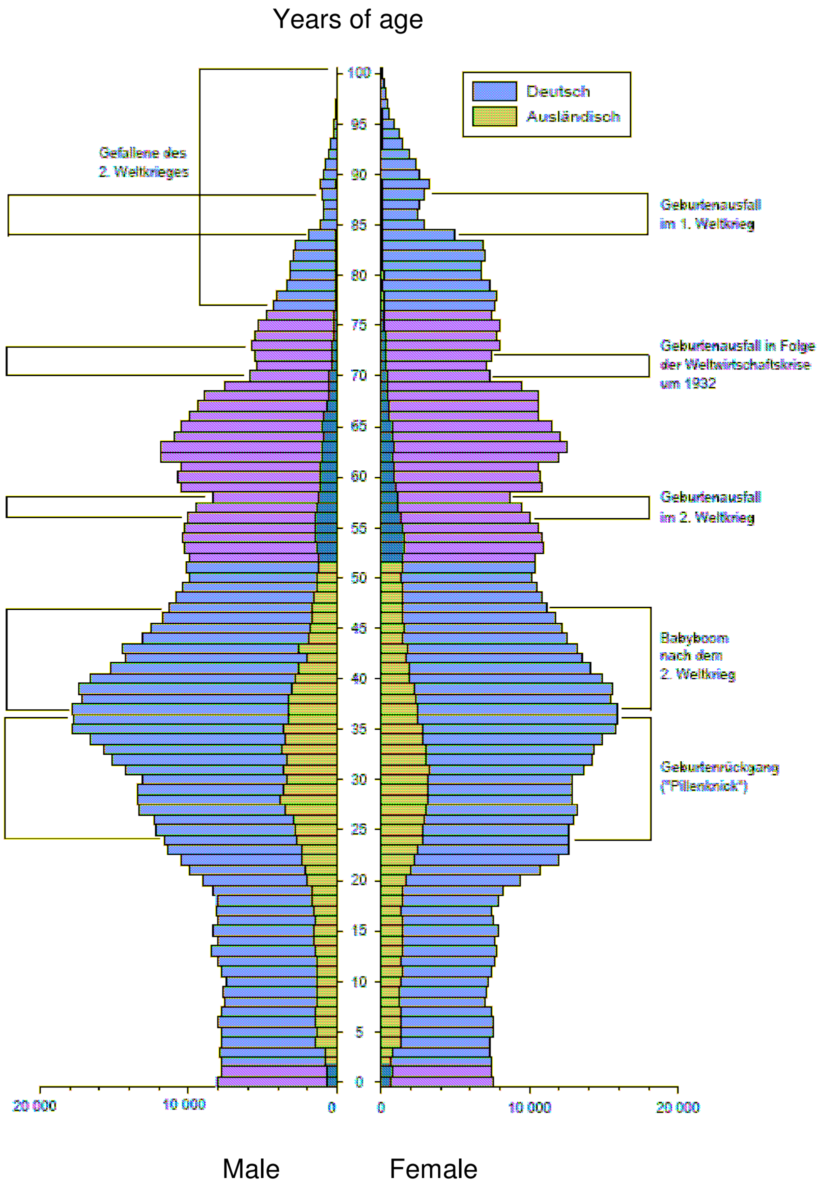


Figure 1: Age structure of the population of Hamburg as at December 31st 2003 (Statistisches Amt für Hamburg und Schleswig-Holstein 2004, 12)

Regarding absolute quantities the HCR data stock contained 340,000 notifications concerning 210,000 patients in 2004. Currently more than 20,000 notifications per year are received and processed corresponding to approximately 8,000 new cases in Hamburg (Figure 2).

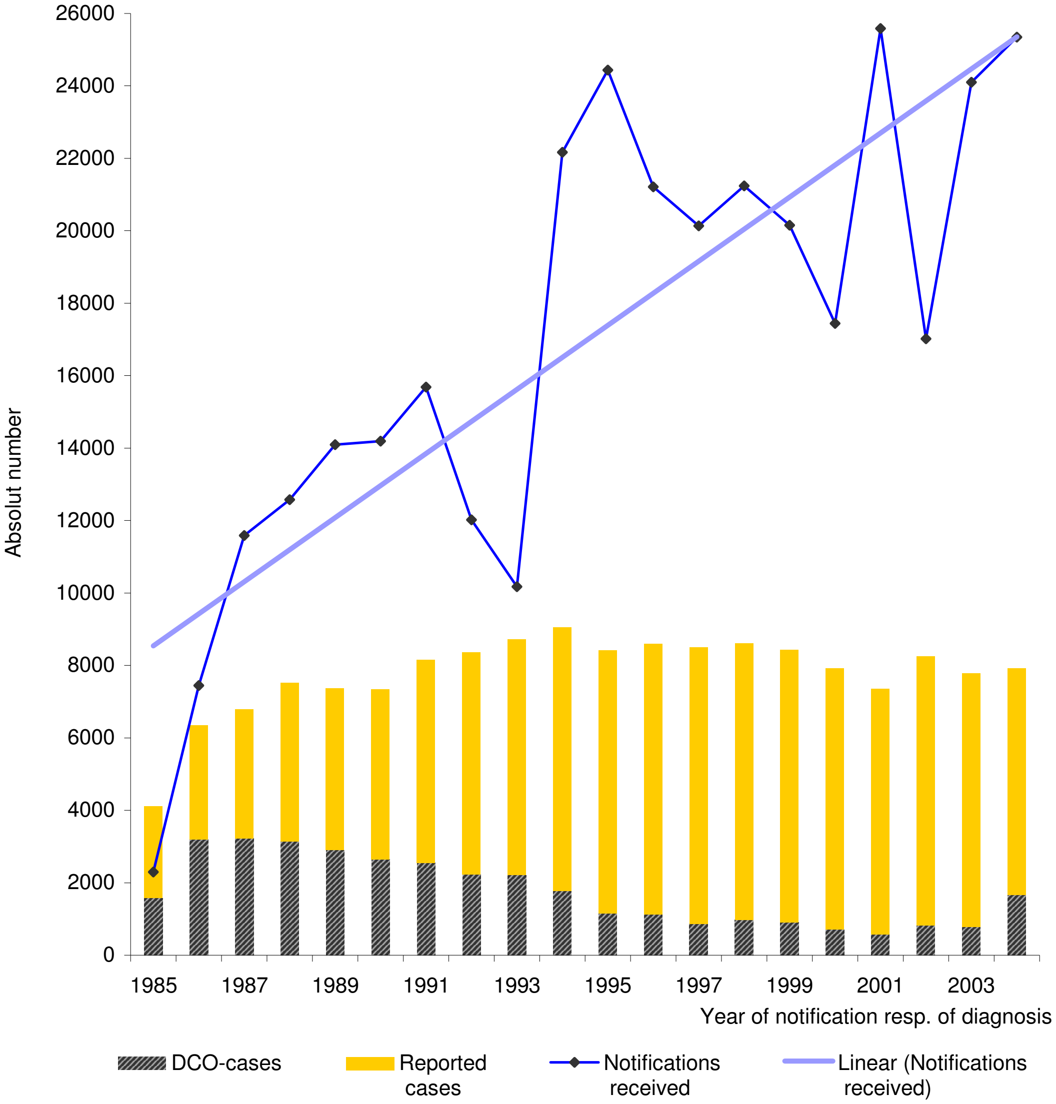


Figure 2: Hamburg cancer registry: Trend of notifications and case-numbers 1985-2004

2.5. Data quality

The estimation of cancer incidence and survival rates in the population at risk requires an accurate enumeration of all newly diagnosed cases, and their complete follow-up until death or migration out of the target population. The extent to which the data represent the true picture of diagnosed cancer occurrence depends on completeness and validity of the recorded information (Parkin et al, 1994, vii). Ideally, at least 90% of all incident casses should be registered, so that comparison of rates between registries reflect true differences in risk of cancer and not artefacts of the registration process (RKI 2005). For various reasons the true incidence of malignancies is unknown, it can only be estimated indirectly using several indicators like number of notifications per case, proportion of DCO-cases and the mortality/incidence ratio (Parkin et al, 1994, 14-31). In Germany the Robert Koch-Institut[3] (RKI) regularly issues estimates of completeness relating to particular and registries cancer sites. The applied method adjusts log-linear models to age- and sex-specific mortality / incidence ratios of reference data from supposedly complete registries, in order to estimate the expected number of incident cases (Haberland et al. 2003, 770-4).

In 2004 the HCR has been rated as overall sufficiently complete, grouped by primary site and year the estimates differ considerably (BMG Pressemitteilung 15/10/04; RKI confidential information 2005). In 1990-2004 the proportion of DCO cases amounted to 17% overall, varying substantially depending on year and topography, the average number of notifications per case was 1.4. A recently performed investigation on the quality of the vital status as documented in the HCR in relation to survival analyses proved the follow-up of patients from Hamburg as valid and reliable: Among a cohort of nearly 3000 cases of colorectal cancer 3,8% proved as moved from Hamburg, 0,7% were falsly documented as alive and 0,7% were lost to follow-up, resulting in a 0.1-year deviation of the median observed survival (Fertmann et al, Freiburg 2005).

2.6. Use of data and current Projects

Comprehensive reports on cancer incidence and mortality in Hamburg are published every third year (Hamburgisches Krebsregister 2004), and the RKI and the IARC are regularly provided by HCR data. Various services and analyses on demand, feedback to hospitals and public information belong to the routine tasks beyond data processing.

---

[3] central German institution for the analysis of public health relevant data

The HCR both initiates and participates in various projects of research and development. The following list refers to some recent subjects without being exhaustive:

- Development and propagation of electronic notification for practitioners and hospitals (Hamburgisches Krebsregister 2004, 12; idem 2005)
- Active participation in the MARIE study (Mammakarzinom-Risikofaktoren-Erhebung) on risk factors for breast carcinoma (MARIE 2006)
- Regional analysis of incidence concerning leukaemia and lymphoma in Hamburg (Schümann et al, 2004)
- Provision of data for a study on acute and post-traumatic stress disorder in breast cancer patients (Mehnert 2005)
- Improvement of clinical data use by invention of regular feedback on long-term survival to notifying institutions, supported by the 'Hamburger Krebsgesellschaft e.V.' (Hamburgisches Krebsregister 2004, 13; Hamburger Krebsgesellschaft e.V. 2006)

Following up the last named issue some general aspects of survival analysis are presented subsequently.

2.7. Basic concepts of survival analysis

Survival analysis refers to the techniques used to analyse the time from a defined starting point to the occurrence of some irreversible event for a given population. The aims are to depict and compare survival time, and to evaluate influential factors (Cutler et al. 1958, 699). Population-based cancer survival analysis requires to consider censored cases, i.e. observations cut off before death occurred. If the quality of long-term follow-up is high by matching to mortality statistics and residential registration the censoring is mainly due to patients still alive at the end of observation, rather than to factual loss of follow-up.

A basic measure of the survival experience of persons diagnosed with a malignancy is the absolute or observed survival rate. It is defined as the proportion of the patients surviving a specified amount of time after cancer diagnosis. A disadvantage of using this measure is that deaths from causes other than the disease of interest lower the observed survival proportion and preclude comparison of results between groups experiencing different general mortality. Therefore it should be interpreted as the likelihood of surviving all causes of death for a certain time after cancer diagnosis, not the likelihood of surviving that cancer.

A possibility to indirectly adjust the survival rate to remove the effect of normal mortality is to compare the observed with an expected proportion of survivors (Berkson et al 1950, 282-285). This concept of relative survival provides an appropriate measure of patient survival corrected for the effect of competing risks of death, but independent of information on cause of death. In the context of cancer, relative survival is defined as the ratio of the observed survival for a group of cancer patients to the survival that would have been expected for members of the general population, who have the same main factors affecting patient survival (e.g., sex, age, area of residence) as the cancer patients (Ederer et al. 1961, 103; Voutilainen et al 2000, 43). Relative survival rates are calculated for constant and consecutive intervals in the course of follow-up, values <1 indicating a higher mortality among the patients compared to the general population and = 1 pointing to identical mortalities, i.e. ‘cured’ patients. Estimates of the relative survival ratio greater than 1 are possible and indicate either incomplete registration of deaths or that the observed survival of the cancer patients is better than that expected from the general population. This can occur for cancers with high survival probability, if patients lead a healthier life or are better treated for co-morbidities than the reference population.

To illustrate the chronological course of survival cumulative survival rates are calculated by multiplication of interval specific survival probabilities. They can be displayed as single values or as survival curves. The 5-year cumulative relative survival rate may be regarded as an internationally common standard measure for comparison of cancer survival. As for survival curves the shape of decrease reflects the ‘mortality power’ of the pertinent malignancy while the existence of an asymptotic limit, the time until that is reached and its level mark the point at which the patient´s mortality is equal to that of the general population.

3. Investigation

3.1. Background

Epidemiological cancer registries provide a basis for cancer research by collecting and analysing data of incidence and mortality. Their priorities are the extensive registration of malignancies in the entire population, the accuracy of the collected data and the high quality of long-term follow-up, while hospital based cancer documentation systems focus on detailed clinical aspects of progress and therapy with regard to non-representative patient samples. Employing registry data for survival analysis can give useful indications regarding the effectiveness of the whole chain of cancer related activities within the healthcare system. Thus population-based cancer survival reports constitute valuable reference materials for clinicians, scientists, quality-managers and decision-makers in the field of public health.

The Hamburg Cancer Registry (HCR) has been in operation since 1927, and has collected a substantial database. Historical changes in the general conditions have caused considerable variations of data quantity and quality. Since 1985, when the corresponding law (HmbKrebsRG) became effective, epidemiological cancer registration in Hamburg has been based on the voluntary right of physicians to notify cases dependent on the patient's informed consent. During the past 20 years the number of notifications received rose from 2,300 to 25,770 annually, including in situ neoplasms and those of uncertain or unknown behaviour, multiple notifications and cases from outside of Hamburg (Figure 1). Concerning exclusively primary invasive malignancies[4] in residents of the 1.7 million metropolitan area, approximately 8000 new cases on average are registered per year from 1991 onwards, with a decreasing proportion of those reported by death certificates only (DCO-cases).

Comprehensive cancer survival analysis based on registry data from Hamburg has not yet been performed, but is intended to improve the clinical usability of the database. The purpose of this study is to assess the HCR's database concerning survival analysis, to perform analyses within selected malignancies, and to evaluate the results in relation to the assessments of clinical specialists and external estimates.

---

[4] according to ICD10 C00-C96, excl. non-melanoma skin cancers (C44)

3.2. Material and Methods

The basic material consisted of all the electronically documented cases in the HCR as diagnosed in 1990-2004, including 123,415 primary invasive malignancies with overall 17% DCO-cases (status: December 2005). The prior period was ignored due to incomplete and heterogeneous data. Routine quality secureing measures had been applied as specified elsewhere (see 2.3.). With regard to an exemplary and explorative analysis, four cancer sites and corresponding periods of diagnoses were selected considering the following criteria. The study was to be to limited to first primary malignancies diagnosed in Hamburg residents. Public health relevance and adequate numbers for stratified survival analysis procedures required at least 100 notified cases per sex and year. A maximum allowance of 20% cases documented as diagnosed at death annually and the provision for estimates of completeness was chosen to keep possible bias of survival estimates at a tolerable level. The dominance of one histological type was preferred to support the assumption of homogeneous tumor entities. Finally a certain heterogeneity concerning the quality of registry data and tumor specific features was meant to cover a range of different conditions.

The selection resulted in malignancies of the colon, female breast, prostate and urinary bladder. The cases were diagnosed between 1992-2003 or 1995-2003. Excluded were second primary tumors and all cases with date of diagnosis documented as equal to death. Urinary bladder invasive and in situ malignancies (ICD10 C67 and D09.0) were grouped together because of period changes in the classification in 1990 and 2000 (Wagner et al 1995, 41.25-.26; DIMDI 2003b, 134). For reasons of calculation ages ≥100 (n=7) were reset to 99 years, the factual range of age at diagnosis in the present study was 18-104.

Information on survival was derived from the comparison with official mortality statistics and the residential registration office's data up to end of 2004, ensuring valid and reliable follow-up (Fertmann et al 2005). Survival time was calculated as the difference in quarters between the date of diagnosis and date of last observation, death or December 31, 2004, whichever was earliest. As measures of survival, cumulative observed (Cobs) and cumulative relative survival ratios (Crel) were calculated for multiple-year cohorts. The observed survival, defined as the proportion of patients surviving a specific amount of time after cancer diagnosis, was computed according to the life-table method (Berkson et al. 1950, 275-80; Cutler et al. 1958, 699-712; Voutilainen et al. 2000, 39-42). Relative survival, defined as the ratio between observed and expected survival in a comparable group of the regional population, was estimated according to Hakulinen (Ederer et al. 1961, 101-110; Hakulinen 1982,933-41; Voutilainen et al. 2000, 43-60).

Reference data for expected survival estimates were derived from sex- and calendar year-specific life tables for Hamburg by the statistical state office (Statistisches Amt für Hamburg und Schleswig-Holstein). The life table's ranges of age (0-90 years) were extended up to the age of 99 according to the GOMPERTZ distribution by means of logistic regression (Manton et al. 1994, B169-90.). Standard errors (SE) of the estimated relative survival were obtained using GREENWOOD'S formula, the 95%-confidence (95%CI) interval was approximated by addition and subtraction of twice the standard error (Greenwood 1926, 1-30; Schön et al. 1999, 39).

Survival ratios were estimated by site, sex, consecutive triennial calendar periods of diagnoses, age-group, staged vs. unstaged cases and stages. The results are presented as tables containing one- and 5-year survival, survival curves and trend diagrams using moving three-year cohorts. The acceptance of calculated values into graphs was limited to the condition, that at the beginning of the resp. interval at least 30 patients were alive and SE ≤ 25%.

Descriptive data analysis was conducted by means of SPSS version 12.0 and Microsoft Excel 2003, and by exemplary checks of the original cancer registry data stock. Survival analysis was performed by using SURV3, a shareware package from the Finnish Cancer Registry (Hakulinen et al. 1988, Finnish Cancer Registry 2002).

Beyond the calculative approach, a written survey was conducted among clinical specialists from Hamburg, selected by combining indicators proving them to be experienced authorities: They ought to have worked in oncological hospital departments as head or senior consultant, or in relevant medical offices in Hamburg for several years, preferably decades. In addition the department's top diagnoses according to the hospital quality reports from 2004, the notification-frequencies to the HCR 1990-2005 and the authorship of oncology guidelines were evaluated, added by personal communication. 45 contacts resulted, there-of 33 at hospitals and 12 in offices, covering one to four tumor sites each. They were addressed in September 2005 receiving a letter and the adequate number of questionnaires, i.e. 18x concerning colon, 16x breast, 17x prostate and 14x urinary bladder (A-13). The single-page forms were designed to be completed casually and to be returned by fax or post, and contained the following issues: estimation of particular cancer survival trend since 1990 by means of a semi-quantitative scale as significantly increased, marginally increased, not changed, rather decreased or heavily decreased; specification of survival relevant developments of diagnostics and therapy and their timing as to Hamburg. Within 10 weeks after dispatch of 65 questionnaires 43 (66%) were returned.

3.3. Results

The selected database shows a homogeneous proportion of histologically verified diagnoses (90±5%) and a range of specified stages (61-77% according to site). The trend of DCO-cases was declining while proportions of first vs. secondary tumors remained stable over time on different levels (Table 2).

Table 2: Selection of database for exemplary survival analysis from Hamburg Cancer Registry

		Colon		**Breast**	**Prostate**	**Urinary bladder**	
		Men	Women	Women	Men	Men	Women
(A)	**Primary malignancies** [1] **1990-2003**	4,291	6,317	16,280	10,360	4,511	1,913
(B)	**First primary malignancies 1990-2003**	3,654	5,433	15,265	9,341	3,780	1,620
	(% of *(A)**)***	*(85)*	*(86)*	*(94)*	*(90)*	*(84)*	*(85)*
(C)	**Selected period** [2]	1995 - 2003		1992-2003	1995-2003	1995 - 2003	
(D)	**First prim. malignancies In selected period**	2,322	3,216	13,355	6,646	2,480	1,017
(E)	**Excluded DCO-cases**	292	515	1,080	818	173	129
	(% of *(D)**)***	*(13)*	*(16)*	*(8)*	*(12)*	*(7)*	*(13)*
(F)	**Excluded cases (other)** [3]	70	117	192	121	27	20
	(% of *(D)**)***	*(3)*	*(4)*	*(1)*	*(2)*	*(1)*	*(2)*
(G)	**Included cases**	**1,960**	**2,584**	**12,083**	**5,707**	**2,280**	**868**
	(% of *(D)**)***	*(84)*	*(80)*	*(91)*	*(86)*	*(92)*	*(85)*
(H)	**Estimate of completeness** [4] in % of expected cases without DCO	74	71	93	81	71	64
(I)	**Predominant histological type of carcinomata** [5]	Adeno ~		Ductal and lobular ~ [6]	Adeno ~	Transitional cell ~	

[1] All primary malignancies of specific site concerning Hamburg residents as registered by HCR; including secondary tumors and cases with documented date of diagnosis equal to death

[2] Period of diagnoses selected for survival analysis by criterion = 25% cases with date of diagnosis equal to death

[3] Cases with documented date of diagnosis equal to death due to temporary use of notification sheets lacking space for date of diagnosis

[4] Estimates of completeness conc. HCR as calculated by the Robert Koch Institut (RKI 2005) , here: average estimates for 1995-2002, resp. for female breast cancer 1992-2003; conc. urinary bladder ICD10 C67 only

[5] Histological type as documented in =80% of included first primary malignancies

[6] According to SAINSBURY et al. (2000, 745-9) ductal and lobular types both arise from terminal lobular units

The results in detail are pointed out site-specific, in each case preceded by the expert's rating. Time statements as to beginning and predominant application of diagnostic and therapeutic measures in Hamburg are not presented because of inaccuracy and partial contrariness. The range of dates covered periods from long before 1990 to the present, or even not yet, concerning most of the items mentioned (Table A1 - A4).

Statements on the particular database are illustrated by table 2 and figure 3.

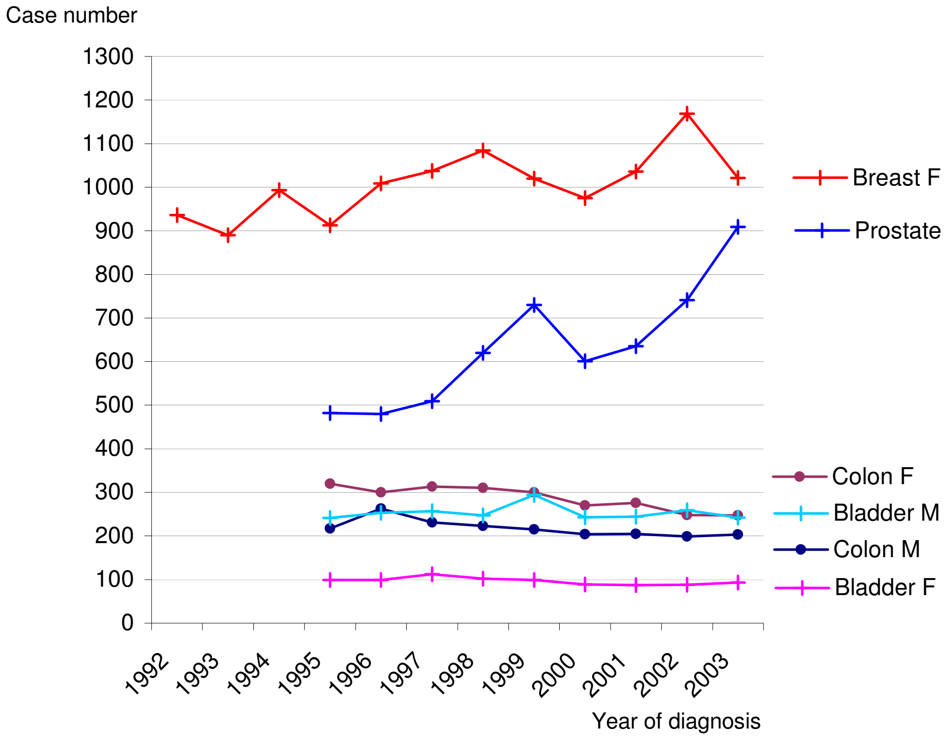
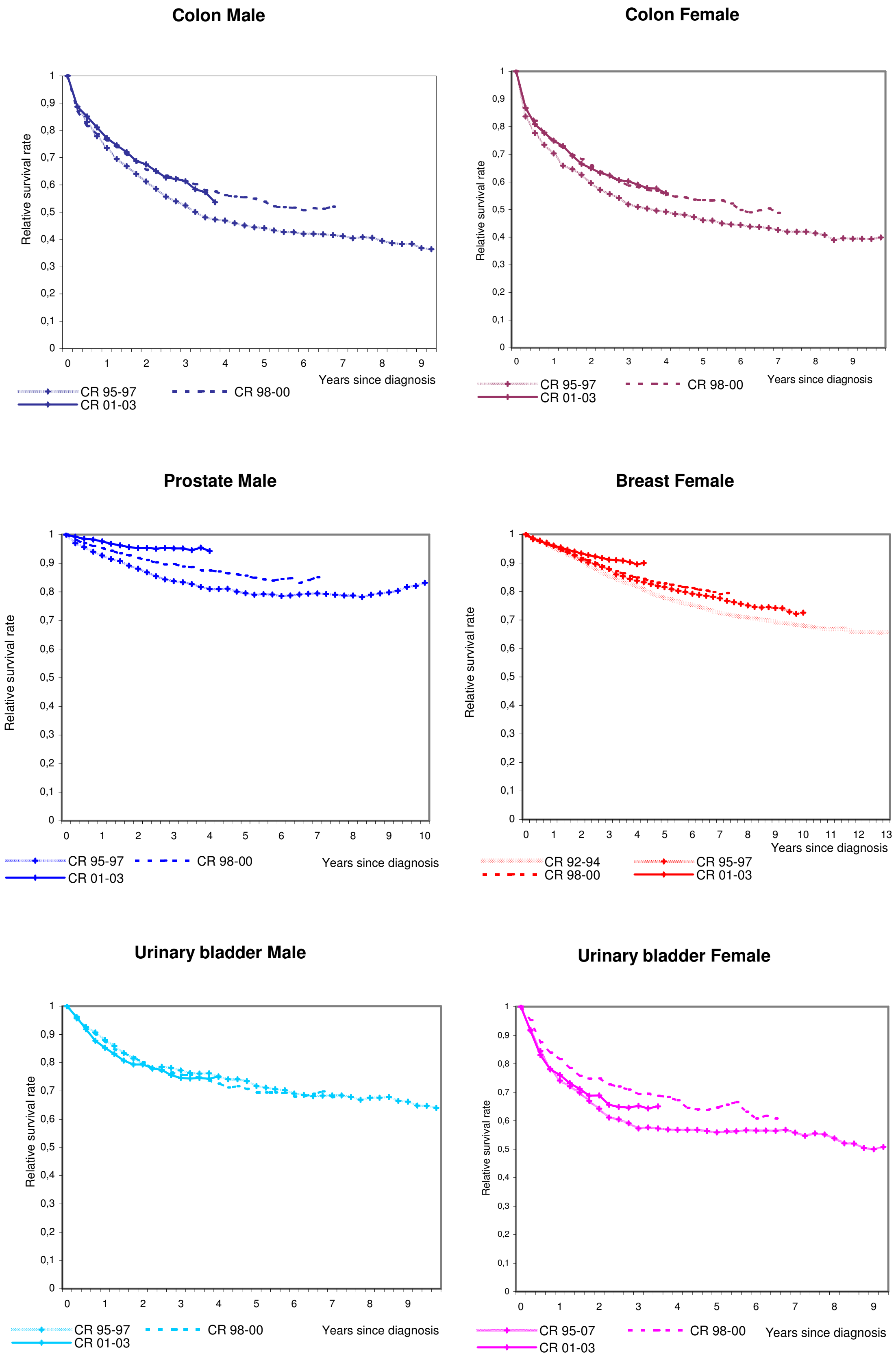


Figure 3: Trends of case numbers for selected cancer sites, including first primary malignancies with survival > 0 according to database of Hamburg Cancer Registry

Summarized results of survival analyses are to be found in table 3 as well as figures 4 and 5. Further information is provided in the appendix.

Table 3: One- and five-year observed and relative survival (%) for selected tumor sites diagnosed in 1992-2003 resp. 1995-2003, by sex and age-group

Tumor site Period of diagnosis		**Age-group**	Number of Patients	One-year survival (%)			Five-year survival (%)		
				Cobs	Crel	*(95% CI)*	Cobs	Crel	*(95% CI)*
Colon (1995-2003)									
	Men	**Total**	1,960	72	**76**	*(73-78)*	38	**50**	*(47-53)*
		18-59	364	79	**80**	*(76-84)*	47	**49**	*(43-55)*
		60-69	600	80	**82**	*(79-85)*	48	**54**	*(49-59)*
		70-79	622	71	**74**	*(70-78)*	35	**46**	*(41-52)*
		80+	374	53	**61**	*(56-67)*	21	**46**	*(37-57)*
	Women	**Total**	2,584	70	**73**	*(71-75)*	39	**51**	*(48-53)*
		18-59	329	87	**87**	*(83-91)*	57	**58**	*(52-64)*
		60-69	471	80	**80**	*(77-84)*	48	**52**	*(46-57)*
		70-79	878	71	**73**	*(70-76)*	41	**50**	*(45-54)*
		80+	906	57	**64**	*(60-67)*	25	**46**	*(40-52)*
Breast (1992-2003)									
	Women	**Total**	12,083	94	**96**	*(95-96)*	74	**82**	*(81-83)*
		18-49	2351	97	**98**	*(97-98)*	81	**82**	*(80-83)*
		50-59	3259	97	**97**	*(97-98)*	82	**84**	*(82-85)*
		60-69	3098	95	**96**	*(95-97)*	77	**82**	*(80-84)*
		70-79	2196	92	**95**	*(94-96)*	67	**80**	*(78-83)*
		80+	1179	79	**88**	*(85-90)*	42	**73**	*(68-79)*
Prostate (1995-2003)									
	Men	**Total**	5,707	92	**96**	*(95-96)*	68	**86**	*(84-88)*
		18-59	829	97	**98**	*(97-99)*	82	**87**	*(83-90)*
		60-69	2,438	97	**99**	*(98-100)*	83	**94**	*(92-96)*
		70-79	1,730	91	**95**	*(94-97)*	63	**83**	*(79-86)*
		80+	710	70	**80**	*(76-84)*	23	**49**	*(42-56)*
Bladder (1995-2003)									
	Men	**Total**	2,280	83	**87**	*(85-89)*	54	**70**	*(67-73)*
		18-59	418	91	**92**	*(89-94)*	76	**79**	*(74-84)*
		60-69	645	89	**91**	*(88-93)*	64	**72**	*(68-77)*
		70-79	781	83	**87**	*(84-89)*	50	**67**	*(61-75)*
		80+	436	66	**76**	*(70-81)*	27	**57**	*(48-68)*
	Women	**Total**	868	74	**77**	*(74-80)*	47	**56**	*(56-65)*
		18-69	297	86	**86**	*(82-90)*	64	**68**	*(61-74)*
		70-79	301	76	**78**	*(73-83)*	52	**62**	*(55-69)*
		80+	270	58	**65**	*(58-71)*	24	**44**	*(35-55)*


Colon Male

Colon Female

Prostate Male

Breast Female

Urinary bladder Male

Urinary bladder Female

Figure 4: Cumulative relative survival rates (CR) stratified by tumor site, sex and period of diagnoses

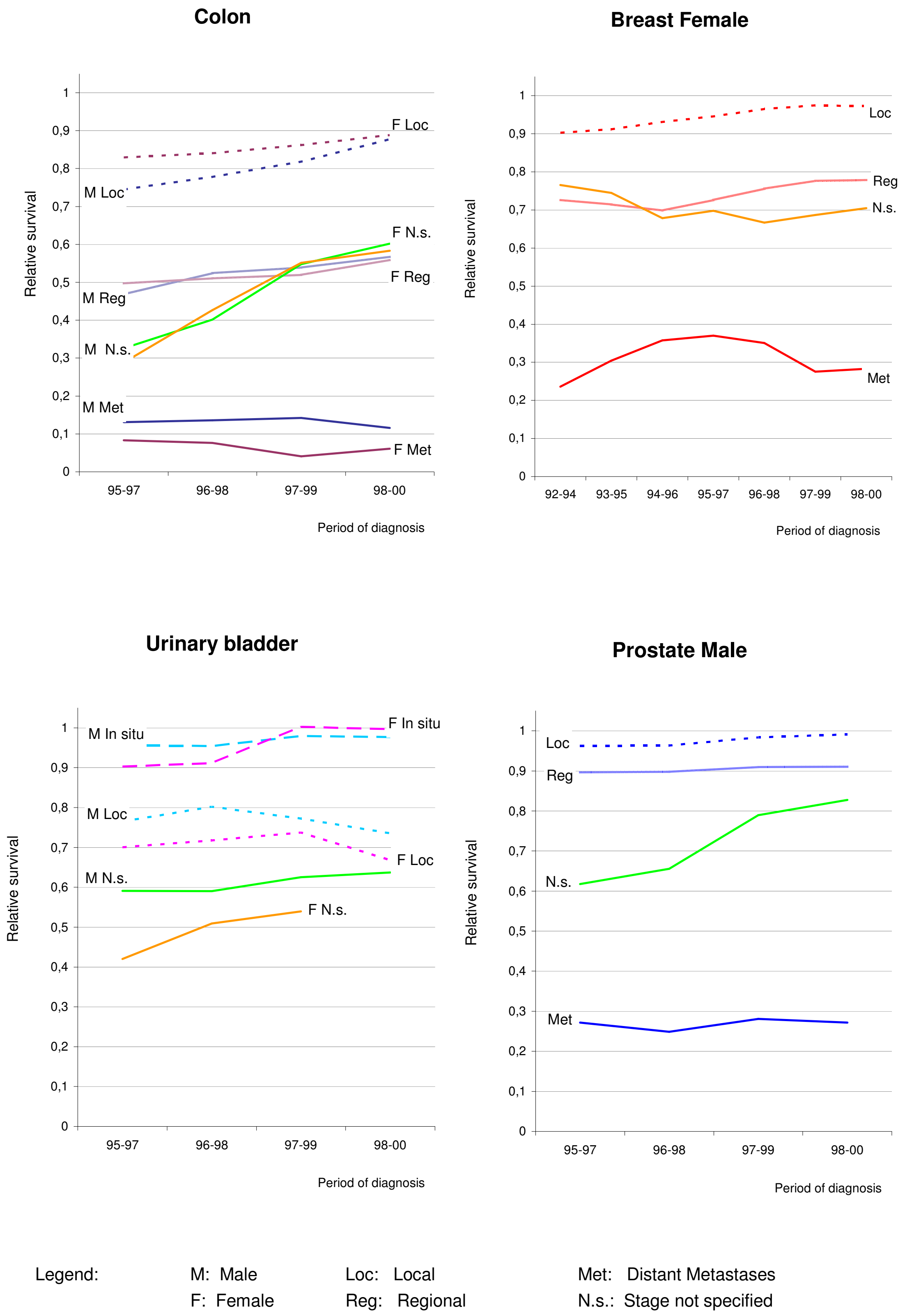


Figure 5: Stage specific 5-year relative survival by site and sex (moving three-year cohorts)

Colon

The responding experts (rate of return: 8/18) assessed the survival of colon cancer patients more marginally than significantly increased since 1990. Predominantly adjuvant and palliative chemotherapy in advanced stages was quoted as relevant therapeutic development, followed by colonoscopy enabling early detection.

The ratio of female to male colon cancer patients was 1.4, the case numbers slowly dropped by approximately 20% in both sexes. 69.8 years represented the median age at diagnosis in men compared to 75.6 years in women. 20% resp. 16% of excluded cases and an estimated completeness of 71% resp. 74% indicate a certain amount of underregistration.

The survival analysis shows similar estimates for both sexes (5-year Crel 50% vs. 51%) except slight differences in the rates by age-groups. A significant increase in long-term Crel is seen between 1995-1997 and 1998-2000, yet no improvement for the 2001-2003-cohort. Stage-specific trends of 5-year Crel survival show gradual improvements for local and regional stages, from unchanged to declined low estimates in the presence of metastases at 10%, and a striking boost for cases without specified extent of disease.

Breast

According to the survey (rate of return 13/16) the survival of female breast cancer patients may have increased marginally since 1990. Nearly all experts mention mammography in the context of 'grey screening' and adjuvant chemotherapy and/or contrahormonal therapy as survival relevant.

The included cases of female breast cancer ranged on a fluctuating level of approximately 1,000 – 1,200 per year. The median age at diagnosis gradually rose from 59.5 years (1992) to 62.0 (2003). The low proportion of exclusions (9%) and an estimated completeness of 93% indicate a high degree of coverage. An outstanding data quality is confirmed by 93% histologically verified diagnoses and 77% specified stages.

The relative survival curves for female breast cancer are almost lineally and slowly declining on a high level (5-year Crel 82%), only patients aged 80 and more years have distinctly inferior rates (5-year Crel 73%) compared to other age-groups. Crel for four consecutive triennials show constant increases beyond the first year after diagnosis, while stratification by stage supports this finding for local and regional stages only. Trends of distant and not specified stages appear to undulate and overall to decrease.

Prostate

Two thirds of the responding prostate cancer specialists (rate of return 12/17) rated survival as having increased significantly, predominantly accounting the early detection by analysis of prostate-specific antigen (PSA). Second came therapeutic developments such as radical prostatectomy, chemotherapy, contrahormonal drugs and brachytherapy.

Prostate cancer case numbers increased constantly from less than 500 cases per year (1995) to more than 900 (2003), simultaneously the median age at diagnosis dropped from 70 to 67 years. 14% of excluded cases correspond to 81% estimated completeness. Of the included, 61% are staged.

Long-term observed and relative survival diverge more distinctly compared to other sites investigated in this study. The descent of Crel is constantly slow for the whole cohort (5-year Crel 86%) as well as for age-groups under 80 years (5-year Crel 83-94%). The 60-69 year-old patients present the best estimates (5-year Crel 94%) in contrast to significantly subjacent rates of those aged 80 years and more (5-year Crel 49%). Successive periods of diagnosis show clear increases for relative survival curves of prostate cancer, which is in accordance with the ascending trend of 5-year Crel in unstaged cases. Local and regional stages are marginally improving, metastases constantly rendered 5-year Crel around 27%.

Urinary bladder

The responding experts (rate of return 10/14) assessed survival of urinary bladder cancer patients as not changed, marginally or significantly increased since 1990. Most often recidive prophylaxis by instillation of BCG or zytostatic drugs and the growing application of radical cystectomy were mentioned.

The cohort shows rather constant annual case numbers, men being affected 2.5 times as often and at a younger age than women (median age at diagnosis 70.7 vs. 73.9 years). Almost a fifth of all cases registered in 1995-2003 had to be excluded as second primary tumors. Concerning indicators of completeness, comparatively minor proportions of cases with date of diagnosis equal to death (8% resp. 15%) contradict the estimates (71% resp. 64%).

Female urinary bladder cancer patients exhibit significantly worse observed and relative survival than male patients (Males 5-year Crel 70% vs. Female 56%). Crel of the age-group 80 years and more is inferior to that of younger patients with a major difference in women. Relative survival curves of consecutive triennials show heterogeneity with scant alterations in men, and an increase in women between 1995-1997 and 1998-2000 followed by a decrease in 2001-2003. Due to small case numbers, the trend graphs for 5-year Crel were limited to early and not specified extents of disease, indicating overall slight improvements of in situ, decrease of local and increases of not specified stages.

3.4. Discussion

The HCR's data stock is heterogeneous with respect to periods, sites and differentiations. Data quality concerning follow-up information and histological verification since the mid-nineties has been shown to be valid and reliable. The two thirds amount of staged cases is in need of enhancement. Decreasing trends of DCO cases indicate a substantial and improving degree of registra-tion, enabling reliable analyses for certain tumor sites. Yet the overall DCO-proportion still exceeds that of many publications on population-based cancer survival analysis (Teppo et al.1999, 284; Schön et al. 1999, 33; Capocaccia et al. 2003, v18).

The selection of malignancies according to criteria, which ought to ensure sufficient representation and significance of population based survival analysis, however revealed a differentiated picture for cancer of the colon, female breast, prostate and urinary bladder. Several findings correspond well to those of recently published German and other Western European and North American population-based cancer survival studies (Schön et al. 1999; GEKID 2006; Brenner et al. 2005b; Sant 2003; SEER 2005; Statistics Canada 2005): Age- and stage-stratified survival estimates turned out in expected patterns, indicating high age and above all stage as strongly influential variables. Relative survival is usually worst in the age-group 80 years and more. In breast and prostate cancer the youngest patients do not have the best rates. Colon malignancies almost uniformly affect survival of both sexes, while male bladder cancer patients have significantly better probabilities than female patients. 5-year relative survival increased since the mid-nineties with respect to the sites colon, female breast and prostate. Particularly the trend of increasing incidence because of PSA testing in prostate cancer patients as main reason for improved survival has been confirmed in former studies (Quinn et al. 2002, 162; Sant et al. 2003, v65). In contrast to that the trend of urinary bladder cancer appears to be stagnant or decreasing, partially interpreted as a consequence of classification changes during the relevant period (Schön et al. 1999, 186; Brenner et al. 2005b, A2630). In the presence of distant malignancies stage-specific trends deny survival improvements, thus consistent with recently published results (Kato et al. 2001, 2214; Schlesinger-Raab et al. 2005, A2706).

The relation of computed survival estimates to statements given by clinical specialists in returned questionnaires show some conformity too. Obvious improvements concerning of breast and prostate malignancies as well as ambiguous results for urinary bladder cancer have been expected and calculated. With regard to colon tumors therapeutic efforts in advanced stages and consecutive survival improvements were stressed, and are reflected by rising 5-year relative survival for regional stages. Measures of early detection (mammography, colonoscopy, PSA-analysis) and adjuvant resp. palliative chemotherapy were emphasized as survival-relevant developments, similar to suppositions in current literature (Sant et al. 2003; Brenner et al. 2005b, A2632). Statements as to time of introduction and propagation of these measures covered broad ranges. This may be interpreted as a reflection of the need for objective data on medical care, with respect to the evaluation of impact on long-term cancer survival.

5-year relative survival ratios, calculated for patients diagnosed during certain periods, may be regarded as an internationally common standard measure for population-based cancer survival. However, any comparison between countries has to be regarded with utmost caution given the differences concerning populations, conditions of registration, inclusion criteria and methodological details. These cautions notwithstanding the 5-year relative survival ratios derived in the present study for female breast and prostate cancer in Hamburg are comparable to or slightly exceed those published for other German and Western European regions and similar periods recently (GEKID 2006; Brenner et al. 2005b; Tumorzentrum Land Brandenburg e.V. 2006; National Statistics 2005; Federico et al. 2005). The rates for colon malignancies remain 5-10 percentage points under estimates for Germany and the Italian Modena area, but are equal to those reported from Brandenburg and England. These discrepancies might be explained by the estimated underregistration of 20-30% in Hamburg and Brandenburg, which according to BRENNER can cause considerable bias (RKI confidential information 2005; Tumorzentrum Land Brandenburg e.V. 2006, 27; Brenner 2005a). Survival estimates concerning urinary bladder cancer are heterogeneous among all cancer registries aforementioned, partially due to lack of stratification by sex and to diverse classification of non-invasive malignancies. The rates for patients from Hamburg are between those for Germany and Modena and those for England, but range around the unisex estimates for Brandenburg and Saarland (GEKID 2006, 80; Tumorzentrum Land Brandenburg e.V. 2006, 68; Brenner et al.2005b, A2630).

Overall North American 5-year relative survival ratios exceed the results of the present study significantly (SEER 2005; Statistics Canada 2005). In breast and prostate cancer cohorts these differences almost disappear if comparing exclusively strata of specified stages, as described by CICCOLALLO (2005) and SANT (2004). With respect to malignant colon and bladder tumors considerable discrepancies remain except for distant metastases.

It can be concluded that the HCR currently provides a database enabling meaningful survival analysis for breast and prostate cancer, while the explanatory power concerning colon and urinary bladder is limited. The usability of registry services will further improve, if the positive trends of data quality and quantity continue in cooperation with physicians and medical institutions.

3.5. Abstract

Background: Population-based cancer survival analysis is an appropriate way of monitoring the effectiveness of prevention and treatment in the healthcare system. The Hamburg Cancer Registry (HCR) intends to apply this tool to improve the usability of its data stock. The objectives of this study are to assess the HCR's database concerning survival analysis, to perform analyses within selected malignancies, and to evaluate the results in relation to the assessments of clinical specialists and external estimates.

Methods: Four cancer sites and corresponding periods of diagnoses were chosen by the criteria minimum of 100 cases annually in Hamburg residents of each sex, ≥80% documented as having survived more than one day, and dominance of a histological type. Included were first primary malignancies of the colon, the prostate and the urinary bladder diagnosed in 1995-2003, as well as of the female breast diagnosed in 1992-2003. Cumulative observed and relative survival was estimated by site, sex, time, age and stage. In addition clinical oncologists from Hamburg were asked per post to estimate particular cancer survival trends since 1990, and to specify survival relevant developments of diagnostics and therapy by subject and time.

Results: The selected database presents a homogeneous proportion of histologically verified diagnoses (90±5%), a declining trend of cases notified by death certificates only, and approximately two thirds of staged cases. Malignancies of the female breast and the prostate show higher degrees of registration, which does not apply for colon and bladder. Overall 5-year relative cancer survival by site and sex were estimated as follows: Breast 82% (female), prostate (male) 86%, colon 50% (male), 51% (female), urinary bladder 70% (male), 56% (female). Patients aged 80 years and more, and those with distant metastases have significantly worse prognosis. The polled oncologists supposed moderately increased survival, and emphasized measures of early detection as survival relevant. Improvements over time were seen to a various extent for all sites except for bladder.

Conclusions: The quality of the HCR's database varies with respect to periods, sites and specifications. It enables meaningful survival analysis for breast and prostate cancer as from the mid-nineties, while the explanatory power concerning colon and urinary bladder is limited. These findings are confirmed by the cautious comparison with national and international 5-year survival estimates. If the positive trends of data quality and quantity continue in cooperation with physicians and medical institutions, the usability of registry services will further improve.

4. Index of Figures

5. Index of Tables

6. Literature

Berkson J, Gage RP: Calculation of survival rates for cancer, in: Proceedings of Staff Meetings of the Mayo Clinic 25 (**1950**): 270–286.

BMG: Mehr vollzählig erfassende Krebsregister in Deutschland, in: Pressemitteilung v. 15.10.**2004**, Berlin, in: http://www.bmg.bund.de/nn_600184/DE/Presse/Pressemitteilungen/Archiv/Presse-BMGS-1-2004/PM-15-10-2004-6152,param=.html (February 15, 2006)

Brenner H, Hakulinen T: Population-based monitoring of cancer patient survival in situations with imperfect completeness of cancer registration, in: British Journal of Cancer 92 (**2005a**) 3: 576-579

Brenner H, Stegmaier C, Ziegler H: Verbesserte Langzeitüberlebensraten von Krebspatienten, in: Deutsches Ärzteblatt 102 (**2005b**) 39: A2628-A2633

Buchhofer B, Weißker J: Krebsregister Hamburg, in: Bevölkerungsbezogene Krebsregister der Bundesrepublik Deutschland (Hrsg.: Hoffmeister H), München (bga-Schriften) 2/**1987**

Capocaccia R, Gatta G, Roazzi P, Carrani E, Santaquilani M, De Angelis R, Tavilla A, EUROCARE Working Group: The EUROCARE-3 database: methodology of data collection, standardisation, quality control and statistical analysis; in: Annals of Oncology 14 (**2003**) Suppl 5: v14–v27

Ciccolallo L, Capocaccia R, Coleman MP, Berrino F, Coebergh JWW, Damhuis RAM, Faivre J, Martinez-Garcia C, Møller H, Ponz de Leon M, Launoy G, Raverdy N, Williams EMI, GattaG: Survival differences between European and US patients with colorectal cancer: role of stage at diagnosis and surgery, in: Gut (**2005**) 54:268-73

Cutler SJ, Ederer F: Maximum utilisation of the life table method in analyzing survival, in: J Chron Dis (**1958**)8: 699-712.

Deutsches Institut für Medizinische Dokumentation und Information (DIMDI), (Hrsg.): ICD10, WHO-Ausgabe, Version 2004. Köln **2003a**, in: http://www.dimdi.de/dynamic/de/klassi/downloadcenter/icd-10-who/vorgaenger/version2004/ (February 15, 2006)

Deutsches Institut für Medizinische Information und Dokumentation (DIMDI), (Hrsg.): Internationale Klassifikation der Krankheiten für die Onkologie. Dritte Revision (ICD-O-3), 1st ed. Köln (videel) **2003b**, in: http://www.dimdi.de/dynamic/de/klassi/downloadcenter/icd-o-3/1auflage2003/o3gp1.zip (February 15, 2006)

Ederer F, Axtell LM, Cutler SJ: The relative survival rate: A statistical methodology, in: National Cancer Institute Monograph (**1961**) 6: 101–121.

Federico M, Rashid I, Artioli ME, Cirilli C, Fracca A, Vinceti M, Maiorana A, De Girolamo G: Cancer in Modena, 2003 (I tumori in provincia di Modena nel 2003) **2005** in: http://www.rtm.unimo.it/dati/2003/libroE.html (February 15, 2006)

Fertmann R, Hentschel S: Langzeitüberleben von Personen mit Colorektal-Krebs, Lecture at 50. Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (gmds), 12. Jahrestagung der Deutschen Arbeitsgemeinschaft für Epidemiologie. Freiburg im Breisgau, 12.-15.09.**2005**, in: http://www.egms.de/en/meetings/gmds2005/05gmds210.shtml (February 15, 2006)

Finnish Cancer Registry: SURV3: Windows Software for Relative Survival Analysis (version 3.01 last update December 20, **2002**, in: http://www.cancerregistry.fi/surv3/ (February 15, 2006)

Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID) (Hrsg.): Umsetzung von TNM in UICC-Stadium und Ausbreitung, Bearbeitungsstand 14.12.**2005**, in: http://www.gekid.de/ (protected domain, February 20, 2006)

Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID) und das RKI (Hrsg.): Krebs in Deutschland. 5. überarbeitete, aktualisierte Ausgabe. Saarbrücken **2006**

Gesetz über Krebsregister (Krebsregistergesetz KRG), veröffentlicht im Bundesgesetzblatt I (**1994**) 79: 3351-3355

Greenwood M: The Errors of Sampling of the Survivorship Tables, in: Reports on Public Health and Medical Subjects 33, London (Her Majesty's Stationery Office) (**1926)**: 1-30.

Haberland J, Schön D, Bertz J, Görsch B: Vollzähligkeitsschätzungen von Krebsregisterdaten in Deutschland, in: Bundesgesundheitsblatt - Gesundheitsforschung – Gesundheitsschutz 46 (**2003**) 9: 770-774

Hakulinen T: Cancer survival corrected for heterogeneity in patient withdrawal, in: Biometrics (**1982**) 38: 933–942.

Hakulinen T, Gibberd R, Abeywickrama K, Söderman B: A Computer Program Package for Cancer Survival Studies, in: Cancer Society of Finland Publication No. 39 (Ed.: Finnish Cancer Registry) Helsinki **1988**

Hamburger Krebsgesellschaft e.V.: Projekt „Verbesserung der klinischen Krebsregistrierung in Hamburg“, in: http://www.hamburger-krebsgesellschaft.de/projekte/projekte.html (February 21, 2006)

Hamburgisches Krebsregister: Datenimport durch Datensatzschnittstelle, Lecture at GEKID-Tagung in Nürnberg (previously unreleased), 16.11.**2005**

Hamburgisches Krebsregister, Freie und Hansestadt Hamburg, Behörde für Wissenschaft und Gesundheit (Hrsg.): Hamburger Krebsdokumentation 1999-2001,Hamburg **2004**

Hoffmeister H, Lingk W (Hrsg.): Das Krebsregister der Freien und Hansestadt Hamburg, in: Krebsregistrierung in der Bundesrepublik Deutschland. Möglichkeiten und Grenzen, bga-Bericht, Berlin (Dietrich Reimer Verlag) **1981**

IARC (International Agency for Research on Cancer), Commission of the European Communities, World Health Organization, “Europe against Cancer”: Facts and Figures of Cancer in the European Community, **1993**, in: http://telescan.nki.nl/iarc.html (February 15, 2006)

Kato I, Severson RK, Schwartz AG: Conditional median survival of patients with advanced carcinoma: surveillance, epidemiology, and end results data. in: Cancer (**2001**) 92: 2211-2219

Manton KG, Stallard E, Woodbury MA, Dowd JE: Time-varying covariates in models of human mortality and aging: Multidimensional generalizations of the Gompertz, in: Journal of Gerontology: Biological Sciences (**1994**)49: B169-B190,

MARIE study, Wer führt MARIE durch?, **2002**, in: http://www.uke.uni-hamburg.de/extern/marie/marie_werfuehrtdurch.html (February 15, 2006)

Mehnert A: Akute und posttraumatische Belastungsstörungen bei Patientinnen mit Brustkrebs, Münster (Lit Verlag) **2005**

National Statistics: Cancer Survival, England, 1998-2003. last updated 9/5/**2005**, in: National Statistics website: www.statistics.gov.uk Crown copyright material is reproduced with the permission of the Controller of HMSO
http://www.statistics.gov.uk/StatBase/Expodata/Spreadsheets/D8982.xls (February 20, 2006)

Parkin DM: Global Cancer Statistics in the Year 2000, in: Lancet Oncology (**2001**)2: 533-543

Parkin DM, Chen VW, Ferlay J, Galceran J, Storm HH, Whelan SL : Comparability and Quality Control in Cancer Registration. IARC Technical Report No. 19 (Ed.: International Agency for Research on Cancer), Lyon **1994**

Quinn M; Babb P: Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons, in: BJU international 90 (**2002**) 2:162-73

Reiche R: Beiträge zur Statistik des Carcinoms, in: Deutsche Medizinische Wochenschrift 26 (**1900**) 7:120-121 and 8:135-137.

RKI Dachdokumentation Krebs: Vollzähligkeitsschätzung **2005**, in: http://www.rki.de/nn_227180/DE/Content/GBE/DachdokKrebs/Vollzaehligkeitsschaetzung/vollzaehligkeitsschaetzung__node.html__nnn=true (February 20, 2006)

Sainsbury JRC, Anderson TJ, Morgan DAL: Breast cancer, in: BMJ (**2000**) 321: 745-749

Sankila R: IARC - Course on Analysis and Presentation of Cancer Registry Data. Entebbe, Uganda (**2005**) in: www.iacr.com.fr/uganda/Sankila-Cancer-Registration-Quality-Control.ppt (February 16, 2006)

Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, Grosclaude P, Hédelin G, Matsuda T, Møller H, Möller T, Verdecchia A, Capocaccia R, Gatta G, Micheli A, Santaquilani M, Roazzi P, Lisi D and the EUROCARE Working Group: EUROCARE-3: survival of cancer patients diagnosed 1990–94 — results and commentary, in: Annals of Oncology 14 (**2003**) Suppl. 5: v61–v118

Sant M, Allemani C, Berrino F, Coleman MP, Aareleid T, Chaplain G, Coebergh JW, Colonna M, Crosignani P, Danzon A, Federico M, Gafa L, Grosclaude P, Hedelin G, Mace-Lesech J, Garcia CM, Moller H, Paci E, Raverdy N, Tretarre B, Williams EM; European Concerted Action on Survival and Care of Cancer Patients (EUROCARE) Working Group: Breast carcinoma survival in Europe and the United States, in: Cancer. 100 (**2004**) 4:715-22

Schlesinger-Raab A, Eckel R, Engel J, Sauer H, Löhrs U, Molls M, Hölzel: Metastasiertes Mammakarzinom: Keine Lebensverlängerung seit 20 Jahren, in: Deutsches Ärzteblatt 102 (**2005**) 40: A2706-A2714

Schleswig-Holsteinischer Landtag : Plenarprotokoll 14/14, Kiel, **1996**

Schön D, Bertz J, Görsch B, Haberland J, Ziegler H, Stegmaier C, Eisinger B, Stabenow R: Entwicklung der Überlebensraten von Krebspatienten in Deutschland, Berlin (Robert Koch-Institut) **1999**

Schümann M, Berger J, Hentschel S, Burkardt N, Wessel M, Dirksen-Kauerz U: Inzidenz und räumliche Verteilung maligner hämatologischer Systemerkrankungen in Hamburg (1988-1999). Hamburg **2004**, in: http://fhh.hamburg.de/stadt/Aktuell/behoerden/wissenschaft-gesundheit/verbraucherschutz/umwelteinfluesse/zz-ladbar/leukaemiestudie-datei,property=source.pdf (February 15, 2006)

Schwanke W: Krebs in Hamburg, in: Bruns Beiträge zur klinischen Chirurgie 151(**1930**) 46:326-330.

Statistics Canada: Cancer survival statistics **2005** http://www.statcan.ca/english/freepub/84-601-XIE/2005001/survival.htm (February 20, 2006)

Statistisches Amt für Hamburg und Schleswig-Holstein: 500 Jahres-Zeitreihen (seit 1970), Stand: 31.12.**2003**, in: http://fhh1.hamburg.de/fhh/behoerden/behoerde_fuer_inneres/statistisches_landesamt/zeit/zeit1Tab1.htm (February 20, 2006)

Statistisches Amt für Hamburg und Schleswig-Holstein (Hrsg.): Statistisches Jahrbuch Hamburg 2004/2005. Hamburg/Kiel **2004**, in: http://fhh1.hamburg.de/fhh/behoerden/behoerde_fuer_inneres/statistisches_landesamt/jahrbuch/Jahrbuch2004_HH_CD-ROM.pdf (February 20, 2006)

Statisches Landesamt in Verbindung mit der Gesundheitsbehörde der Freien und Hansestadt Hamburg (Hrsg.): Hamburger Krebsdokumentation 1956 bis 1971. Sonderdruck des Heftes 105 der Reihe „Statistik des Hamburger Staates“ **1973**

Surveillance, Epidemiology, and End Results (SEER) Program: SEER Survival Statistics, based on the November 2004 submission , released April **2005** in: http://seer.cancer.gov/canques/survival.html (February 20, 2006)

Teppo L, Dickman PW, Hakulinen T, Luostarinen T, Pukkala E, Sankila R, Söderman B: Cancer patient survival -- patterns, comparisons, trends -- a population-based Cancer Registry study in Finland, in: Acta oncologica, 38 (**1999**) 3: 283-294

Tumorzentrum Land Brandenburg e.V.und Qualitätskonferenz Onkologie: Qualitätssicherung durch klinische Krebsregister: Sachbericht Onkologie 2004/2005. Frankfurt (Oder) **2006**, in: http://www.tumorzentrum-brandenburg.de/files/Sachbericht_2004-2005.pdf (February 20, 2006)

Voutilainen ET, Dickman PW, Hakulinen T: SURV2: Relative Survival Analysis Program. Software Manual Program version 2.02β (Ed.: Finnish Cancer Registry) Helsinki 1998, Manual updated August 9, **2000**, in: http://www.cancerregistry.fi/surv2/(February 20, 2006)

Wagner G, Hermanek P: Organspezifische Tumordokumentation, Prinzipien und Verschlüsselungsanweisungen für Klinik und Praxis, Berlin, Heidelberg (Springer) **1995**

Wittekind D, Meyer HJ, Bootz F (Hrsg.): TNM Klassifikation maligner Tumoren, 6. Aufl., Heidelberg (Springer) **2002**

7. Declaration

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgment has been made in the text.

Hamburg, February 27th 2006