Prostate Cancer and Prostatic Diseases (1999) 2, 253–256
 1365–7852/99 $15.00
www.nature.com/pcan

Paper

Morbidity in patients with clinically localized prostate cancer managed with non-curative intent. A population-based case–control study

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To compare the morbidity in patients with newly diagnosed clinically localized prostate cancer managed conservatively with the morbidity in a randomly selected age-matched background population with no history of prostate cancer.

Patients younger than 75 y at diagnosis with newly diagnosed clinically localized prostate cancer reported to the Danish Cancer Registry in the period 1977–1992. Morbidity in patients and age-matched controls was extracted from The Danish Hospital Discharge Registry. Admissions were stratified by discharge diagnosis.

Overall 4744 patients were hospitalized for 251,695 days within the first 10 y following diagnosis compared with 74,563 days in 4774 age-matched controls. The patients were admitted 6.7 (6.4–7.1) times more often than controls in the year following diagnosis, and 2.7 (2.6–2.8) times more often in the following 9 y. Excess morbidity declined over time. When prostate cancer-related admissions were excluded, the relative risk of admission was reduced to 1.35 (1.3–1.4) and 0.86 (0.83–0.89), respectively. The estimated costs associated with deferred therapy in patients with clinically localized prostate cancer exceeded the estimated cost in age-matched controls by approximately US$88 million, equivalent to an average extra cost per patient of approximately US$18,500.

Patients with clinically localized prostate cancer managed conservatively had a significantly higher morbidity than age-matched controls due to admissions associated with prostate cancer. In future comparisons of treatment strategies, morbidity following treatment and impact on quality of life have to be included when evaluating the outcome.

Keywords: prostate cancer; deferred endocrine therapy; morbidity; case–control study

Introduction

No clear consensus exists as to the optimal management of clinically localized prostate cancer (PC).[1,2] In younger patients managed expectantly, localized PC will progress, leading to morbidity associated with advanced PC. Previous studies have demonstrated that patients with PC managed with deferred therapy need repeated hospital admissions and palliative treatments. However, these studies have included patients in different clinical stages, and morbidity has not been compared to the background population.[3–6]

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Received 1 September 1999; accepted 1 November 1999

The Danish attitude towards PC has been conservative. Nationwide registries on incident cancer cases and hospitalizations, added to the possibility of accurate linkage across registries, offer unique opportunities for studying the impact of PC managed with deferred endocrine therapy. In a historical prospective population-based case–control study we have compared the morbidity in patients with newly diagnosed clinically localized PC to the morbidity in an age-matched background population.

Materials and methods

The study is based on a computerized linkage between two population-based registries; the Danish Cancer Registry (DCR) and the Danish Hospital Discharge Registry (DHDR).

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis in Denmark since 1943. Reporting was voluntary until 1987, when reporting became mandatory. The registry is regarded as almost complete.[7] Records on PC include information on the clinical age at diagnosis recorded as localized, regional, metastatic or unknown.

The DHDR, established in 1977, contains information on hospitalizations in Denmark with the general exception of psychiatric wards. Records include information on the duration of hospitalization and discharge diagnoses based on the International Classification of Diseases (ICD). In both registries the identification of individual patients is based on a unique Central Personal Registration number.

All patients with newly diagnosed PC reported to the DCR in the period from 1977 to 1992 were identified. Patients age 74 or younger with clinically localized PC at diagnosis were extracted. Patients in whom diagnosis was based on autopsy findings or death certificate information only were excluded.

Each case was matched with one control. Suitable controls should meet the following criteria:

1. Same year and month of birth as the matching case.
2. Alive with residence in Denmark at the time of diagnosis of the matching case.
3. No record of PC before 1992 in DCR.

A random match procedure based on the Central Personal Registration number was performed. Information on the number and duration of hospitalizations was extracted from DHDR in the period 1 January 1977 to 31 December 1994. Admissions were considered related to PC if PC (ICD8 code 185 or ICD10 code DC61.9) was recorded as discharge diagnosis. The linkage between registers and data analysis was based on specially designed computer software (Data Medica, Copenhagen). Follow-up on cases and controls were terminated 31 December 1994, or earlier if one of the pair died before.

The morbidity of patients compared to controls is described as the ratio between admission (adm.) rates, *relative morbidity*, defined as ((no. adm./patient/y)/(no. adm./control/y)), and as the difference between time spent in hospital, *excess morbidity*, defined as (no. days/patient/y) − (no. days/control/y). The admission-rate and the need for hospitalization were analyzed for the year of diagnosis, ie 365 days following the date of diagnosis and the following 9 y, respectively. The cost associated with hospital care was calculated based on the average price for hospitalization in Denmark.[8]

Trends were analyzed using a χ^2-test for trend. Differences between admission rates were tested using a rate-ratio and score test[9] and reported as relative risks (RR) with 95% confidence limits.

Results

A total of 4884 patients with clinically localized PC age 74 or younger at diagnosis were identified; 94 patients were excluded since diagnosis was based on either autopsy findings or death certificate only. In 4713 (98.4%) of the patients diagnosis was based on histological examination, and in a further 23 (0.5%) on cytological examination. In 54 patients (1.1%) no information on verification was available. Median age at diagnosis was 69 y, range 37–74. Following the matching procedure, an additional 16 patients were excluded as no matching controls were found for technical reasons. The study population thus consists of 4774 matched pairs.

In the year of diagnosis patients on average had 2.2 admissions. When admissions related to PC were excluded, the average number of admissions fell to 0.44. The relative morbidity was 6.75 (6.39–7.13) and 1.35 (1.26–1.44) after exclusion of PC-related admissions. In the following 9 y patients were still admitted significantly more often than controls RR = 2.69 (2.61–2.77). However, when PC-related admissions were excluded, the RR was close to unity 0.86 (0.83–0.89; Figure 1).

Overall, the 4774 patients were hospitalized 251,695 days within the first 10 y following diagnosis compared with 74,563 days in age-matched controls. In the year of diagnosis patients were hospitalized 100,269 days compared to 15,658 days among controls. The total number of days and the number of days spent in hospital after exclusion of discharges with PC as one of the discharge diagnosis is shown in Figure 2. The following 9 y patients spent 151,426 days in hospital compared with 58,905 days among controls (Table 1).

Admissions with PC as discharge diagnosis accounted for 76% of the days spent in hospital. When admissions

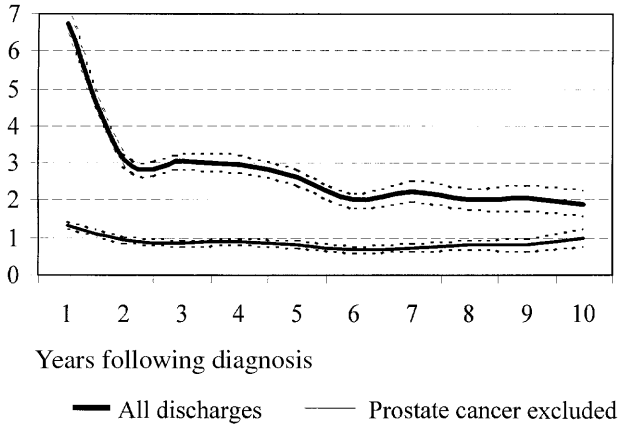

Figure 1 *Relative morbidity ((no. admissions/patient/y)/(no. admissions/control/y)) in patients with clinically localized PC (95% CI). All discharges, and PC discharges excluded.*

Table 1 Length of and costs associated with hospitalization of patients with clinically localized PC compared with controls

Year	Years at risk	Patients ($n=4774$) all discharges	Patients ($n=4774$) prostate cancer discharges excluded	Controls ($n=4774$)
1	4488	100,269 days US$50.1 million	17,050 days US$8.5 million	15,658 days US$7.8 million
2–10	15,100	151,426 days US$75.7 million	43,481 US$21.7 million	58,905 days US$29.5 million
Total	19,598	251,695 days US$125.8 million	60,981 US$30.2 million	74,563 US$37.3 million

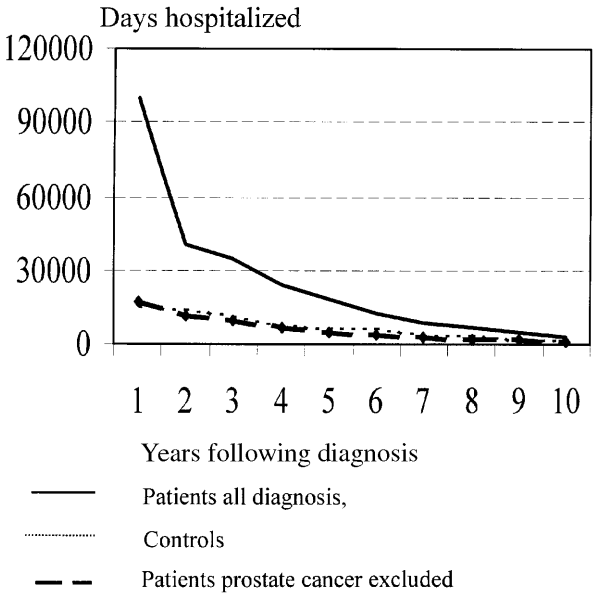

Figure 2 *The number of days per year hospitalized for PC patients, all discharges and PC discharges excluded, respectively. The number of days per year hospitalized for controls.*

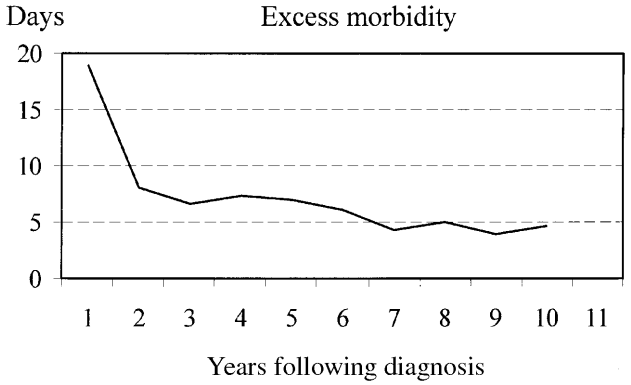

Figure 3 *Excess morbidity (no. days/patient/y) − (no. days/control/y) in patients with clinically localized PC.*

with PC as discharge diagnosis were excluded patients were hospitalized 17,050 days in the year of diagnosis and 43,481 in the following 9 y.

In the year of diagnosis patients were on average hospitalized for 22.3 days compared with 3.5 days among controls. In the following 9 y a significant decline in excess morbidity was found (Figure 3). From the second to the tenth year following diagnosis patients on average were hospitalized 6.1 days more than controls.

Table 1 shows the estimated costs associated with hospitalizations of patients and controls. The overall cost from the year of diagnosis and the following 9 y was approximately, US$125.8 million in the patients compared with US$37.3 million in the controls. This difference in need for hospital care amounted to an approximate extra cost per patient of US$18,500.

Discussion

Until 1994, expectant management of localized PC has been the routine strategy in Denmark and no early detection policy has been implemented.[10] Deferred endocrine therapy, regardless of age and stage, has been routine treatment for PC in Denmark, and only a few patients have been treated with curative intent.[11]

In this study, we described morbidity based on information from the DHDR. This registry has previously been found suitable for epidemiological studies[12] and good correlation between hospital records and information recorded in the registry has been demonstrated.[13]

The morbidity in patients with PC was compared to a randomly selected age-matched background population assuming that possible differences between patients and controls were due to PC.

Theoretically, the results may be biased by the selection procedure. The controls were only accepted if they had no previous or *subsequent* clinical diagnosis of PC. If histological sub-clinical PC increases the morbidity, the selection of controls may have lead to an underestimation of the morbidity in that group. Still, since PC is a frequent finding at autopsy,[14, 15] histological PC must be frequent among controls. This could result in an underestimation of the impact of PC, and a larger difference in morbidity might have been found if controls without even histological PC could have been identified. These considerations, however, are purely academic, and our study demonstrates the difference between clinical PC and no clinical PC.

We found that the morbidity was significantly higher among patients with clinically localized PC than among age-matched controls. The difference in admission-rate was highest in the year of diagnosis. Since the majority of PC cases in Denmark during the study period were diagnosed during hospitalization, the morbidity in the year of diagnosis may overestimate the morbidity associated with PC. However, in the 9 y following the year of diagnosis, admission rates showed only minor variations and patients were on average admitted 2.7 times more often than controls. When admissions related to PC were excluded, the relative morbidity was 0.86, thus close to unity. This finding indicates that if morbidity associated with PC is eliminated, the PC patients would exhibit

morbidity comparable to the background population. The fact that the relative morbidity was significantly below 1 may be explained by misclassification of PC as discharge diagnosis in cases where PC was not the direct cause of admission.

Excess morbidity declined during the period of follow-up. There are several explanations to this finding. Patients with the most aggressive PC have been shown to have the highest need for hospitalization.[3] These patients also have the worst prognosis and will be lost from follow-up first. Also, with extended follow-up, increasing competing morbidity will tend to reduce the relative impact of PC morbidity on the total morbidity.

The cost of hospitalization in Denmark varies from US$350 to 625, with an average of around US$500 per day.[8] Overall, the patients were hospitalized a total of 177,132 days more than controls, or approximately 37 days per patient. This difference was equivalent to a cost of approximately US$88.5 million, and represents a potential gain if a curative therapy without complications existed. This gain is, however, overestimated as both treatment, treatment failures and complications following curatively intended therapy will add to the costs of a curative treatment strategy.[16, 17]

The patients in our material represent a subgroup of patients believed to have had a clinically localized PC; further, their life expectancy would have made them candidates for curatively intended therapy.[18,19] When managed expectantly, this group of patients was found to have a significant excess morbidity leading to significant costs compared to the background population. Our findings demonstrate that these patients endure considerable morbidity related to PC and a significant impact on quality of life must be assumed. However, not all patients included in the study had truly localized, ie organ-confined PC, since the retroactive selection makes a significant under-staging likely. Thus, they would not all have been candidates for curative therapy. Nonetheless, it seems justified to question whether curative therapy in this group of patients would have reduced morbidity and cost.

In future studies of early prostate cancer, not only mortality and quality of life, but also morbidity and costs have to be considered when evaluating the outcome of various treatment strategies.

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