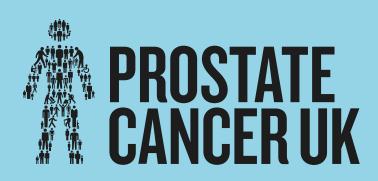
The characteristics of men who die of Prostate Cancer: An Evidence Review of Prostate Cancer Mortality

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Introduction

Prostate cancer is the third most common cause of cancer death in the UK and accounts for more than 12,000 deaths a year. As such, prostate cancer deaths account for 14% of all male cancer deaths in the UK from 2017-2019 (1). When compared to 31 European countries in 2018, the UK had the 9th highest mortality rate from prostate cancer, affecting 40 in every 100,000 men, compared to the European average of 33 deaths in every 100,000 (2). Prostate cancer mortality also differs between the UK nations, as shown in **Table 1** below.

Table 1 Prostate Cancer Age Standardised Mortality Rate in the UK Nations

Nation	Year	Age Standardised Mortality Rate per 100,000 men
England	2021	43.0 (3)
Wales	2021	41.7 (4)
Northern Ireland	2021	43.6 (5)
Scotland	2021	48.3 (6)

Evidence Gaps

Despite being a common cause of cancer death, there remains a significant evidence gap in our understanding of prostate cancer mortality. Perhaps the biggest questions pertain to who is affected by prostate cancer mortality and why. In the pursuit of understanding who is affected by prostate cancer mortality, it is imperative to identify (a.) the characteristics of this population, and (b.) whether there is any association between these characteristics and risk of prostate cancer mortality. Fulfilling this evidence gap could help inform preventative measures and/or further research that could help reduce prostate cancer mortality.

Prostate Cancer Mortality & Age at Diagnosis

Several studies have found a correlation with older age at diagnosis and an increased likelihood of prostate cancer death. This includes a population-based retrospective cohort study by Clark et al., 2022 that evaluated the association of prostate cancer mortality and age at diagnosis using U.S. Surveillance, Epidemiology, and End Results (SEER) data. 116,796 men (of which 12.5% were Black) were diagnosed between 1992 and 1997 and were assessed with a 25-year of follow-up. A total of 92,590 died, of which 18.7% died of prostate cancer-specific mortality (PCSM). The study found that prostate cancer-specific mortality increased with age at diagnosis. The mean annual prostate cancer-specific mortality rate 20 years after diagnosis was 0.9% for men diagnosed under 60, 1.2% for men diagnosed aged 60-70, and 2.1% for men diagnosed aged 70 or above. This study had the limitations of potential misclassification of high-grade prostate cancer with updates to the Gleason scoring system, the wider adoption of PSA testing, and the evolution of the diagnostic pathway (i.e. 6-core biopsy) (7).

Pettersson et al., 2018 conducted a similar cohort study using data from the National Prostate Cancer Register of Sweden. Of the cohort that included 121,392 men, 19% (23,649) men died of prostate cancer. Pettersson et al found that old age at diagnosis was associated with higher risk of prostate cancer death after adjusting for cancer characteristics, primary treatment, year of diagnosis, mode of detection, and comorbidity. Conversely to radical prostatectomy, deferred treatment, or ADT, old age was not associated with a higher risk of PCSM for men treated with radiotherapy. This study concluded that old men with prostate cancer receive insufficient diagnostic care and curative treatment (8).

A third study by MacKintosh et al., 2016 evaluated data from the U.S.'s Veterans Administration to determine the risk of prostate cancer death according to age and PSA level at diagnosis. They assessed a cohort of 24,142 men who died from PCSM between 1999 and 2009. 77% of the prostate cancer deaths occurred in men diagnosed at age 70-89. They determined that PSA and age at diagnosis are strong independent predictors of PCSM when compared to no cancer death but are more predictive in comparison. The limitations of this study include not controlling for treatment and other variables, not recording if the purpose of PSA testing was screening or diagnostic in nature, and a short follow up of 3.7 years (9).

Prostate Cancer Mortality & Age at Mortality

There is a clear association between prostate cancer mortality and age at mortality. According to Cancer Research UK, 75% of prostate cancer deaths occur in men aged 75 and over, based on 2017–2019 UK data (10).

Because older men have a higher risk of prostate cancer death, the years of life lost (YLL) due to prostate cancer is not as high as other common cancers. The average YLL for prostate cancer using UK data from 2013-2017 was 9.1 as opposed to a 17.2 average YLL for breast cancer, or 14.1 average YLL for lung cancer. For further comparison, Prostate cancer mortality made up 13% of all cancer mortality in males in the UK from 2013-2017, but only 9% of all YLL in males in the same period (11).

Despite the majority of prostate cancer deaths attributed to older men, there remains a percentage of younger men who die from prostate cancer as well. Prostate cancer in younger men is sometimes referred to as 'early onset prostate cancer'.

Prostate Cancer Mortality & Stage of Prostate Cancer at Diagnosis

The association between stage and grade at diagnosis and prostate cancer mortality is less clear. Understanding whether late diagnoses lead to prostate cancer mortality could elucidate key information, such as the course of disease progression. There have been a few studies that have retrospectively evaluated prostate cancer deaths to assess the stage of cancer at diagnosis.

Roy and Morgan et al., 2019 conducted a population-based study using data from the U.S. SEER database with the aim of characterising men who die of prostate cancer, focusing on risk group distribution. The study included data from men who had been diagnosed with prostate cancer between 1990 and 2015. Data for the risk group and cause of death was available for 635,733 patients. After the median follow-up of 83 months, 29% of the cohort (187,358 patients) had died, and 30% of this cohort (55,128 patients) had died from prostate cancer. From the cohort of men who died, the risk group distribution was as follows: 3.9% low-risk localised, 29.4% intermediate-risk localised, 40.9% high-risk localised, 3.2% node-positive, and 22.8% M1. Some study limitations to consider is the incomplete risk stratification information for 22% of patients and the potential for misclassification bias that arises from risk stratification based on TNM and biopsy grade before 2004 as opposed to PSA and Gleason score, among other reasons (12).

Another important study is that by Lycken et al., 2022 which also aimed to understand the diagnostic characteristics of men who died from prostate cancer. Lycken et al., 2022 evaluated data from 54, 645 men that died from prostate cancer between 1992 and 2016 as reported in the Swedish Cancer Registry. The study assessed the risk group distribution of men that died from prostate cancer over time between 1992 and 2016. They found that from the men who died of prostate cancer, 34% and 48% were diagnosed with localised disease in 1992 and 2016. The rate of distant metastases in 1992 and 2016 were 56% and 42%, respectively (13).

Helgstrand et al., 2017 also executed a population-based study investigating the diagnostic characteristics of 19, 487 men who died from prostate cancer between 1995 and 2013 as recorded within the Danish Prostate Cancer Registry. Of this cohort, 46.9% has metastatic disease, 16.8% had locally advanced/lymph node positive disease, and 36.3% had localised disease at diagnosis. The median age of men diagnosed with localised disease at diagnosis was 75.1 years (14).

Andersen et al., 2022 also assessed the Danish Registry of Causes of Death (RCOD) to evaluate the characteristics of men who died of prostate cancer-specific death between 2007 and 2016. A total of 8325 men died of prostate cancer-specific death, with 35.5% diagnosed with localised disease, 29% diagnosed with locally advanced disease, and 35.5% with metastatic disease. Overall, two thirds of men (65%) of these men had advanced disease. Limitations of this study include risk of overestimation of prostate cancer as the primary cause of death, and lack of recording co-morbidities and treatments, among others (15).

Parmi et al., 2020 evaluated the characteristics from 1,256 men who died of prostate cancer as reported within the BC Cancer database. The data shows that within this cohort, 32% presented with metastatic disease, 3% presented as regional (node positive), 29% presented with localised high risk, 9% presented with localised intermediate risk, 4% with localised low risk, 6% presented with localised not otherwise specified, and 7% with unknown. Overall, 80.3% of these patients were diagnosed with localised high-risk, regional, or metastatic disease at diagnosis. Limitations of this study include small patient numbers, and the data being collected from a time before docetaxel or abiraterone were adopted for the metastatic castration sensitive setting (16).

Finally, Mensah et al., 2023 evaluated data between 2013-2022 of 234 men who died of prostate cancer within a tertiary hospital in Ghana. 81.7% of the patients presented with metastatic stage cancer at diagnosis. 8.10% presented with localised disease, and 9.4% presented with locally advanced disease. Overall, 80% of patients presented with advanced stage disease at diagnosis. Mensah et al reflects on the surprising result of patients presented with localised disease that died despite receiving curative treatment (radical prostatectomy, brachytherapy, or external beam radiotherapy). They stipulate that inadequate local treatment, or undetected metastatic deposits may be the culprit for this alarming statistic. Limitations and considerations of this study include the small patient numbers and potential bias towards shorter survival duration, as these medical records are more likely to be complete. In addition, Ghana has a different diagnostic and treatment pathway than Western countries (17).

The evidence above shows alarming rates of prostate cancer deaths that were originally diagnosed as localised or locally advanced disease. This contradicts the idea that late diagnosis is to blame for all prostate cancer deaths. The cause for this trend is unclear and may hint at weaknesses in diagnostic and treatment pathways. The experts on the studies mentioned above have formed hypotheses on why this trend is observed. Helgstrand et al., 2017 attribute the prostate cancer deaths in men presenting with localised disease as 'old and harbouring [ing] aggressive tumours (14).' Lycken et al., 2022 pointed out that the number of prostate cancer deaths presenting with localised diagnosis increased during the study period (1992–2016) and highlighted a clinical need to identify markers which can signal to localised disease that needs aggressive treatment (13). Finally, Andersen et al mentions the conservative treatment guideline which dictate, that curative treatment is recommended only to men with at least 10 years of life expectancy, meaning treatment was not offered to men above the age of 70. Therefore, older men diagnosed with localised prostate cancer may have been under-treated (15).

Table 2 Studies evaluating stage at diagnosis in cohorts of men with PCSM

Study	Cohort	Localised	Locally advanced/ node positive	Metastatic
Helgstrand et al., 2017	Danish Prostate Cancer Registry (1995-2013) N=19,487	36.3%	16.8%	46.9%
Roy & Morgan., 2019	SEER (1990-2015) N= unknown	3.9% LRL 29.4% IRL 40.9% HRL	3.2%	22.8%
Andersen et al., 2022	Danish Prostate Cancer Registry (2007- 2016) N= 8,325	35.5%	29%	35.5%
Lycken et al., 2022	Swedish Cancer Registry (1992-2016) N=56,645	34% (1992) 48% (2016)	-	[Distant Metastases] 56% (1992) 42% (2016)
Parimi et al., 2020	British Columbia Cancer Databases (2013- 2015) N=1,256	4% LRL 9% IRL 39% HRL 6% localised (not otherwise specified)	3%	32%
Mensah et al., 2023	Medical records at a tertiary hospital in Ghana N=234	8.1%	9.4%	81.7%

Prostate Cancer Mortality & Deprivation

It is unclear whether there is a causal link between deprivation and prostate cancer mortality, as there are many confounding factors (various socioeconomic factors, access to health services, patient characteristics, etc). However, a similar trend of data showing an increased prostate cancer mortality rate in more deprived areas is seen in England, Scotland, and Wales.

According to NHS England's 'Cancer Registration Statistics, England 2020', the prostate cancer mortality rate was 14% higher for people living in the most deprived areas compared to the least deprived areas (18).

A 2017 report from the NHS National Services Scotland, in collaboration with Macmillan Cancer Support found that people living in the most deprived areas were found to have a 98% higher risk of death from prostate cancer than those in the least deprived. When this model is adjusted to include factors such as patient characteristics, tumour and health services, and treatments, the excess risk of death from prostate cancer was found to be 21% higher in the most deprived compared to the least deprived (19).

Public Health Wales reported that the prostate cancer mortality rate gap between the most and least deprived was small in 2022. The age-standardised prostate cancer mortality was highest in the next most deprived areas (as opposed to the most deprived) with a rate of 50.9 per 100,000 persons (20).

CRUK reports that prostate cancer mortality rates are 11% higher in the most deprived quantile compared with the least in the UK, and that 740 deaths annually are associated with deprivation (10).

Prostate Cancer Mortality & Ethnicity

Prostate cancer mortality affects Black men differently than white men. In England, Black men have twice the lifetime risk of dying from prostate cancer, with a 1 in 12 chance compared to a 1 in 24 chance that white men have. The data also shows that Black men have a higher age-standardised mortality rate (ASMR) regardless of minor ethnic group. According to 2017–2019 England & Wales Office for National Statistics Data on ASMR for prostate cancer in males stratified by age and ethnicity, the ASMR for Black African, Black Caribbean, and Black Other for men aged 65 and older was 267.6, 380.6, and 304.3. For comparison, the ASMR for white men was 229.5. The ASMR for other ethnicity groups such as Asian, Indian, and Mixed, was lower than that of white men (21). However, it is important to note that once diagnosed, Black men and white men have the same likelihood of dying from prostate cancer (22).

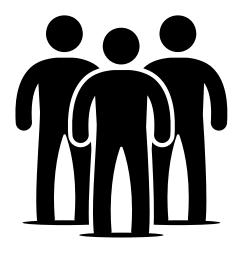
Time between Diagnosis and Prostate Cancer Mortality

The time between a diagnosis of prostate cancer and a prostate cancer specific mortality can vary depending on several factors (stage at diagnosis, disease aggressiveness, age, etc.) Certain studies have evaluated these criteria. The Lycken et al., 2022 study mentioned prior also investigated the 'disease duration', defined as the time between prostate cancer diagnosis and death. Using the Swedish Cancer Registry database to identify men who died from prostate cancer between 1992 and 2016, they found that the median disease duration in 1992 was 3.3 years, and 5.9 years in 2016 (13).

Clark et al., 2022 investigated the time to death of a U.S. SEER cohort of men diagnosed with prostate cancer between 1992 and 1997. Of the total 21, 896 men who died of prostate cancer, the median time to death was 5 years. For men diagnosed under 60 years of age, the median time from diagnosis to death was 7.5 years. For men aged between 60 to 70, the time to death was 7.8 years. Finally, the time to death for those aged 70 and up was 4.8 years. Of the entire cohort, 69.3% of the deaths occurred in the first ten years, and 30.7% occurred after ten years (7). The limitations of this study are mentioned above in the 'Prostate Cancer Mortality & Age at Diagnosis' section.

According to the Mensah et al., study mentioned prior in this report, 51.3% of this Ghanaian cohort of men died within 24 months of diagnosis, 23% between 2-5 years after diagnosis, and 25% survived over 5 years. It's important to bear in mind that 80% of this cohort originally presented with advanced disease (17). Andersen et al., a study also mentioned prior in this report, also had an endpoint of measuring time to death from diagnosis in a Danish cohort of men. They found the predicted time from diagnosis to death increased from 3.1 years in 2007 to 6.2 years in 2016. In this case, 35.5% of the cohort of men that died of PCSM had metastatic disease at diagnosis 2016 (15).

As we can see from these studies, the time between diagnosis and time of death will vary depending on stage at diagnosis, diagnostic pathway, national differences in healthcare, and age of patient, among other interrelated factors.



Prostate Cancer Mortality & Obesity

Several studies have sought to determine whether there is an association between obesity and risk of prostate cancer mortality. A prospective analysis and meta-analysis by Perez-Cornago et al., 2022 evaluated the relationship between adiposity and prostate cancer mortality. Perez-Cornago et al., 2022 assessed data from 218,237 men as reported within the UK Biobank over an average of 11.6 year follow-up, of which 661 men died from prostate cancer. The evidence showed that the hazard ratio for prostate cancer death was 1.07 per 5kg/m2 higher BMI, 1.00 per 5% increase in total body fat percentage, and 1.06 per 10cm increase in waist circumference. The results suggested that men with higher adiposity could have a higher risk of dying from prostate cancer than men with a healthy weight, although more research is needed to disentangle all the confounding factors. Limitations of this study include potential selection bias (lack of representation of whole UK population, potential confounding such as co-morbidities, etc., potential misclassification of cause of death, and a small sample size of 661 deaths. The authors were also unsure if the increased risk of prostate cancer mortality was due to biological reasons or cancer detection (23).

A systematic review and meta-analysis by Riviera-Izquierdo et al., 2021 aimed to determine if obesitywas a prognostic factor for mortality. 59 analyses were included for evaluation. The evidence presented found that a BMI >30 was associated with prostate cancer-specific mortality and all-cause mortality compared with a healthy weight, and that there was a dose-response relationship between mortality outcomes with every 5kg/m2 unit increase in BMI. According to the Bradford Hill principles of causation, the evidence shows moderate strength of association, consistency, temporality, dose-response gradient, biological plausibility, and analogy (24).

Another resource is the 2018 'Diet, nutrition, physical activity and prostate cancer' report by the World Cancer Research Fund. This report discusses 12 studies with dose-response meta-analysis that found a 11% higher risk of prostate cancer mortality per 5kg/m2 in BMI (25).

Conclusions

In summary, there are a few patient characteristics with well-evidenced associations with prostate cancer-specific mortality. For example, Black men are twice as likely to die from prostate cancer if undiagnosed. This review highlights concerning rates of prostate cancer mortality among men diagnosed with non-metastatic prostate cancer, challenging the common assumption that the majority of men who die from prostate cancer are initially diagnosed with metastatic disease. Additionally, our findings suggest a potential association between prostate cancer mortality and factors such as socioeconomic deprivation and obesity; however, these relationships remain insufficiently understood and require further investigation. Understanding the characteristics of men who die from prostate cancer is paramount to our understanding of the disease at large and to guiding the development of strategies to reduce prostate cancer mortality.

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