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ORIGINAL ARTICLE

Prostate Cancer

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.[1–4] Men with a long life expectancy may benefit from a later cessation of prostate cancer screening, and individualized risk-adapted strategies have been suggested.[5,6] 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.[2–4] The socioeconomic status is another factor found associated with life expectancy.[7,8] 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.[9] 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

Patient 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.[10] 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

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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.[8,9] As in our sample, in a recent Swedish study, a lower level of education was associated with increased cancer mortality.[16] 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.[16] 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	
Sample size (*n*)	2630
Median (mean) age	65.0 (64.3) years
Median (mean) follow-up (censored patients)	9.6 (10.0) years
Median (mean) PSA level*	7.3 (10.7) ng ml^{-1}
Median (mean) body mass index	26.8 (27.1) kg m^{-2}
Neoadjuvant hormonal treatment (%)	381 (14.5)
Organ confined disease** (%)	1816 (69.0)
Positive lymph nodes (%)	225 (8.6)
Gleason score 8–10 (%)	497 (18.9)
ASA Class 3 (%)	449 (17.1)
Charlson score 2 or higher (%)	401 (15.2)
Current smokers (%)	285 (10.8)
College or university degree or master (%)	1238 (47.1)
Deaths from noncancer causes***	186
Deaths from prostate cancer	110
Deaths from second cancers***	126
Deaths from unknown causes***	9

*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	
Mean PSA* (ng ml^{-1})	11.1	10.3	0.1246
Organ confined disease**	864 (70.0)	952 (68.4)	0.4738
Positive lymph nodes	104 (8.3)	121 (8.7)	0.7802
Gleason score 8–10	234 (18.9)	263 (18.9)	0.9890
Mean age (years)	64.5	64.2	0.2514
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. BMI: body mass index; ASA: American Society of Anesthesiologists

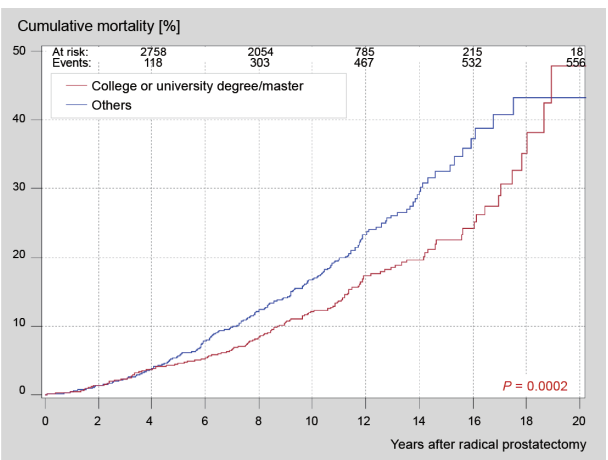

Figure 1: Cumulative overall mortality curves stratified by the level of education. *P* values are given for log-rank test (Kaplan–Meier analysis and log-rank test *P* value).

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	0.0154
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

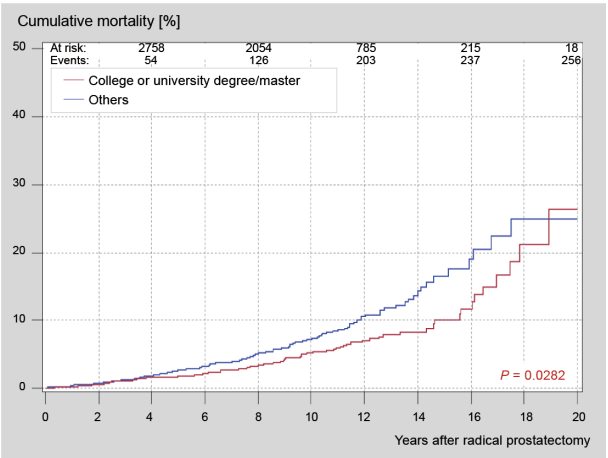

Figure 2: Cumulative noncancer mortality curves stratified by the level of education (univariate competing risk analysis and Pepe–Mori test *P* value).

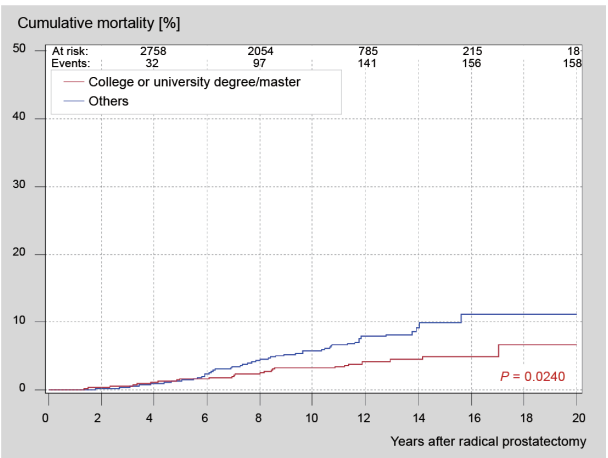

Figure 3: Cumulative second cancer mortality curves stratified by the level of education (univariate competing risk analysis and Pepe–Mori test *P* value).

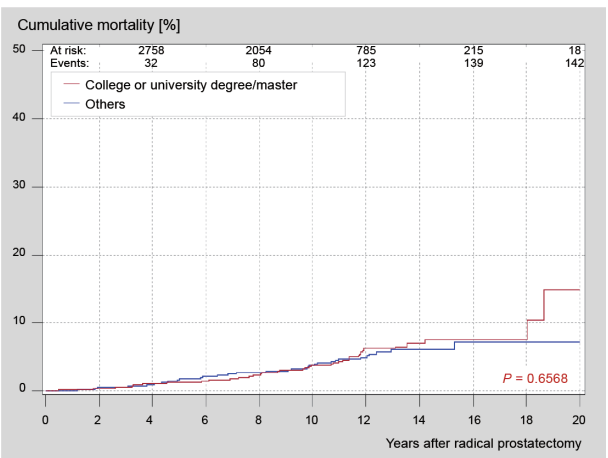

Figure 4: Cumulative prostate cancer mortality curves stratified by the level of education (univariate competing risk analysis and Pepe–Mori test *P* value).

Smoking is another risk factor with higher prevalence in this population[23] and has been held responsible for a portion of the lower education-related life year loss.[8,24] 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.[25] This study indicates that this is not necessarily the case among patients selected for radical prostatectomy in accordance with the findings by others.[26] 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[25]) are largely eliminated by selection.

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.[27] 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,[6] 2.4–3.9 years,[9] 3.4–4.7 years,[24] 3.4 years,[28] and 1.4–2.8 years,[29] 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%,[30] 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.[5]

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.

REFERENCES

1 Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, *et al*. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 2014; 65: 124–37.
2 Daskivich TJ, Fan KH, Koyama T, Albertsen PC, Goodman M, *et al*. Effect of age, tumor risk, and comorbidity on competing risks for survival in a U.S. population-based cohort of men with prostate cancer. *Ann Intern Med* 2013; 158: 709–17.
3 Daskivich TJ, Kwan L, Dash A, Greenfield S, Litwin MS. Weighted versus unweighted Charlson score to predict long-term other-cause mortality in men with early-stage prostate cancer. *Eur Urol* 2014; 66: 1002–9.
4 Daskivich TJ, Kwan L, Dash A, Saigal C, Litwin MS. An age adjusted comorbidity index to predict long-term, other cause mortality in men with prostate cancer. *J Urol* 2015; 194: 73–8.
5 Lansdorp-Vogelaar I, Gulati R, Mariotto AB, Schechter CB, de Carvalho TM, *et al*. Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. *Ann Intern Med* 2014; 161: 104–12.
6 Kitagawa Y, Namiki M. Prostate-specific antigen-based population screening for prostate cancer: current status in Japan and future perspective in Asia. *Asian J Androl* 2015; 17: 475–80.
7 Perna L, Thien-Seitz U, Ladwig KH, Meisinger C, Mielck A. Socio-economic differences in life expectancy among persons with diabetes mellitus or myocardial infarction: results from the German MONICA/KORA study. *BMC Public Health* 2010; 10: 135.
8 Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. *N Engl J Med* 2002; 347: 1585–92.
9 Guralnik JM, Land KC, Blazer D, Fillenbaum GG, Branch LG. Educational status and active life expectancy among older blacks and whites. *N Engl J Med* 1993; 329: 110–6.
10 Bundesministerium für Bildung und Forschung [Federal Ministry of Education and Research]: Deutscher Qualifikationsrahmen (DQR) [German Qualification Frame]. Available from: http://www.dqr.de/. [Last accessed on 2016 Jan 26].
11 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987; 40: 373–83.
12 American Society of Anesthesiologists. ASA Physical Status Classification System. Available from: http://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system. [Last accessed on 2016 Jan 26].
13 Parmar MK, Machin D. Survival Analysis. A Practical Approach. Chichester, England: John Wiley & Sons; 1996. p. 75–87.
14 Pintilie M. Competing Risks: A Practical Perspective. Chichester, England, Hoboken, NJ: John Wiley & Sons; 2006. p. 195–207.
15 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509.
16 Abdoli G, Bottai M, Moradi T. Cancer mortality by country of birth, sex, and socioeconomic position in Sweden, 1961-2009. *PLoS One* 2014; 9: e93174.
17 Smith D, Taylor R, Coates M. Socioeconomic differentials in cancer incidence and mortality in urban New South Wales, 1987–1991. *Aust N Z J Public Health* 1996; 20: 129–37.
18 Puigpinós R, Borrell C, Antunes JL, Puigpinós R, Cano-Serral G, *et al*. Trends in socioeconomic inequalities in cancer mortality in Barcelona: 1992-2003. *BMC Public Health* 2009; 9: 35.

19 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003; 348: 1625–38.
20 Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, *et al*. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006; 355: 763–8.
21 Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013; 309: 71–82.
22 Hermann S, Rohrmann S, Linseisen J, May AM, Kunst A, *et al*. The association of education with body mass index and waist circumference in the EPIC-PANACEA study. *BMC Public Health* 2011; 11: 169.
23 Pampel F, Legleye S, Goffette C, Piontek D, Kraus L, *et al*. Cohort changes in educational disparities in smoking: France, Germany and the United States. *Soc Sci Med* 2015; 127: 41–50.
24 Martikainen P, Ho JY, Preston S, Elo IT. The changing contribution of smoking to educational differences in life expectancy: indirect estimates for Finnish men and women from 1971 to 2010. *J Epidemiol Community Health* 2013; 67: 219–24.
25 Klein J, von dem Knesebeck O. Socioeconomic inequalities in prostate cancer survival: a review of the evidence and explanatory factors. *Soc Sci Med* 2015; 142: 9–18.
26 Papa N, Lawrentschuk N, Muller D, MacInnis R, Ta A, *et al*. Rural residency and prostate cancer specific mortality: results from the Victorian Radical Prostatectomy Register. *Aust N Z J Public Health* 2014; 38: 449–54.
27 Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, *et al*. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014; 370: 932–42.
28 Kulhánová I, Hoffmann R, Eikemo TA, Eikemo TA, Menvielle G, *et al*. Educational inequalities in mortality by cause of death: first national data for the Netherlands. *Int J Public Health* 2014; 59: 687–96.
29 Mäki NE, Martikainen PT, Eikemo T, Menvielle G, Lundberg O, *et al*. The potential for reducing differences in life expectancy between educational groups in five European countries: the effects of obesity, physical inactivity and smoking. *J Epidemiol Community Health* 2014; 68: 635–40.
30 Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, *et al*. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012; 367: 203–13.