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Screening for Prostate Cancer—Necessity or Nonsense?

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INTRODUCTION

PROSTATE CANCER is a common disease among men above the age of 50 years. The 85 000 new cases diagnosed in the European Community every year amount to 13% of all cases of cancer in men. Prostate cancer in most countries is now the second most frequent malignancy in men after lung cancer. Death from prostate cancer accounts for 9% of all cancer death in males—this is evident from a recent review of prostate cancer incidence and mortality in European Community countries by Møller Jensen *et al.* [1]. The incidence and mortality of prostate cancer is also increasing in most Western countries. Part of this is due to the increase of male life expectancy. However, after correction for life expectancy, there remains a true increase, which at this moment is unexplained. This has been shown clearly in a recent survey in The Netherlands [2].

In 1982 Mettlin and co-workers [3] have published data from a short- and long-term survey of prostate cancer of the American College of Surgeons. Their data include the stage distribution in 20 166 (long-term) and 14 079 (short-term) patients with this disease. Although their data may be biased by the inclusion of an unusually high proportion of incidentally detected, usually focal prostate cancer (23 and 27%), this study still shows that roughly half of patients who are diagnosed as having prostate cancer present with locally advanced and/or metastatic disease at the time of first diagnosis. The prognosis of patients with advanced prostate cancer, even with the most aggressive treatment, is poor. Cure is impossible, median time to progression and median survival of metastatic patients is in the range of 18 and 30 months, respectively [4, 5]. These figures contrast sharply with the results of radical prostatectomy or radiotherapy for localised disease, usually cancer that is palpable on rectal examination. Such data were recently subject to a United States National Cancer Institute (NCI) consensus development conference and the conclusion was that both radical prostatectomy and radiotherapy are "clearly effective forms of treatment" in this disease [6]. Median survival was shown by Gibbons [7] to be longer than 15 years in 57 patients with clinical stage B disease who were followed for more than 15 years. The observed crude survival rates were identical to the expected survival of 59-year-old American men.

Obviously, if a high risk for patients suffering from localised prostate cancer and effectiveness of treatment could be documented, a systematic search for early stages of prostate cancer should lead to a decrease of the mortality of this disease. However, uncertainties concerning the natural history, especially in the individual patient, and the lack of randomised treatment studies comparing radiotherapy or radical prostatectomy to delayed treatment or placebo, still cast doubt on the potential usefulness of population screening for prostate cancer.

Recent progress has been made concerning the available screening tests for prostate cancer. While for a long period of time rectal examination was considered to be the most sensitive test for the detection of prostate cancer, it has recently been shown by Catalona *et al.* [8] that serum prostate specific antigen (PSA) measured by the tandem-R technique of Hybriteck is a much more sensitive method of detecting prostate cancer than rectal examination alone. 12 of 37 cancers (32%) detected by PSA would have been missed by rectal examination. Transrectal ultrasonography, another new modality used for early detection of prostate cancer, has been shown by Lee *et al.* [9] to increase, in conjunction with a novel automatic biopsy device, the detection rate of prostate cancer 2-fold when compared to rectal examination. Prostate cancer is identified with this technique by its characteristic of frequently presenting as a hypoechogenic area within the prostate. At this moment it is, however, unclear how much of the higher detection rate is due to the ultrasonography as opposed to the novel, automatic biopsy technique, used by these and other authors. Detection rates are in the range of 2–3%. It is difficult for lay people and potential patients to understand why readily available early detection which is not associated with heavy physical or mental trauma should not be used, especially in a situation when effective treatment seems to be available. As a consequence, screening ouside of studies or official programmes is carried out with increasing frequency upon the request of men who have heard about these tests. Such pressure and increasing use of the available tests is one important reason to carry out careful studies of screening for prostate cancer. Such a study has recently been designed by a task force of the U.S. National Institutes of Health.

There is consensus that at this moment it would be premature to recommend prostate cancer screening as a public health policy. Relevant arguments have recently been summarised by Hinman [10] and by a task force of the International Union Against Cancer (UICC) [11].

Most authors agree that randomised treatment studies and randomised screening studies must be conducted prior to considering the introduction of the new screening technology into routine health care. Wilson and Jungner [12] have identified a number of criteria which can be used as prerequisites for the evaluation of screening programs. The 10 criteria address the following issues:
(1) Is the disease under study an important health problem? (2) There must be an effective treatment for patients suffering from localised disease. (3) The facilities for further diagnosis and treatment must be available. (4) There must be an identifiable latent or early symptomatic stage of the disease. (5) The technique to be used for screening must be effective. (6) The tests must be acceptable to the screened population. (7) The natural history of the disease, including the development of the latent phase, to clinical disease must be sufficiently known. (8) There must be a generally accepted strategy allowing

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determination of which patients should be treated and which ones should remain untreated. (9) The expenses of the screening must be acceptable. (10) Management of the disease in early stages must have favourable impact on prognosis.

Clearly, a number of these parameters are related to health care routines and not to screening studies. Within a prospective, randomised study, facilities for diagnosis and treatment will be part of the study organisation. The expenses of screening should be subject to such a study. The importance of prostate cancer as a general health problem has already been addressed above. The remaining issues, mainly concerning the natural history of the small lesion, the effectiveness of treatment and the acceptability of the screening tests will be dealt with in the subsequent text.

IS THERE AN IDENTIFIABLE LATENT OR EARLY SYMPTOMATIC STAGE OF PROSTATE CANCER?

Locally confined prostatic cancer is usually asymptomatic. It is often diagnosed because of symptoms of associated benign prostatic hyperplasia (BPH). In the TNM system locally confined disease is described as T1a or T1b if the tumour is found unexpectedly by the pathologist examining the apparently benign tissue removed for treatment of BPH and is also called incidental prostate cancer. Incidental prostate cancer is seen in 8–12% of such cases [13]. These tumours are not palpable on rectal examination. Some may be visualised by ultrasonography. Prostate cancer confined to the prostate but palpable on rectal examination is classified in the TNM system as T2 disease. Obviously, these tumours will be diagnosed at the time of preventive check-ups, since these are customary in several European countries such as Belgium, Germany and France. According to the survey of the American College of Surgeons [3] the proportion of category T1 and T2 tumours amounts to 23 and 34% of 20 166 identified prostate cancers (long-term survey). The frequency at which these early stages, especially the small palpable tumours, are diagnosed in Europe may be lower than in the U.S.A. The incidence of all early lesions is strongly dependent on age. While there is no doubt that some of these lesions are prognostically very favourable and probably do not require treatment, only the small focal and well-differentiated lesions (T1a) can be identified as progressing sufficiently slowly to warrant observation rather than aggressive treatment in elderly men. For palpable lesions there is a great need to identify reliable prognostic factors which allow prediction of progression to metastatic disease in the individual patient prior to treatment.

THE NATURAL HISTORY OF THE DISEASE MUST BE SUFFICIENTLY KNOWN

In the pathogenesis of human prostate cancer a number of steps can be identified by morphological and functional criteria. These are summarised in Table 1. Bostwick [14], in a recent survey of the literature, differentiates between three putative premalignant lesions of the prostate, PIN1, PIN2 and PIN3 which have different morphological characteristics. At this moment it is not entirely clear whether transition from PIN to focal carcinoma, respectively, to infiltrating adenocarcinoma actually occurs. A strong argument for considering true focal disease as a separate entity lies in the fact that its incidence is not geographically variable as opposed to the locally extensive or metastatic disease [15, 16].

The incidence of all steps in the development of prostate cancer is age-dependent. In this context it is important to consider that Franks [17] in his autopsy studies found that 52 of 69 very small tumours already showed invasion of the fibrous capsule of the prostate. The total autopsy incidence, independent of age, in the studies by Gaynor [18] and Franks [17] average 18.2 and 32.9%, respectively. The incidence, besides being related to age, seems to be mainly dependent on the step sectioning technique applied to the specimens. The progression from focal carcinoma to clinical disease, androgen-dependent or androgen-independent may be an endocrine-dependent process. Very little is known about the genetic changes that are probably associated with the stepwise pathogenesis of prostate carcinoma.

Table 1. Pathogenesis of prostatic carcinoma—morphological and functional development

Normal epithelial cell
↓
Prostatic intraepithelial (neoplasia) PIN
↓
Focal carcinoma
↓
Adenocarcinoma, hormone dependent
↓
Adenocarcinoma, hormone independent

The natural history of T1a and T1b disease

Fortunately, a number of recent studies have contributed very significantly to a better understanding of the natural course of carcinoma of the prostate. A number of representative references are given in Table 2. All series cited deal with incidental prostatic cancer which has remained otherwise untreated. Progression rates clearly are dependent on time, grade of differentiation and on the extent of the primary lesion (T1a, T1b). Lowe *et al.* [23] have calculated median times to progression for T1a lesions of 13.5 years and for T1b lesions of 4.75 years. Most prostate cancer patients die of other causes. Death from intercurrent disease is very common in this age group. Blute *et al.* [22] point to a higher probability of progression and death from prostate cancer in younger males. This finding is not confirmed by Lowe and Liström [23]. Not all reports differentiate between local and distant progression. Out of 121 cited patients, including 12 with progression, 3 (25%) showed progression locally while 9 (75%) progressed to the metastatic stage. With a 50% chance of progression within 4.75 years, treatment is obviously desirable for T1b lesions.

Prediction of progression.

Cantrell *et al.* [20] were the first to study factors influencing progression rates of incidentally detected prostate cancer in a multivariate analysis. They found that the involvement by tumour of less than 5% of the total surface of the histological slides was the most important prognostic factor. It did not appear significant, in his hands, whether this was judged by a complicated morphometrical technique or by just viewing the slides with low magnification. Obviously, this parameter strongly depends on preparative techniques. Still, the 5% cut-off has become very common in differentiating between focal and extensive incidental disease. In the same multivariate analysis the grade of differentiation was the second most important parameter. Low and Liström [23] used age, grade and involvement of more or less than 5% of the slide surface to design a probability score for progression. Their tables allow the prediction of progression rates according to these parameters at 5- and 10-year periods.

Table 2. Progression rates and cancer deaths due to untreated prostatic carcinoma T1a and T1b (TNM 1987)

Reference	T1a/T1b *n*	Average time of follow-up		PD *n* (%)	Cancer deaths *n*	
19	45	62 months		13 (28.8)	2	
20	48 T1a	> 48 months		1 (2.0)	0	
	34 T1b	> 48 months		11 (32.0)	5/23	
21	50 T1a	> 96 months		8 (16.0)	6/26	
22	15 T1a	10.2 years		4 (26.6)	1/8	
(age < 60 years)	8 T1b	10.2 years		21 (25.0)		
23	143 T1a	13.5 years*	60	50%*	3	38
	55 T1b	4.75 years*		50%*	12	
24	76 T0pT1†	7 (10)		3/22		
	38 T0pT2–3†	6.5 years		11 (32)	5/10	

* Kaplan–Meier projections of median time to progression. † TNM 1982. PD = Progressive disease.

On the basis of these findings it has become common practice to not treat truly focal disease if it can be diagnosed with reasonable certainty in older men. Younger men (below the age of 60) may outlive the progression of their tumour and might be considered candidates for an aggressive approach. Treatment is warranted for T1b lesions which represent an immediate threat to anyone who has a life expectancy of at least 5 years. The best form of treatment for T1b lesions is not known at this time. Radical prostatectomy in a series of 45 patients with incidental prostate cancer revealed a 45% cancer death rate over a 50-year follow-up period after radical prostatectomy [25]. Clearly, some of these lesions are too extensive to be cured by local measures.

THE NATURAL HISTORY OF PALPABLE, CONFINED DISEASE (CATEGORY T2)

A classical article reviewing the natural history of prostatic cancer has been contributed by Whitmore [26]. A recent update was given by the same author [27]. Data resulting from a recent review of the literature are summarised in Table 3. It is evident from these data that median time to progression is in the range of 6 years and varied with the subclassifications of the T2 category. The data presented by Johansson *et al.* [24] may not be representative because while they were collected during a number of years, an unknown number of G3 lesions have been excluded. This is reflected in a very low proportion (only 4.5%) of G3 lesions in this study. In series of patients treated by means of radical prostatectomy G3 lesions are usually present in 25–30% of cases. Also, the number of grade 1 lesions (66%) is unusually high. In general, the proportion of patients dying of locally confined prostate cancer is low. This again is most likely due to a high presentation of men dying due to intercurrent disease; the short duration of follow-up may also be an important factor. The number of patients in whom cancer death can be prevented will be low in this group of patients. In the protocol on "A European randomised study for screening of adenocarcinoma of the prostate" by Schröder and Denis [31], Damhuis calculated the risk of dying of prostate cancer within 10 years for a group of men aged 60–74 years. Life table methods were used, exclusion of larger tumours by PSA prescreening was taken into account. The 10-year risk of dying of prostate cancer is approximately 0.5%.

Table 3. Progression rates and cancer deaths due to confined, palpable prostate cancer (category T2a and T2b, TNM 1987 and B1, B2, B3)

Reference	*n*	Stage	No. (%) progressing	Average follow-up (months)	No./(%) cancer deaths
19	20	T2	7 (35)	91	1/6
29	117	T1	49 (42)	120	8/56
		T2		(66–150)	
27, 30	29	B1	19 (66)	124	
	37	B2	29 (78)	120	18/75
	9	B3	4 (44)	96	= 24%

Unfortunately, no parameter exists which allows a reliable prediction of progression in the individual patient. The grade of differentiation as determined on radical prostatectomy specimens has been shown to be the most powerful predictor in several series of cases. However, as Ackermann and Müller [33] have shown, the true grade of locally confined prostate cancer cannot be predicted on the basis of biopsy evidence. DNA ploidy, proliferation labelling and tumour volume estimated by ultrasonography may be more reliable prognostic factors. Their clinical impact, however, is insufficiently documented at present. A preselection of patients with larger tumours for surveillance and aggressive treatment, therefore, is not possible at this time.

STRATEGY FOR INCLUDING AND EXCLUDING PATIENTS FROM TREATMENT

The only group of patients that can be excluded from treatment on the basis of pretreatment evaluation are those who have well-differentiated focal incidental prostate carcinoma. This group has been described above. Unfortunately, as mentioned in the previous section, it is impossible to preselect patients with localised, palpable disease. The possibility of overtreatment in this particular group cannot be excluded. The development of prognostic factors of sufficient predictive value is a high priority of clinical research in this field.

EFFECTIVE TREATMENT MUST BE AVAILABLE AND MANAGEMENT IN THE EARLY STAGES MUST HAVE A FAVOURABLE IMPACT ON THE PROGNOSIS

The effectiveness of radiotherapy and radical prostatectomy in managing patients with localised prostate cancer has recently been dealt with extensively during a U.S. National Cancer Institute consensus development conference. The results of this conference have been widely published [6, 33]. A very distinguished group of radiotherapists and urologists, after discussing the issue, came to the conclusion that "radical prostatectomy and radiation therapy are clearly effective forms of treatment in physicians' attempts to cure tumours limited to the prostate for appropriately selected patients". Unfortunately, this consensus statement, although based on a sound argument, does not resolve the issue of whether surgery, radiotherapy or surveillance with delayed treatment will produce better results.

There is very little doubt that a number of patients can be cured by means of radiotherapy as well as by radical prostatectomy. In an early report on his radiotherapy experience, Bagshaw [34] had included 6 patients who had undergone autopsy after definitive external beam radiotherapy. These men had died of other causes. At step sectioning of the prostates, no evidence of the previously biopsy-proven tumour was found. However, this initially very favourable report of excellent local control by means of external beam radiotherapy was followed by an increasing volume of data showing that local control is not achieved in a large proportion of patients. The difficulty is how to define local control clinically. If systematic aspiration biopsy of postradiotherapy patients is carried out over periods up to 2 years, apparently vital tumour cells are recovered in up to 90% of cases [35]. Van der Werf-Messing [36] was first to show conclusively that patients who have a positive biopsy have a 35% higher incidence of later occurrence of metastases in comparison with the biopsy-negative control population. This was confirmed by several other authors. The issue of local control by means of radiotherapy (external beam and brachy therapy) was recently reviewed by Schellhammer and El-Mahdi [37]. Local progression to larger tumours or a higher T category after external beam radiotherapy is seen much more rarely than positive biopsies. It is unclear which parameter should be used to determine local failure after this form of treatment.

Local control after radical prostatectomy has been extensively studied. The data are summarised by Schellhammer and El-Mahdi [37]. Local failure after radical prostatectomy without any use of adjuvant endocrine treatment was calculated to average 19% in five representative series of a total of 258 clinical stage B and 31% in two representative series of a total of 51 patients with clinical stage C disease. These local failure rates are similar to those reported for external beam radiotherapy (without considering the biopsy data) but are clearly lower in comparison with those reported for interstitial brachy therapy, especially in the more advanced stages. Also after surgery a high correlation between local recurrence and the later development of distant metastases is found. This correlation is similar to the one seen between positive biopsies and later distant recurrences after external beam radiotherapy. It may, therefore, be more appropriate to consider positive biopsies after prolonged periods after radiotherapy as a local failure.

The only randomised prospective study comparing radiotherapy and radical prostatectomy after lymphadenectomy in locally confined prostatic cancer was reported by Paulson *et al.* [38]. The study was discontinued because a significant difference occurred in favour of radical prostatectomy. This study was, however, heavily criticised mainly because of the organisation of the radiotherapy group. Historical comparison of large series of patients treated by means of radiotherapy and similar series treated by means of radical prostatectomy has not shown a clear advantage in cancer death and survival rates for either of the treatment modalities. This is well documented in the NCI consensus monograph [6]. Theoretically this may be due to equal effectiveness of the two treatment modalities. More likely, the selection bias that is present in each individual series makes historical comparison impossible. Considering the presence of strong prognostic factors and the difficulty of their reliable pretreatment evaluation, comparison after correction for such factors must also be considered non-feasible. Another explanation for the similarity of the survival data obtained with both modalities lies in the fact that the treatment advantage to be expected with consideration of the natural history will not be very large. In the large series of Schröder and Belt [40] with an average follow-up of almost 10 years, only 11.5% of 132 patients with histological stage B disease and 29.9% of 213 patients with histological stage C disease died of prostate cancer. The lymph node status was not considered in this series of patients. These data are quite similar to the percentages of cancer deaths seen in the surveillance series, referenced in Table 3. Again, prognostic factors are very important in this context and historical comparison is not feasible.

Unfortunately, only one prospective randomised study using radical prostatectomy vs. surveillance has ever been reported in the literature [41, 42]. This study was never completed, only 66 patients with stage II disease (T2) were randomised, only 50 (20 in placebo and 30 in the radical prostatectomy arm) could be analysed. Similar numbers were obtained for stage I (incidental carcinoma). No significant differences were found in the early analysis and in a later analysis presenting a 15-year follow-up. The power of this study is insufficient to draw any conclusions.

In summarising this section on the effectiveness of treatment and the modulation of the natural course in locally confined disease, it can be stated that clear evidence exists that confined prostate cancer can be eradicated by either radiotherapy or radical prostatectomy. Unfortunately, no evidence from randomised studies exists that patients with localised prostatic cancer benefit from early treatment in terms of overall mortality and cancer-related mortality. The open questions have been phrased by Whitmore [43]: is cure necessary for those in whom it is possible? Is cure possible for those for whom it is necessary?

A prospective randomised study comparing radical prostatectomy with surveillance has been initiated in Sweden recently. If this study can be properly conducted and completed, an answer to the question may be available 10–15 years after completion of recruitment. In the meantime, very large numbers of radical prostatectomies and of radiotherapy treatments are carried out around the world. The morbidity of radical prostatectomy has been significantly reduced by recent technical developments [44]. Patients who present with locally confined prostate cancer do not wish to take the risk that they may belong to the group of rapidly progressing tumours that will kill within a short period of time and which still cannot be properly identified by pretreatment parameters. Patients presenting with this disease usually wish to take advantage of available treatment modalities to eliminate this tumour. A randomised screening study for localised prostate cancer with well-defined criteria of entry and the provision of early treatment in one arm as compared to standard health care patterns in the control arm, is likely to provide an answer to the pending questions.

THE SCREENING TESTS MUST BE ACCEPTABLE TO THE SCREENED POPULATION

Rectal examination, transrectal ultrasonography and plasma determination of PSA are the screening tests under question. No permanent damage and a good general acceptance of these procedures is widely reported in the literature. If suspicion is raised on the basis of one or a combination of these screening tests, a prostatic biopsy will have to be carried out. Such biopsies are outpatient procedures and are usually done via the transrectal route under ultrasonographic control. With proper antibiotic prophylaxis complications are rare and occur at a frequency of 0.1–2.0%. Complications are usually minor. Still, the fact that 60–75% of screened subjects who are found to have suspicious parameters for the presence of prostate cancer will undergo a biopsy without having the disease, is very disturbing. The possible adverse reactions from the screening procedure itself certainly will have to be part of any screening study for prostate cancer. The following parameters should be separately considered as suggested by Hinman [10]: the morbidity resulting from the tests, the emotional trauma resulting from the tests and the costs of the false-positive tests. The morbidity and mortality from unnecessary treatment of those patients who have incurable disease and the detection of clinically insignificant disease with resulting emotional trauma, are points that are of great relevance but may be very difficult to evaluate at the present time.

CONCLUSIONS

From this discussion it is evident that most of the criteria of Wilson and Jungner [12] can be met. The present uncertainties about the natural history in the individual case are disturbing facts. Evidence of cure of prostate cancer from phase II studies of radiotherapy and radical prostatectomy is firm. The high progression rates known from surveillance studies, the death rates observed in these patients together with the decreasing morbidity of treatment and the possibility of cure by means of the available treatment modalities, have led to widespread use of radiotherapy and radical prostatectomy. Still, the lack of evidence from randomised treatment studies concerning prolongation of life and the decrease of the number of cancer deaths, must be considered prohibitive at this time for the introduction of screening as a health care policy. In the present situation, however, also considering the difficulty of conducting randomised treatment studies with a surveillance control arm, well-controlled screening studies of this problem should be encouraged. This recommendation is in line with UICC policy [11] and the fact that the National Cancer Institute is at this moment sponsoring such a protocol.

Screening studies of prostate cancer intended to make a contribution to these relevant unanswered questions, must have a control arm in which at least some of the screening procedures are not applied. Clear treatment policies for the screened and the control population should be included in the protocol. Endpoints should include prostate cancer morbidity and mortality. Screening protocols should be preceded by pilot studies which address the issue of the response rate to the invitation to participate, the sensitivity and specificity of the screening test, morbidity and inconvenience resulting from the screening procedure as a whole and the screening tests in particular and costs of the early detection procedure and subsequent treatment.

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Cancer Epidemiology and Privacy Laws: Recent Trends in Germany

PARALLEL TO the efforts to establish modern epidemiological research in the Federal Republic of Germany came a rapid increase in public awareness of privacy of various kinds of person-related data. Epidemiological research became a victim of this trend. Mainly affected from this development were (a) projects of analytical epidemiology which needed access to death certificates of the official mortality statistics, (b) descriptive epidemiology despite its use of only aggregated data, and (c) , of course, cancer registration. Publications from that time [1, 2] deplored the restrictions which led to considerable delays of time needed to carry out epidemiological studies.

Those reports may have given rise to the misunderstanding that chiefly the new data protection laws have caused the problems in conducting epidemiological studies in Germany. In fact, however, data were never unprotected. Previous to the privacy laws of the late 1970s, regulations on access to, e.g. death certificates or data of the official mortality statistics existed, but, at the beginning of our first historical cohort studies, *awareness* of those regulations was relatively low. Thus, one effect of the passionate public discussion on data protection was that awareness of existing regulations increased and began to hamper epidemiological research.

On the other hand, hinderance of valuable scientific research has been recognised from the very beginning as an *unwanted* side-effect of the discussion on privacy and the respective legislation. Efforts have been undertaken to specify updates of privacy regulations in order to guarantee prerequisites for scientific research. At present, research regulations of privacy laws can widely be accepted by epidemiologists. However, because problems of epidemiologists do not actually originate from that legislation (or, at least, not only), some of our problems, nevertheless, persist, and will need some further efforts to achieve corresponding improvements in neighbouring fields of legislation.

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Well-suited examples for these developments were our experiences during the follow-up of the historical follow-up studies cited above [1, 2]. Parts of the inquiries, especially at the beginning of the follow-up, proceeded without problems, and we were able to get death certificates from the respective health offices through official channels. Later, however, inquiries were increasingly blocked. Importantly, the reasons were quite different and generally not due to the newly passed privacy acts:

(1) Death certificates may by law (*burial laws!*) only be used for the official mortality statistics: these laws do not take scientific research into account; thus, the request for informations has been rejected. The burial laws originated from 1970 and earlier [3].
(2) According to a decree of the respective Federal government, cause of death may, besides the official mortality statistics, only be reported to pension offices. This governmental act originated from 1965.
(3) Professional confidentiality of physicians prohibits communication of causes of death to "third persons". This is regulated in the penal code.
(4) According to decrees of several Federal state governments, cause of death may be communicated, but only if the German