Level of education and mortality after radical prostatectomy

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Estimating the risk of competing mortality is of importance in men with early prostate cancer to choose the most appropriate way of management and to avoid over- or under-treatment. In this study, we investigated the impact of the level of education in this context. The study sample consisted of 2630 patients with complete data on level of education (college, university degree, master craftsmen, comparable profession, or others), histopathological tumor stage (organ confined or extracapsular), lymph node status (negative or positive), and prostatectomy specimen Gleason score (<7, 7, or 8–10) who underwent radical prostatectomy between 1992 and 2007. Overall, prostate cancer-specific, competing, and second cancer-related mortalities were study endpoints. Cox proportional hazard models for competing risks were used to study combined effects of the variables on these endpoints. A higher level of education was independently associated with decreased overall mortality after radical prostatectomy (hazard ratio [HR]: 0.75, 95% confidence interval [95% CI]: 0.62–0.91, P = 0.0037). The mortality difference was attributable to decreased second cancer mortality (HR: 0.59, 95% CI: 0.40–0.85, P = 0.0052) and noncancer mortality (HR: 0.73, 95% CI: 0.55–0.98, P = 0.0345) but not to differences in prostate cancer-specific mortality (HR: 1.16, 95% CI: 0.79–1.69, P = 0.4536 in the full model). In conclusion, the level of education might serve as an independent prognostic parameter supplementary to age, comorbidity, and smoking status to estimate the risk of competing mortality and to choose optimal treatment for men with early prostate cancer who are candidates for radical prostatectomy.

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INTRODUCTION

Estimating the risk of competing mortality is of importance in men with early prostate cancer to choose the most appropriate way of management and to avoid over- or under-treatment. Men with a long life expectancy may benefit from a later cessation of prostate cancer screening, and individualized risk-adapted strategies have been suggested. Age and comorbidity are factors used to determine the further life expectancy; nevertheless, life expectancy estimation is not yet sufficiently integrated into clinical decision-making in men with early prostate cancer. The socioeconomic status is another factor found associated with life expectancy. In one study, persons at age of 65 years with 12 or more years of education (as a measure of the socioeconomic status) had up to 3.9 years longer life expectancy than those with less education. We investigated the association of the level of education with different causes of death after radical prostatectomy to evaluate its possible value as a prognostic factor.

PATIENTS AND METHODS

Patien sample

Among 2961 consecutive patients who underwent radical prostatectomy at our institution (University Hospital Dresden, Germany) between December 1, 1992, and December 31, 2007, 2630 patients with complete data on level of education, histopathological tumor stage (organ confined or extracapsular), lymph node status (negative or positive), and prostatectomy specimen Gleason score (<7, 7, or 8–10) were included in this analysis. Institutional Review Board approval was obtained (EK268092009).

Variables

The level of education was stratified by the presence or absence of college or university degree. Master craftsmen and comparable professions were considered equivalent to college or university degree since they are classified equivalent to the first academic degree (bachelor) in Germany. Information was obtained from the patient charts. Comorbidity data (American Society of Anesthesiologists [ASA] physical status classification [Class 1, 2, or 3]11 and Charlson score,12 as a continuous variable) were derived from premedication and discharge records. Beside these data, smoking status (current smokers, former smokers, nonsmokers, or unknown smoking status), the presence of neoadjuvant hormonal treatment, preoperative prostate-specific
antigen (PSA) level (<10 ng ml\(^{-1}\) and no neoadjuvant hormonal treatment, 10 ng ml\(^{-1}\), higher or neoadjuvant hormonal treatment), and body mass index (as a continuous variable) were obtained from the patient charts.

**Follow-up data collection**

Follow-up data were collected from urologists, general practitioners, the patients themselves and their relatives, health insurance companies, local authorities, or the local tumor register. Prostate cancer was considered the cause of death when uncontrolled disease progression was present at the time of death. Second cancers were considered the cause of death when an uncontrolled second malignancy was present at the time of death. Deaths in the absence of uncontrolled prostate or second cancer or where the cause was unknown at the time of analysis were considered deaths from noncancer causes. Deaths from causes other than prostate cancer were considered deaths from competing causes (Table 1).

**Statistical analysis**

The cumulative incidences of deaths from prostate cancer, competing causes altogether, noncancer causes, and second cancers were determined by univariate and multivariate competing risk analysis. The univariate analyses were performed using SAS macros and Pepe–Mori tests.\(^{13,14}\) Cox proportional hazard models for competing risks according to Fine and Gray\(^{15}\) were used to study combined effects of the variables on overall, competing, noncancer, second cancer, and prostate cancer-specific mortality. The analyses were done with the Statistical Analysis Systems Version 9.4 statistical package (SAS Institute, Cary, NC, USA).

**RESULTS**

Demographic details of the whole sample are given in Table 1 and stratified by the level of education in Table 2. Patients with a higher level of education were less frequently current smokers (\(P < 0.001\)), had a lower mean body mass index (\(P < 0.001\)) and somewhat less severe comorbid conditions. The mean age- and prostate cancer-related risk profile did not differ by the level of education (Table 2).

A higher level of education was associated with decreased overall mortality (\(P = 0.002\)), attributable to both decreased noncancer (\(P = 0.0282\)) and second cancer mortality (\(P = 0.0240\)) (Figures 1–3). No difference in prostate cancer-specific mortality was seen (Figure 4). In the multivariate analysis with controlling for age, smoking status, prostate cancer risk profile, and two comorbidity classifications, a higher level of education was an independent predictor of lower mortality from all investigated causes except for prostate cancer (Table 3).

**DISCUSSION**

In this study, the level of education was independently associated with increased overall mortality after radical prostatectomy. The excess mortality in men with lower level of education was attributable to noncancer causes and second cancers but not to prostate cancer.

The level of education as a measure of the socioeconomic status has been found associated with life expectancy.\(^{16-18}\) As in our sample, in a recent Swedish study, a lower level of education was associated with increased cancer mortality.\(^{19}\) Similar observations have been made in Australia and Spain.\(^{17,18}\) Differences in healthcare-seeking behavior, unfavorable lifestyle, and comorbidities have been discussed as possible explanations for this observation.\(^{19}\) Overweight and obesity have been found associated with increased mortality from cancer as well as from noncancer causes\(^{19,21}\) and are (as in this study) more common in persons with a lower level of education.\(^{22}\)

### Table 1: Demographic details of the patient sample

| Parameter | College or university degree or master (%) | Others (%) | \(P\) |
|-----------|------------------------------------------|------------|------|
| Sample size \((n)\) | 1239 | 1391 | 0.1246 |
| Mean PSA\(^*\) (ng ml\(^{-1}\)) | 11.1 | 10.3 | 0.4738 |
| Organ confined disease\(^**\) (%) | 864 (70.0) | 952 (68.4) | 0.7802 |
| Positive lymph nodes (%) | 104 (8.3) | 121 (8.7) | 0.9980 |
| Gleason score 8–10 (%) | 234 (18.9) | 263 (18.9) | 0.2514 |
| Mean age (years) | 64.5 | 64.2 | 0.0001 |
| Mean BMI (kg m\(^{-2}\)) | 26.7 | 27.3 | <0.0001 |
| ASA Class 3 (%) | 187 (15.1) | 262 (18.8) | 0.0109 |
| Charlson score 2 or higher (%) | 174 (14.0) | 227 (16.3) | 0.1051 |
| Current smokers (%) | 102 (8.2) | 183 (13.2) | <0.0001 |

\(^*\)In patients without neoadjuvant hormonal treatment; \(^**\)Regardless of lymph node status; \(^**\)These three categories were considered competing causes of death. PSA: prostate-specific antigen; ASA: American Society of Anesthesiologists

### Table 2: Age-, tumor-, and patient-related risk profiles stratified by the level of education

| Parameter | College or university degree or master (%) | Others (%) | \(P\) |
|-----------|------------------------------------------|------------|------|
| Sample size \((n)\) | 1239 | 1391 | 0.1246 |
| Mean PSA\(^*\) (ng ml\(^{-1}\)) | 11.1 | 10.3 | 0.4738 |
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\(^*\)In patients without neoadjuvant hormonal treatment; \(^**\)Regardless of lymph node status. BMI: body mass index; ASA: American Society of Anesthesiologists

**Figure 1:** Cumulative overall mortality curves stratified by the level of education. \(P\) values are given for log-rank test (Kaplan–Meier analysis and log-rank test \(P\) value).
Smoking is another risk factor with higher prevalence in this population and has been held responsible for a portion of the lower education-related life year loss. The higher mean body mass index combined with the increased prevalence of smoking may therefore in part explain the increased second cancer and noncancer mortality rates in patients with a lower level of education. Since a lower level of education was an independent predictor of mortality after controlling for age, smoking status, body mass index, and comorbidity, an association with further unmeasured (for instance occupational, environmental or lifestyle-related) risk factors may be hypothesized. A lower level of education has repeatedly been found associated with worse prostate-cancer-specific survival. This study indicates that this is not necessarily the case among patients selected for radical prostatectomy in accordance with the findings by others. It is conceivable that some factors possibly contributing to adverse prostate-cancer-related outcome in men with a lower level of education (later diagnosis with more advanced tumors, differences in treatment choice) are largely eliminated by selection.

### Table 3: Optimal Cox proportional hazard models for overall, prostate cancer-specific, competing, noncancer, and second cancer mortality

| Category                              | HR   | 95% CI | P         |
|---------------------------------------|------|--------|-----------|
| **Endpoint overall mortality**        |      |        |           |
| Age (continuous variable, per year increase) | 1.06 | 1.04–1.08 | <0.0001  |
| Charlson score (continuous variable, per unit increase) | 1.31 | 1.20–1.43 | <0.0001  |
| ASA Class 2 (vs 1)                    | 1.48 | 0.96–2.26 | 0.0730   |
| ASA Class 3 (vs 1)                    | 2.17 | 1.34–3.50 | 0.0016   |
| Current smoker (vs not or unknown)    | 2.12 | 1.64–2.73 | <0.0001  |
| Extracapsular disease (vs organ confined) | 1.30 | 1.05–1.62 | 0.1514   |
| Positive lymph nodes (vs negative lymph nodes) | 1.54 | 1.16–2.04 | 0.0026   |
| Gleason score 7 (vs <7)               | 1.15 | 0.91–1.46 | 0.2349   |
| Gleason score 8–10 (vs <7)            | 1.93 | 1.48–2.51 | <0.0001  |
| College or university degree/master (vs none) | 0.75 | 0.62–0.91 | 0.0037   |
| **Endpoint prostate cancer-specific mortality** |      |        |           |
| Extracapsular disease (vs organ confined) | 3.09 | 1.89–5.03 | <0.0001  |
| Positive lymph nodes (vs negative lymph nodes) | 2.73 | 1.82–4.10 | <0.0001  |
| Gleason score 7 (vs <7)               | 2.87 | 1.39–5.93 | 0.0043   |
| Gleason score 8–10 (vs <7)            | 8.40 | 4.14–17.07 | <0.0001  |
| **Endpoint competing mortality**      |      |        |           |
| Age (continuous variable, per year increase) | 1.08 | 1.06–1.10 | <0.0001  |
| Charlson score (continuous variable, per unit increase) | 1.31 | 1.19–1.44 | <0.0001  |
| ASA Class 2 (vs 1)                    | 2.17 | 1.19–3.97 | 0.0116   |
| ASA Class 3 (vs 1)                    | 3.54 | 1.86–6.72 | 0.0001   |
| Current smoker (vs not or unknown)    | 2.29 | 1.73–3.02 | <0.0001  |
| College or university degree/master (vs none) | 0.65 | 0.52–0.82 | 0.0002   |
| **Endpoint noncancer mortality**      |      |        |           |
| Age (continuous variable, per year increase) | 1.07 | 1.04–1.10 | <0.0001  |
| Charlson score (continuous variable, per unit increase) | 1.34 | 1.19–1.50 | <0.0001  |
| ASA Class 2 (vs 1)                    | 3.50 | 1.32–9.31 | 0.0120   |
| ASA Class 3 (vs 1)                    | 6.62 | 2.41–18.15 | 0.0002  |
| Current smoker (vs not or unknown)    | 2.16 | 1.52–3.07 | <0.0001  |
| College or university degree/master (vs none) | 0.73 | 0.55–0.98 | 0.0345   |
| **Endpoint second cancer mortality**  |      |        |           |
| Age (continuous variable, per year increase) | 1.08 | 1.05–1.12 | <0.0001  |
| Charlson score (continuous variable, per unit increase) | 1.23 | 1.07–1.42 | 0.0042   |
| Current smoker (vs not or unknown)    | 2.15 | 1.35–3.42 | 0.0013   |
| College or university degree/master (vs none) | 0.59 | 0.40–0.85 | 0.0052   |

*College or university degree/master (vs none) in the full model: HR: 1.16, 95% CI: 0.79–1.69, P=0.4536. ASA: American Society of Anesthesiologists; CI: confidence interval; HR: hazard ratio.

### Figures
- **Figure 2:** Cumulative noncancer mortality curves stratified by the level of education (univariate competing risk analysis and Pepe–Mori test P value).
- **Figure 3:** Cumulative second cancer mortality curves stratified by the level of education (univariate competing risk analysis and Pepe–Mori test P value).
- **Figure 4:** Cumulative prostate cancer mortality curves stratified by the level of education (univariate competing risk analysis and Pepe–Mori test P value).
With hazard ratios (HRs) of 0.70 (95% CI: 0.58–0.84) in the univariate analysis and 0.75 (95% CI: 0.62–0.91) in the multivariate analysis, in this study, the size of the difference in overall mortality between men with high versus low level of education was comparable to that of radical prostatectomy versus watchful waiting (HR: 0.71, 95% CI: 0.59–0.86) in the Scandinavian Prostate Cancer Group Study Number 4. In our study, the overall mortality difference between men with high versus low level of education was narrowly equivalent to one point of the Charlson comorbidity score (Table 3). With the qualification that the 50% overall mortality level has no yet been reached, it may be estimated that the medium-term difference between the overall mortality curves of patients with or without a higher level of education was approximately 3 years (Figure 1), which was in a similar range as in comparable studies (3.8 years, 2.4–3.9 years, 3.4–4.7 years, and 1.4–2.8 years, respectively). Such a relatively large mortality difference may be clinically significant, particularly since the level of education may be used supplementary to age, ASA classification (evaluating the general physical status focused on the perioperative risk), Charlson score (counting and weighting of concomitant diseases), and smoking status (Table 3) to estimate the further life expectancy in candidates for radical prostatectomy. The capability to predict the risk of second cancer mortality (accounting for 39% of competing deaths in our sample) as well as the risk of competing noncancer mortality is a possible clinically useful property of the level of education as a prognostic factor. In patients aged 65 years or older, the 10-year competing mortality rate was 6% (95% CI: 3–9) in nonsmokers with a higher level of education and no relevant comorbidity (ASA Classes 1–2 and Charlson score 0, n = 285) but 54% (95% CI: 26–82) in smokers with a lower degree of education and serious comorbidity (ASA Class 3 or Charlson score 2 or higher, n = 20). Compared with the high 10-year competing mortality rate in the Prostate Cancer Intervention versus Observation Trial (PIVOT) of approximately 33%, the healthiest elderly patients in this study had a more than 5 times lower competing mortality whereas the highest risk group had an even higher 10-year competing mortality rate. These data suggest that the predictors of competing mortality identified in this study (age, comorbidity classifications, smoking status, and level of education) may rather have clinical importance in the identification of elderly patients with a very long life expectancy who could particularly benefit from early detection and treatment of prostate cancer, who represent a meaningful proportion among elderly candidates for radical prostatectomy than in the identification of patients with a shorter life expectancy, and who represent only a small minority in patients selected for radical prostatectomy. Identifying men with particularly long life expectancy may be of particular clinical concern in tailoring individualized prostate cancer screening strategies to improve the harm/benefit ratio.

This study has several limitations. Because of the unicentric study design, verification in different samples would be desirable. Data were obtained in the setting of a public healthcare system; in different healthcare systems, results might be different. The results apply to men selected for radical prostatectomy. In different clinical settings (unselected patients or patients selected for different treatment modalities), different effects are conceivable. The classification of the level of education relied on relatively sparse information in the patient records. Misclassification in individual cases may not be ruled out and is, however, unlikely of having influenced the results meaningfully since it would rather dilute than pretend effects. Comorbidity assessment relied on preoperative data in a highly selected and carefully investigated patient sample and might not necessarily apply to different populations.

CONCLUSIONS
A higher level of education was independently associated with decreased overall mortality after radical prostatectomy. This mortality gap was attributable both to competing second cancers and to noncancer causes but not to differences in prostate cancer mortality. The level of education might serve as an independent prognostic parameter supplementary to age, comorbidity, and smoking status to estimate the risk of competing mortality and to choose optimal management for men who are candidates for radical prostatectomy.

AUTHOR CONTRIBUTIONS
MF, RK, and MPW were responsible for the concept and framework of the paper. MF, SP, MH, RK, DL, OWH, GBB, and MPW participated in collecting and evaluating the data. MF wrote the paper. MF, RK, MH, and MPW were largely responsible for the drafting and final editing. All authors read and approved the final manuscript.

COMPETING FINANCIAL INTERESTS
The authors declared no potential conflicts of interest related to the matter discussed in this submission.

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