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Influence of variation in use of definitive therapy on risk-adjusted prostate cancer mortality in England and the US

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Abstract

Objectives: Prostate cancer mortality (PCM) in the US is amongst the lowest in the world, whereas PCM in England is amongst the highest in Europe. This paper aims to assess the influence of variation in use of definitive therapy on risk-adjusted PCM in England as compared to the US.

Design: Observational study

Setting: Cancer registry data from England and the US

Participants: Men diagnosed with non-metastatic prostate cancer (PCa) in England and the US between 2004 and 2008

Outcome measures: Competing-risks survival analyses to estimate sub-hazard ratios (SHR) of prostate cancer mortality adjusted for age, ethnicity, year of diagnosis, Gleason score (GS), and clinical tumor stage (cT).

Results: 222,163 men were eligible for inclusion. Compared to American patients, English patients were more likely to present at an older age (70-79 years: England 44.2%, US 29.3%, p<0.001), with higher tumour stage (cT3-4: England 25.1%, US 8.6%, p<0.001) and higher Gleason score (GS 8-10: England 20.7%, US 11.2%, p<0.001). They were also less likely to receive definitive therapy (England 38%, US 77%, p<0.001).

English patients were more likely to die of PCa (SHR 1.9, 95% confidence interval 1.7-2.0, p<0.001). However, this difference was no longer statistically significant when also adjusted for use of definitive therapy (SHR 1.0, 95% confidence interval 1.0-1.1, p=0.3).

Conclusions: Risk-adjusted PCM is significantly higher in England compared to the US. This difference may be explained by less frequent use of definitive therapy in England.

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Article summary

Strengths and limitations of this study:

- Variation in prostate cancer management in England and the US provides an observational setting to study potential determinants of prostate cancer outcomes. We report the first risk-adjusted comparison of prostate cancer mortality in these two countries, to assess the influence of variation in use of definitive therapy.
- A key strength of this paper is the use of routinely collected data from hospital episode statistics linked to cancer registry data, providing a large dataset to make accurate estimates of relative prostate cancer mortality.
- Lack of PSA data and a relatively short follow-up period of 6 years are the key limitations of this study.

Background

Outcomes following a diagnosis of cancer vary markedly around the world. In the United States of America (US), cancer-related deaths have been demonstrated to be amongst the lowest. For example, US breast cancer mortality is 65% lower than the European average while death from colorectal cancer is 30% lower.[1] On the other hand, cancer mortality rates in England are amongst the highest in Europe.[2] The disparity in cancer outcomes appears greatest for prostate cancer for which 5-year mortality has been reported to be six times higher in England compared to the US.[1]

A number of disease and treatment-related factors may account for the observed variation in prostate cancer outcomes between the US and England. These include variation in policy concerning prostate cancer screening between the two countries together with variation in use of definitive prostate cancer therapy. Other factors that may be at play include the methods by which data on cancer diagnoses and cancer related deaths are both collected and processed.

In the US, the vast majority of men diagnosed with localized prostate cancer have definitive therapy, either by radical radiation therapy or radical surgery. For example, three quarters of men diagnosed with prostate cancer between 1988 and 2006 were reported to have undergone definitive therapy for their disease.[3] This figure compares to only about one third in England.[4 5]

We report differences in risk-adjusted prostate cancer mortality between the US and England. Furthermore, we investigate whether prostate cancer outcomes are related to the use of definitive therapy between the two countries. This study is part of a program of work assessing the value of procedure-specific and disease-specific

metrics derived from English hospital admission records to assess the performance of English National Health Service (NHS) providers.

Methods

Study design

We performed a population-based observational cohort study using patient-level cancer registry data from England and the US.

Data sources

Data collected by the eight regional cancer registries[6] for all men diagnosed with prostate cancer in England were linked to the Hospital Episodes Statistics (HES) database[7] and national mortality records provided by the Office for National Statistics.

The Surveillance, Epidemiology and End Results (SEER) database was used to identify American patients with prostate cancer from 18 regional cancer registries.[8] This database covers 28% of the US population and is linked to mortality data provided by the National Center for Health Statistics.

Participants

Men diagnosed with prostate cancer between 2004 and 2008, and aged between 35 and 80 years at the time of diagnosis were identified from both countries. The years 2004 to 2008 were selected as comparable English and American data were available for this period. Diagnosis of prostate cancer was confirmed using the 'C61'

International Classification of Diseases (ICD-10) diagnosis code in the HES and SEER databases. Follow-up data were available through to 16th April 2010 for the English cohort, and 31st December 2010 for the American cohort.

Patients were included if prostate cancer was histologically confirmed as their only primary malignancy. Patients with lymph node involvement or distant metastases were excluded, as they would not be candidates for primary definitive therapy. Where data on metastatic disease were missing, we considered the use of chemotherapy as a surrogate marker for metastases. Patients who underwent chemotherapy within 6 months of diagnosis were therefore also excluded. Twenty-one patients in the English dataset were noted to have negative survival data (i.e. date of diagnosis was chronologically after the date of death), and were therefore excluded. Those with missing data concerning pathological Gleason score (GS) or clinical tumour (cT) stage were excluded from the primary analysis, as they would not be amenable to risk stratification.

Variable definition

English patients were considered to have undergone definitive therapy if their HES record contained the 'M61' Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) code[9] indicating radical prostatectomy within 1 year of diagnosis, or alternatively if their cancer registry record indicated the use of radiotherapy.

Patients from the SEER dataset were considered to have undergone definitive therapy if they underwent radical prostatectomy or radiation therapy as part of their first

course of therapy. American patients were considered to have undergone radical prostatectomy if they had undergone cancer-directed surgery, coded as any of the following: Radical/total prostatectomy, or Prostatectomy with resection in continuity with other organs/pelvic exenteration. All forms of radiotherapy were assumed to be definitive in nature, as treatment doses are not routinely recorded in the SEER or English cancer registries.

Risk stratification

Patients were classified into risk groups using a modified version of the National Comprehensive Cancer Network (NCCN) prostate cancer risk classification,[10] based on clinical tumour (cT) stage and Gleason score (GS). Risk groups were defined as follows: low risk (cT1 stage and GS 2-6), intermediate risk (cT2 stage or GS 7), and high risk (cT3-T4 stage or GS 8-10). Since prostate-specific antigen (PSA) levels are not recorded in the HES database or English cancer registries, this variable was not used for risk stratification in this study.

Outcome measurement

The cause of death amongst English patients was extracted from national mortality records provided by the Office for National Statistics, which were linked to cancer registry and HES data. Similarly, cause of death is routinely recorded as part of the SEER dataset for US patients. Where the cause of death was listed as the disease code for prostate cancer, C61, it was classified as a prostate cancer death.

Statistical analysis

Chi square test was used to compare proportions between the two countries. A Cox regression model was used to calculate adjusted hazard ratios (HRs) for all-cause mortality (ACM), comparing mortality in England and the US. Similarly, adjusted sub-hazard ratios (SHRs) were calculated for prostate cancer mortality (PCM) using a maximum likelihood competing risk regression model, according to the method of Fine and Gray.[11] Failure event for PCM was defined as death due to prostate cancer, while death due to a cause other than prostate cancer was defined as the competing event. All analyses were performed using STATA version 11 (StataCorp, College station, TX, USA).

All regression models were adjusted for age group, year of diagnosis, ethnicity, clinical tumour stage, and Gleason score (model 1). Next, the impact of variation in use of definitive therapy was assessed by additionally including use of definitive therapy in a separate regression model (model 2). Separate regression models were built to test for differences between the two countries for each individual risk group. This resulted in 20 regression models in total: 5 patient groups (all eligible patients, all patients with complete data, low, intermediate, and high risk) x 2 adjustment models (model 1 and model 2) x 2 outcomes (ACM and PCM).

Sensitivity Analysis

In order to investigate the influence of excluding patients for whom tumour stage and Gleason grade data were missing, we performed a sensitivity analysis where all eligible patients were included.

Role of Funding Source

The study benefited from a grant from the Academy of Medical Royal Colleges supporting a project assessing the value of procedure-specific and disease-specific metrics derived from routinely collected data to assess the performance of NHS providers. Sponsors were not involved in the study design; the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

Participants

Data were available on 328,182 men (111,917 from England and 216,265 from the US) of which 301,989 (97,079 from England and 204,910 from the US) met the selection criteria. Reasons for exclusion are described in Figure 1.

Complete data to enable risk stratification (i.e. cT stage and Gleason score) were available for 222,163 men (23,235 from England and 196,928 from the US). These data were used to undertake the primary analysis.

Men diagnosed with prostate cancer in England tended to be older and less ethnically diverse, to present with higher clinical tumour stage, and to have higher pathological Gleason scores (Table 1, Appendix 1), with each of these differences reaching statistical significance at $p < 0.001$. Amongst patients for whom complete data were available, men diagnosed with prostate cancer in England were more likely to present

with high-risk prostate cancer according to our modified NCCN criteria (34.5% in England and 17.2% in US, Table 1).

Men diagnosed with prostate cancer in England were less likely to receive definitive therapy (38.2% in England and 77.1% in US), and this difference was observed in all risk groups (Table 1).

Mortality

The median follow-up for the entire cohort was 43.3 months. Unadjusted 6-year ACM amongst English men was higher compared to American men (21.0% versus 9.6%). Similarly, unadjusted 6-year PCM amongst English men was also higher, as compared to American men (9.6% versus 2.6%). This trend was similar amongst patients with complete data, whose outcomes are described below (Table 2).

Primary analysis

The primary analysis was conducted using data from the 222,163 patients for whom clinical tumour stage and Gleason score were available, to allow risk stratification.

Unadjusted 6-year ACM amongst patients who had definitive therapy was 7.3% in England and 4.9% in the US. Corresponding ACM figures amongst those who did not have definitive treatment were 19.5% in England and 15.5% in the US. The greatest difference was observed in patients at high prostate cancer risk undergoing definitive treatment with a 6-year ACM of 15.1% in England and 8.1% in the US, with the smallest difference observed in patients with low-risk prostate cancer who did not undergo definitive therapy (9.5% in England and 9.9% in the US).

Unadjusted 6-year PCM amongst patients from all risk groups who underwent definitive therapy was 2.4% in England and 1.2% in the US. This compared to 8.8% amongst patients who did not receive definitive therapy in England and 4.5% in the US. Differences in unadjusted 6-year PCM were smallest amongst patients with low-risk disease undergoing definitive therapy (0.4% in England and 0.5% in the US), and greatest amongst patients with high-risk disease undergoing definitive therapy (7.6% in England and 3.7% in the US).

When comparing all patients with complete data amenable for risk stratification, following adjustment for age group, ethnicity, year of diagnosis, and tumour characteristics (model 1), significantly higher ACM (adjusted HR 1.60, 95% CI 1.52 to 1.68) and PCM (adjusted SHR 1.88, 95% CI 1.72 to 2.05) were found in England than in the US (Table 2). Within each of the three risk groups, with adjustment for patient and tumour characteristics (model 1), the greatest difference in ACM and PCM was noted amongst the intermediate-risk and high-risk patients (Table 4). PCM was not significantly different at 0.9% in both countries at six years amongst men with low-risk disease.

When treatment allocation was included in the multivariate model (model 2), no difference in ACM and PCM was noted between the US and England for all men (ACM: adjusted HR 1.03, 95% CI 0.97 to 1.08; PCM: adjusted SHR 0.97, 95% CI 0.88 to 1.07) or within each of the individual risk groups (Table 4).

Sensitivity Analysis

Multivariate analysis for the entire cohort of 301,989 patients, including patients for whom data regarding either clinical tumour stage or Gleason score were missing, revealed a similar trend (Appendix 2). Adjustment for age group, ethnicity and year of

diagnosis, revealed higher ACM (adjusted HR 2.19, 95% CI 2.13 to 2.26) and PCM (adjusted SHR 3.67, 95% CI 3.50 to 3.85) amongst English patients.

Additional adjustment for the use of definitive therapy appeared, in part, to account for variation in ACM (adjusted HR 1.55, 95% CI 1.50 to 1.59) and PCM (adjusted HR 2.37, 95% CI 2.25 to 2.50).

Discussion

Prostate cancer death in intermediate to high-risk cases is higher in England than it is in the US. When we adjusted for the different rates of definitive therapy in the two countries, the rates of prostate cancer death were similar. This suggests that the differences in mortality may be explained by a lower use of definitive therapy in England.

Methodological considerations

First, the English dataset contained a high proportion of missing data for clinical tumour stage and Gleason score. Excluded English patients tended to be older, to have more advanced disease, and they less frequently received definitive therapy (Appendix 1). This limitation is unlikely to have had a marked influence on our results, as inclusion of these patients would have increased the observed difference in PCM noted between the two countries. Thus, these data provide a conservative estimate of the spread of prostate cancer risk amongst the general English population.

Nevertheless it is worthwhile to note that these are the only population-wide data currently available for comparing management of PCa in the two countries.

Furthermore, a sensitivity analysis was performed to investigate the influence of excluding patients with missing cT stage or Gleason score. This showed that PCM is significantly higher in England than the US, though this difference is partly explained upon additional adjustment for the variation in use of definitive treatment in the two countries. Due to the higher proportion of men with low or intermediate risk disease in the US, the variation in use of definitive treatment becomes more apparent upon risk stratification in our primary analysis.

Secondly, the SEER dataset did not contain information concerning patient comorbidity. We feel our findings remain valid despite this potential limitation as PCM is less strongly influenced by comorbid conditions than ACM.[12] In addition, there were also differences between England and the US in the PCM of young patients aged between 35 and 59 years who are least likely to have comorbid conditions at the time of diagnosis (adjusted SHR 2.66, 95% CI 1.99 to 3.56, $p<0.001$).

Thirdly, "lead time bias" could be an explanation for PCM being lower in the US than in the UK given that the uptake of PSA testing is much higher in the US, the effect of which is likely to be that men in the US are diagnosed with less advanced prostate cancer at an earlier age. In an attempt to minimise the effect of this limitation we adjusted for clinical stage at diagnosis and patient age at diagnosis together with Gleason score in our primary analysis.

Lastly, PSA levels were not available for English patients and therefore they could not be used to adjust the differences in PCM between England and the US. To investigate

this limitation further, we evaluated if the inclusion of PSA into our risk stratification model resulted in significant re-categorisation of a patient's prostate cancer risk for the US patients. We found little movement between risk groups with, for example, only 7.4% US patients being re-classified as intermediate-risk having initially been assigned a low-risk status.

Despite the above-mentioned limitations, routinely collected data provide a rich resource to explain performance of health care providers in different countries. However, differences in coding practices and differences in healthcare frameworks must be acknowledged.

Comparison with other studies

Mortality

PCM was found to be significantly higher in England compared to the US amongst men with intermediate and high-risk prostate cancer. In the current study, we used SEER data of men diagnosed between 2004 and 2008 and found that 6-year ACM was 9.3% and PCM 2.4%. A study using SEER data of men diagnosed between 1992 and 2005 found very similar figures (5-year ACM 14.3% and PCM 1.7%).[13] Improvements in management of prostate cancer and other comorbidities may explain why our figures for ACM are slightly lower.

In comparison, our analysis of the English HES database found that 6-year ACM was 18.5% and PCM 7.6%. A study reporting outcome of 50,066 men diagnosed with prostate cancer in the London area between 1997 and 2006 with a median follow up

of 3.5 years reported a PCM for men who had undergone definitive treatment of about 2%, which corresponds closely to the figures we found in this study.[14]

The only two relevant randomised controlled trials[15 16] demonstrated benefit of definitive therapy in patients with high-risk disease, which is consistent with the results of our study.

Differences between England and the US

A study using the EUROCARE and SEER registries including men diagnosed between 1985 and 1989 reported a 2.8 times relative excess risk of death amongst European men with prostate cancer compared to their American counterparts.[17] A more recent study using SEER data between 1975 and 2004 together with UK cancer mortality statistics found that age-adjusted PCM rates in the US were significantly lower than in England with the decline in PCM being 4.2% per year since the 1990s, a figure about four times higher than that reported for England.[18]

The investigators of both these studies suggested that difference in PCM between England and the US is the result of variation in disease burden brought about by the higher incidence of prostate cancer screening in the US. However, neither study adjusted for prostate cancer risk. In this study, we have identified for the first time that irrespective of prostate cancer stage and Gleason score, prostate cancer outcomes in terms of ACM and PCM are better in the US than in England, which does not support the increased use of prostate cancer screening in the US as an explanation for the difference in prostate cancer mortality. Instead, our data suggest that the better

prostate cancer outcome seen in the US may be due to the more frequent use of definitive treatment.

Clinical implication

The decision to offer definitive prostate cancer therapy is influenced by both disease characteristics and patient characteristics. As noted in our results, variations in healthcare systems have direct and indirect affects on both these factors. The expected survival benefit of definitive prostate cancer therapy must therefore also be balanced against the associated probability of side effects, including urinary incontinence and erectile dysfunction.

Our analysis suggests that prostate cancer mortality in England may be improved by an increase in the use of definitive treatment. This increase should be directed at men with intermediate and high-risk prostate cancer, as the differences in outcomes between England and the US for men with low-risk disease were very small. These results have to be interpreted in the context of differences between the two countries in the way prostate cancer is diagnosed, with higher uptake of PSA testing in the US.

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Data sharing: No additional data available.

Declaration of transparency: AS and PJC affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9(8):730-56.

2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *The lancet oncology* 2013.

3. Abdollah F, Sun M, Thuret R, Jeldres C, Tian Z, Briganti A, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* 2011;59(1):88-95.

4. Fairley L, Baker M, Whiteway J, Cross W, Forman D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 2009;101(11):1839-45.

5. Lyratzopoulos G, Barbiere JM, Greenberg DC, Wright KA, Neal DE. Population based time trends and socioeconomic variation in use of radiotherapy and radical surgery for prostate cancer in a UK region: continuous survey. *BMJ* 2010;340:c1928.

6. *National Cancer Data Repository 1990-2010*. National Cancer Intelligence Network; [cited 2014 October 1]; Available from: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/.

7. *Hospital Episode Statistics*. [Website]: NHS Health and Social Care Information Centre; [cited 2014 October 1]; Available from: http://www.hesonline.nhs.uk/.

8. *Surveillance, Epidemiology, and End Results (SEER) Program 1975-2010*. [Website] Bethesda, MD: National Cancer Institute; [cited 2014 October 1]; Available from: http://seer.cancer.gov/csr/1975_2010/.

9. NHS Connecting for Health. *Office of Population, Censuses, and Surveys (OPCS) Classification of Interventions and Procedures Version 4.6 (April 2011)*: The Stationery Office.

10. *NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer*. National Comprehensive Care Network; 2014 [cited 2014 October 1]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94(446):496-509.

12. Briganti A, Spahn M, Joniau S, Gontero P, Bianchi M, Kneitz B, et al. Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. *Eur Urol* 2013;63(4):693-701.

13. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. *Eur Urol* 2011;60(5):920-30.

14. Chowdhury S, Robinson D, Cahill D, Rodriguez-Vida A, Holmberg L, Moller H. Causes of death in men with prostate cancer: an analysis of 50,000 men from the Thames Cancer Registry. *BJU Int* 2013;112(2):182-9.

15. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011;364(18):1708-17.

16. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367(3):203-13.

17. Gatta G, Capocaccia R, Coleman MP, Gloeckler Ries LA, Hakulinen T, Micheli A, et al. Toward a comparison of survival in American and European cancer patients. *Cancer* 2000;89(4):893-900.

18. Collin SM, Martin RM, Metcalfe C, Gunnell D, Albertsen PC, Neal D, et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncol* 2008;9(5):445-52.

Comparison of prostate cancer outcomes in England and US

Table 1: Patient demographics by country (n = 222,163).

	England	US	*p* value
	(n = 25,235)	**(n = 196,928)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	36,172 (18.4)	<0.001
2005	4,959 (19.7)	34,403 (17.5)	
2006	5,172 (20.5)	40,531 (20.6)	
2007	5,009 (19.9)	43,800 (22.2)	
2008	4,717 (18.7)	42,022 (21.3)	
Age group (%)			
35-59	3,620 (14.4)	56,399 (28.6)	<0.001
60-64	4,361 (17.3)	40,287 (20.5)	
65-69	6,104 (24.2)	42,439 (21.6)	
70-74	6,145 (24.4)	33,912 (17.2)	
75-79	5,005 (19.8)	23,891 (12.1)	
Ethnicity (%)			
White	17,924 (94.8)	154,077 (80.4)	<0.001
African/Caribbean	571 (3.0)	28,361 (14.8)	
Asian	318 (1.7)	8,638 (4.5)	
Other	105 (0.6)	626 (0.3)	
Missing	6,317	5,226	
Clinical tumour stage (%)			
cT1	9,374 (37.2)	72,407 (36.8)	<0.001
cT2	9,538 (37.8)	107,762 (54.7)	
cT3	5,577 (22.1)	15,482 (7.9)	
cT4	746 (3.0)	1,277 (0.7)	
Gleason score (%)			
2-6	10,909 (43.2)	99,661 (50.6)	<0.001
7	9,112 (36.1)	75,247 (38.2)	
8-10	5,214 (20.7)	22,020 (11.2)	
Modified NCCN risk (%)			
Low risk	6,151 (24.4)	45,045 (22.9)	<0.001
Intermediate risk	10,386 (41.2)	118,074 (60.0)	
High risk	8,698 (34.5)	33,809 (17.1)	
Treatment – all risk groups (%)			
No definitive therapy	15,583 (61.8)	45,113 (22.9)	<0.001
Definitive therapy	9,652 (38.2)	151,815 (77.1)	
Treatment – low risk (%)			
No definitive therapy	3,799 (61.8)	17,516 (38.9)	<0.001
Definitive therapy	2,352 (38.2)	27,529 (61.1)	
Treatment – intermediate risk (%)			
No definitive therapy	5,696 (54.8)	21,999 (18.6)	<0.001
Definitive therapy	4,690 (45.2)	96,075 (81.4)	
Treatment – high risk (%)			
No definitive therapy	6,088 (70.0)	5,598 (16.6)	<0.001
Definitive therapy	2,610 (30.0)	28,211 (83.4)	

cT = Clinical tumour stage

Comparison of prostate cancer mortality in England and the US

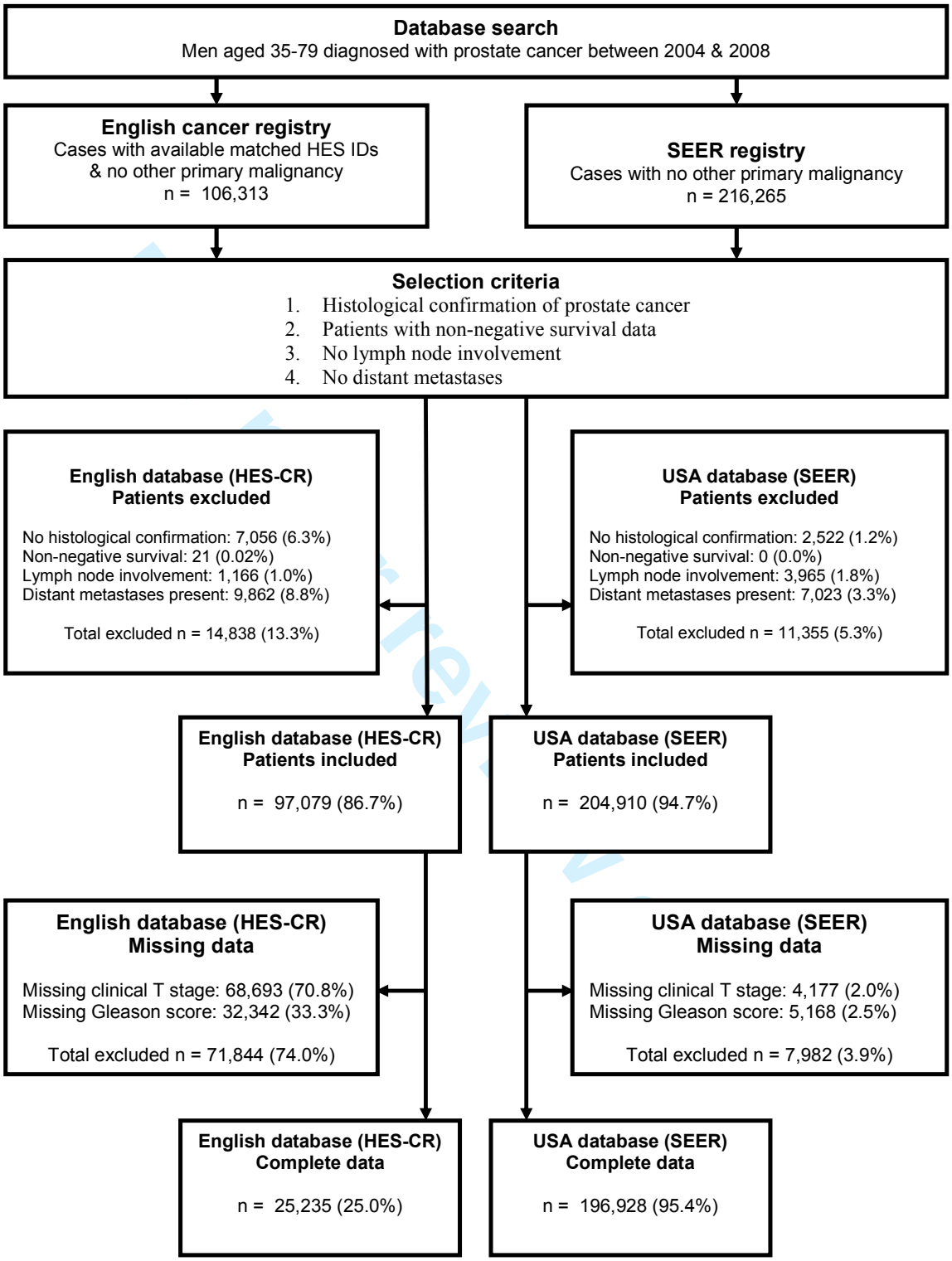
Table 2: All-cause mortality (ACM) and prostate cancer mortality (PCM) according to country of treatment and modified NCCN risk (n = 222,163).

	6 year All Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)		Model 2 (Model 1 and definitive therapy)	
Risk group	**US**	**England**	**Adj HR (95% CI)**	***p* value**	**Adj HR (95% CI)**	***p* value**
	n = 196,928	n = 25,235				
All risk groups	9.3%	18.5%	1.60 (1.52 to 1.68)	<0.001	1.03 (0.97 to 1.08)	0.336
Low risk	8.7%	10.3%	1.30 (1.15 to 1.48)	<0.001	1.06 (0.93 to 1.21)	0.397
Intermediate risk	7.6%	12.5%	1.44 (1.32 to 1.58)	<0.001	0.98 (0.90 to 1.08)	0.740
High risk	16.3%	31.8%	1.92 (1.78 to 2.06)	<0.001	0.99 (0.92 to 1.08)	0.863
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)**		**Model 2 (Model 1 and definitive therapy)**	
Risk group	**US**	**England**	**Adj SHR (95% CI)**	***p* value**	**Adj SHR (95% CI)**	***p* value**
All risk groups	2.4%	7.6%	1.88 (1.72 to 2.05)	<0.001	0.97 (0.88 to 1.07)	0.568
Low risk	0.9%	0.9%	1.57 (1.08 to 2.30)	0.018	1.31 (0.89 to 1.93)	0.169
Intermediate risk	1.4%	2.8%	1.71 (1.40 to 2.09)	<0.001	1.00 (0.81 to 1.23)	0.994
High risk	8.1%	18.8%	2.06 (1.87 to 2.28)	<0.001	0.96 (0.86 to 1.08)	0.537

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence Interval

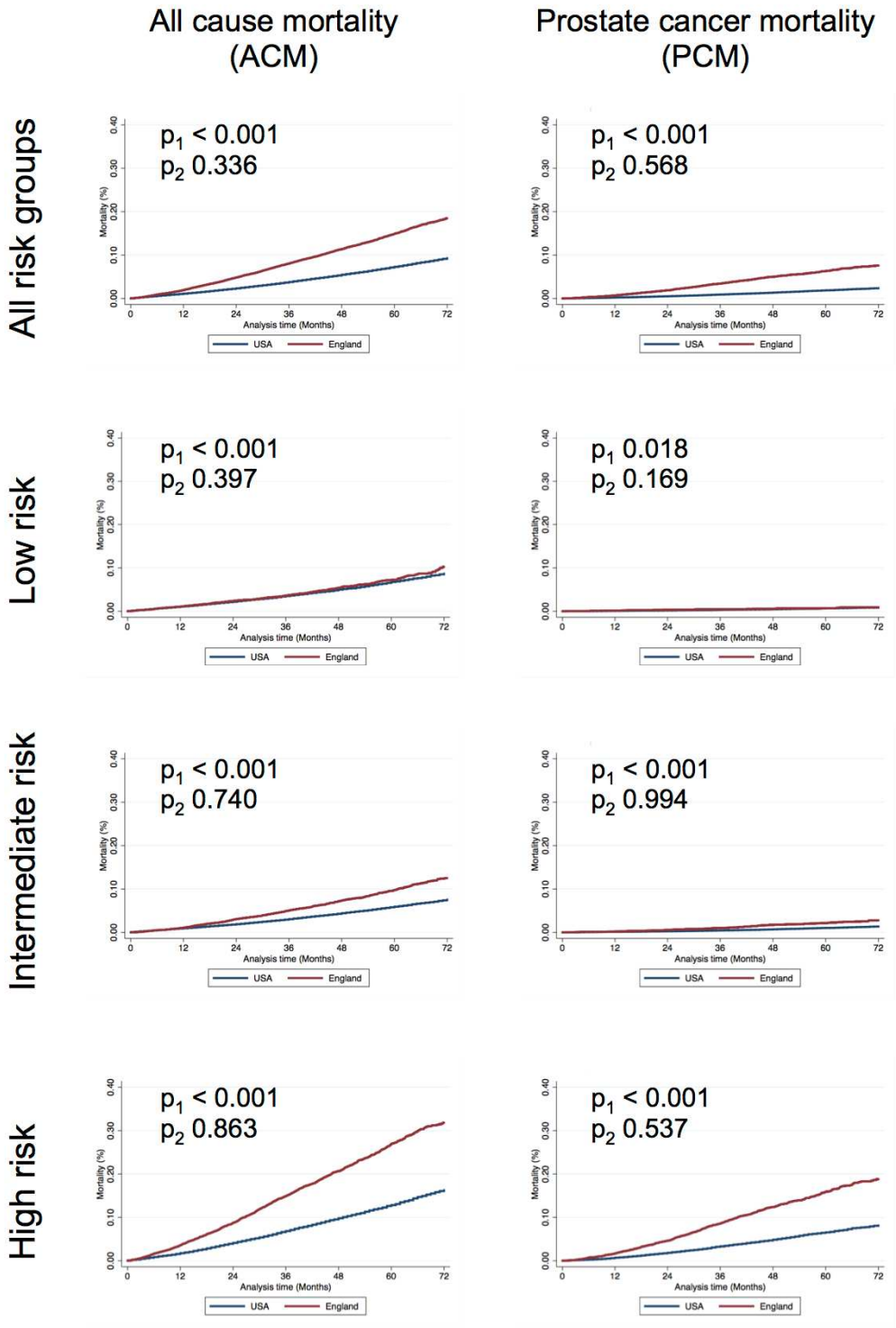
Comparison of prostate cancer outcomes in England and US

Figure 1: Study flow diagram



Comparison of prostate cancer mortality in England and the US

Figure 2: Unadjusted Kaplan-Meier plots for all-cause mortality (ACM) and prostate cancer mortality (PCM). Separate p values are reported for regression models with (Model 1, p1) and without (Model 2, p2) the inclusion of definitive therapy.



Appendix 1: Sensitivity analysis. Demographic and disease characteristics of all eligible patients by country (n = 328,182).

	England	US	*p* value
	(n = 97,079)	**(n = 204,910)**	
Year of diagnosis			
2004	18,883 (19.5)	37,686 (18.4)	<0.001
2005	18,392 (19.0)	35,656 (17.4)	
2006	19,847 (20.4)	41,938 (20.5)	
2007	20,061 (20.7)	45,612 (22.3)	
2008	19,896 (20.5)	44,018 (21.5)	
Age group			
35-59	13,593 (14.5)	57,992 (28.9)	<0.001
60-64	16,643 (17.8)	41,601 (20.7)	
65-69	22,782 (24.3)	44,116 (22.0)	
70-74	23,565 (25.1)	35,612 (17.7)	
75-79	17,139 (18.3)	21,592 (10.8)	
Ethnicity			
White	68,618 (93.8)	159,399 (80.4)	<0.001
African/Caribbean	2,796 (3.8)	29,362 (14.8)	
Asian	1,343 (1.8)	8,983 (4.5)	
Other	430 (0.6)	654 (0.3)	
Missing	23,892	6,512	
Clinical tumour stage			
cT1	10,331 (36.4)	74,169 (37.0)	<0.001
cT2	10,779 (38.0)	109,680 (54.6)	
cT3	6,421 (22.6)	15,562 (7.8)	
cT4	855 (3.0)	1,322 (0.7)	
Missing	68,693	4,177	
Gleason score			
2-6	28,119 (43.4)	101,123 (50.6)	<0.001
7	23,527 (36.3)	76,049 (38.1)	
8-10	13,091 (20.2)	22,570 (11.3)	
Missing	32,342	5,168	
Use of definitive therapy			
No definitive therapy	63,716 (65.6)	51,100 (24.9)	<0.001
Definitive therapy	33,363 (34.4)	153,810 (75.1)	

Appendix 2: Sensitivity analysis. Relative all-cause mortality (ACM) and prostate cancer mortality (PCM) of all eligible patients according to country (n = 328,182).

	6 year All-Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity)		Model 2 (Model 1 and definitive therapy)	
	US	England	Adj HR (95% CI)	*p* value	Adj HR (95% CI)	*p* value
All patients	n = 204,910 9.6%	n = 97,079 21.0%	2.19 (2.13 to 2.26)	<0.001	1.55 (1.50 to 1.59)	<0.001
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity)**		**Model 2 (Model 1 and definitive therapy)**	
	US	England	Adj SHR (95% CI)	*p* value	Adj SHR (95% CI)	*p* value
All patients	2.6%	9.6%	3.67 (3.50 to 3.85)	<0.001	2.37 (2.25 to 2.50)	<0.001

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence interval

Appendix 3: Comparison of demographic and disease characteristics of all eligible included and excluded English patients. Patients with either missing clinical tumour stage or missing Gleason score were classified as "excluded patients".

	Included patients	Excluded patients	*p* value
	(n = 25,235)	**(n = 71,844)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	13,505 (18.8)	<0.001
2005	4,959 (19.7)	13,433 (18.7)	
2006	5,172 (20.5)	14,675 (20.4)	
2007	5,009 (19.9)	15,052 (21.0)	
2008	4,717 (18.7)	15,179 (21.1)	
Age group (%)			
35-59	3,620 (14.4)	9,973 (13.9)	<0.001
60-64	4,361 (17.3)	12,282 (17.1)	
65-69	6,104 (24.2)	16,678 (23.2)	
70-74	6,145 (24.4)	17,420 (24.3)	
75-79	5,005 (19.8)	15,491 (21.6)	
Ethnicity (%)			
White	17,924 (94.8)	50,694 (93.4)	<0.001
African/Caribbean	571 (3.0)	2,225 (4.1)	
Asian	318 (1.7)	1,025 (1.9)	
Other	105 (0.6)	325 (0.6)	
Missing	*6,317*	*17,575*	
Socio-economic quartile			
1	6,262 (24.9)	17,588 (24.5)	<0.001
2	6,101 (24.2)	16,975 (23.7)	
3	5,392 (21.4)	14,693 (20.5)	
4	4,073 (16.2)	12,023 (16.8)	
5	3,363 (13.4)	10,409 (14.5)	
Missing	44	156	
Charlson co-morbidity index			
0	11,261 (44.6)	33,914 (47.2)	<0.001
1	11,761 (46.6)	30,861 (43.0)	
2 or more	2,213 (8.8)	7,069 (9.8)	
Clinical tumour stage			
cT1	9,374 (37.2)	957 (30.37)	<0.001
cT2	9,538 (37.8)	1,241 (39.4)	
cT3	5,577 (22.1)	844 (26.8)	
cT4	746 (3.0)	109 (3.5)	
Missing	0	68,693	
Gleason score			
2-6	10,909 (43.2)	17,210 (43.6)	0.083
7	9,112 (36.1)	14,415 (36.5)	
8-10	5,214 (20.7)	7,877 (19.9)	
Missing	0	32,342	
Treatment (%)			
No definitive therapy	15,583 (61.8)	48,133 (67.0)	<0.001
Definitive therapy	9,652 (38.3)	23,711 (33.0)	

STROBE Statement—checklist of items that should be included in reports of observational studies

Evidence of inclusion of checklist items is provided as relevant page numbers in the last column.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**
Methods			
Study design	4	Present key elements of study design early in the paper	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**5, 6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**5, 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**6, 7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5**
Bias	9	Describe any efforts to address potential sources of bias	**7, 8**
Study size	10	Explain how the study size was arrived at	**9, 22**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**8**
		(*b*) Describe any methods used to examine subgroups and interactions	**8**
		(*c*) Explain how missing data were addressed	**8**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**8**
		(*e*) Describe any sensitivity analyses	**8**

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**9, 22**
		(b) Give reasons for non-participation at each stage	**9, 22**
		(c) Consider use of a flow diagram	**22**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**20**
		(b) Indicate number of participants with missing data for each variable of interest	**22**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	**10**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	**10**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**-**
		Cross-sectional study—Report numbers of outcome events or summary measures	**-**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**10**
		(*b*) Report category boundaries when continuous variables were categorized	**6, 7, 20**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**-**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**11, 12**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**12, 13, 14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**16**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**14, 15**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**9**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluating variation in use of definitive therapy and risk-adjusted prostate cancer mortality in England and the US

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Evaluating variation in use of definitive therapy and risk-adjusted prostate cancer mortality in England and the US

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Abstract

Objectives: Prostate cancer mortality (PCM) in the US is amongst the lowest in the world, whereas PCM in England is amongst the highest in Europe. This paper aims to assess the influence of variation in use of definitive therapy on risk-adjusted PCM in England as compared to the US.

Design: Observational study

Setting: Cancer registry data from England and the US

Participants: Men diagnosed with non-metastatic prostate cancer (PCa) in England and the US between 2004 and 2008

Outcome measures: Competing-risks survival analyses to estimate sub-hazard ratios (SHR) of prostate cancer mortality adjusted for age, ethnicity, year of diagnosis, Gleason score (GS), and clinical tumor stage (cT).

Results: 222,163 men were eligible for inclusion. Compared to American patients, English patients were more likely to present at an older age (70-79 years: England 44.2%, US 29.3%, p<0.001), with higher tumour stage (cT3-4: England 25.1%, US 8.6%, p<0.001) and higher Gleason score (GS 8-10: England 20.7%, US 11.2%, p<0.001). They were also less likely to receive definitive therapy (England 38%, US 77%, p<0.001).

English patients were more likely to die of PCa (SHR 1.9, 95% confidence interval 1.7-2.0, p<0.001). However, this difference was no longer statistically significant when also adjusted for use of definitive therapy (SHR 1.0, 95% confidence interval 1.0-1.1, p=0.3).

Conclusions: Risk-adjusted PCM is significantly higher in England compared to the US. This difference may be explained by less frequent use of definitive therapy in England.

Word count: 236

Article summary

Strengths and limitations of this study:

- A key strength of this paper is the use of routinely collected data from hospital episode statistics linked to cancer registry data, providing a large dataset to make accurate estimates of relative prostate cancer mortality.
- Lack of PSA data and a relatively short follow-up period of 6 years are the key limitations of this study.

Background

Outcomes following a diagnosis of cancer vary markedly around the world. In the United States of America (US), cancer-related deaths have been demonstrated to be amongst the lowest. For example, US breast cancer mortality is 65% lower than the European average while death from colorectal cancer is 30% lower.[1] On the other hand, cancer mortality rates in England are amongst the highest in Europe.[2] The disparity in cancer outcomes appears greatest for prostate cancer for which 5-year mortality has been reported to be six times higher in England compared to the US.[1]

A number of disease and treatment-related factors may account for the observed variation in prostate cancer outcomes between the US and England. These include variation in policy concerning prostate cancer screening between the two countries together with variation in use of definitive prostate cancer therapy. Other factors that may be at play include the methods by which data on cancer diagnoses and cancer related deaths are both collected and processed.

In the US, the vast majority of men diagnosed with localized prostate cancer have definitive therapy, either by radical radiation therapy or radical surgery. For example, three quarters of men diagnosed with prostate cancer between 1988 and 2006 were reported to have undergone definitive therapy for their disease.[3] This figure compares to only about one third in England.[4 5]

We report differences in risk-adjusted prostate cancer mortality between the US and England. Furthermore, we investigate whether prostate cancer outcomes are related to the use of definitive therapy between the two countries. This study is part of a program of work assessing the value of procedure-specific and disease-specific

metrics derived from English hospital admission records to assess the performance of English National Health Service (NHS) providers.

Methods

Study design

We performed a population-based observational cohort study using patient-level cancer registry data from England and the US.

Data sources

Data collected by the eight regional cancer registries[6] for all men diagnosed with prostate cancer in England were linked to the Hospital Episodes Statistics (HES) database[7] and national mortality records provided by the Office for National Statistics.

The Surveillance, Epidemiology and End Results (SEER) database was used to identify American patients with prostate cancer from 18 regional cancer registries.[8] This database covers 28% of the US population and is linked to mortality data provided by the National Center for Health Statistics.

Participants

Men diagnosed with prostate cancer between 2004 and 2008, and aged between 35 and 80 years at the time of diagnosis were identified from both countries. The years 2004 to 2008 were selected as comparable English and American data were available for this period. Diagnosis of prostate cancer was confirmed using the 'C61'

International Classification of Diseases (ICD-10) diagnosis code in the HES and SEER databases. Follow-up data were available through to 16th April 2010 for the English cohort, and 31st December 2010 for the American cohort.

Patients were included if prostate cancer was histologically confirmed as their only primary malignancy. Patients with lymph node involvement or distant metastases were excluded, as they would not be candidates for primary definitive therapy. Where data on metastatic disease were missing, we considered the use of chemotherapy as a surrogate marker for metastases. Patients who underwent chemotherapy within 6 months of diagnosis were therefore also excluded. Twenty-one patients in the English dataset were noted to have negative survival data (i.e. date of diagnosis was chronologically after the date of death), and were therefore excluded. Those with missing data concerning pathological Gleason score (GS) or clinical tumour (cT) stage were excluded from the primary analysis, as they would not be amenable to risk stratification.

Variable definition

English patients were considered to have undergone definitive therapy if their HES record contained the 'M61' Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) code[9] indicating radical prostatectomy within 1 year of diagnosis, or alternatively if their cancer registry record indicated the use of radiotherapy.

Patients from the SEER dataset were considered to have undergone definitive therapy if they underwent radical prostatectomy or radiation therapy as part of their first

course of therapy. American patients were considered to have undergone radical prostatectomy if they had undergone cancer-directed surgery, coded as any of the following: Radical/total prostatectomy, or Prostatectomy with resection in continuity with other organs/pelvic exenteration. All forms of radiotherapy were assumed to be definitive in nature, as treatment doses are not routinely recorded in the SEER or English cancer registries.

Risk stratification

Patients were classified into risk groups using a modified version of the National Comprehensive Cancer Network (NCCN) prostate cancer risk classification,[10] based on clinical tumour (cT) stage and Gleason score (GS). Risk groups were defined as follows: low risk (cT1 stage and GS 2-6), intermediate risk (cT2 stage or GS 7), and high risk (cT3-T4 stage or GS 8-10). Since prostate-specific antigen (PSA) levels are not recorded in the HES database or English cancer registries, this variable was not used for risk stratification in this study.

Outcome measurement

The cause of death amongst English patients was extracted from national mortality records provided by the Office for National Statistics, which were linked to cancer registry and HES data. Similarly, cause of death is routinely recorded as part of the SEER dataset for US patients. Where the cause of death was listed as the disease code for prostate cancer, C61, it was classified as a prostate cancer death.

Statistical analysis

Chi square test was used to compare proportions between the two countries. A Cox regression model was used to calculate adjusted hazard ratios (HRs) for all-cause mortality (ACM), comparing mortality in England and the US. Similarly, adjusted sub-hazard ratios (SHRs) were calculated for prostate cancer mortality (PCM) using a maximum likelihood competing risk regression model, according to the method of Fine and Gray.[11] Failure event for PCM was defined as death due to prostate cancer, while death due to a cause other than prostate cancer was defined as the competing event. All analyses were performed using STATA version 11 (StataCorp, College station, TX, USA).

All regression models were adjusted for age group, year of diagnosis, ethnicity, clinical tumour stage, and Gleason score (model 1). Next, the impact of variation in use of definitive therapy was assessed by additionally including use of definitive therapy in a separate regression model (model 2). Separate regression models were built to test for differences between the two countries for each individual risk group. This resulted in 20 regression models in total: 5 patient groups (all eligible patients, all patients with complete data, low, intermediate, and high risk) x 2 adjustment models (model 1 and model 2) x 2 outcomes (ACM and PCM).

Sensitivity Analysis

In order to investigate the influence of excluding patients for whom tumour stage and Gleason grade data were missing, we performed a sensitivity analysis where all eligible patients were included.

Role of Funding Source

The study benefited from a grant from the Academy of Medical Royal Colleges supporting a project assessing the value of procedure-specific and disease-specific metrics derived from routinely collected data to assess the performance of NHS providers. Sponsors were not involved in the study design; the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

Participants

Data were available on 328,182 men (111,917 from England and 216,265 from the US) of which 301,989 (97,079 from England and 204,910 from the US) met the selection criteria. Reasons for exclusion are described in Figure 1.

Complete data to enable risk stratification (i.e. cT stage and Gleason score) were available for 222,163 men (23,235 from England and 196,928 from the US). These data were used to undertake the primary analysis.

Men diagnosed with prostate cancer in England tended to be older and less ethnically diverse, to present with higher clinical tumour stage, and to have higher pathological Gleason scores (Table 1, Appendix 1), with each of these differences reaching statistical significance at $p < 0.001$. Amongst patients for whom complete data were available, men diagnosed with prostate cancer in England were more likely to present

with high-risk prostate cancer according to our modified NCCN criteria (34.5% in England and 17.2% in US, Table 1).

Men diagnosed with prostate cancer in England were less likely to receive definitive therapy (38.2% in England and 77.1% in US), and this difference was observed in all risk groups (Table 1).

Mortality

The median follow-up for the entire cohort was 43.3 months. Unadjusted 6-year ACM amongst English men was higher compared to American men (21.0% versus 9.6%). Similarly, unadjusted 6-year PCM amongst English men was also higher, as compared to American men (9.6% versus 2.6%). This trend was similar amongst patients with complete data, whose outcomes are described below (Table 2).

Primary analysis

The primary analysis was conducted using data from the 222,163 patients for whom clinical tumour stage and Gleason score were available, to allow risk stratification.

Unadjusted 6-year ACM amongst patients who had definitive therapy was 7.3% in England and 4.9% in the US. Corresponding ACM figures amongst those who did not have definitive treatment were 19.5% in England and 15.5% in the US. The greatest difference was observed in patients at high prostate cancer risk undergoing definitive treatment with a 6-year ACM of 15.1% in England and 8.1% in the US, with the smallest difference observed in patients with low-risk prostate cancer who did not undergo definitive therapy (9.5% in England and 9.9% in the US).

Unadjusted 6-year PCM amongst patients from all risk groups who underwent definitive therapy was 2.4% in England and 1.2% in the US. This compared to 8.8% amongst patients who did not receive definitive therapy in England and 4.5% in the US. Differences in unadjusted 6-year PCM were smallest amongst patients with low-risk disease undergoing definitive therapy (0.4% in England and 0.5% in the US), and greatest amongst patients with high-risk disease undergoing definitive therapy (7.6% in England and 3.7% in the US).

When comparing all patients with complete data amenable for risk stratification, following adjustment for age group, ethnicity, year of diagnosis, and tumour characteristics (model 1), significantly higher ACM (adjusted HR 1.60, 95% CI 1.52 to 1.68) and PCM (adjusted SHR 1.88, 95% CI 1.72 to 2.05) were found in England than in the US (Table 2). Within each of the three risk groups, with adjustment for patient and tumour characteristics (model 1), the greatest difference in ACM and PCM was noted amongst the intermediate-risk and high-risk patients (Table 2). PCM was not significantly different at 0.9% in both countries at six years amongst men with low-risk disease.

When treatment allocation was included in the multivariate model (model 2), no difference in ACM and PCM was noted between the US and England for all men (ACM: adjusted HR 1.03, 95% CI 0.97 to 1.08; PCM: adjusted SHR 0.97, 95% CI 0.88 to 1.07) or within each of the individual risk groups (Table 2).

Sensitivity Analysis

Multivariate analysis for the entire cohort of 301,989 patients, including patients for whom data regarding either clinical tumour stage or Gleason score were missing, revealed a similar trend (Appendix 2). Adjustment for age group, ethnicity and year of

diagnosis, revealed higher ACM (adjusted HR 2.19, 95% CI 2.13 to 2.26) and PCM (adjusted SHR 3.67, 95% CI 3.50 to 3.85) amongst English patients.

Additional adjustment for the use of definitive therapy appeared, in part, to account for variation in ACM (adjusted HR 1.55, 95% CI 1.50 to 1.59) and PCM (adjusted HR 2.37, 95% CI 2.25 to 2.50).

Discussion

Prostate cancer death in intermediate to high-risk cases is higher in England than it is in the US. When we adjusted for the different rates of definitive therapy in the two countries, the rates of prostate cancer death were similar. This suggests that the differences in mortality may be explained by a lower use of definitive therapy in England.

Methodological considerations

First, the English dataset contained a high proportion of missing data for clinical tumour stage and Gleason score. The high proportion of patients with missing data in the English dataset may be due to poor data capture. Excluded English patients tended to be older, to have more advanced disease, and they less frequently received definitive therapy (Appendix 3). This limitation is unlikely to have had a marked influence on our results, as inclusion of these patients would have increased the observed difference in PCM noted between the two countries. Thus, these data provide a conservative estimate of the spread of prostate cancer risk amongst the

general English population. Nevertheless it is worthwhile to note that these are the only population-wide data currently available for comparing management of PCa in the two countries.

Furthermore, a sensitivity analysis was performed to investigate the influence of excluding patients with missing cT stage or Gleason score. This showed that PCM is significantly higher in England than the US, though this difference is partly explained upon additional adjustment for the variation in use of definitive treatment in the two countries. Due to the higher proportion of men with low or intermediate risk disease in the US, the variation in use of definitive treatment becomes more apparent upon risk stratification in our primary analysis.

Secondly, the SEER dataset did not contain information concerning patient comorbidity. We feel our findings remain valid despite this potential limitation as PCM is less strongly influenced by comorbid conditions than ACM.[12] In addition, there were also differences between England and the US in the PCM of young patients aged between 35 and 59 years who are least likely to have comorbid conditions at the time of diagnosis (adjusted SHR 2.66, 95% CI 1.99 to 3.56, $p<0.001$).

Thirdly, "lead time bias" could be an explanation for PCM being lower in the US than in the UK given that the uptake of PSA testing is much higher in the US, the effect of which is likely to be that men in the US are diagnosed with less advanced prostate cancer at an earlier age. In an attempt to minimise the effect of this limitation we adjusted for clinical stage at diagnosis and patient age at diagnosis together with Gleason score in our primary analysis.

Lastly, PSA levels were not available for English patients and therefore they could not be used to adjust the differences in PCM between England and the US. To investigate this limitation further, we evaluated if the inclusion of PSA into our risk stratification model resulted in significant re-categorisation of a patient's prostate cancer risk for the US patients. We found little movement between risk groups with, for example, only 7.4% US patients being re-classified as intermediate-risk having initially been assigned a low-risk status. Furthermore, Elliott et al have previously shown that while it is advantageous to have all three clinical variables (including PSA, cT stage and Gleason score) available for risk stratification, patients with high-risk disease can still be correctly identified even if one of these variable (such as PSA) is missing.[13]

Despite the above-mentioned limitations, routinely collected data provide a rich resource to explain performance of health care providers in different countries. However, differences in coding practices and differences in healthcare frameworks must be acknowledged.

Comparison with other studies

Mortality

PCM was found to be significantly higher in England compared to the US amongst men with intermediate and high-risk prostate cancer. In the current study, we used SEER data of men diagnosed between 2004 and 2008 and found that 6-year ACM was 9.3% and PCM 2.4%. A study using SEER data of men diagnosed between 1992 and 2005 found very similar figures (5-year ACM 14.3% and PCM 1.7%).[14]

Improvements in management of prostate cancer and other comorbidities may explain why our figures for ACM are slightly lower.

In comparison, our analysis of the English HES database found that 6-year ACM was 18.5% and PCM 7.6%. A study reporting outcome of 50,066 men diagnosed with prostate cancer in the London area between 1997 and 2006 with a median follow up of 3.5 years reported a PCM for men who had undergone definitive treatment of about 2%, which corresponds closely to the figures we found in this study.[15]

The only two relevant randomised controlled trials[16 17] demonstrated benefit of definitive therapy in patients with high-risk disease, which is consistent with the results of our study.

Differences between England and the US

A study using the EUROCARE and SEER registries including men diagnosed between 1985 and 1989 reported a 2.8 times relative excess risk of death amongst European men with prostate cancer compared to their American counterparts.[18] A more recent study using SEER data between 1975 and 2004 together with UK cancer mortality statistics found that age-adjusted PCM rates in the US were significantly lower than in England with the decline in PCM being 4.2% per year since the 1990s, a figure about four times higher than that reported for England.[19]

The investigators of both these studies suggested that difference in PCM between England and the US is the result of variation in disease burden brought about by the higher incidence of prostate cancer screening in the US. However, neither study adjusted for prostate cancer risk. In this study, we have identified for the first time

that irrespective of prostate cancer stage and Gleason score, prostate cancer outcomes in terms of ACM and PCM are better in the US than in England, which does not support the increased use of prostate cancer screening in the US as an explanation for the difference in prostate cancer mortality. Instead, our data suggest that the better prostate cancer outcome seen in the US may be due to the more frequent use of definitive treatment.

Clinical implication

The decision to offer definitive prostate cancer therapy is influenced by both disease characteristics and patient characteristics. As noted in our results, variations in healthcare systems have direct and indirect affects on both these factors. The expected survival benefit of definitive prostate cancer therapy must therefore also be balanced against the associated probability of side effects, including urinary incontinence and erectile dysfunction.

Our analysis suggests that prostate cancer mortality in England may be improved by an increase in the use of definitive treatment. This increase should be directed at men with intermediate and high-risk prostate cancer, as the differences in outcomes between England and the US for men with low-risk disease were very small. These results have to be interpreted in the context of differences between the two countries in the way prostate cancer is diagnosed, with higher uptake of PSA testing in the US.

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electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

References

1. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9(8):730-56.

2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *The lancet oncology* 2013.

3. Abdollah F, Sun M, Thuret R, Jeldres C, Tian Z, Briganti A, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* 2011;59(1):88-95.

4. Fairley L, Baker M, Whiteway J, Cross W, Forman D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 2009;101(11):1839-45.

5. Lyratzopoulos G, Barbiere JM, Greenberg DC, Wright KA, Neal DE. Population based time trends and socioeconomic variation in use of radiotherapy and radical surgery for prostate cancer in a UK region: continuous survey. *BMJ* 2010;340:c1928.

6. *National Cancer Data Repository 1990-2010*. National Cancer Intelligence Network; [cited 2014 October 1]; Available from: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/.

7. *Hospital Episode Statistics*. [Website]: NHS Health and Social Care Information Centre; [cited 2014 October 1]; Available from: http://www.hesonline.nhs.uk/.

8. *Surveillance, Epidemiology, and End Results (SEER) Program 1975-2010*. [Website] Bethesda, MD: National Cancer Institute; [cited 2014 October 1]; Available from: http://seer.cancer.gov/csr/1975_2010/.

9. NHS Connecting for Health. *Office of Population, Censuses, and Surveys (OPCS) Classification of Interventions and Procedures Version 4.6 (April 2011)*: The Stationery Office.

10. *NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer*. National Comprehensive Care Network; 2014 [cited 2014 October 1]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94(446):496-509.

12. Briganti A, Spahn M, Joniau S, Gontero P, Bianchi M, Kneitz B, et al. Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. *Eur Urol* 2013;63(4):693-701.

13. Elliott SP, Johnson DP, Jarosek SL, Konety BR, Adejoro OO, Virnig BA. Bias due to missing SEER data in D'Amico risk stratification of prostate cancer. *The Journal of urology* 2012;187(6):2026-31.

14. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. *Eur Urol* 2011;60(5):920-30.

15. Chowdhury S, Robinson D, Cahill D, Rodriguez-Vida A, Holmberg L, Moller H. Causes of death in men with prostate cancer: an analysis of 50,000 men from the Thames Cancer Registry. *BJU Int* 2013;112(2):182-9.

16. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011;364(18):1708-17.

17. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367(3):203-13.

18. Gatta G, Capocaccia R, Coleman MP, Gloeckler Ries LA, Hakulinen T, Micheli A, et al. Toward a comparison of survival in American and European cancer patients. *Cancer* 2000;89(4):893-900.

19. Collin SM, Martin RM, Metcalfe C, Gunnell D, Albertsen PC, Neal D, et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncol* 2008;9(5):445-52.

Comparison of prostate cancer outcomes in England and US

Table 1: Patient demographics by country (n = 222,163).

	England	US	*p* value
	(n = 25,235)	**(n = 196,928)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	36,172 (18.4)	<0.001
2005	4,959 (19.7)	34,403 (17.5)	
2006	5,172 (20.5)	40,531 (20.6)	
2007	5,009 (19.9)	43,800 (22.2)	
2008	4,717 (18.7)	42,022 (21.3)	
Age group (%)			
35-59	3,620 (14.4)	56,399 (28.6)	<0.001
60-64	4,361 (17.3)	40,287 (20.5)	
65-69	6,104 (24.2)	42,439 (21.6)	
70-74	6,145 (24.4)	33,912 (17.2)	
75-79	5,005 (19.8)	23,891 (12.1)	
Ethnicity (%)			
White	17,924 (94.8)	154,077 (80.4)	<0.001
African/Caribbean	571 (3.0)	28,361 (14.8)	
Asian	318 (1.7)	8,638 (4.5)	
Other	105 (0.6)	626 (0.3)	
Missing	6,317	5,226	
Clinical tumour stage (%)			
cT1	9,374 (37.2)	72,407 (36.8)	<0.001
cT2	9,538 (37.8)	107,762 (54.7)	
cT3	5,577 (22.1)	15,482 (7.9)	
cT4	746 (3.0)	1,277 (0.7)	
Gleason score (%)			
2-6	10,909 (43.2)	99,661 (50.6)	<0.001
7	9,112 (36.1)	75,247 (38.2)	
8-10	5,214 (20.7)	22,020 (11.2)	
Modified NCCN risk (%)			
Low risk	6,151 (24.4)	45,045 (22.9)	<0.001
Intermediate risk	10,386 (41.2)	118,074 (60.0)	
High risk	8,698 (34.5)	33,809 (17.1)	
Treatment – all risk groups (%)			
No definitive therapy	15,583 (61.8)	45,113 (22.9)	<0.001
Definitive therapy	9,652 (38.2)	151,815 (77.1)	
Treatment – low risk (%)			
No definitive therapy	3,799 (61.8)	17,516 (38.9)	<0.001
Definitive therapy	2,352 (38.2)	27,529 (61.1)	
Treatment – intermediate risk (%)			
No definitive therapy	5,696 (54.8)	21,999 (18.6)	<0.001
Definitive therapy	4,690 (45.2)	96,075 (81.4)	
Treatment – high risk (%)			
No definitive therapy	6,088 (70.0)	5,598 (16.6)	<0.001
Definitive therapy	2,610 (30.0)	28,211 (83.4)	

cT = Clinical tumour stage

Comparison of prostate cancer mortality in England and the US

Table 2: All-cause mortality (ACM) and prostate cancer mortality (PCM) according to country of treatment and modified NCCN risk (n = 222,163).

	6 year All Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)		Model 2 (Model 1 and definitive therapy)	
Risk group	**US**	**England**	**Adj HR (95% CI)**	***p* value**	**Adj HR (95% CI)**	***p* value**
	n = 196,928	n = 25,235				
All risk groups	9.3%	18.5%	1.60 (1.52 to 1.68)	<0.001	1.03 (0.97 to 1.08)	0.336
Low risk	8.7%	10.3%	1.30 (1.15 to 1.48)	<0.001	1.06 (0.93 to 1.21)	0.397
Intermediate risk	7.6%	12.5%	1.44 (1.32 to 1.58)	<0.001	0.98 (0.90 to 1.08)	0.740
High risk	16.3%	31.8%	1.92 (1.78 to 2.06)	<0.001	0.99 (0.92 to 1.08)	0.863
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)**		**Model 2 (Model 1 and definitive therapy)**	
Risk group	**US**	**England**	**Adj SHR (95% CI)**	***p* value**	**Adj SHR (95% CI)**	***p* value**
All risk groups	2.4%	7.6%	1.88 (1.72 to 2.05)	<0.001	0.97 (0.88 to 1.07)	0.568
Low risk	0.9%	0.9%	1.57 (1.08 to 2.30)	0.018	1.31 (0.89 to 1.93)	0.169
Intermediate risk	1.4%	2.8%	1.71 (1.40 to 2.09)	<0.001	1.00 (0.81 to 1.23)	0.994
High risk	8.1%	18.8%	2.06 (1.87 to 2.28)	<0.001	0.96 (0.86 to 1.08)	0.537

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence Interval

~~Influence of~~Evaluating variation in use of definitive therapy ~~on~~ and risk-adjusted prostate cancer mortality in England and the US

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Abstract

Objectives: Prostate cancer mortality (PCM) in the US is amongst the lowest in the world, whereas PCM in England is amongst the highest in Europe. This paper aims to assess the influence of variation in use of definitive therapy on risk-adjusted PCM in England as compared to the US.

Design: Observational study

Setting: Cancer registry data from England and the US

Participants: Men diagnosed with non-metastatic prostate cancer (PCa) in England and the US between 2004 and 2008

Outcome measures: Competing-risks survival analyses to estimate sub-hazard ratios (SHR) of prostate cancer mortality adjusted for age, ethnicity, year of diagnosis, Gleason score (GS), and clinical tumor stage (cT).

Results: 222,163 men were eligible for inclusion. Compared to American patients, English patients were more likely to present at an older age (70-79 years: England 44.2%, US 29.3%, p<0.001), with higher tumour stage (cT3-4: England 25.1%, US 8.6%, p<0.001) and higher Gleason score (GS 8-10: England 20.7%, US 11.2%, p<0.001). They were also less likely to receive definitive therapy (England 38%, US 77%, p<0.001).

English patients were more likely to die of PCa (SHR 1.9, 95% confidence interval 1.7-2.0, p<0.001). However, this difference was no longer statistically significant when also adjusted for use of definitive therapy (SHR 1.0, 95% confidence interval 1.0-1.1, p=0.3).

Conclusions: Risk-adjusted PCM is significantly higher in England compared to the US. This difference may be explained by less frequent use of definitive therapy in England.

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Article summary

Strengths and limitations of this study:

- ~~Variation in prostate cancer management in England and the US provides an observational setting to study potential determinants of prostate cancer outcomes. We report the first risk-adjusted comparison of prostate cancer mortality in these two countries, to assess the influence of variation in use of definitive therapy.~~
- A key strength of this paper is the use of routinely collected data from hospital episode statistics linked to cancer registry data, providing a large dataset to make accurate estimates of relative prostate cancer mortality.
- Lack of PSA data and a relatively short follow-up period of 6 years are the key limitations of this study.

Background

Outcomes following a diagnosis of cancer vary markedly around the world. In the United States of America (US), cancer-related deaths have been demonstrated to be amongst the lowest. For example, US breast cancer mortality is 65% lower than the European average while death from colorectal cancer is 30% lower.[1] On the other hand, cancer mortality rates in England are amongst the highest in Europe.[2] The disparity in cancer outcomes appears greatest for prostate cancer for which 5-year mortality has been reported to be six times higher in England compared to the US.[1]

A number of disease and treatment-related factors may account for the observed variation in prostate cancer outcomes between the US and England. These include variation in policy concerning prostate cancer screening between the two countries together with variation in use of definitive prostate cancer therapy. Other factors that may be at play include the methods by which data on cancer diagnoses and cancer related deaths are both collected and processed.

In the US, the vast majority of men diagnosed with localized prostate cancer have definitive therapy, either by radical radiation therapy or radical surgery. For example, three quarters of men diagnosed with prostate cancer between 1988 and 2006 were reported to have undergone definitive therapy for their disease.[3] This figure compares to only about one third in England.[4 5]

We report differences in risk-adjusted prostate cancer mortality between the US and England. Furthermore, we investigate whether prostate cancer outcomes are related to the use of definitive therapy between the two countries. This study is part of a program of work assessing the value of procedure-specific and disease-specific

metrics derived from English hospital admission records to assess the performance of English National Health Service (NHS) providers.

Methods

Study design

We performed a population-based observational cohort study using patient-level cancer registry data from England and the US.

Data sources

Data collected by the eight regional cancer registries[6] for all men diagnosed with prostate cancer in England were linked to the Hospital Episodes Statistics (HES) database[7] and national mortality records provided by the Office for National Statistics.

The Surveillance, Epidemiology and End Results (SEER) database was used to identify American patients with prostate cancer from 18 regional cancer registries.[8] This database covers 28% of the US population and is linked to mortality data provided by the National Center for Health Statistics.

Participants

Men diagnosed with prostate cancer between 2004 and 2008, and aged between 35 and 80 years at the time of diagnosis were identified from both countries. The years 2004 to 2008 were selected as comparable English and American data were available for this period. Diagnosis of prostate cancer was confirmed using the 'C61'

International Classification of Diseases (ICD-10) diagnosis code in the HES and SEER databases. Follow-up data were available through to 16th April 2010 for the English cohort, and 31st December 2010 for the American cohort.

Patients were included if prostate cancer was histologically confirmed as their only primary malignancy. Patients with lymph node involvement or distant metastases were excluded, as they would not be candidates for primary definitive therapy. Where data on metastatic disease were missing, we considered the use of chemotherapy as a surrogate marker for metastases. Patients who underwent chemotherapy within 6 months of diagnosis were therefore also excluded. Twenty-one patients in the English dataset were noted to have negative survival data (i.e. date of diagnosis was chronologically after the date of death), and were therefore excluded. Those with missing data concerning pathological Gleason score (GS) or clinical tumour (cT) stage were excluded from the primary analysis, as they would not be amenable to risk stratification.

Variable definition

English patients were considered to have undergone definitive therapy if their HES record contained the 'M61' Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) code[9] indicating radical prostatectomy within 1 year of diagnosis, or alternatively if their cancer registry record indicated the use of radiotherapy.

Patients from the SEER dataset were considered to have undergone definitive therapy if they underwent radical prostatectomy or radiation therapy as part of their first

course of therapy. American patients were considered to have undergone radical prostatectomy if they had undergone cancer-directed surgery, coded as any of the following: Radical/total prostatectomy, or Prostatectomy with resection in continuity with other organs/pelvic exenteration. All forms of radiotherapy were assumed to be definitive in nature, as treatment doses are not routinely recorded in the SEER or English cancer registries.

Risk stratification

Patients were classified into risk groups using a modified version of the National Comprehensive Cancer Network (NCCN) prostate cancer risk classification,[10] based on clinical tumour (cT) stage and Gleason score (GS). Risk groups were defined as follows: low risk (cT1 stage and GS 2-6), intermediate risk (cT2 stage or GS 7), and high risk (cT3-T4 stage or GS 8-10). Since prostate-specific antigen (PSA) levels are not recorded in the HES database or English cancer registries, this variable was not used for risk stratification in this study.

Outcome measurement

The cause of death amongst English patients was extracted from national mortality records provided by the Office for National Statistics, which were linked to cancer registry and HES data. Similarly, cause of death is routinely recorded as part of the SEER dataset for US patients. Where the cause of death was listed as the disease code for prostate cancer, C61, it was classified as a prostate cancer death.

Statistical analysis

Chi square test was used to compare proportions between the two countries. A Cox regression model was used to calculate adjusted hazard ratios (HRs) for all-cause mortality (ACM), comparing mortality in England and the US. Similarly, adjusted sub-hazard ratios (SHRs) were calculated for prostate cancer mortality (PCM) using a maximum likelihood competing risk regression model, according to the method of Fine and Gray.[11] Failure event for PCM was defined as death due to prostate cancer, while death due to a cause other than prostate cancer was defined as the competing event. All analyses were performed using STATA version 11 (StataCorp, College station, TX, USA).

All regression models were adjusted for age group, year of diagnosis, ethnicity, clinical tumour stage, and Gleason score (model 1). Next, the impact of variation in use of definitive therapy was assessed by additionally including use of definitive therapy in a separate regression model (model 2). Separate regression models were built to test for differences between the two countries for each individual risk group. This resulted in 20 regression models in total: 5 patient groups (all eligible patients, all patients with complete data, low, intermediate, and high risk) x 2 adjustment models (model 1 and model 2) x 2 outcomes (ACM and PCM).

Sensitivity Analysis

In order to investigate the influence of excluding patients for whom tumour stage and Gleason grade data were missing, we performed a sensitivity analysis where all eligible patients were included.

Role of Funding Source

The study benefited from a grant from the Academy of Medical Royal Colleges supporting a project assessing the value of procedure-specific and disease-specific metrics derived from routinely collected data to assess the performance of NHS providers. Sponsors were not involved in the study design; the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

Participants

Data were available on 328,182 men (111,917 from England and 216,265 from the US) of which 301,989 (97,079 from England and 204,910 from the US) met the selection criteria. Reasons for exclusion are described in Figure 1.

Complete data to enable risk stratification (i.e. cT stage and Gleason score) were available for 222,163 men (23,235 from England and 196,928 from the US). These data were used to undertake the primary analysis.

Men diagnosed with prostate cancer in England tended to be older and less ethnically diverse, to present with higher clinical tumour stage, and to have higher pathological Gleason scores (Table 1, Appendix 1), with each of these differences reaching statistical significance at $p < 0.001$. Amongst patients for whom complete data were available, men diagnosed with prostate cancer in England were more likely to present

with high-risk prostate cancer according to our modified NCCN criteria (34.5% in England and 17.2% in US, Table 1).

Men diagnosed with prostate cancer in England were less likely to receive definitive therapy (38.2% in England and 77.1% in US), and this difference was observed in all risk groups (Table 1).

Mortality

The median follow-up for the entire cohort was 43.3 months. Unadjusted 6-year ACM amongst English men was higher compared to American men (21.0% versus 9.6%). Similarly, unadjusted 6-year PCM amongst English men was also higher, as compared to American men (9.6% versus 2.6%). This trend was similar amongst patients with complete data, whose outcomes are described below (Table 2).

Primary analysis

The primary analysis was conducted using data from the 222,163 patients for whom clinical tumour stage and Gleason score were available, to allow risk stratification.

Unadjusted 6-year ACM amongst patients who had definitive therapy was 7.3% in England and 4.9% in the US. Corresponding ACM figures amongst those who did not have definitive treatment were 19.5% in England and 15.5% in the US. The greatest difference was observed in patients at high prostate cancer risk undergoing definitive treatment with a 6-year ACM of 15.1% in England and 8.1% in the US, with the smallest difference observed in patients with low-risk prostate cancer who did not undergo definitive therapy (9.5% in England and 9.9% in the US).

Unadjusted 6-year PCM amongst patients from all risk groups who underwent definitive therapy was 2.4% in England and 1.2% in the US. This compared to 8.8% amongst patients who did not receive definitive therapy in England and 4.5% in the US. Differences in unadjusted 6-year PCM were smallest amongst patients with low-risk disease undergoing definitive therapy (0.4% in England and 0.5% in the US), and greatest amongst patients with high-risk disease undergoing definitive therapy (7.6% in England and 3.7% in the US).

When comparing all patients with complete data amenable for risk stratification, following adjustment for age group, ethnicity, year of diagnosis, and tumour characteristics (model 1), significantly higher ACM (adjusted HR 1.60, 95% CI 1.52 to 1.68) and PCM (adjusted SHR 1.88, 95% CI 1.72 to 2.05) were found in England than in the US (Table 2). Within each of the three risk groups, with adjustment for patient and tumour characteristics (model 1), the greatest difference in ACM and PCM was noted amongst the intermediate-risk and high-risk patients (Table 42). PCM was not significantly different at 0.9% in both countries at six years amongst men with low-risk disease.

When treatment allocation was included in the multivariate model (model 2), no difference in ACM and PCM was noted between the US and England for all men (ACM: adjusted HR 1.03, 95% CI 0.97 to 1.08; PCM: adjusted SHR 0.97, 95% CI 0.88 to 1.07) or within each of the individual risk groups (Table 42).

Sensitivity Analysis

Multivariate analysis for the entire cohort of 301,989 patients, including patients for whom data regarding either clinical tumour stage or Gleason score were missing, revealed a similar trend (Appendix 2). Adjustment for age group, ethnicity and year of

diagnosis, revealed higher ACM (adjusted HR 2.19, 95% CI 2.13 to 2.26) and PCM (adjusted SHR 3.67, 95% CI 3.50 to 3.85) amongst English patients.

Additional adjustment for the use of definitive therapy appeared, in part, to account for variation in ACM (adjusted HR 1.55, 95% CI 1.50 to 1.59) and PCM (adjusted HR 2.37, 95% CI 2.25 to 2.50).

Discussion

Prostate cancer death in intermediate to high-risk cases is higher in England than it is in the US. When we adjusted for the different rates of definitive therapy in the two countries, the rates of prostate cancer death were similar. This suggests that the differences in mortality may be explained by a lower use of definitive therapy in England.

Methodological considerations

First, the English dataset contained a high proportion of missing data for clinical tumour stage and Gleason score. The high proportion of patients with missing data in the English dataset may be due to poor data capture. Excluded English patients tended to be older, to have more advanced disease, and they less frequently received definitive therapy (Appendix ~~1~~3). This limitation is unlikely to have had a marked influence on our results, as inclusion of these patients would have increased the observed difference in PCM noted between the two countries. Thus, these data provide a conservative estimate of the spread of prostate cancer risk amongst the

general English population. Nevertheless it is worthwhile to note that these are the only population-wide data currently available for comparing management of PCa in the two countries.

Furthermore, a sensitivity analysis was performed to investigate the influence of excluding patients with missing cT stage or Gleason score. This showed that PCM is significantly higher in England than the US, though this difference is partly explained upon additional adjustment for the variation in use of definitive treatment in the two countries. Due to the higher proportion of men with low or intermediate risk disease in the US, the variation in use of definitive treatment becomes more apparent upon risk stratification in our primary analysis.

Secondly, the SEER dataset did not contain information concerning patient comorbidity. We feel our findings remain valid despite this potential limitation as PCM is less strongly influenced by comorbid conditions than ACM.[12] In addition, there were also differences between England and the US in the PCM of young patients aged between 35 and 59 years who are least likely to have comorbid conditions at the time of diagnosis (adjusted SHR 2.66, 95% CI 1.99 to 3.56, $p<0.001$).

Thirdly, "lead time bias" could be an explanation for PCM being lower in the US than in the UK given that the uptake of PSA testing is much higher in the US, the effect of which is likely to be that men in the US are diagnosed with less advanced prostate cancer at an earlier age. In an attempt to minimise the effect of this limitation we adjusted for clinical stage at diagnosis and patient age at diagnosis together with Gleason score in our primary analysis.

Lastly, PSA levels were not available for English patients and therefore they could not be used to adjust the differences in PCM between England and the US. To investigate this limitation further, we evaluated if the inclusion of PSA into our risk stratification model resulted in significant re-categorisation of a patient's prostate cancer risk for the US patients. We found little movement between risk groups with, for example, only 7.4% US patients being re-classified as intermediate-risk having initially been assigned a low-risk status. Furthermore, Elliott et al have previously shown that while it is advantageous to have all three clinical variables (including PSA, cT stage and Gleason score) available for risk stratification, patients with high-risk disease can still be correctly identified even if one of these variable (such as PSA) is missing.[13]

Despite the above-mentioned limitations, routinely collected data provide a rich resource to explain performance of health care providers in different countries. However, differences in coding practices and differences in healthcare frameworks must be acknowledged.

Comparison with other studies

Mortality

PCM was found to be significantly higher in England compared to the US amongst men with intermediate and high-risk prostate cancer. In the current study, we used SEER data of men diagnosed between 2004 and 2008 and found that 6-year ACM was 9.3% and PCM 2.4%. A study using SEER data of men diagnosed between 1992 and 2005 found very similar figures (5-year ACM 14.3% and PCM 1.7%).[14]

Comparison of prostate cancer outcomes in England and US

Improvements in management of prostate cancer and other comorbidities may explain why our figures for ACM are slightly lower.

In comparison, our analysis of the English HES database found that 6-year ACM was 18.5% and PCM 7.6%. A study reporting outcome of 50,066 men diagnosed with prostate cancer in the London area between 1997 and 2006 with a median follow up of 3.5 years reported a PCM for men who had undergone definitive treatment of about 2%, which corresponds closely to the figures we found in this study.[15]

The only two relevant randomised controlled trials[16 17] demonstrated benefit of definitive therapy in patients with high-risk disease, which is consistent with the results of our study.

Differences between England and the US

A study using the EUROCARE and SEER registries including men diagnosed between 1985 and 1989 reported a 2.8 times relative excess risk of death amongst European men with prostate cancer compared to their American counterparts.[18] A more recent study using SEER data between 1975 and 2004 together with UK cancer mortality statistics found that age-adjusted PCM rates in the US were significantly lower than in England with the decline in PCM being 4.2% per year since the 1990s, a figure about four times higher than that reported for England.[19]

The investigators of both these studies suggested that difference in PCM between England and the US is the result of variation in disease burden brought about by the higher incidence of prostate cancer screening in the US. However, neither study adjusted for prostate cancer risk. In this study, we have identified for the first time

that irrespective of prostate cancer stage and Gleason score, prostate cancer outcomes in terms of ACM and PCM are better in the US than in England, which does not support the increased use of prostate cancer screening in the US as an explanation for the difference in prostate cancer mortality. Instead, our data suggest that the better prostate cancer outcome seen in the US may be due to the more frequent use of definitive treatment.

Clinical implication

The decision to offer definitive prostate cancer therapy is influenced by both disease characteristics and patient characteristics. As noted in our results, variations in healthcare systems have direct and indirect affects on both these factors. The expected survival benefit of definitive prostate cancer therapy must therefore also be balanced against the associated probability of side effects, including urinary incontinence and erectile dysfunction.

Our analysis suggests that prostate cancer mortality in England may be improved by an increase in the use of definitive treatment. This increase should be directed at men with intermediate and high-risk prostate cancer, as the differences in outcomes between England and the US for men with low-risk disease were very small. These results have to be interpreted in the context of differences between the two countries in the way prostate cancer is diagnosed, with higher uptake of PSA testing in the US.

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Conflicts of interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: (1) No authors received support for the submitted work; (2) ME has received funding from GSK, Sonacare, STEBA Biotech and Sanofi-Aventis, outside the submitted work. He acts as a consultant to these companies and has received honoraria for speaking and organising and participating in educational activities. JvdM has received a one-year unrestricted research grant from Sanofi-Aventis, outside the submitted work. (3) Their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) all authors have no non-financial interests that may be relevant to the submitted work.

Ethical approval: Not required for this study.

Data sharing: No additional data available.

Declaration of transparency: AS and PJC affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

References

1. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9(8):730-56.

2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *The lancet oncology* 2013.

3. Abdollah F, Sun M, Thuret R, Jeldres C, Tian Z, Briganti A, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* 2011;59(1):88-95.

4. Fairley L, Baker M, Whiteway J, Cross W, Forman D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 2009;101(11):1839-45.

5. Lyratzopoulos G, Barbiere JM, Greenberg DC, Wright KA, Neal DE. Population based time trends and socioeconomic variation in use of radiotherapy and radical surgery for prostate cancer in a UK region: continuous survey. *BMJ* 2010;340:c1928.

6. *National Cancer Data Repository 1990-2010*. National Cancer Intelligence Network; [cited 2014 October 1]; Available from: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/.

7. *Hospital Episode Statistics*. [Website]: NHS Health and Social Care Information Centre; [cited 2014 October 1]; Available from: http://www.hesonline.nhs.uk/.

8. *Surveillance, Epidemiology, and End Results (SEER) Program 1975-2010*. [Website] Bethesda, MD: National Cancer Institute; [cited 2014 October 1]; Available from: http://seer.cancer.gov/csr/1975_2010/.

9. NHS Connecting for Health. *Office of Population, Censuses, and Surveys (OPCS) Classification of Interventions and Procedures Version 4.6 (April 2011)*: The Stationery Office.

10. *NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer*. National Comprehensive Care Network; 2014 [cited 2014 October 1]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94(446):496-509.

12. Briganti A, Spahn M, Joniau S, Gontero P, Bianchi M, Kneitz B, et al. Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. *Eur Urol* 2013;63(4):693-701.

13. Elliott SP, Johnson DP, Jarosek SL, Konety BR, Adejoro OO, Virnig BA. Bias due to missing SEER data in D'Amico risk stratification of prostate cancer. *The Journal of urology* 2012;187(6):2026-31.

14. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. *Eur Urol* 2011;60(5):920-30.

15. Chowdhury S, Robinson D, Cahill D, Rodriguez-Vida A, Holmberg L, Moller H. Causes of death in men with prostate cancer: an analysis of 50,000 men from the Thames Cancer Registry. *BJU Int* 2013;112(2):182-9.

16. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011;364(18):1708-17.

17. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367(3):203-13.

18. Gatta G, Capocaccia R, Coleman MP, Gloeckler Ries LA, Hakulinen T, Micheli A, et al. Toward a comparison of survival in American and European cancer patients. *Cancer* 2000;89(4):893-900.

19. Collin SM, Martin RM, Metcalfe C, Gunnell D, Albertsen PC, Neal D, et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncol* 2008;9(5):445-52.

Comparison of prostate cancer outcomes in England and US

Table 1: Patient demographics by country (n = 222,163).

	England	US	*p* value
	(n = 25,235)	**(n = 196,928)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	36,172 (18.4)	<0.001
2005	4,959 (19.7)	34,403 (17.5)	
2006	5,172 (20.5)	40,531 (20.6)	
2007	5,009 (19.9)	43,800 (22.2)	
2008	4,717 (18.7)	42,022 (21.3)	
Age group (%)			
35-59	3,620 (14.4)	56,399 (28.6)	<0.001
60-64	4,361 (17.3)	40,287 (20.5)	
65-69	6,104 (24.2)	42,439 (21.6)	
70-74	6,145 (24.4)	33,912 (17.2)	
75-79	5,005 (19.8)	23,891 (12.1)	
Ethnicity (%)			
White	17,924 (94.8)	154,077 (80.4)	<0.001
African/Caribbean	571 (3.0)	28,361 (14.8)	
Asian	318 (1.7)	8,638 (4.5)	
Other	105 (0.6)	626 (0.3)	
Missing	6,317	5,226	
Clinical tumour stage (%)			
cT1	9,374 (37.2)	72,407 (36.8)	<0.001
cT2	9,538 (37.8)	107,762 (54.7)	
cT3	5,577 (22.1)	15,482 (7.9)	
cT4	746 (3.0)	1,277 (0.7)	
Gleason score (%)			
2-6	10,909 (43.2)	99,661 (50.6)	<0.001
7	9,112 (36.1)	75,247 (38.2)	
8-10	5,214 (20.7)	22,020 (11.2)	
Modified NCCN risk (%)			
Low risk	6,151 (24.4)	45,045 (22.9)	<0.001
Intermediate risk	10,386 (41.2)	118,074 (60.0)	
High risk	8,698 (34.5)	33,809 (17.1)	
Treatment – all risk groups (%)			
No definitive therapy	15,583 (61.8)	45,113 (22.9)	<0.001
Definitive therapy	9,652 (38.2)	151,815 (77.1)	
Treatment – low risk (%)			
No definitive therapy	3,799 (61.8)	17,516 (38.9)	<0.001
Definitive therapy	2,352 (38.2)	27,529 (61.1)	
Treatment – intermediate risk (%)			
No definitive therapy	5,696 (54.8)	21,999 (18.6)	<0.001
Definitive therapy	4,690 (45.2)	96,075 (81.4)	
Treatment – high risk (%)			
No definitive therapy	6,088 (70.0)	5,598 (16.6)	<0.001
Definitive therapy	2,610 (30.0)	28,211 (83.4)	

cT = Clinical tumour stage

Comparison of prostate cancer mortality in England and the US

Table 2: All-cause mortality (ACM) and prostate cancer mortality (PCM) according to country of treatment and modified NCCN risk (n = 222,163).

	6 year All Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)		Model 2 (Model 1 and definitive therapy)	
Risk group	**US**	**England**	**Adj HR (95% CI)**	***p* value**	**Adj HR (95% CI)**	***p* value**
	n = 196,928	n = 25,235				
All risk groups	9.3%	18.5%	1.60 (1.52 to 1.68)	<0.001	1.03 (0.97 to 1.08)	0.336
Low risk	8.7%	10.3%	1.30 (1.15 to 1.48)	<0.001	1.06 (0.93 to 1.21)	0.397
Intermediate risk	7.6%	12.5%	1.44 (1.32 to 1.58)	<0.001	0.98 (0.90 to 1.08)	0.740
High risk	16.3%	31.8%	1.92 (1.78 to 2.06)	<0.001	0.99 (0.92 to 1.08)	0.863
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)**		**Model 2 (Model 1 and definitive therapy)**	
Risk group	**US**	**England**	**Adj SHR (95% CI)**	***p* value**	**Adj SHR (95% CI)**	***p* value**
All risk groups	2.4%	7.6%	1.88 (1.72 to 2.05)	<0.001	0.97 (0.88 to 1.07)	0.568
Low risk	0.9%	0.9%	1.57 (1.08 to 2.30)	0.018	1.31 (0.89 to 1.93)	0.169
Intermediate risk	1.4%	2.8%	1.71 (1.40 to 2.09)	<0.001	1.00 (0.81 to 1.23)	0.994
High risk	8.1%	18.8%	2.06 (1.87 to 2.28)	<0.001	0.96 (0.86 to 1.08)	0.537

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence Interval

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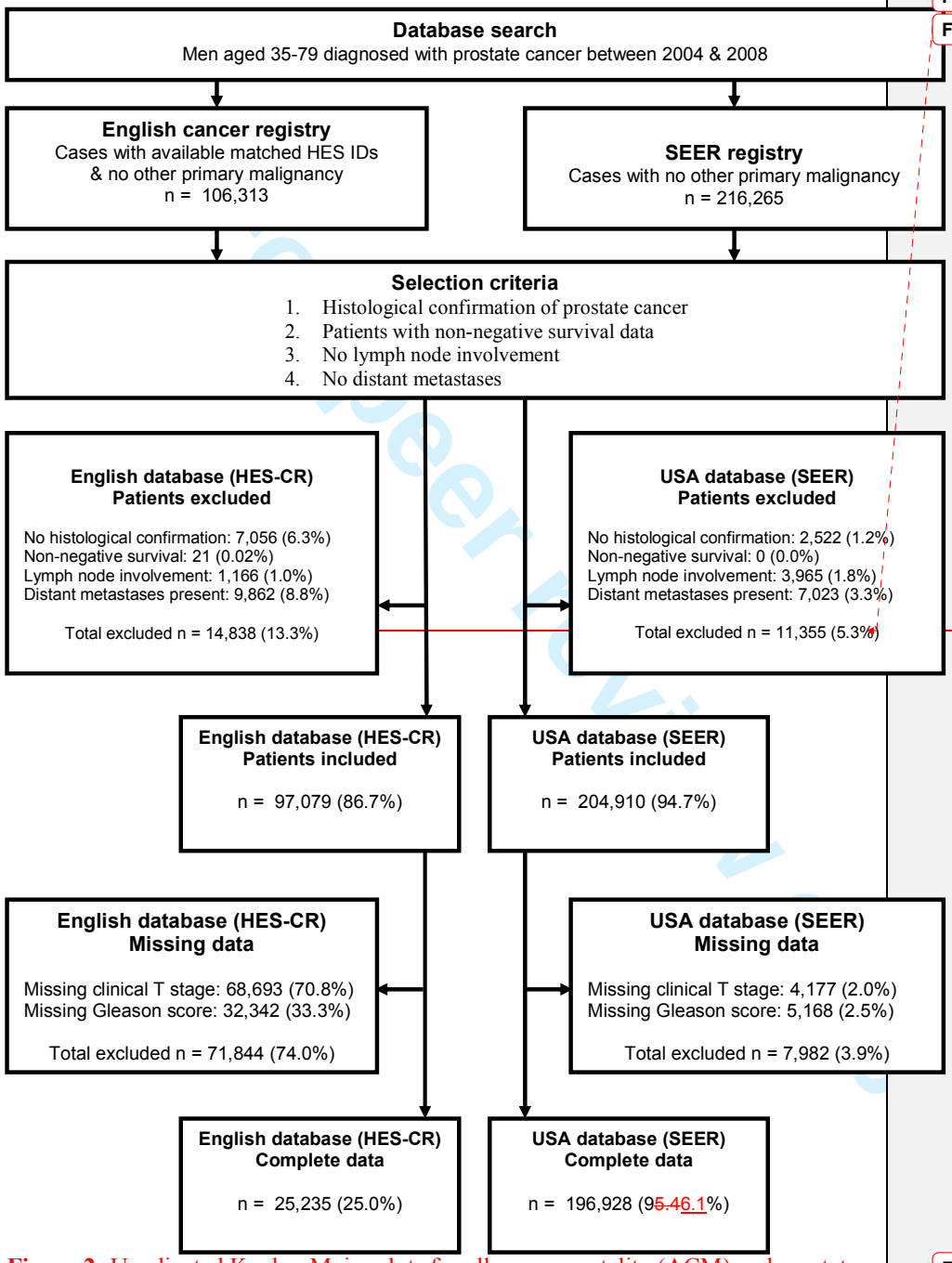
Comparison of prostate cancer outcomes in England and US

~~**Figure 1:** Study flow diagram~~



~~**Figure 2:** Unadjusted Kaplan-Meier plots for all-cause mortality (ACM) and prostate cancer mortality (PCM). Separate p-values are reported for regression models with (Model 1, p1) and without (Model 2, p2) the inclusion of definitive therapy.~~

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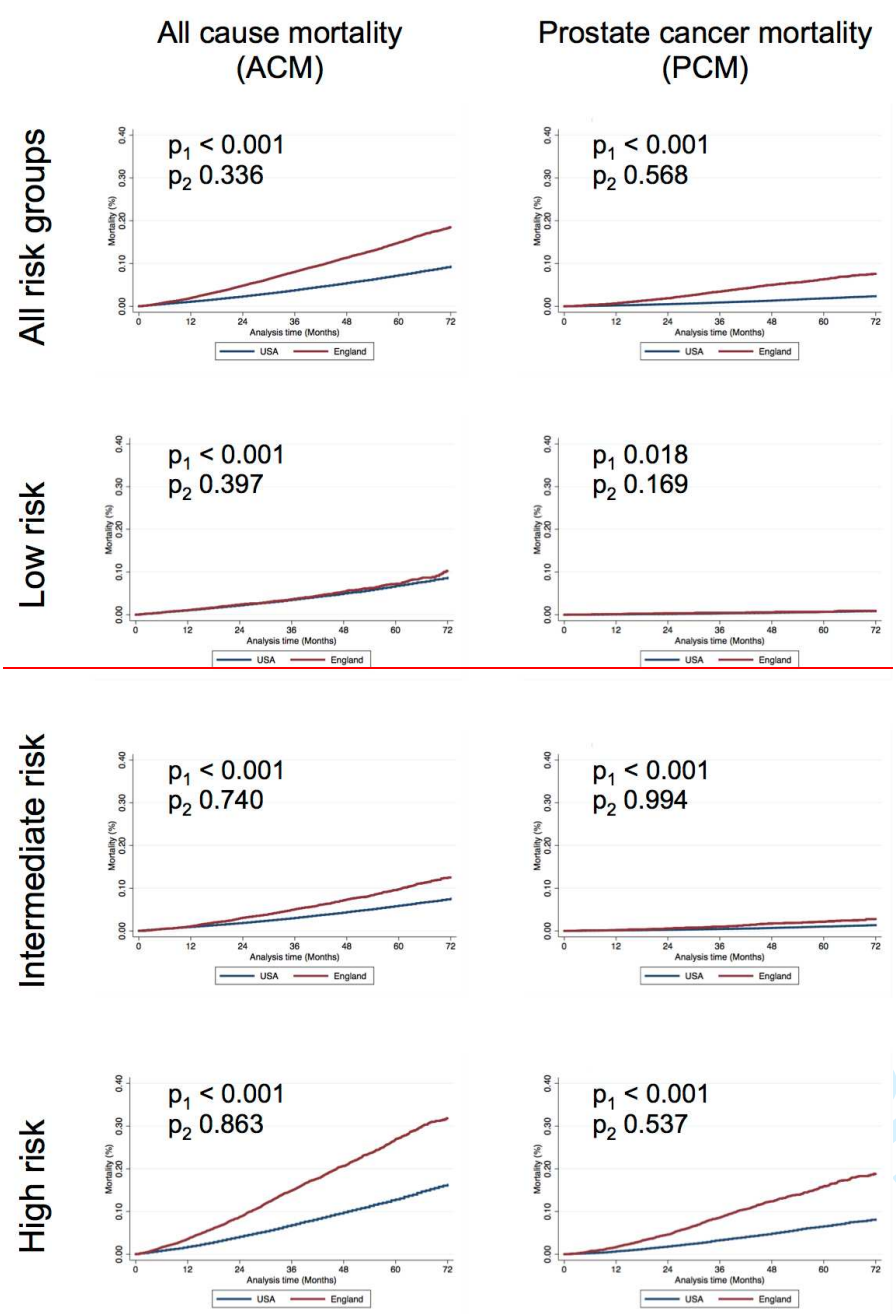
Comparison of prostate cancer mortality in England and the US



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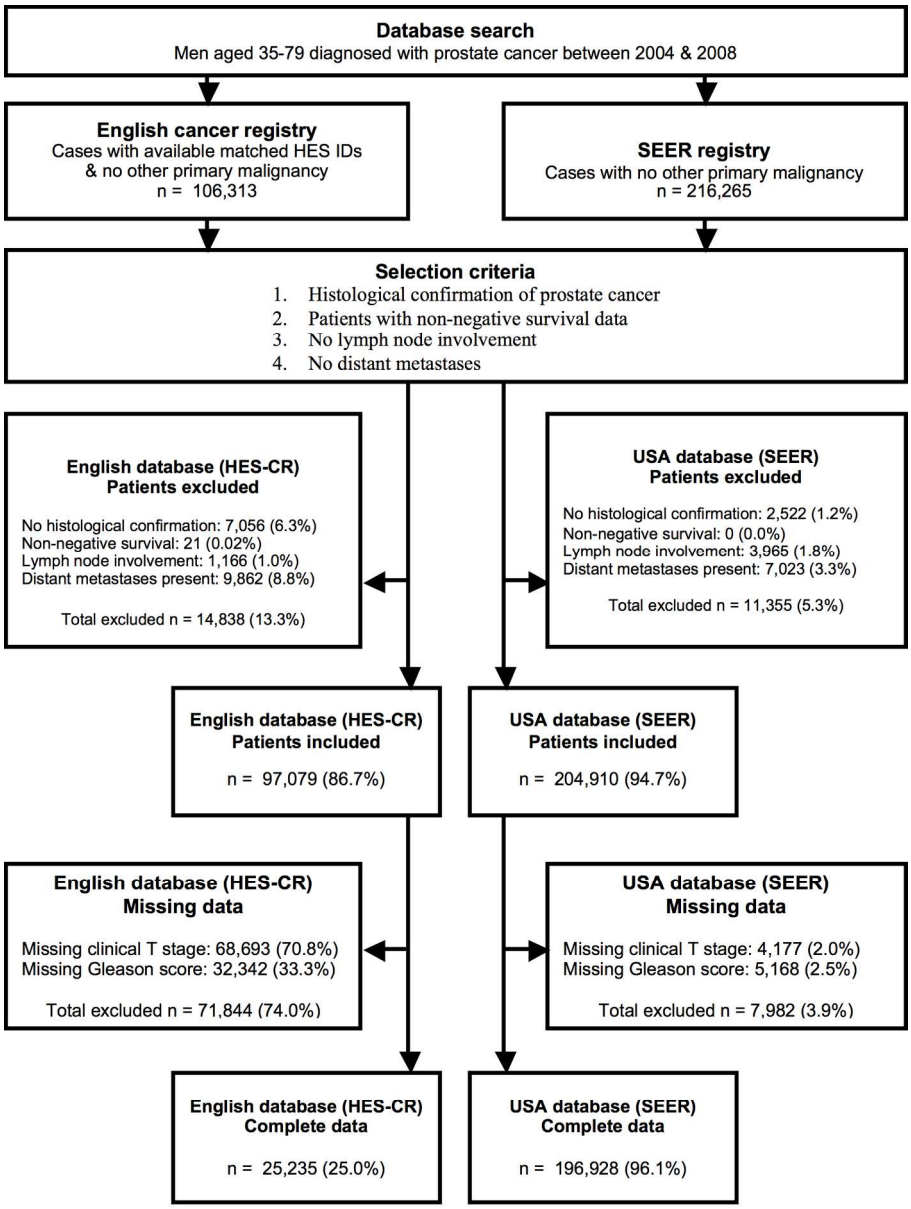

Figure 1: Study flow diagram
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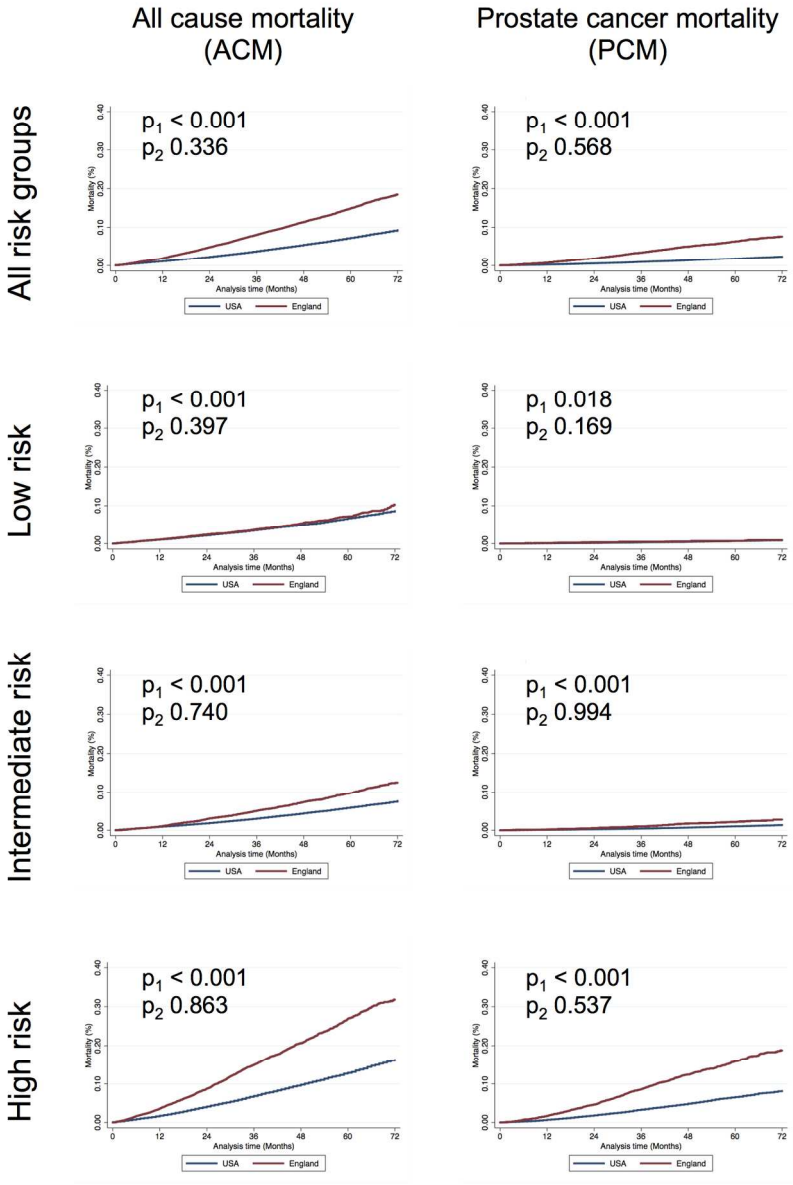

Figure 2: Unadjusted Kaplan-Meier plots for all-cause mortality (ACM) and prostate cancer mortality (PCM). Separate p values are reported for regression models with (Model 1, p1) and without (Model 2, p2) the inclusion of definitive therapy.
145x216mm (300 x 300 DPI)

Appendix 1: Sensitivity analysis. Demographic and disease characteristics of all eligible patients by country (n = 328,182).

	England	US	*p* value
	(n = 97,079)	**(n = 204,910)**	
Year of diagnosis			
2004	18,883 (19.5)	37,686 (18.4)	<0.001
2005	18,392 (19.0)	35,656 (17.4)	
2006	19,847 (20.4)	41,938 (20.5)	
2007	20,061 (20.7)	45,612 (22.3)	
2008	19,896 (20.5)	44,018 (21.5)	
Age group			
35-59	13,593 (14.5)	57,992 (28.9)	<0.001
60-64	16,643 (17.8)	41,601 (20.7)	
65-69	22,782 (24.3)	44,116 (22.0)	
70-74	23,565 (25.1)	35,612 (17.7)	
75-79	17,139 (18.3)	21,592 (10.8)	
Ethnicity			
White	68,618 (93.8)	159,399 (80.4)	<0.001
African/Caribbean	2,796 (3.8)	29,362 (14.8)	
Asian	1,343 (1.8)	8,983 (4.5)	
Other	430 (0.6)	654 (0.3)	
Missing	23,892	6,512	
Clinical tumour stage			
cT1	10,331 (36.4)	74,169 (37.0)	<0.001
cT2	10,779 (38.0)	109,680 (54.6)	
cT3	6,421 (22.6)	15,562 (7.8)	
cT4	855 (3.0)	1,322 (0.7)	
Missing	68,693	4,177	
Gleason score			
2-6	28,119 (43.4)	101,123 (50.6)	<0.001
7	23,527 (36.3)	76,049 (38.1)	
8-10	13,091 (20.2)	22,570 (11.3)	
Missing	32,342	5,168	
Use of definitive therapy			
No definitive therapy	63,716 (65.6)	51,100 (24.9)	<0.001
Definitive therapy	33,363 (34.4)	153,810 (75.1)	

Appendix 2: Sensitivity analysis. Relative all-cause mortality (ACM) and prostate cancer mortality (PCM) of all eligible patients according to country (n = 328,182).

	6 year All-Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity)		Model 2 (Model 1 and definitive therapy)	
	US	**England**	**Adj HR (95% CI)**	***p* value**	**Adj HR (95% CI)**	***p* value**
All patients	n = 204,910 9.6%	n = 97,079 21.0%	2.19 (2.13 to 2.26)	<0.001	1.55 (1.50 to 1.59)	<0.001
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity)**		**Model 2 (Model 1 and definitive therapy)**	
	US	**England**	**Adj SHR (95% CI)**	***p* value**	**Adj SHR (95% CI)**	***p* value**
All patients	2.6%	9.6%	3.67 (3.50 to 3.85)	<0.001	2.37 (2.25 to 2.50)	<0.001

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence interval

Appendix 3: Comparison of demographic and disease characteristics of all eligible included and excluded English patients. Patients with either missing clinical tumour stage or missing Gleason score were classified as "excluded patients".

	Included patients	Excluded patients	*p* value
	(n = 25,235)	**(n = 71,844)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	13,505 (18.8)	<0.001
2005	4,959 (19.7)	13,433 (18.7)	
2006	5,172 (20.5)	14,675 (20.4)	
2007	5,009 (19.9)	15,052 (21.0)	
2008	4,717 (18.7)	15,179 (21.1)	
Age group (%)			
35-59	3,620 (14.4)	9,973 (13.9)	<0.001
60-64	4,361 (17.3)	12,282 (17.1)	
65-69	6,104 (24.2)	16,678 (23.2)	
70-74	6,145 (24.4)	17,420 (24.3)	
75-79	5,005 (19.8)	15,491 (21.6)	
Ethnicity (%)			
White	17,924 (94.8)	50,694 (93.4)	<0.001
African/Caribbean	571 (3.0)	2,225 (4.1)	
Asian	318 (1.7)	1,025 (1.9)	
Other	105 (0.6)	325 (0.6)	
Missing	*6,317*	*17,575*	
Socio-economic quartile			
1	6,262 (24.9)	17,588 (24.5)	<0.001
2	6,101 (24.2)	16,975 (23.7)	
3	5,392 (21.4)	14,693 (20.5)	
4	4,073 (16.2)	12,023 (16.8)	
5	3,363 (13.4)	10,409 (14.5)	
Missing	44	156	
Charlson co-morbidity index			
0	11,261 (44.6)	33,914 (47.2)	<0.001
1	11,761 (46.6)	30,861 (43.0)	
2 or more	2,213 (8.8)	7,069 (9.8)	
Clinical tumour stage			
cT1	9,374 (37.2)	957 (30.37)	<0.001
cT2	9,538 (37.8)	1,241 (39.4)	
cT3	5,577 (22.1)	844 (26.8)	
cT4	746 (3.0)	109 (3.5)	
Missing	0	68,693	
Gleason score			
2-6	10,909 (43.2)	17,210 (43.6)	0.083
7	9,112 (36.1)	14,415 (36.5)	
8-10	5,214 (20.7)	7,877 (19.9)	
Missing	0	32,342	
Treatment (%)			
No definitive therapy	15,583 (61.8)	48,133 (67.0)	<0.001
Definitive therapy	9,652 (38.3)	23,711 (33.0)	

STROBE Statement—checklist of items that should be included in reports of observational studies

Evidence of inclusion of checklist items is provided as relevant page numbers in the last column.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**
Methods			
Study design	4	Present key elements of study design early in the paper	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**5, 6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**5, 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**6, 7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5**
Bias	9	Describe any efforts to address potential sources of bias	**7, 8**
Study size	10	Explain how the study size was arrived at	**9, 22**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**8**
		(*b*) Describe any methods used to examine subgroups and interactions	**8**
		(*c*) Explain how missing data were addressed	**8**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**8**
		(*e*) Describe any sensitivity analyses	**8**

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**9, 22**
		(b) Give reasons for non-participation at each stage	**9, 22**
		(c) Consider use of a flow diagram	**22**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**20**
		(b) Indicate number of participants with missing data for each variable of interest	**22**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	**10**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	**10**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**-**
		Cross-sectional study—Report numbers of outcome events or summary measures	**-**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**10**
		(*b*) Report category boundaries when continuous variables were categorized	**6, 7, 20**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**-**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**11, 12**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**12, 13, 14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**16**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**14, 15**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**9**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Evaluating variation in use of definitive therapy and risk-adjusted prostate cancer mortality in England and the US

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Evaluating variation in use of definitive therapy and risk-adjusted prostate cancer mortality in England and the US

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Abstract

Objectives: Prostate cancer mortality (PCM) in the US is amongst the lowest in the world, whereas PCM in England is amongst the highest in Europe. This paper aims to assess the association of variation in use of definitive therapy on risk-adjusted PCM in England as compared to the US.

Design: Observational study

Setting: Cancer registry data from England and the US

Participants: Men diagnosed with non-metastatic prostate cancer (PCa) in England and the US between 2004 and 2008

Outcome measures: Competing-risks survival analyses to estimate sub-hazard ratios (SHR) of prostate cancer mortality adjusted for age, ethnicity, year of diagnosis, Gleason score (GS), and clinical tumor stage (cT).

Results: 222,163 men were eligible for inclusion. Compared to American patients, English patients were more likely to present at an older age (70-79 years: England 44.2%, US 29.3%, p<0.001), with higher tumour stage (cT3-4: England 25.1%, US 8.6%, p<0.001) and higher Gleason score (GS 8-10: England 20.7%, US 11.2%, p<0.001). They were also less likely to receive definitive therapy (England 38%, US 77%, p<0.001).

English patients were more likely to die of PCa (SHR 1.9, 95% confidence interval 1.7-2.0, p<0.001). However, this difference was no longer statistically significant when also adjusted for use of definitive therapy (SHR 1.0, 95% confidence interval 1.0-1.1, p=0.3).

Conclusions: Risk-adjusted PCM is significantly higher in England compared to the US. This difference may be explained by less frequent use of definitive therapy in England.

Word count: 236

Article summary

Strengths and limitations of this study:

- A key strength of this paper is the use of routinely collected data from hospital episode statistics linked to cancer registry data, providing a large dataset to make accurate estimates of relative prostate cancer mortality.
- Lack of PSA data and a relatively short follow-up period of 6 years are the key limitations of this study.
- Given that this is an observational study, there is some uncertainty about the causes for the observed differences in prostate cancer mortality.

Background

Outcomes following a diagnosis of cancer vary markedly around the world. In the United States of America (US), cancer-related deaths have been demonstrated to be amongst the lowest. For example, US breast cancer mortality is 65% lower than the European average while death from colorectal cancer is 30% lower.[1] On the other hand, cancer mortality rates in England are amongst the highest in Europe.[2] The disparity in cancer outcomes appears greatest for prostate cancer for which 5-year mortality has been reported to be six times higher in England compared to the US.[1]

A number of disease and treatment-related factors may account for the observed variation in prostate cancer outcomes between the US and England. These include variation in policy concerning prostate cancer screening between the two countries together with variation in use of definitive prostate cancer therapy. Other factors that may be at play include the methods by which data on cancer diagnoses and cancer related deaths are both collected and processed.

In the US, the vast majority of men diagnosed with localized prostate cancer have definitive therapy, either by radical radiation therapy or radical surgery. For example, three quarters of men diagnosed with prostate cancer between 1988 and 2006 were reported to have undergone definitive therapy for their disease.[3] This figure compares to only about one third in England.[4 5]

We report differences in risk-adjusted prostate cancer mortality between the US and England. Furthermore, we investigate whether prostate cancer outcomes are related to the use of definitive therapy between the two countries. This study is part of a program of work assessing the value of procedure-specific and disease-specific

metrics derived from English hospital admission records to assess the performance of English National Health Service (NHS) providers.

Methods

Study design

We performed a population-based observational cohort study using patient-level cancer registry data from England and the US.

Data sources

Data collected by the eight regional cancer registries[6] for all men diagnosed with prostate cancer in England were linked to the Hospital Episodes Statistics (HES) database[7] and national mortality records provided by the Office for National Statistics.

The Surveillance, Epidemiology and End Results (SEER) database was used to identify American patients with prostate cancer from 18 regional cancer registries.[8] This database covers 28% of the US population and is linked to mortality data provided by the National Center for Health Statistics.

Participants

Men diagnosed with prostate cancer between 2004 and 2008, and aged between 35 and 80 years at the time of diagnosis were identified from both countries. The years 2004 to 2008 were selected as comparable English and American data were available for this period. Diagnosis of prostate cancer was confirmed using the 'C61'

International Classification of Diseases (ICD-10) diagnosis code in the HES and SEER databases. Follow-up data were available through to 16th April 2010 for the English cohort, and 31st December 2010 for the American cohort.

Patients were included if prostate cancer was histologically confirmed as their only primary malignancy. Patients with lymph node involvement or distant metastases were excluded, as they would not be candidates for primary definitive therapy. Where data on metastatic disease were missing, we considered the use of chemotherapy as a surrogate marker for metastases. Patients who underwent chemotherapy within 6 months of diagnosis were therefore also excluded. Twenty-one patients in the English dataset were noted to have negative survival data (i.e. date of diagnosis was chronologically after the date of death), and were therefore excluded. Those with missing data concerning pathological Gleason score (GS) or clinical tumour (cT) stage were excluded from the primary analysis, as they would not be amenable to risk stratification.

Variable definition

English patients were considered to have undergone definitive therapy if their HES record contained the 'M61' Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) code[9] indicating radical prostatectomy within 1 year of diagnosis, or alternatively if their cancer registry record indicated the use of radiotherapy.

Patients from the SEER dataset were considered to have undergone definitive therapy if they underwent radical prostatectomy or radiation therapy as part of their first

course of therapy. American patients were considered to have undergone radical prostatectomy if they had undergone cancer-directed surgery, coded as any of the following: Radical/total prostatectomy, or Prostatectomy with resection in continuity with other organs/pelvic exenteration. All forms of radiotherapy were assumed to be definitive in nature, as treatment doses are not routinely recorded in the SEER or English cancer registries.

Risk stratification

Patients were classified into risk groups using a modified version of the National Comprehensive Cancer Network (NCCN) prostate cancer risk classification,[10] based on clinical tumour (cT) stage and Gleason score (GS). Risk groups were defined as follows: low risk (cT1 stage and GS 2-6), intermediate risk (cT2 stage or GS 7), and high risk (cT3-T4 stage or GS 8-10). Since prostate-specific antigen (PSA) levels are not recorded in the HES database or English cancer registries, this variable was not used for risk stratification in this study.

Outcome measurement

The cause of death amongst English patients was extracted from national mortality records provided by the Office for National Statistics, which were linked to cancer registry and HES data. Similarly, cause of death is routinely recorded as part of the SEER dataset for US patients. Where the cause of death was listed as the disease code for prostate cancer, C61, it was classified as a prostate cancer death.

Statistical analysis

Chi square test was used to compare proportions between the two countries. A Cox regression model was used to calculate adjusted hazard ratios (HRs) for all-cause mortality (ACM), comparing mortality in England and the US. Similarly, adjusted sub-hazard ratios (SHRs) were calculated for prostate cancer mortality (PCM) using a maximum likelihood competing risk regression model, according to the method of Fine and Gray.[11] Failure event for PCM was defined as death due to prostate cancer, while death due to a cause other than prostate cancer was defined as the competing event. All analyses were performed using STATA version 11 (StataCorp, College station, TX, USA).

All regression models were adjusted for age group, year of diagnosis, ethnicity, clinical tumour stage, and Gleason score (model 1). Next, the impact of variation in use of definitive therapy was assessed by additionally including use of definitive therapy in a separate regression model (model 2). Separate regression models were built to test for differences between the two countries for each individual risk group. This resulted in 20 regression models in total: 5 patient groups (all eligible patients, all patients with complete data, low, intermediate, and high risk) x 2 adjustment models (model 1 and model 2) x 2 outcomes (ACM and PCM).

Sensitivity Analysis

In order to investigate the influence of excluding patients for whom tumour stage and Gleason grade data were missing, we performed a sensitivity analysis where all eligible patients were included.

Role of Funding Source

The study benefited from a grant from the Academy of Medical Royal Colleges supporting a project assessing the value of procedure-specific and disease-specific metrics derived from routinely collected data to assess the performance of NHS providers. Sponsors were not involved in the study design; the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

Participants

Data were available on 328,182 men (111,917 from England and 216,265 from the US) of which 301,989 (97,079 from England and 204,910 from the US) met the selection criteria. Reasons for exclusion are described in Figure 1.

Complete data to enable risk stratification (i.e. cT stage and Gleason score) were available for 222,163 men (23,235 from England and 196,928 from the US). These data were used to undertake the primary analysis.

Men diagnosed with prostate cancer in England tended to be older and less ethnically diverse, to present with higher clinical tumour stage, and to have higher pathological Gleason scores (Table 1, Appendix 1), with each of these differences reaching statistical significance at $p < 0.001$. Amongst patients for whom complete data were available, men diagnosed with prostate cancer in England were more likely to present

with high-risk prostate cancer according to our modified NCCN criteria (34.5% in England and 17.2% in US, Table 1).

Men diagnosed with prostate cancer in England were less likely to receive definitive therapy (38.2% in England and 77.1% in US), and this difference was observed in all risk groups (Table 1).

Mortality

The median follow-up for the entire cohort was 43.3 months. Unadjusted 6-year ACM amongst English men was higher compared to American men (21.0% versus 9.6%). Similarly, unadjusted 6-year PCM amongst English men was also higher, as compared to American men (9.6% versus 2.6%). This trend was similar amongst patients with complete data, whose outcomes are described below (Table 2, Figure 2).

Primary analysis

The primary analysis was conducted using data from the 222,163 patients for whom clinical tumour stage and Gleason score were available, to allow risk stratification.

Unadjusted 6-year ACM amongst patients who had definitive therapy was 7.3% in England and 4.9% in the US. Corresponding ACM figures amongst those who did not have definitive treatment were 19.5% in England and 15.5% in the US. The greatest difference was observed in patients at high prostate cancer risk undergoing definitive treatment with a 6-year ACM of 15.1% in England and 8.1% in the US, with the smallest difference observed in patients with low-risk prostate cancer who did not undergo definitive therapy (9.5% in England and 9.9% in the US).

Unadjusted 6-year PCM amongst patients from all risk groups who underwent definitive therapy was 2.4% in England and 1.2% in the US. This compared to 8.8% amongst patients who did not receive definitive therapy in England and 4.5% in the US. Differences in unadjusted 6-year PCM were smallest amongst patients with low-risk disease undergoing definitive therapy (0.4% in England and 0.5% in the US), and greatest amongst patients with high-risk disease undergoing definitive therapy (7.6% in England and 3.7% in the US).

When comparing all patients with complete data amenable for risk stratification, following adjustment for age group, ethnicity, year of diagnosis, and tumour characteristics (model 1), significantly higher ACM (adjusted HR 1.60, 95% CI 1.52 to 1.68) and PCM (adjusted SHR 1.88, 95% CI 1.72 to 2.05) were found in England than in the US (Table 2). Within each of the three risk groups, with adjustment for patient and tumour characteristics (model 1), the greatest difference in ACM and PCM was noted amongst the intermediate-risk and high-risk patients (Table 2). PCM was not significantly different at 0.9% in both countries at six years amongst men with low-risk disease.

When treatment allocation was included in the multivariate model (model 2), no difference in ACM and PCM was noted between the US and England for all men (ACM: adjusted HR 1.03, 95% CI 0.97 to 1.08; PCM: adjusted SHR 0.97, 95% CI 0.88 to 1.07) or within each of the individual risk groups (Table 2).

Sensitivity Analysis

Multivariate analysis for the entire cohort of 301,989 patients, including patients for whom data regarding either clinical tumour stage or Gleason score were missing, revealed a similar trend (Appendix 2). Adjustment for age group, ethnicity and year of

diagnosis, revealed higher ACM (adjusted HR 2.19, 95% CI 2.13 to 2.26) and PCM (adjusted SHR 3.67, 95% CI 3.50 to 3.85) amongst English patients.

Additional adjustment for the use of definitive therapy appeared, in part, to account for variation in ACM (adjusted HR 1.55, 95% CI 1.50 to 1.59) and PCM (adjusted HR 2.37, 95% CI 2.25 to 2.50).

Discussion

Prostate cancer death in intermediate to high-risk cases is higher in England than it is in the US. When we adjusted for the different rates of definitive therapy in the two countries, the rates of prostate cancer death were similar. This suggests that the differences in mortality may be explained by a lower use of definitive therapy in England.

Methodological considerations

First, the English dataset contained a high proportion of missing data for clinical tumour stage and Gleason score. The high proportion of patients with missing data in the English dataset may be due to poor data capture. Excluded English patients tended to be older, to have more advanced disease, and they less frequently received definitive therapy (Appendix 3). This limitation is unlikely to have had a marked influence on our results, as inclusion of these patients would have increased the observed difference in PCM noted between the two countries. Thus, these data provide a conservative estimate of the spread of prostate cancer risk amongst the

general English population. Nevertheless it is worthwhile to note that these are the only population-wide data currently available for comparing management of PCa in the two countries.

Furthermore, a sensitivity analysis was performed to investigate the influence of excluding patients with missing cT stage or Gleason score. This showed that PCM is significantly higher in England than the US, though this difference is partly explained upon additional adjustment for the variation in use of definitive treatment in the two countries. Due to the higher proportion of men with low or intermediate risk disease in the US, the variation in use of definitive treatment becomes more apparent upon risk stratification in our primary analysis.

Secondly, the SEER dataset did not contain information concerning patient comorbidity. We feel our findings remain valid despite this potential limitation as PCM is less strongly influenced by comorbid conditions than ACM.[12] In addition, there were also differences between England and the US in the PCM of young patients aged between 35 and 59 years who are least likely to have comorbid conditions at the time of diagnosis (adjusted SHR 2.66, 95% CI 1.99 to 3.56, $p<0.001$).

Thirdly, "lead time bias" could be an explanation for PCM being lower in the US than in the UK given that the uptake of PSA testing is much higher in the US, the effect of which is likely to be that men in the US are diagnosed with less advanced prostate cancer at an earlier age. In an attempt to minimise the effect of this limitation we adjusted for clinical stage at diagnosis and patient age at diagnosis together with Gleason score in our primary analysis.

Lastly, PSA levels were not available for English patients and therefore they could not be used to adjust the differences in PCM between England and the US. To investigate this limitation further, we evaluated if the inclusion of PSA into our risk stratification model resulted in significant re-categorisation of a patient's prostate cancer risk for the US patients. We found little movement between risk groups with, for example, only 7.4% US patients being re-classified as intermediate-risk having initially been assigned a low-risk status. Furthermore, Elliott et al have previously shown that while it is advantageous to have all three clinical variables (including PSA, cT stage and Gleason score) available for risk stratification, patients with high-risk disease can still be correctly identified even if one of these variable (such as PSA) is missing.[13]

Despite the above-mentioned limitations, routinely collected data provide a rich resource to explain performance of health care providers in different countries. However, differences in coding practices and differences in healthcare frameworks must be acknowledged.

Comparison with other studies

Mortality

PCM was found to be significantly higher in England compared to the US amongst men with intermediate and high-risk prostate cancer. In the current study, we used SEER data of men diagnosed between 2004 and 2008 and found that 6-year ACM was 9.3% and PCM 2.4%. A study using SEER data of men diagnosed between 1992 and 2005 found very similar figures (5-year ACM 14.3% and PCM 1.7%).[14]

Improvements in management of prostate cancer and other comorbidities may explain why our figures for ACM are slightly lower.

In comparison, our analysis of the English HES database found that 6-year ACM was 18.5% and PCM 7.6%. A study reporting outcome of 50,066 men diagnosed with prostate cancer in the London area between 1997 and 2006 with a median follow up of 3.5 years reported a PCM for men who had undergone definitive treatment of about 2%, which corresponds closely to the figures we found in this study.[15]

The only two relevant randomised controlled trials[16 17] demonstrated benefit of definitive therapy in patients with high-risk disease, which is consistent with the results of our study.

Differences between England and the US

A study using the EUROCARE and SEER registries including men diagnosed between 1985 and 1989 reported a 2.8 times relative excess risk of death amongst European men with prostate cancer compared to their American counterparts.[18] A more recent study using SEER data between 1975 and 2004 together with UK cancer mortality statistics found that age-adjusted PCM rates in the US were significantly lower than in England with the decline in PCM being 4.2% per year since the 1990s, a figure about four times higher than that reported for England.[19]

The investigators of both these studies suggested that difference in PCM between England and the US is the result of variation in disease burden brought about by the higher incidence of prostate cancer screening in the US. However, neither study adjusted for prostate cancer risk. In this study, we have identified for the first time

that irrespective of prostate cancer stage and Gleason score, prostate cancer outcomes in terms of ACM and PCM are better in the US than in England, which does not support the increased use of prostate cancer screening in the US as an explanation for the difference in prostate cancer mortality. Instead, our data suggest that the better prostate cancer outcome seen in the US may be due to the more frequent use of definitive treatment.

Clinical implication

The decision to offer definitive prostate cancer therapy is influenced by both disease characteristics and patient characteristics. As noted in our results, variations in healthcare systems have direct and indirect affects on both these factors. The expected survival benefit of definitive prostate cancer therapy must therefore also be balanced against the associated probability of side effects, including urinary incontinence and erectile dysfunction.

Our analysis suggests that prostate cancer mortality in England may be improved by an increase in the use of definitive treatment. However, due to the retrospective nature of this analysis, there could be other factors such as lead time bias which account for this difference. Only randomised trials can address these differences directly.

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Conflicts of interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: (1) No authors received support for the submitted work; (2) ME has received funding from GSK, Sonacare, STEBA Biotech and Sanofi-Aventis, outside the submitted work. He acts as a consultant to these companies and has received honoraria for speaking and organising and participating in educational activities. JvdM has received a one-year unrestricted research grant from Sanofi-Aventis, outside the submitted work. (3) Their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) all authors have no non-financial interests that may be relevant to the submitted work.

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Data sharing: No additional data available.

Declaration of transparency: AS and PJC affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

References

1. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9(8):730-56.

2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *The lancet oncology* 2013.

3. Abdollah F, Sun M, Thuret R, Jeldres C, Tian Z, Briganti A, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* 2011;59(1):88-95.

4. Fairley L, Baker M, Whiteway J, Cross W, Forman D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 2009;101(11):1839-45.

5. Lyratzopoulos G, Barbiere JM, Greenberg DC, Wright KA, Neal DE. Population based time trends and socioeconomic variation in use of radiotherapy and radical surgery for prostate cancer in a UK region: continuous survey. *BMJ* 2010;340:c1928.

6. *National Cancer Data Repository 1990-2010*. National Cancer Intelligence Network; [cited 2014 October 1]; Available from: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/.

7. *Hospital Episode Statistics*. [Website]: NHS Health and Social Care Information Centre; [cited 2014 October 1]; Available from: http://www.hesonline.nhs.uk/.

8. *Surveillance, Epidemiology, and End Results (SEER) Program 1975-2010*. [Website] Bethesda, MD: National Cancer Institute; [cited 2014 October 1]; Available from: http://seer.cancer.gov/csr/1975_2010/.

9. NHS Connecting for Health. *Office of Population, Censuses, and Surveys (OPCS) Classification of Interventions and Procedures Version 4.6 (April 2011)*: The Stationery Office.

10. *NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer*. National Comprehensive Care Network; 2014 [cited 2014 October 1]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94(446):496-509.

12. Briganti A, Spahn M, Joniau S, Gontero P, Bianchi M, Kneitz B, et al. Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. *Eur Urol* 2013;63(4):693-701.

13. Elliott SP, Johnson DP, Jarosek SL, Konety BR, Adejoro OO, Virnig BA. Bias due to missing SEER data in D'Amico risk stratification of prostate cancer. *The Journal of urology* 2012;187(6):2026-31.

14. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. *Eur Urol* 2011;60(5):920-30.

15. Chowdhury S, Robinson D, Cahill D, Rodriguez-Vida A, Holmberg L, Moller H. Causes of death in men with prostate cancer: an analysis of 50,000 men from the Thames Cancer Registry. *BJU Int* 2013;112(2):182-9.

16. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011;364(18):1708-17.

17. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367(3):203-13.

18. Gatta G, Capocaccia R, Coleman MP, Gloeckler Ries LA, Hakulinen T, Micheli A, et al. Toward a comparison of survival in American and European cancer patients. *Cancer* 2000;89(4):893-900.

19. Collin SM, Martin RM, Metcalfe C, Gunnell D, Albertsen PC, Neal D, et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncol* 2008;9(5):445-52.

Comparison of prostate cancer outcomes in England and US

Table 1: Patient demographics by country (n = 222,163).

	England	US	*p* value
	(n = 25,235)	**(n = 196,928)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	36,172 (18.4)	<0.001
2005	4,959 (19.7)	34,403 (17.5)	
2006	5,172 (20.5)	40,531 (20.6)	
2007	5,009 (19.9)	43,800 (22.2)	
2008	4,717 (18.7)	42,022 (21.3)	
Age group (%)			
35-59	3,620 (14.4)	56,399 (28.6)	<0.001
60-64	4,361 (17.3)	40,287 (20.5)	
65-69	6,104 (24.2)	42,439 (21.6)	
70-74	6,145 (24.4)	33,912 (17.2)	
75-79	5,005 (19.8)	23,891 (12.1)	
Ethnicity (%)			
White	17,924 (94.8)	154,077 (80.4)	<0.001
African/Caribbean	571 (3.0)	28,361 (14.8)	
Asian	318 (1.7)	8,638 (4.5)	
Other	105 (0.6)	626 (0.3)	
Missing	6,317	5,226	
Clinical tumour stage (%)			
cT1	9,374 (37.2)	72,407 (36.8)	<0.001
cT2	9,538 (37.8)	107,762 (54.7)	
cT3	5,577 (22.1)	15,482 (7.9)	
cT4	746 (3.0)	1,277 (0.7)	
Gleason score (%)			
2-6	10,909 (43.2)	99,661 (50.6)	<0.001
7	9,112 (36.1)	75,247 (38.2)	
8-10	5,214 (20.7)	22,020 (11.2)	
Modified NCCN risk (%)			
Low risk	6,151 (24.4)	45,045 (22.9)	<0.001
Intermediate risk	10,386 (41.2)	118,074 (60.0)	
High risk	8,698 (34.5)	33,809 (17.1)	
Treatment – all risk groups (%)			
No definitive therapy	15,583 (61.8)	45,113 (22.9)	<0.001
Definitive therapy	9,652 (38.2)	151,815 (77.1)	
Treatment – low risk (%)			
No definitive therapy	3,799 (61.8)	17,516 (38.9)	<0.001
Definitive therapy	2,352 (38.2)	27,529 (61.1)	
Treatment – intermediate risk (%)			
No definitive therapy	5,696 (54.8)	21,999 (18.6)	<0.001
Definitive therapy	4,690 (45.2)	96,075 (81.4)	
Treatment – high risk (%)			
No definitive therapy	6,088 (70.0)	5,598 (16.6)	<0.001
Definitive therapy	2,610 (30.0)	28,211 (83.4)	

cT = Clinical tumour stage

Comparison of prostate cancer mortality in England and the US

Table 2: All-cause mortality (ACM) and prostate cancer mortality (PCM) according to country of treatment and modified NCCN risk (n = 222,163).

	6 year All Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)		Model 2 (Model 1 and definitive therapy)	
Risk group	**US**	**England**	**Adj HR (95% CI)**	***p* value**	**Adj HR (95% CI)**	***p* value**
	n = 196,928	n = 25,235				
All risk groups	9.3%	18.5%	1.60 (1.52 to 1.68)	<0.001	1.03 (0.97 to 1.08)	0.336
Low risk	8.7%	10.3%	1.30 (1.15 to 1.48)	<0.001	1.06 (0.93 to 1.21)	0.397
Intermediate risk	7.6%	12.5%	1.44 (1.32 to 1.58)	<0.001	0.98 (0.90 to 1.08)	0.740
High risk	16.3%	31.8%	1.92 (1.78 to 2.06)	<0.001	0.99 (0.92 to 1.08)	0.863
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)**		**Model 2 (Model 1 and definitive therapy)**	
Risk group	**US**	**England**	**Adj SHR (95% CI)**	***p* value**	**Adj SHR (95% CI)**	***p* value**
All risk groups	2.4%	7.6%	1.88 (1.72 to 2.05)	<0.001	0.97 (0.88 to 1.07)	0.568
Low risk	0.9%	0.9%	1.57 (1.08 to 2.30)	0.018	1.31 (0.89 to 1.93)	0.169
Intermediate risk	1.4%	2.8%	1.71 (1.40 to 2.09)	<0.001	1.00 (0.81 to 1.23)	0.994
High risk	8.1%	18.8%	2.06 (1.87 to 2.28)	<0.001	0.96 (0.86 to 1.08)	0.537

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence Interval

~~Influence of~~Evaluating variation in use of definitive therapy ~~on~~ and risk-adjusted prostate cancer mortality in England and the US

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Abstract

Objectives: Prostate cancer mortality (PCM) in the US is amongst the lowest in the world, whereas PCM in England is amongst the highest in Europe. This paper aims to assess the influence of variation in use of definitive therapy on risk-adjusted PCM in England as compared to the US.

Design: Observational study

Setting: Cancer registry data from England and the US

Participants: Men diagnosed with non-metastatic prostate cancer (PCa) in England and the US between 2004 and 2008

Outcome measures: Competing-risks survival analyses to estimate sub-hazard ratios (SHR) of prostate cancer mortality adjusted for age, ethnicity, year of diagnosis, Gleason score (GS), and clinical tumor stage (cT).

Results: 222,163 men were eligible for inclusion. Compared to American patients, English patients were more likely to present at an older age (70-79 years: England 44.2%, US 29.3%, p<0.001), with higher tumour stage (cT3-4: England 25.1%, US 8.6%, p<0.001) and higher Gleason score (GS 8-10: England 20.7%, US 11.2%, p<0.001). They were also less likely to receive definitive therapy (England 38%, US 77%, p<0.001).

English patients were more likely to die of PCa (SHR 1.9, 95% confidence interval 1.7-2.0, p<0.001). However, this difference was no longer statistically significant when also adjusted for use of definitive therapy (SHR 1.0, 95% confidence interval 1.0-1.1, p=0.3).

Conclusions: Risk-adjusted PCM is significantly higher in England compared to the US. This difference may be explained by less frequent use of definitive therapy in England.

Word count: 236

Article summary

Strengths and limitations of this study:

- ~~Variation in prostate cancer management in England and the US provides an observational setting to study potential determinants of prostate cancer outcomes. We report the first risk-adjusted comparison of prostate cancer mortality in these two countries, to assess the influence of variation in use of definitive therapy.~~
- A key strength of this paper is the use of routinely collected data from hospital episode statistics linked to cancer registry data, providing a large dataset to make accurate estimates of relative prostate cancer mortality.
- Lack of PSA data and a relatively short follow-up period of 6 years are the key limitations of this study.

Background

Outcomes following a diagnosis of cancer vary markedly around the world. In the United States of America (US), cancer-related deaths have been demonstrated to be amongst the lowest. For example, US breast cancer mortality is 65% lower than the European average while death from colorectal cancer is 30% lower.[1] On the other hand, cancer mortality rates in England are amongst the highest in Europe.[2] The disparity in cancer outcomes appears greatest for prostate cancer for which 5-year mortality has been reported to be six times higher in England compared to the US.[1]

A number of disease and treatment-related factors may account for the observed variation in prostate cancer outcomes between the US and England. These include variation in policy concerning prostate cancer screening between the two countries together with variation in use of definitive prostate cancer therapy. Other factors that may be at play include the methods by which data on cancer diagnoses and cancer related deaths are both collected and processed.

In the US, the vast majority of men diagnosed with localized prostate cancer have definitive therapy, either by radical radiation therapy or radical surgery. For example, three quarters of men diagnosed with prostate cancer between 1988 and 2006 were reported to have undergone definitive therapy for their disease.[3] This figure compares to only about one third in England.[4 5]

We report differences in risk-adjusted prostate cancer mortality between the US and England. Furthermore, we investigate whether prostate cancer outcomes are related to the use of definitive therapy between the two countries. This study is part of a program of work assessing the value of procedure-specific and disease-specific

metrics derived from English hospital admission records to assess the performance of English National Health Service (NHS) providers.

Methods

Study design

We performed a population-based observational cohort study using patient-level cancer registry data from England and the US.

Data sources

Data collected by the eight regional cancer registries[6] for all men diagnosed with prostate cancer in England were linked to the Hospital Episodes Statistics (HES) database[7] and national mortality records provided by the Office for National Statistics.

The Surveillance, Epidemiology and End Results (SEER) database was used to identify American patients with prostate cancer from 18 regional cancer registries.[8] This database covers 28% of the US population and is linked to mortality data provided by the National Center for Health Statistics.

Participants

Men diagnosed with prostate cancer between 2004 and 2008, and aged between 35 and 80 years at the time of diagnosis were identified from both countries. The years 2004 to 2008 were selected as comparable English and American data were available for this period. Diagnosis of prostate cancer was confirmed using the 'C61'

International Classification of Diseases (ICD-10) diagnosis code in the HES and SEER databases. Follow-up data were available through to 16th April 2010 for the English cohort, and 31st December 2010 for the American cohort.

Patients were included if prostate cancer was histologically confirmed as their only primary malignancy. Patients with lymph node involvement or distant metastases were excluded, as they would not be candidates for primary definitive therapy. Where data on metastatic disease were missing, we considered the use of chemotherapy as a surrogate marker for metastases. Patients who underwent chemotherapy within 6 months of diagnosis were therefore also excluded. Twenty-one patients in the English dataset were noted to have negative survival data (i.e. date of diagnosis was chronologically after the date of death), and were therefore excluded. Those with missing data concerning pathological Gleason score (GS) or clinical tumour (cT) stage were excluded from the primary analysis, as they would not be amenable to risk stratification.

Variable definition

English patients were considered to have undergone definitive therapy if their HES record contained the 'M61' Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (4th revision) code[9] indicating radical prostatectomy within 1 year of diagnosis, or alternatively if their cancer registry record indicated the use of radiotherapy.

Patients from the SEER dataset were considered to have undergone definitive therapy if they underwent radical prostatectomy or radiation therapy as part of their first

course of therapy. American patients were considered to have undergone radical prostatectomy if they had undergone cancer-directed surgery, coded as any of the following: Radical/total prostatectomy, or Prostatectomy with resection in continuity with other organs/pelvic exenteration. All forms of radiotherapy were assumed to be definitive in nature, as treatment doses are not routinely recorded in the SEER or English cancer registries.

Risk stratification

Patients were classified into risk groups using a modified version of the National Comprehensive Cancer Network (NCCN) prostate cancer risk classification,[10] based on clinical tumour (cT) stage and Gleason score (GS). Risk groups were defined as follows: low risk (cT1 stage and GS 2-6), intermediate risk (cT2 stage or GS 7), and high risk (cT3-T4 stage or GS 8-10). Since prostate-specific antigen (PSA) levels are not recorded in the HES database or English cancer registries, this variable was not used for risk stratification in this study.

Outcome measurement

The cause of death amongst English patients was extracted from national mortality records provided by the Office for National Statistics, which were linked to cancer registry and HES data. Similarly, cause of death is routinely recorded as part of the SEER dataset for US patients. Where the cause of death was listed as the disease code for prostate cancer, C61, it was classified as a prostate cancer death.

Statistical analysis

Chi square test was used to compare proportions between the two countries. A Cox regression model was used to calculate adjusted hazard ratios (HRs) for all-cause mortality (ACM), comparing mortality in England and the US. Similarly, adjusted sub-hazard ratios (SHRs) were calculated for prostate cancer mortality (PCM) using a maximum likelihood competing risk regression model, according to the method of Fine and Gray.[11] Failure event for PCM was defined as death due to prostate cancer, while death due to a cause other than prostate cancer was defined as the competing event. All analyses were performed using STATA version 11 (StataCorp, College station, TX, USA).

All regression models were adjusted for age group, year of diagnosis, ethnicity, clinical tumour stage, and Gleason score (model 1). Next, the impact of variation in use of definitive therapy was assessed by additionally including use of definitive therapy in a separate regression model (model 2). Separate regression models were built to test for differences between the two countries for each individual risk group. This resulted in 20 regression models in total: 5 patient groups (all eligible patients, all patients with complete data, low, intermediate, and high risk) x 2 adjustment models (model 1 and model 2) x 2 outcomes (ACM and PCM).

Sensitivity Analysis

In order to investigate the influence of excluding patients for whom tumour stage and Gleason grade data were missing, we performed a sensitivity analysis where all eligible patients were included.

Role of Funding Source

The study benefited from a grant from the Academy of Medical Royal Colleges supporting a project assessing the value of procedure-specific and disease-specific metrics derived from routinely collected data to assess the performance of NHS providers. Sponsors were not involved in the study design; the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Results

Participants

Data were available on 328,182 men (111,917 from England and 216,265 from the US) of which 301,989 (97,079 from England and 204,910 from the US) met the selection criteria. Reasons for exclusion are described in Figure 1.

Complete data to enable risk stratification (i.e. cT stage and Gleason score) were available for 222,163 men (23,235 from England and 196,928 from the US). These data were used to undertake the primary analysis.

Men diagnosed with prostate cancer in England tended to be older and less ethnically diverse, to present with higher clinical tumour stage, and to have higher pathological Gleason scores (Table 1, Appendix 1), with each of these differences reaching statistical significance at $p < 0.001$. Amongst patients for whom complete data were available, men diagnosed with prostate cancer in England were more likely to present

with high-risk prostate cancer according to our modified NCCN criteria (34.5% in England and 17.2% in US, Table 1).

Men diagnosed with prostate cancer in England were less likely to receive definitive therapy (38.2% in England and 77.1% in US), and this difference was observed in all risk groups (Table 1).

Mortality

The median follow-up for the entire cohort was 43.3 months. Unadjusted 6-year ACM amongst English men was higher compared to American men (21.0% versus 9.6%). Similarly, unadjusted 6-year PCM amongst English men was also higher, as compared to American men (9.6% versus 2.6%). This trend was similar amongst patients with complete data, whose outcomes are described below (Table 2).

Primary analysis

The primary analysis was conducted using data from the 222,163 patients for whom clinical tumour stage and Gleason score were available, to allow risk stratification.

Unadjusted 6-year ACM amongst patients who had definitive therapy was 7.3% in England and 4.9% in the US. Corresponding ACM figures amongst those who did not have definitive treatment were 19.5% in England and 15.5% in the US. The greatest difference was observed in patients at high prostate cancer risk undergoing definitive treatment with a 6-year ACM of 15.1% in England and 8.1% in the US, with the smallest difference observed in patients with low-risk prostate cancer who did not undergo definitive therapy (9.5% in England and 9.9% in the US).

Unadjusted 6-year PCM amongst patients from all risk groups who underwent definitive therapy was 2.4% in England and 1.2% in the US. This compared to 8.8% amongst patients who did not receive definitive therapy in England and 4.5% in the US. Differences in unadjusted 6-year PCM were smallest amongst patients with low-risk disease undergoing definitive therapy (0.4% in England and 0.5% in the US), and greatest amongst patients with high-risk disease undergoing definitive therapy (7.6% in England and 3.7% in the US).

When comparing all patients with complete data amenable for risk stratification, following adjustment for age group, ethnicity, year of diagnosis, and tumour characteristics (model 1), significantly higher ACM (adjusted HR 1.60, 95% CI 1.52 to 1.68) and PCM (adjusted SHR 1.88, 95% CI 1.72 to 2.05) were found in England than in the US (Table 2). Within each of the three risk groups, with adjustment for patient and tumour characteristics (model 1), the greatest difference in ACM and PCM was noted amongst the intermediate-risk and high-risk patients (Table 42). PCM was not significantly different at 0.9% in both countries at six years amongst men with low-risk disease.

When treatment allocation was included in the multivariate model (model 2), no difference in ACM and PCM was noted between the US and England for all men (ACM: adjusted HR 1.03, 95% CI 0.97 to 1.08; PCM: adjusted SHR 0.97, 95% CI 0.88 to 1.07) or within each of the individual risk groups (Table 42).

Sensitivity Analysis

Multivariate analysis for the entire cohort of 301,989 patients, including patients for whom data regarding either clinical tumour stage or Gleason score were missing, revealed a similar trend (Appendix 2). Adjustment for age group, ethnicity and year of

diagnosis, revealed higher ACM (adjusted HR 2.19, 95% CI 2.13 to 2.26) and PCM (adjusted SHR 3.67, 95% CI 3.50 to 3.85) amongst English patients.

Additional adjustment for the use of definitive therapy appeared, in part, to account for variation in ACM (adjusted HR 1.55, 95% CI 1.50 to 1.59) and PCM (adjusted HR 2.37, 95% CI 2.25 to 2.50).

Discussion

Prostate cancer death in intermediate to high-risk cases is higher in England than it is in the US. When we adjusted for the different rates of definitive therapy in the two countries, the rates of prostate cancer death were similar. This suggests that the differences in mortality may be explained by a lower use of definitive therapy in England.

Methodological considerations

First, the English dataset contained a high proportion of missing data for clinical tumour stage and Gleason score. The high proportion of patients with missing data in the English dataset may be due to poor data capture. Excluded English patients tended to be older, to have more advanced disease, and they less frequently received definitive therapy (Appendix ~~1~~3). This limitation is unlikely to have had a marked influence on our results, as inclusion of these patients would have increased the observed difference in PCM noted between the two countries. Thus, these data provide a conservative estimate of the spread of prostate cancer risk amongst the

general English population. Nevertheless it is worthwhile to note that these are the only population-wide data currently available for comparing management of PCa in the two countries.

Furthermore, a sensitivity analysis was performed to investigate the influence of excluding patients with missing cT stage or Gleason score. This showed that PCM is significantly higher in England than the US, though this difference is partly explained upon additional adjustment for the variation in use of definitive treatment in the two countries. Due to the higher proportion of men with low or intermediate risk disease in the US, the variation in use of definitive treatment becomes more apparent upon risk stratification in our primary analysis.

Secondly, the SEER dataset did not contain information concerning patient comorbidity. We feel our findings remain valid despite this potential limitation as PCM is less strongly influenced by comorbid conditions than ACM.[12] In addition, there were also differences between England and the US in the PCM of young patients aged between 35 and 59 years who are least likely to have comorbid conditions at the time of diagnosis (adjusted SHR 2.66, 95% CI 1.99 to 3.56, $p<0.001$).

Thirdly, "lead time bias" could be an explanation for PCM being lower in the US than in the UK given that the uptake of PSA testing is much higher in the US, the effect of which is likely to be that men in the US are diagnosed with less advanced prostate cancer at an earlier age. In an attempt to minimise the effect of this limitation we adjusted for clinical stage at diagnosis and patient age at diagnosis together with Gleason score in our primary analysis.

Lastly, PSA levels were not available for English patients and therefore they could not be used to adjust the differences in PCM between England and the US. To investigate this limitation further, we evaluated if the inclusion of PSA into our risk stratification model resulted in significant re-categorisation of a patient's prostate cancer risk for the US patients. We found little movement between risk groups with, for example, only 7.4% US patients being re-classified as intermediate-risk having initially been assigned a low-risk status. Furthermore, Elliott et al have previously shown that while it is advantageous to have all three clinical variables (including PSA, cT stage and Gleason score) available for risk stratification, patients with high-risk disease can still be correctly identified even if one of these variable (such as PSA) is missing.[13]

Despite the above-mentioned limitations, routinely collected data provide a rich resource to explain performance of health care providers in different countries. However, differences in coding practices and differences in healthcare frameworks must be acknowledged.

Comparison with other studies

Mortality

PCM was found to be significantly higher in England compared to the US amongst men with intermediate and high-risk prostate cancer. In the current study, we used SEER data of men diagnosed between 2004 and 2008 and found that 6-year ACM was 9.3% and PCM 2.4%. A study using SEER data of men diagnosed between 1992 and 2005 found very similar figures (5-year ACM 14.3% and PCM 1.7%).[14]

Comparison of prostate cancer outcomes in England and US

Improvements in management of prostate cancer and other comorbidities may explain why our figures for ACM are slightly lower.

In comparison, our analysis of the English HES database found that 6-year ACM was 18.5% and PCM 7.6%. A study reporting outcome of 50,066 men diagnosed with prostate cancer in the London area between 1997 and 2006 with a median follow up of 3.5 years reported a PCM for men who had undergone definitive treatment of about 2%, which corresponds closely to the figures we found in this study.[15]

The only two relevant randomised controlled trials[16 17] demonstrated benefit of definitive therapy in patients with high-risk disease, which is consistent with the results of our study.

Differences between England and the US

A study using the EUROCARE and SEER registries including men diagnosed between 1985 and 1989 reported a 2.8 times relative excess risk of death amongst European men with prostate cancer compared to their American counterparts.[18] A more recent study using SEER data between 1975 and 2004 together with UK cancer mortality statistics found that age-adjusted PCM rates in the US were significantly lower than in England with the decline in PCM being 4.2% per year since the 1990s, a figure about four times higher than that reported for England.[19]

The investigators of both these studies suggested that difference in PCM between England and the US is the result of variation in disease burden brought about by the higher incidence of prostate cancer screening in the US. However, neither study adjusted for prostate cancer risk. In this study, we have identified for the first time

that irrespective of prostate cancer stage and Gleason score, prostate cancer outcomes in terms of ACM and PCM are better in the US than in England, which does not support the increased use of prostate cancer screening in the US as an explanation for the difference in prostate cancer mortality. Instead, our data suggest that the better prostate cancer outcome seen in the US may be due to the more frequent use of definitive treatment.

Clinical implication

The decision to offer definitive prostate cancer therapy is influenced by both disease characteristics and patient characteristics. As noted in our results, variations in healthcare systems have direct and indirect affects on both these factors. The expected survival benefit of definitive prostate cancer therapy must therefore also be balanced against the associated probability of side effects, including urinary incontinence and erectile dysfunction.

Our analysis suggests that prostate cancer mortality in England may be improved by an increase in the use of definitive treatment. This increase should be directed at men with intermediate and high-risk prostate cancer, as the differences in outcomes between England and the US for men with low-risk disease were very small. These results have to be interpreted in the context of differences between the two countries in the way prostate cancer is diagnosed, with higher uptake of PSA testing in the US.

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Ethical approval: Not required for this study.

Data sharing: No additional data available.

Declaration of transparency: AS and PJC affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

References

1. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). *Lancet Oncol* 2008;9(8):730-56.

2. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. *The lancet oncology* 2013.

3. Abdollah F, Sun M, Thuret R, Jeldres C, Tian Z, Briganti A, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. *Eur Urol* 2011;59(1):88-95.

4. Fairley L, Baker M, Whiteway J, Cross W, Forman D. Trends in non-metastatic prostate cancer management in the Northern and Yorkshire region of England, 2000-2006. *Br J Cancer* 2009;101(11):1839-45.

5. Lyratzopoulos G, Barbiere JM, Greenberg DC, Wright KA, Neal DE. Population based time trends and socioeconomic variation in use of radiotherapy and radical surgery for prostate cancer in a UK region: continuous survey. *BMJ* 2010;340:c1928.

6. *National Cancer Data Repository 1990-2010*. National Cancer Intelligence Network; [cited 2014 October 1]; Available from: http://www.ncin.org.uk/collecting_and_using_data/national_cancer_data_repository/.

7. *Hospital Episode Statistics*. [Website]: NHS Health and Social Care Information Centre; [cited 2014 October 1]; Available from: http://www.hesonline.nhs.uk/.

8. *Surveillance, Epidemiology, and End Results (SEER) Program 1975-2010*. [Website] Bethesda, MD: National Cancer Institute; [cited 2014 October 1]; Available from: http://seer.cancer.gov/csr/1975_2010/.

9. NHS Connecting for Health. *Office of Population, Censuses, and Surveys (OPCS) Classification of Interventions and Procedures Version 4.6 (April 2011)*: The Stationery Office.

10. *NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer*. National Comprehensive Care Network; 2014 [cited 2014 October 1]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American Statistical Association* 1999;94(446):496-509.

12. Briganti A, Spahn M, Joniau S, Gontero P, Bianchi M, Kneitz B, et al. Impact of age and comorbidities on long-term survival of patients with high-risk prostate cancer treated with radical prostatectomy: a multi-institutional competing-risks analysis. *Eur Urol* 2013;63(4):693-701.

13. Elliott SP, Johnson DP, Jarosek SL, Konety BR, Adejoro OO, Virnig BA. Bias due to missing SEER data in D'Amico risk stratification of prostate cancer. *The Journal of urology* 2012;187(6):2026-31.

14. Abdollah F, Sun M, Schmitges J, Tian Z, Jeldres C, Briganti A, et al. Cancer-specific and other-cause mortality after radical prostatectomy versus observation in patients with prostate cancer: competing-risks analysis of a large North American population-based cohort. *Eur Urol* 2011;60(5):920-30.

15. Chowdhury S, Robinson D, Cahill D, Rodriguez-Vida A, Holmberg L, Moller H. Causes of death in men with prostate cancer: an analysis of 50,000 men from the Thames Cancer Registry. *BJU Int* 2013;112(2):182-9.

16. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011;364(18):1708-17.

17. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med* 2012;367(3):203-13.

18. Gatta G, Capocaccia R, Coleman MP, Gloeckler Ries LA, Hakulinen T, Micheli A, et al. Toward a comparison of survival in American and European cancer patients. *Cancer* 2000;89(4):893-900.

19. Collin SM, Martin RM, Metcalfe C, Gunnell D, Albertsen PC, Neal D, et al. Prostate-cancer mortality in the USA and UK in 1975-2004: an ecological study. *Lancet Oncol* 2008;9(5):445-52.

Comparison of prostate cancer outcomes in England and US

Table 1: Patient demographics by country (n = 222,163).

	England	US	*p* value
	(n = 25,235)	**(n = 196,928)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	36,172 (18.4)	<0.001
2005	4,959 (19.7)	34,403 (17.5)	
2006	5,172 (20.5)	40,531 (20.6)	
2007	5,009 (19.9)	43,800 (22.2)	
2008	4,717 (18.7)	42,022 (21.3)	
Age group (%)			
35-59	3,620 (14.4)	56,399 (28.6)	<0.001
60-64	4,361 (17.3)	40,287 (20.5)	
65-69	6,104 (24.2)	42,439 (21.6)	
70-74	6,145 (24.4)	33,912 (17.2)	
75-79	5,005 (19.8)	23,891 (12.1)	
Ethnicity (%)			
White	17,924 (94.8)	154,077 (80.4)	<0.001
African/Caribbean	571 (3.0)	28,361 (14.8)	
Asian	318 (1.7)	8,638 (4.5)	
Other	105 (0.6)	626 (0.3)	
Missing	6,317	5,226	
Clinical tumour stage (%)			
cT1	9,374 (37.2)	72,407 (36.8)	<0.001
cT2	9,538 (37.8)	107,762 (54.7)	
cT3	5,577 (22.1)	15,482 (7.9)	
cT4	746 (3.0)	1,277 (0.7)	
Gleason score (%)			
2-6	10,909 (43.2)	99,661 (50.6)	<0.001
7	9,112 (36.1)	75,247 (38.2)	
8-10	5,214 (20.7)	22,020 (11.2)	
Modified NCCN risk (%)			
Low risk	6,151 (24.4)	45,045 (22.9)	<0.001
Intermediate risk	10,386 (41.2)	118,074 (60.0)	
High risk	8,698 (34.5)	33,809 (17.1)	
Treatment – all risk groups (%)			
No definitive therapy	15,583 (61.8)	45,113 (22.9)	<0.001
Definitive therapy	9,652 (38.2)	151,815 (77.1)	
Treatment – low risk (%)			
No definitive therapy	3,799 (61.8)	17,516 (38.9)	<0.001
Definitive therapy	2,352 (38.2)	27,529 (61.1)	
Treatment – intermediate risk (%)			
No definitive therapy	5,696 (54.8)	21,999 (18.6)	<0.001
Definitive therapy	4,690 (45.2)	96,075 (81.4)	
Treatment – high risk (%)			
No definitive therapy	6,088 (70.0)	5,598 (16.6)	<0.001
Definitive therapy	2,610 (30.0)	28,211 (83.4)	

cT = Clinical tumour stage

Comparison of prostate cancer mortality in England and the US

Table 2: All-cause mortality (ACM) and prostate cancer mortality (PCM) according to country of treatment and modified NCCN risk (n = 222,163).

	6 year All Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)		Model 2 (Model 1 and definitive therapy)	
Risk group	**US**	**England**	**Adj HR (95% CI)**	***p* value**	**Adj HR (95% CI)**	***p* value**
	n = 196,928	n = 25,235				
All risk groups	9.3%	18.5%	1.60 (1.52 to 1.68)	<0.001	1.03 (0.97 to 1.08)	0.336
Low risk	8.7%	10.3%	1.30 (1.15 to 1.48)	<0.001	1.06 (0.93 to 1.21)	0.397
Intermediate risk	7.6%	12.5%	1.44 (1.32 to 1.58)	<0.001	0.98 (0.90 to 1.08)	0.740
High risk	16.3%	31.8%	1.92 (1.78 to 2.06)	<0.001	0.99 (0.92 to 1.08)	0.863
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity, clinical tumour stage & Gleason score)**		**Model 2 (Model 1 and definitive therapy)**	
Risk group	**US**	**England**	**Adj SHR (95% CI)**	***p* value**	**Adj SHR (95% CI)**	***p* value**
All risk groups	2.4%	7.6%	1.88 (1.72 to 2.05)	<0.001	0.97 (0.88 to 1.07)	0.568
Low risk	0.9%	0.9%	1.57 (1.08 to 2.30)	0.018	1.31 (0.89 to 1.93)	0.169
Intermediate risk	1.4%	2.8%	1.71 (1.40 to 2.09)	<0.001	1.00 (0.81 to 1.23)	0.994
High risk	8.1%	18.8%	2.06 (1.87 to 2.28)	<0.001	0.96 (0.86 to 1.08)	0.537

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence Interval

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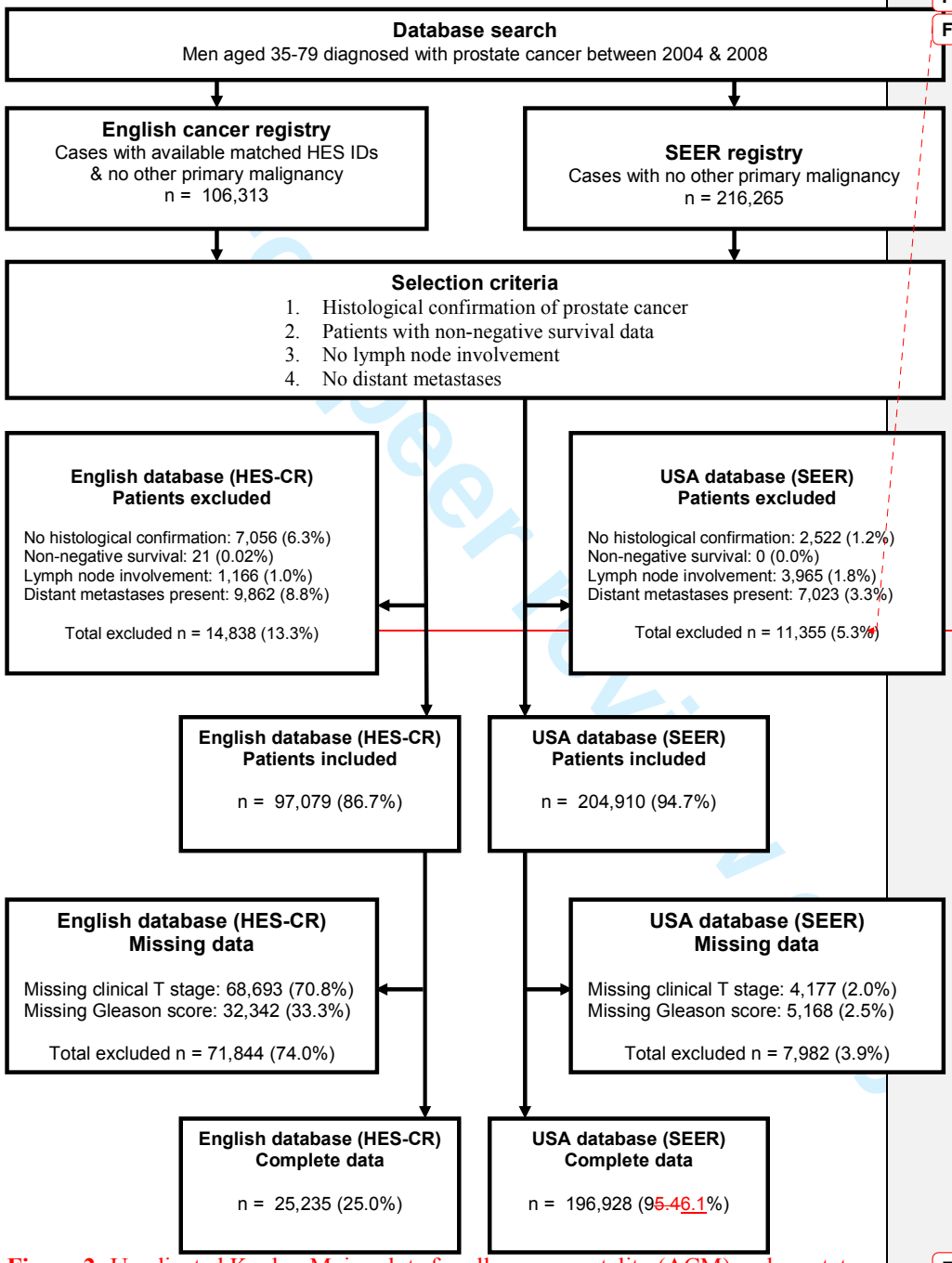
Comparison of prostate cancer outcomes in England and US

~~**Figure 1:** Study flow diagram~~



~~**Figure 2:** Unadjusted Kaplan-Meier plots for all-cause mortality (ACM) and prostate cancer mortality (PCM). Separate p-values are reported for regression models with (Model 1, p1) and without (Model 2, p2) the inclusion of definitive therapy.~~

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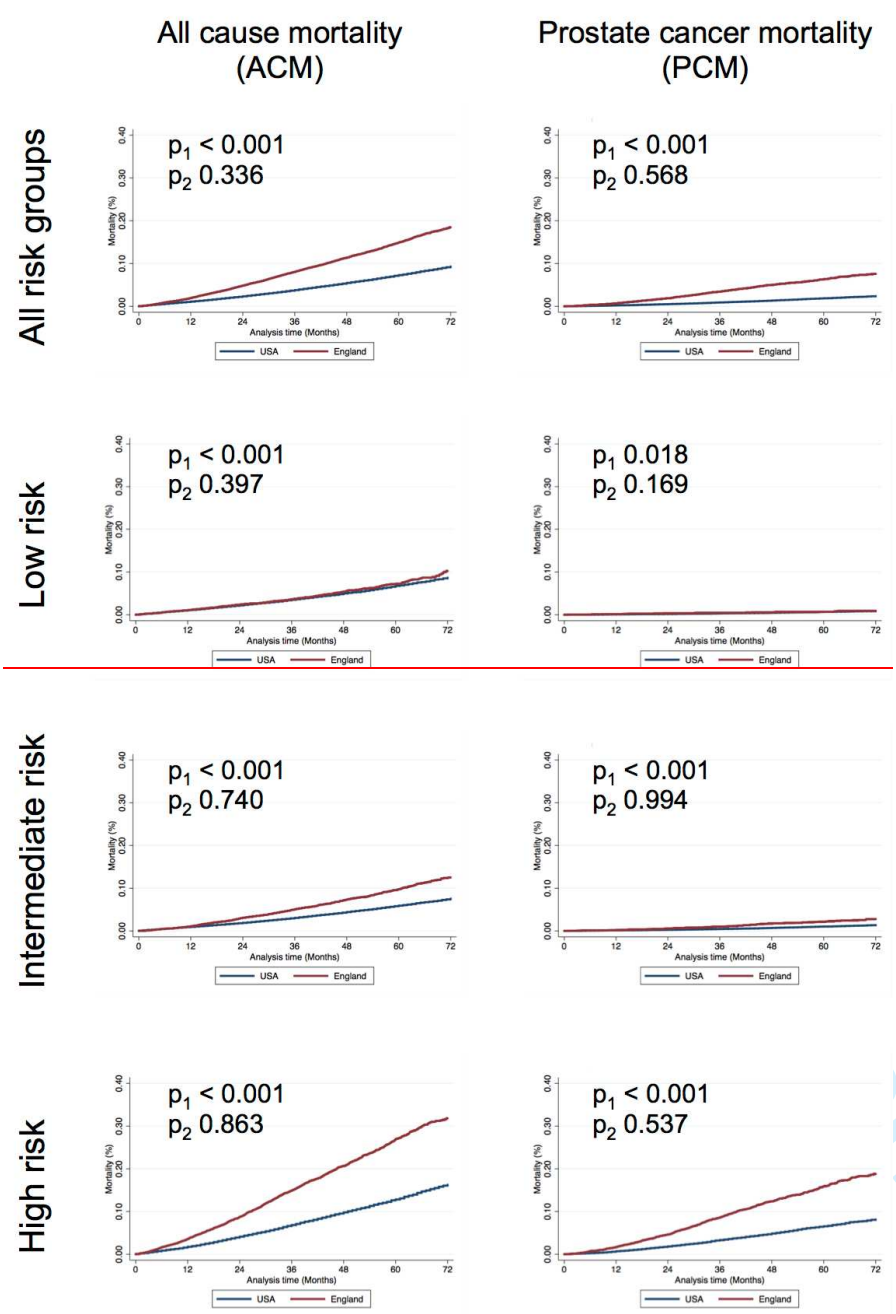
Comparison of prostate cancer mortality in England and the US



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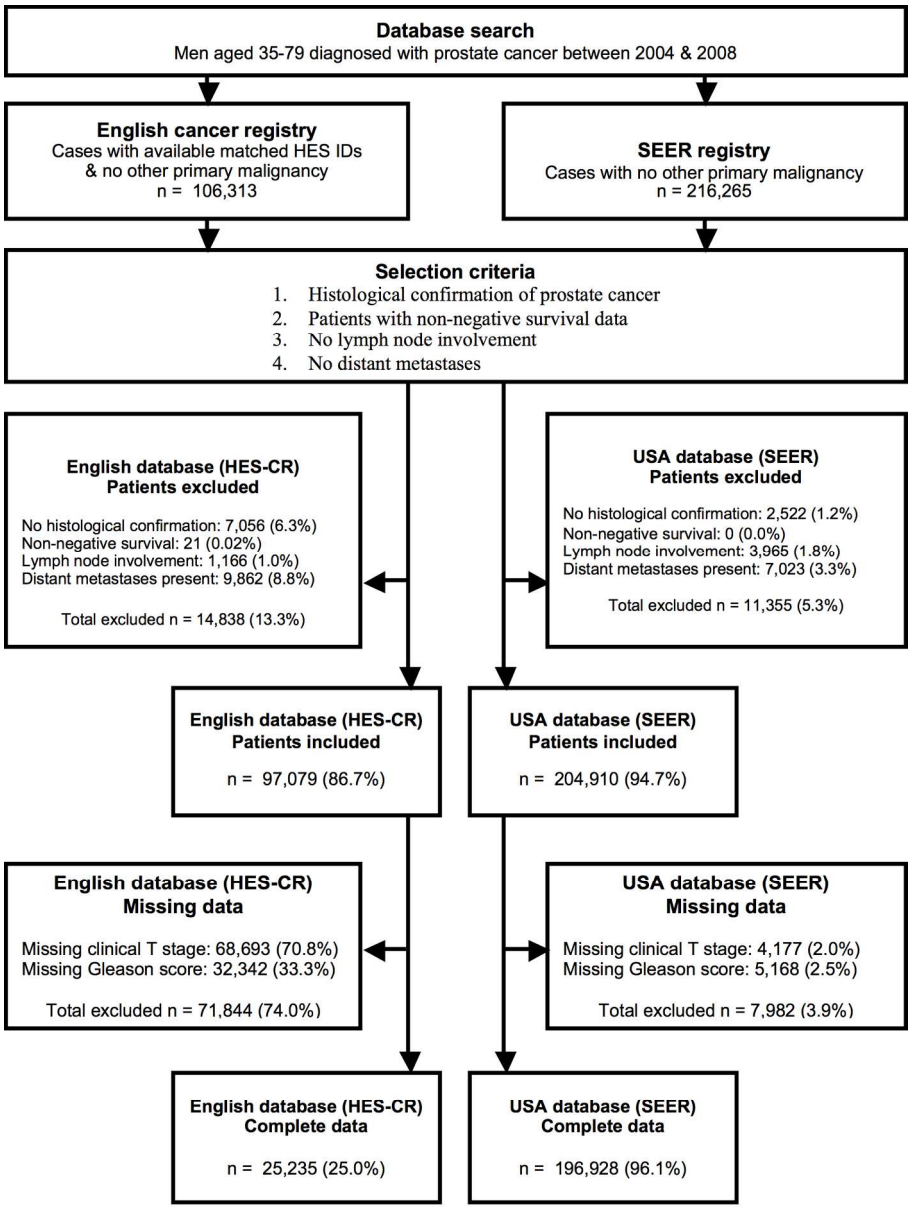

Figure 1: Study flow diagram
160x212mm (300 x 300 DPI)

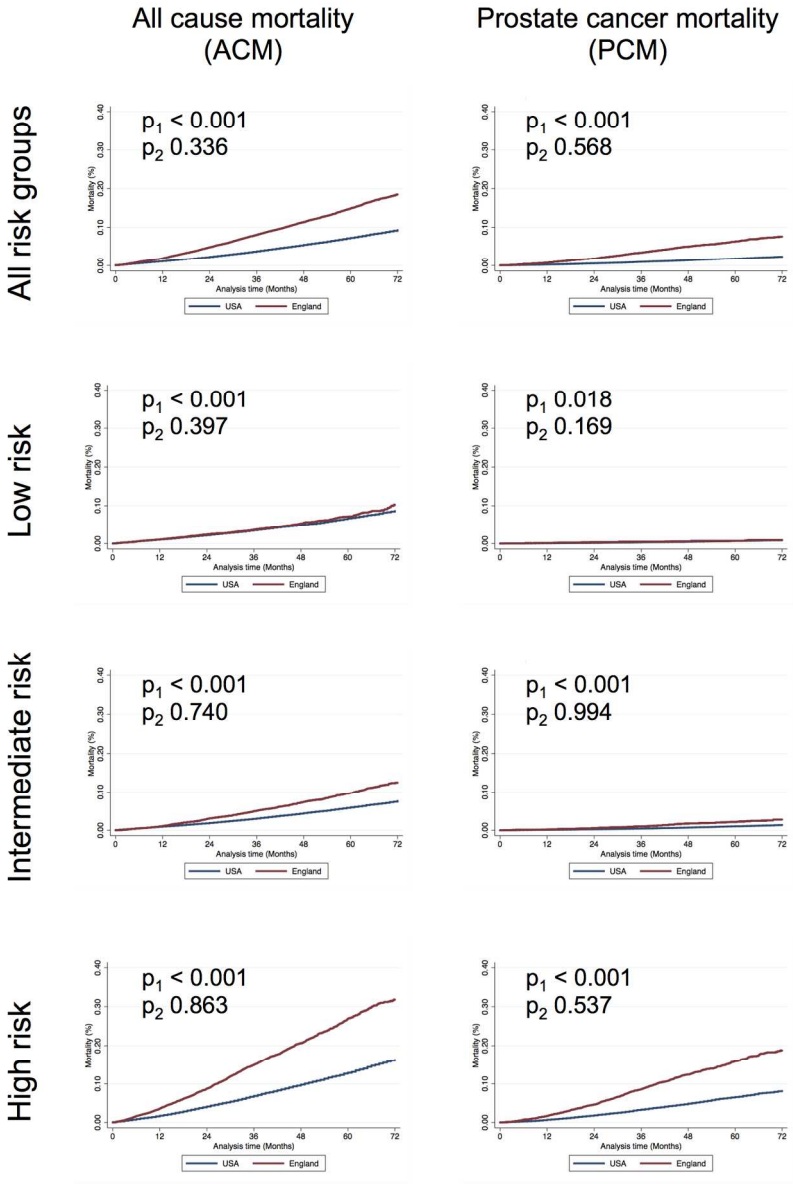

Figure 2: Unadjusted Kaplan-Meier plots for all-cause mortality (ACM) and prostate cancer mortality (PCM). Separate p values are reported for regression models with (Model 1, p1) and without (Model 2, p2) the inclusion of definitive therapy.
145x216mm (300 x 300 DPI)

Appendix 1: Sensitivity analysis. Demographic and disease characteristics of all eligible patients by country (n = 328,182).

	England	US	*p* value
	(n = 97,079)	**(n = 204,910)**	
Year of diagnosis			
2004	18,883 (19.5)	37,686 (18.4)	<0.001
2005	18,392 (19.0)	35,656 (17.4)	
2006	19,847 (20.4)	41,938 (20.5)	
2007	20,061 (20.7)	45,612 (22.3)	
2008	19,896 (20.5)	44,018 (21.5)	
Age group			
35-59	13,593 (14.5)	57,992 (28.9)	<0.001
60-64	16,643 (17.8)	41,601 (20.7)	
65-69	22,782 (24.3)	44,116 (22.0)	
70-74	23,565 (25.1)	35,612 (17.7)	
75-79	17,139 (18.3)	21,592 (10.8)	
Ethnicity			
White	68,618 (93.8)	159,399 (80.4)	<0.001
African/Caribbean	2,796 (3.8)	29,362 (14.8)	
Asian	1,343 (1.8)	8,983 (4.5)	
Other	430 (0.6)	654 (0.3)	
Missing	23,892	6,512	
Clinical tumour stage			
cT1	10,331 (36.4)	74,169 (37.0)	<0.001
cT2	10,779 (38.0)	109,680 (54.6)	
cT3	6,421 (22.6)	15,562 (7.8)	
cT4	855 (3.0)	1,322 (0.7)	
Missing	68,693	4,177	
Gleason score			
2-6	28,119 (43.4)	101,123 (50.6)	<0.001
7	23,527 (36.3)	76,049 (38.1)	
8-10	13,091 (20.2)	22,570 (11.3)	
Missing	32,342	5,168	
Use of definitive therapy			
No definitive therapy	63,716 (65.6)	51,100 (24.9)	<0.001
Definitive therapy	33,363 (34.4)	153,810 (75.1)	

Appendix 2: Sensitivity analysis. Relative all-cause mortality (ACM) and prostate cancer mortality (PCM) of all eligible patients according to country (n = 328,182).

	6 year All-Cause Mortality (ACM)		Model 1 (Age at diagnosis, year of diagnosis, ethnicity)		Model 2 (Model 1 and definitive therapy)	
	US	**England**	**Adj HR (95% CI)**	***p* value**	**Adj HR (95% CI)**	***p* value**
All patients	n = 204,910 9.6%	n = 97,079 21.0%	2.19 (2.13 to 2.26)	<0.001	1.55 (1.50 to 1.59)	<0.001
	6 year Prostate Cancer Mortality (PCM)		**Model 1 (Age at diagnosis, year of diagnosis, ethnicity)**		**Model 2 (Model 1 and definitive therapy)**	
	US	**England**	**Adj SHR (95% CI)**	***p* value**	**Adj SHR (95% CI)**	***p* value**
All patients	2.6%	9.6%	3.67 (3.50 to 3.85)	<0.001	2.37 (2.25 to 2.50)	<0.001

Adj HR = Adjusted Hazard Ratio, Adj SHR = Adjusted Sub-Hazard Ratio, CI = Confidence interval

Appendix 3: Comparison of demographic and disease characteristics of all eligible included and excluded English patients. Patients with either missing clinical tumour stage or missing Gleason score were classified as "excluded patients".

	Included patients	Excluded patients	*p* value
	(n = 25,235)	**(n = 71,844)**	
Year of diagnosis (%)			
2004	5,378 (21.3)	13,505 (18.8)	<0.001
2005	4,959 (19.7)	13,433 (18.7)	
2006	5,172 (20.5)	14,675 (20.4)	
2007	5,009 (19.9)	15,052 (21.0)	
2008	4,717 (18.7)	15,179 (21.1)	
Age group (%)			
35-59	3,620 (14.4)	9,973 (13.9)	<0.001
60-64	4,361 (17.3)	12,282 (17.1)	
65-69	6,104 (24.2)	16,678 (23.2)	
70-74	6,145 (24.4)	17,420 (24.3)	
75-79	5,005 (19.8)	15,491 (21.6)	
Ethnicity (%)			
White	17,924 (94.8)	50,694 (93.4)	<0.001
African/Caribbean	571 (3.0)	2,225 (4.1)	
Asian	318 (1.7)	1,025 (1.9)	
Other	105 (0.6)	325 (0.6)	
Missing	*6,317*	*17,575*	
Socio-economic quartile			
1	6,262 (24.9)	17,588 (24.5)	<0.001
2	6,101 (24.2)	16,975 (23.7)	
3	5,392 (21.4)	14,693 (20.5)	
4	4,073 (16.2)	12,023 (16.8)	
5	3,363 (13.4)	10,409 (14.5)	
Missing	44	156	
Charlson co-morbidity index			
0	11,261 (44.6)	33,914 (47.2)	<0.001
1	11,761 (46.6)	30,861 (43.0)	
2 or more	2,213 (8.8)	7,069 (9.8)	
Clinical tumour stage			
cT1	9,374 (37.2)	957 (30.37)	<0.001
cT2	9,538 (37.8)	1,241 (39.4)	
cT3	5,577 (22.1)	844 (26.8)	
cT4	746 (3.0)	109 (3.5)	
Missing	0	68,693	
Gleason score			
2-6	10,909 (43.2)	17,210 (43.6)	0.083
7	9,112 (36.1)	14,415 (36.5)	
8-10	5,214 (20.7)	7,877 (19.9)	
Missing	0	32,342	
Treatment (%)			
No definitive therapy	15,583 (61.8)	48,133 (67.0)	<0.001
Definitive therapy	9,652 (38.3)	23,711 (33.0)	

STROBE Statement—checklist of items that should be included in reports of observational studies

Evidence of inclusion of checklist items is provided as relevant page numbers in the last column.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**2**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**
Methods			
Study design	4	Present key elements of study design early in the paper	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**5, 6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**5, 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**6, 7**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**5**
Bias	9	Describe any efforts to address potential sources of bias	**7, 8**
Study size	10	Explain how the study size was arrived at	**9, 22**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**7**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**8**
		(*b*) Describe any methods used to examine subgroups and interactions	**8**
		(*c*) Explain how missing data were addressed	**8**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**8**
		(*e*) Describe any sensitivity analyses	**8**

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**9, 22**
		(b) Give reasons for non-participation at each stage	**9, 22**
		(c) Consider use of a flow diagram	**22**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**20**
		(b) Indicate number of participants with missing data for each variable of interest	**22**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	**10**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	**10**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**-**
		Cross-sectional study—Report numbers of outcome events or summary measures	**-**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**10**
		(*b*) Report category boundaries when continuous variables were categorized	**6, 7, 20**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**-**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**11, 12**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**12**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**12, 13, 14**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**16**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**14, 15**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**9**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.