Prostate cancer incidence and mortality in Europe and implications for screening activities: population based study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2024;386:e077738 http://dx.doi.org/10.1136/bmj-2023-077738

Accepted: 04 July 2024

ABSTRACT

OBJECTIVE

To provide a baseline comparative assessment of the main epidemiological features of prostate cancer in European populations as background for the proposed EU screening initiatives.

DESIGN

Population based study.

SETTING

26 European countries, 19 in the EU, 1980-2017. National or subnational incidence data were extracted from population based cancer registries from the International Agency for Research on Cancer's Global Cancer Observatory, and mortality data from the World Health Organization.

POPULATION

Men aged 35-84 years from 26 eligible countries.

RESULTS

Over the past decades, incidence rates for prostate cancer varied markedly in both magnitude and rate of change, in parallel with temporal variations in prostate specific antigen testing. The variation in incidence across countries was largest around the mid-2000s, with rates spanning from 46 (Ukraine) to 336 (France) per 100 000 men. Thereafter, incidence started to decline in several countries, but with the latest rates nevertheless remaining raised and increasing again in the most recent quinquennium in several countries. Mortality rates during 1980-2020 were much lower and less variable than incidence rates, with steady declines in most countries and lesser temporal differences between countries. Overall, the up to 20-fold variation in prostate cancer incidence contrasts with a corresponding fivefold variation in mortality. Also, the inverse U-shape of the age specific curves for incidence contrasted with the mortality pattern, which increased progressively with age. The difference between the highest and lowest incidence rates across countries ranged from 89.6 per 100 000 men in 1985 to 385.8 per 100 000 men in 2007, while mortality rates across countries ranged from 23.7 per 100 000 men in 1983 to 35.6 per 100 000 men in 2006.

CONCLUSIONS

The epidemiological features of prostate cancer presented here are indicative of overdiagnosis varying over time and across populations. Although the results are ecological in nature and must be interpreted with caution, they do support previous recommendations that any future implementation of prostate cancer screening must be carefully designed with an emphasis on minimising the harms of overdiagnosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Unregulated and opportunistic testing of prostate specific antigen has been, and still is, common in Europe

The EU Beating Cancer Plan recently released the European Commission's council recommendations proposing a new strategy for prostate cancer screening programmes

A baseline assessment of the main epidemiological features of prostate cancer outcomes in Europe is needed before the possible initiation of screening with new approaches

WHAT THIS STUDY ADDS

This study found that the magnitude of prostate cancer incidence rates varied markedly across European countries and over time, in parallel with national trends of prostate specific antigen testing. Conversely, the mild and steady declines in mortality rates were at much lower levels and showed a more homogeneous and less variable pattern

The epidemiological features analysed in this study suggest that unregulated and opportunistic screening with prostate specific antigen likely leads to a population effect on prostate cancer outcomes that is less than optimal compared to that observed in randomised clinical trials

The present results are ecological in nature and should be interpreted with caution, but they reinforce the need for prudently planned prostate cancer screening programmes, especially to mitigate harms from overdiagnosis

Introduction

Prostate cancer is currently the most diagnosed malignancy among men and the third most common cause of death from male specific cancers in EU member states.[1] In the European Economic Area, which includes the 26 EU member states, Iceland, Lichtenstein, and Norway, and comprises 219 million men, around 341 000 men were diagnosed as having prostate cancer in 2020 (equivalent to 23% of all cancers in men) and about 71 000 men died from the disease (10% of all deaths from male specific cancers) in the same year.[1]

Screening men to check their prostate specific antigen (PSA) levels aims to reduce mortality from prostate cancer.[2] The European Randomized Study of Screening for Prostate Cancer found a reduction in deaths from prostate cancer (after around 10 years),[3 4] whereas the other large randomised trials—the Prostate, Lung, Colorectal and Ovarian trial,[5] which reported no reduction in mortality (although likely the results were affected by contamination),[6] and the CAP (cluster randomised trial of PSA testing for prostate cancer) in the UK—found similarly negative results based on a single screen. In addition, PSA based screening may lead to overdiagnosis through the detection of low risk tumours that are unlikely to progress, with the risk of overtreatment and adverse effects that could lower

men's quality of life.[7 8] The potential for overdiagnosis and overtreatment is higher when screening for prostate cancer than when screening for breast, cervix, and colorectal cancers, with autopsy studies reporting that up to one third of men of screening age harbour an indolent prostate cancer.[9]

Because of the delicate risk-benefit balance, almost all European countries, except Lithuania, have thus far opted against establishing prostate cancer screening programmes in favour of shared decision making about PSA testing between men and their doctors.[10] Differing individual attitudes and local practices towards PSA testing against a backdrop of on-demand and opportunistic screening unguided by clear protocols (in particular, the testing of older men) are likely to have a less than optimal effect on the population, with a possibly different net balance between the benefits and harms at population level than that observed in randomised clinical trials.[11 12]

The EU Beating Cancer Plan recently released the European Commission's council recommendations proposing a gradual and well planned implementation of screening programmes for prostate cancer in men younger than 70.[13 14] The suggested approach involves PSA testing initially, followed by magnetic resonance imaging (MRI) or other diagnostic tests for men with raised PSA levels before considering biopsy. The aim of the proposed approach is to maintain the benefit of mortality reduction while reducing overdiagnosis.[15] Modelling studies have suggested that this could be a cost effective procedure.[16]

Given that opportunistic PSA testing has largely been carried out in Europe, it is important to assess the effect on prostate cancer incidence and mortality at population level. In addition, baseline data on national levels and trends in prostate cancer outcomes before the possible initiation of screening with new approaches are needed. We therefore carried out a comparative assessment of the main epidemiological features of prostate cancer in 26 European countries, quantifying the range of variability in incidence rates against temporal variations in PSA testing and relative to mortality rates as a contribution to the evaluation of the population level impact of the EU initiative.

Methods

Data sources

We obtained long term data on the annual incidence of prostate cancer (international classification of diseases, 10th revision, ICD-10 code C61) from the International Agency for Research on Cancer's CI5plus (Cancer Incidence in Five Continents Plus) database and the Global Cancer Observatory.[1 17 18] From population based cancer registries we retrieved national or subnational recorded incidence data for 26 European countries during 1980-2017. Countries with populations less than 1 000 000 (Iceland and Malta) were not analysed. Coverage and availability of data within this period varied by country, but for most of the countries, the last year with incidence data was 2017 (see supplementary table S1). We obtained mortality data for the 26 European countries for 1980-2020 based on national vital registration from the World Health Organization.[19] Population coverage of the mortality database was nearly 100% in all selected countries, except Cyprus (86%).[19] Supplementary table S2 shows data availability and missing data points within the study period. We also extracted the most recent (2020) national incidence and mortality estimates from GLOBOCAN 2020 (with UK countries combined).[1]

Review on PSA testing

We carried out a review of the literature on PSA testing across European countries. PubMed was searched using keywords (time trend *OR* trend) *AND* (prostate-specific antigen) *AND* (testing *OR* screening *OR* testing rate). The reference lists of relevant articles were also checked to identify additional eligible studies. We selected only studies that provided information on trends in PSA testing in European countries for at least three years. When several studies reported the time trends of PSA testing for one country, we selected the study with the longest periods of data. Overall, information on trends in PSA testing was available for 12 countries (see supplementary table S3), although quality and type of information varied. Therefore we were unable to derive precise characterisation of prevalence, patterns, and trends in PSA testing from the literature, and the available estimates were not directly comparable across countries because they referred to different indicators, age groups, and data sources across populations. Consequently, it was not possible to carry out a quantitative analysis linking levels of PSA testing with incidence of prostate cancer across countries but only to provide a visual assessment of the temporal trajectory of PSA testing against that of incidence by country.

Statistical analysis

We restricted all analyses to the age group 35-84 years, with missing mortality data points removed. Annual age standardised rates of prostate cancer incidence and mortality per 100 000 men were calculated using the world standard population as a reference.[20] To assess the temporal trends of prostate cancer incidence and mortality by country, we plotted the line chart of annual age standardised rates against calendar years based on all available data points. We assessed trends by country continuously by single year, whereas when emphasis was put on the range of variability in incidence and mortality across the continent, we smoothed trends using Loess regression. The average annual percentage change was calculated as $100\times(e^{\beta}-1)$, where β is the regression coefficient in the generalised linear regression models between natural logarithm of annual age standardised rate and year, with a gaussian distribution and identity link function.[21]

Information on trends in PSA testing was retrieved from the literature for the 12 studied countries and is displayed against the corresponding trend in incidence.

doi: 10.1136/bmj-2023-077738 | *BMJ* 2024;386:e077738 | the bmj

To assess the discrepancy between incidence and mortality, we grouped calendar years into four periods of five years each (1998-2002, 2003-07, 2008-12, and 2013-17). We calculated the standardised rate ratios of annual age standardised rates between incidence and mortality and then compared the standardised rate ratio across periods.[22] Age curves were also plotted for both incidence and mortality over the four periods.

All analyses were performed using R software (version 4.0.3).

Patient and public involvement

This study used deidentified and aggregated registration data provided by patients and collected by staff from local registries in the countries studied. No patients were involved in the development of the research question, outcome measures, study design, or implementation of the study, as it is not possible nor permitted to attempt to identify and engage them. Although no patients were directly involved in this paper, one impetus for this research was the clinical context of the proposed prostate cancer screening programmes in the EU. Results will be disseminated to the public through media and a press release written using layman's terms.

Results

Time trends of prostate cancer incidence and mortality rates

Figure 1, figure 2, figure 3, and supplementary figure S1 show trends in prostate cancer incidence and mortality by country on an arithmetic scale (more suitable to assess and compare absolute values) and semi-log scale (more suitable to assess and compare relative changes over time), respectively. Supplementary figure S2 shows the trajectory of incidence and mortality over time by country. Increases in incidence were seen in almost every country, although the pace of increase varied greatly across countries. Increases in incidence were highest in northern Europe, France, and the Baltic countries—notably in Lithuania where the rates peaked at 435 per 100 000 men in 2007. In several countries (France, Switzerland, Italy, and Lithuania) the rates showed a parabolic increase, culminating after the mid-2000s and followed by subsequent declines, whereas in other countries the rates stabilised (Denmark, Sweden, Norway, Ireland, Spain, and Slovenia). Increases in incidence were, however, observed in the most recent quinquennium (2013-17) in several countries. In contrast, mortality rates decreased in most countries after the early 2000s, except in the Baltic countries and eastern Europe (eg, Estonia, Latvia, Belarus, Bulgaria, Poland, and Ukraine), where marked increasing trends, from previously low rates, were observed.

Three patterns can be distinguished in trends for prostate cancer incidence and mortality. Among the European countries included, nearly half exhibited upward trends in incidence (generally from the early 1990s to the late 2000s), followed by stable or downward trends, with corresponding mortality rates in uniform decline (such as the Nordic countries, France, Switzerland, and Italy). A second pattern involved increasing incidence rates throughout the study period, accompanied by downward mortality trends, as was observed in Britain (England, Wales, and Scotland) and the Czech Republic. The incidence of prostate cancer increased with stable or increasing mortality in the remaining countries, particularly in eastern and Baltic Europe (including Croatia, Estonia, Latvia, Belarus, Ukraine, Poland, Slovakia, and Bulgaria). Supplementary table S4 shows the average annual percentage changes of prostate cancer incidence and mortality.

Range of geographical and temporal variations in incidence and mortality rates

Figure 4 shows the range of variability in the annual age standardised rates for prostate cancer incidence and mortality across European countries and over time, highlighting the contrasting levels and magnitudes of differences in incidence versus mortality. Overall, prostate cancer incidence rates tended to rise during the study period, but with a variable pace and peak incidence in different countries and calendar periods. Consequently, the range varied considerably over time, the lowest rates being at the beginning of the study period in 1980 (from 17.6 in Belarus to 109.4 in Sweden per 100 000), then increasing substantially up until around 2005 (from 46.0 in Ukraine to 335.6 in France) and thereafter somewhat narrowing (from 62.7 in Ukraine to 299.3 in Lithuania) until around 2012, although rising trends were observed thereafter in several countries. The difference between the highest and lowest incidence rates across countries ranged from 89.6 per 100 000 men in 1985 to 385.8 per 100 000 men in 2007.

Compared with incidence, mortality rates were much lower in absolute terms and, despite the declines observed in most countries, presented a smaller range of values, spanning from 12 (Ukraine and Belarus) in 1981 to 53 (Latvia) deaths per 100 000 men in 2006. Considering all countries and periods, the 20-fold maximum variation in prostate cancer incidence contrasts with the fivefold variation in mortality. The difference between the highest and lowest mortality rates across countries ranged from 23.7 per 100 000 men in 1983 to 35.6 per 100 000 men in 2006.

Trends in incidence against trends in PSA testing

Supplementary figure S3 shows the trends in incidence of prostate cancer against trends in PSA testing for the 12 countries where information on both indicators was available. A correlation was evident between the direction and rate of change in incidence relative to PSA testing across all countries assessed, although data on PSA trends are subject to major limitations. Supplementary table S3 provides detailed information on the review of PSA testing in Europe.

Divergence between incidence and mortality

The divergence between incidence and mortality increased in all countries over two decades (fig 5).

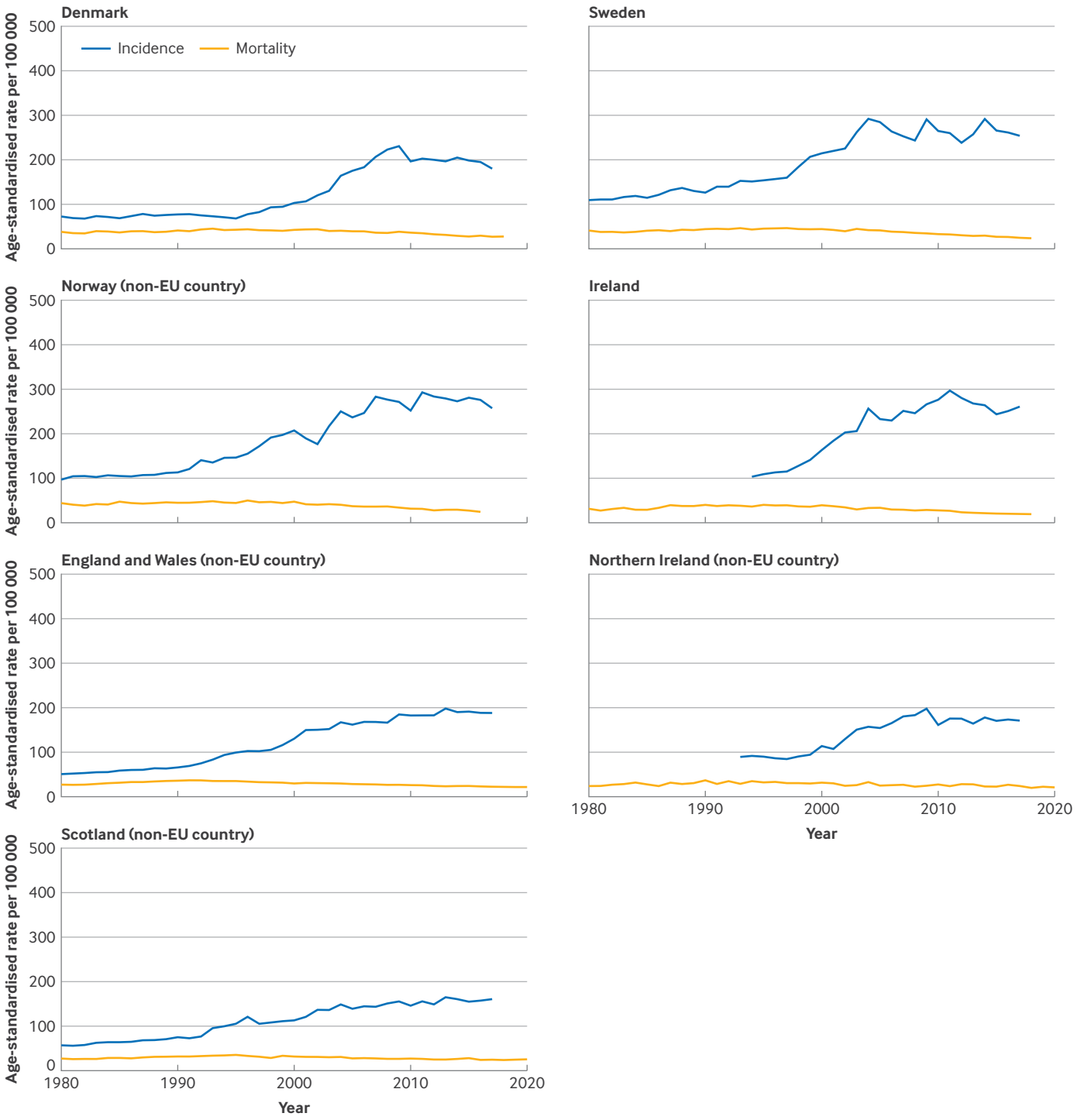

Fig 1 | Time trends of age standardised incidence and mortality rates for prostate cancer per 100 000 men aged 35-84 years on an arithmetic scale in northern Europe

The standardised rate ratios between incidence and mortality were around 2~4 in most countries during 1998-2002, but higher values (5~7) were observed for several central European countries (Germany, Austria, France, Switzerland, Italy, and Spain). The standardised rate ratios almost doubled by 2013-17 compared with 1998-2012 and reached over 5 for almost all included countries other than Croatia, Latvia, and several countries in eastern Europe. High standardised rate ratios (>10) were found in Ireland, France, Italy, and Spain in 2013-17.

Supplementary figure S4 also shows age standardised incidence rates for incidence and mortality in Europe in 2020, ranked by increasing order of incidence. Higher incidence rates were not consistently associated with the level of mortality rates.

doi: 10.1136/bmj-2023-077738 | *BMJ* 2024;386:e077738 | the bmj

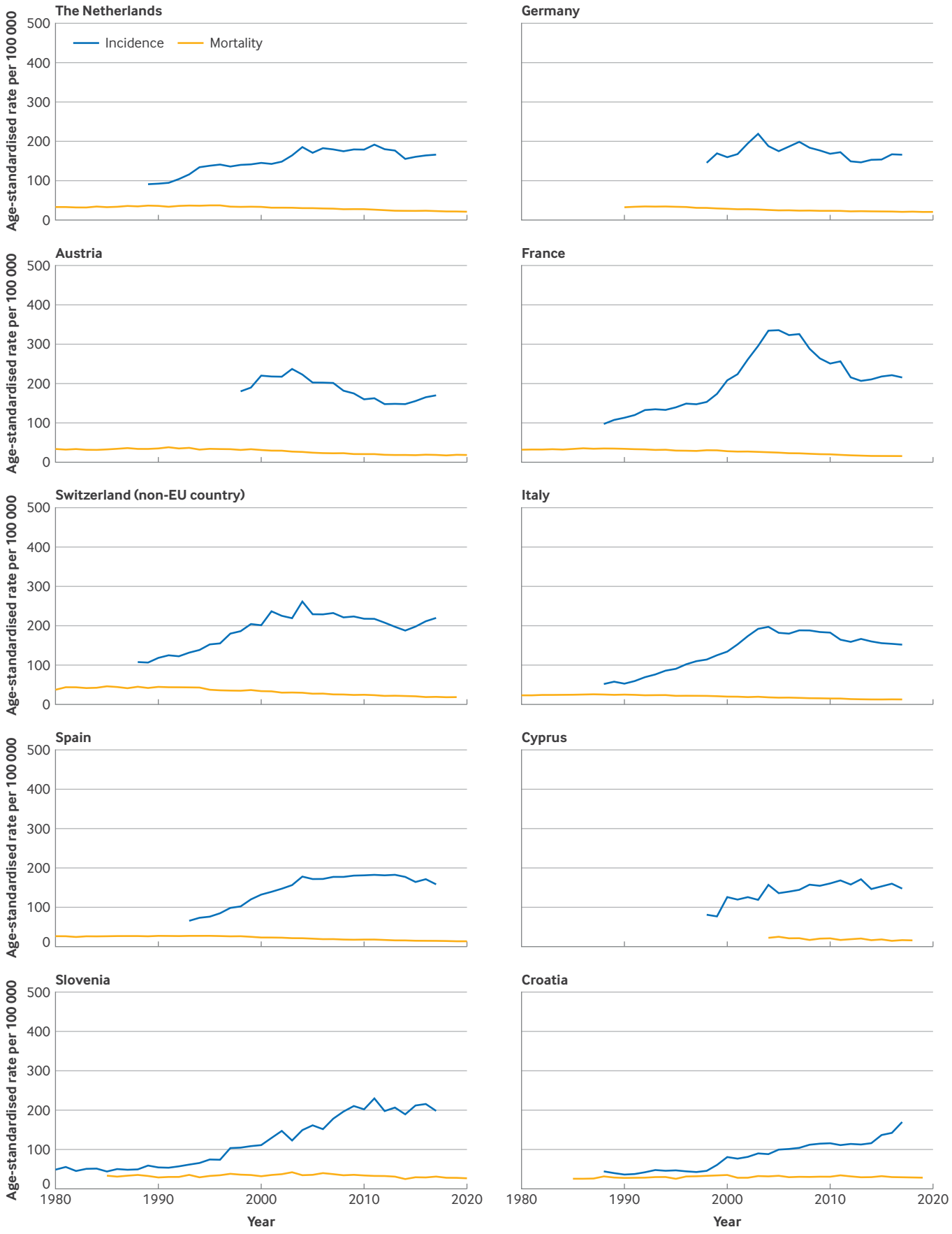

Fig 2 | Time trends of age standardised incidence and mortality rates for prostate cancer per 100 000 men aged 35-84 years on an arithmetic scale in central and southern Europe

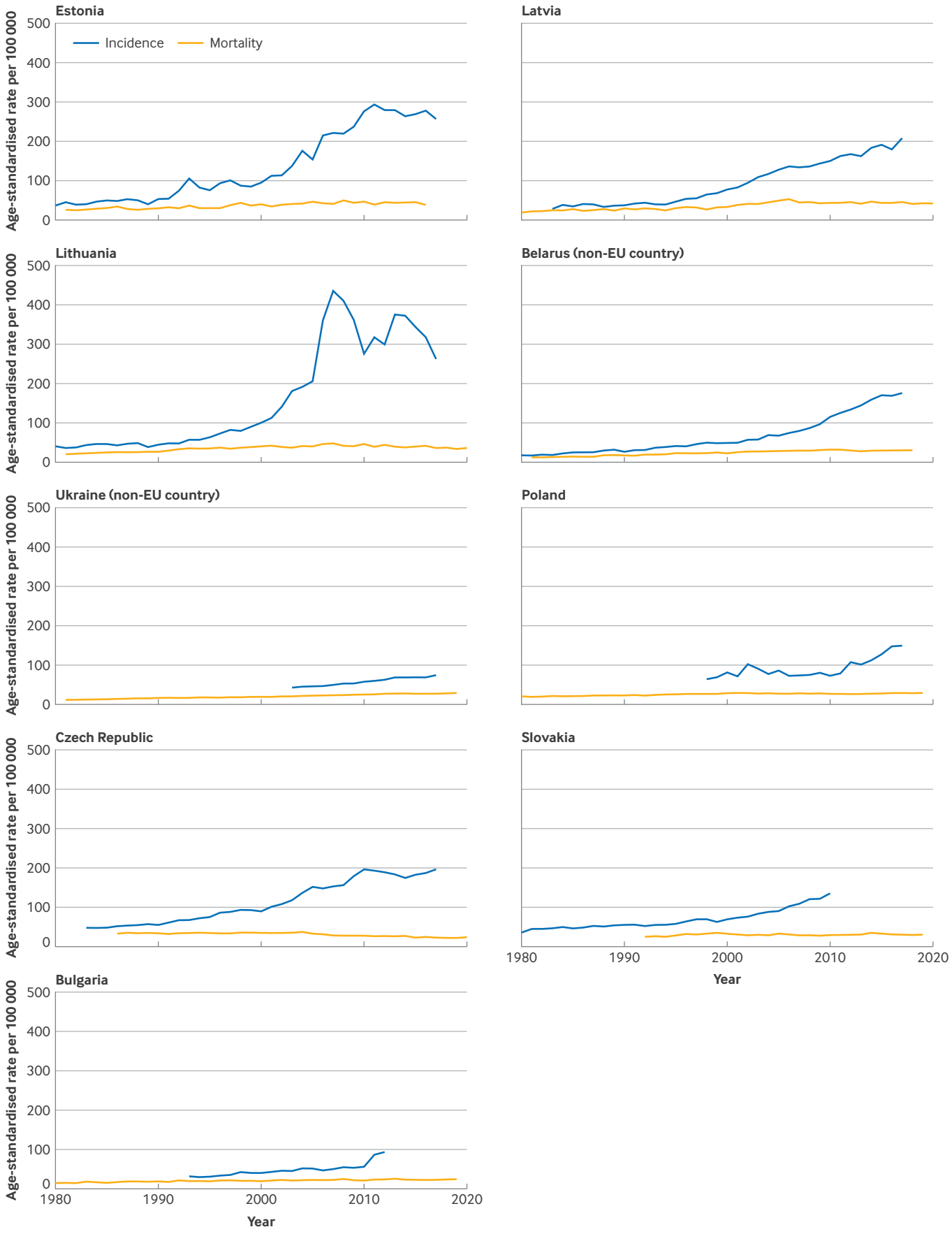

Fig 3 | Time trends of age standardised incidence and mortality rates for prostate cancer per 100 000 men aged 35-84 years on an arithmetic scale in the Baltic countries and eastern Europe

doi: 10.1136/bmj-2023-077738 | *BMJ* 2024;386:e077738 | the bmj

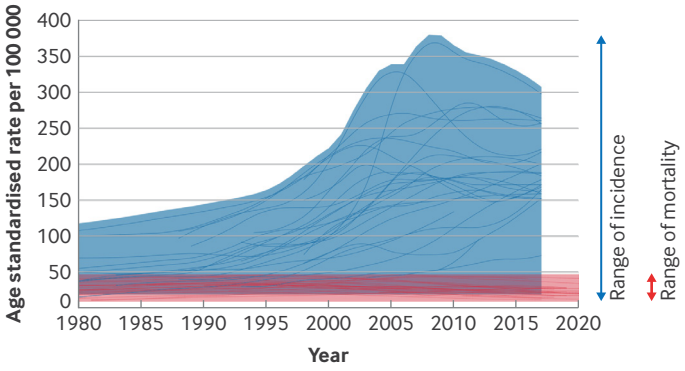

Fig 4 | Range of age standardised incidence and mortality rates of prostate cancer per 100 000 men aged 35-84 years over time among the included European countries. Lines are smoothed by the Loess regression algorithm (bandwidth: 0.4)

Changes in age curves of prostate cancer incidence and mortality over time

Figure 6, figure 7, figure 8 (all on arithmetic scale), and supplementary figure S5 (on logarithmic scale) show the temporal change in age specific incidence and mortality. The age specific profiles changed markedly for incidence, but not for mortality. The incidence curves resembled an inverse U-shape peaking at around 70 years of age during the period 1998-2017, as seen in France, Sweden, Denmark, Norway, Ireland, Estonia, Lithuania, Slovenia, and the Czech Republic. The corresponding age specific curves in the central European countries decreased in 2008-12 after an earlier peak around 2003-07, although increases were observed in the recent quinquennium 2013-17 in some countries in the region. In contrast, the mortality curves remained relatively stable over time, showing a consistent increase with age in all European countries.

Discussion

Our study found noticeable differences in both the magnitude of prostate cancer incidence rates across Europe and the rate of change in the generally upward trends over the past decades. The divergence between countries reached its maximum around the period 2000-10. Thereafter the rates declined in several countries, with somewhat reduced variability in rates, even though they remained high, and even increased in several countries in the most recent years. Such temporal variations in prostate cancer incidence correlated with the national variations in PSA testing. In contrast, mortality rates were substantially lower and showed less variability than incidence, with a more homogeneous pattern over time. Uniform declines in mortality were generally seen across the European continent, although less marked than the increases in incidence. In the Baltic countries and eastern Europe, however, mortality trends remained relatively flat.

The delivery and uptake of PSA testing have been shown to have a rapid effect on the number of new diagnoses of prostate cancer and corresponding incidence rates at the population level. It is widely acknowledged that in the US the large increase (starting in the 1970s and peaking around 2000) and subsequent decline in incidence resulted from the initial increasing use of transurethral resections of the prostate (from the 1970s) and subsequent use of PSA testing (from the mid-1980s)[23] and was followed by a decline, partly as a result of the US Preventive Services Task Force's recommendation aimed to discourage the practice.[24] Our study confirmed this pattern for incidence in Europe yet also found large heterogeneity across countries. Conversely, the extent of the effect of PSA testing on mortality at the population level is less clear. In the US, the decline in mortality from the mid-1990s followed by a period of stability could be attributed to the use of PSA testing as well as to advances in effective treatment for late stage prostate cancer (whereas the cancers are localised at diagnosis). Yet, disentangling the contribution of the two components is challenging. The patterns of prostate cancer in Europe appear to replicate the

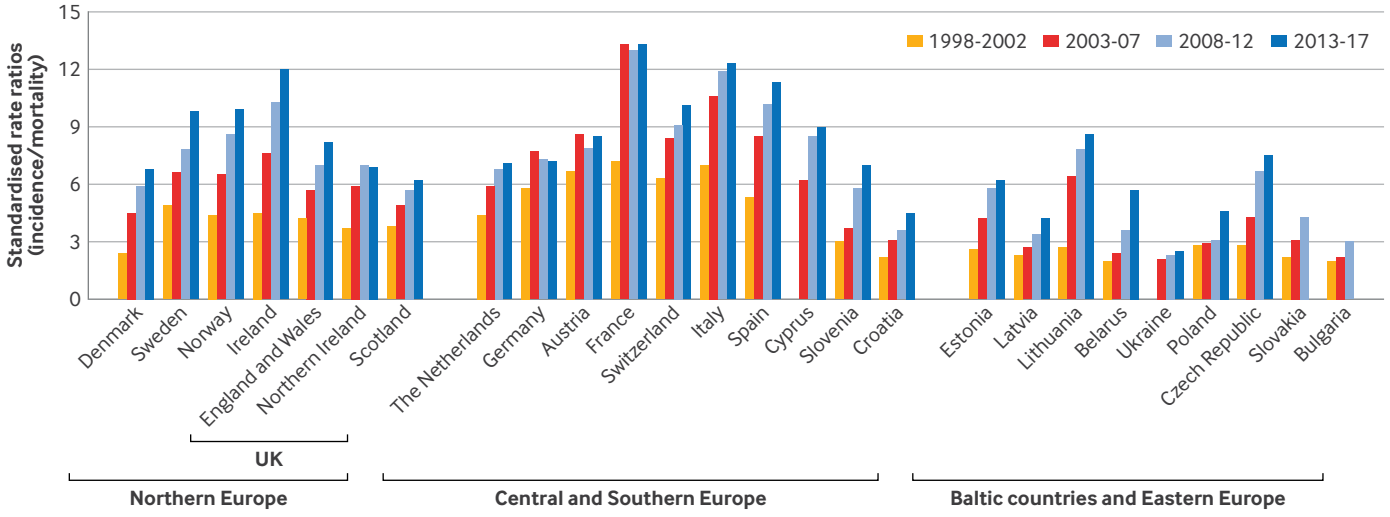

Fig 5 | Standardised rate ratios between incidence and mortality for prostate cancer across different periods among men aged 35-84 years

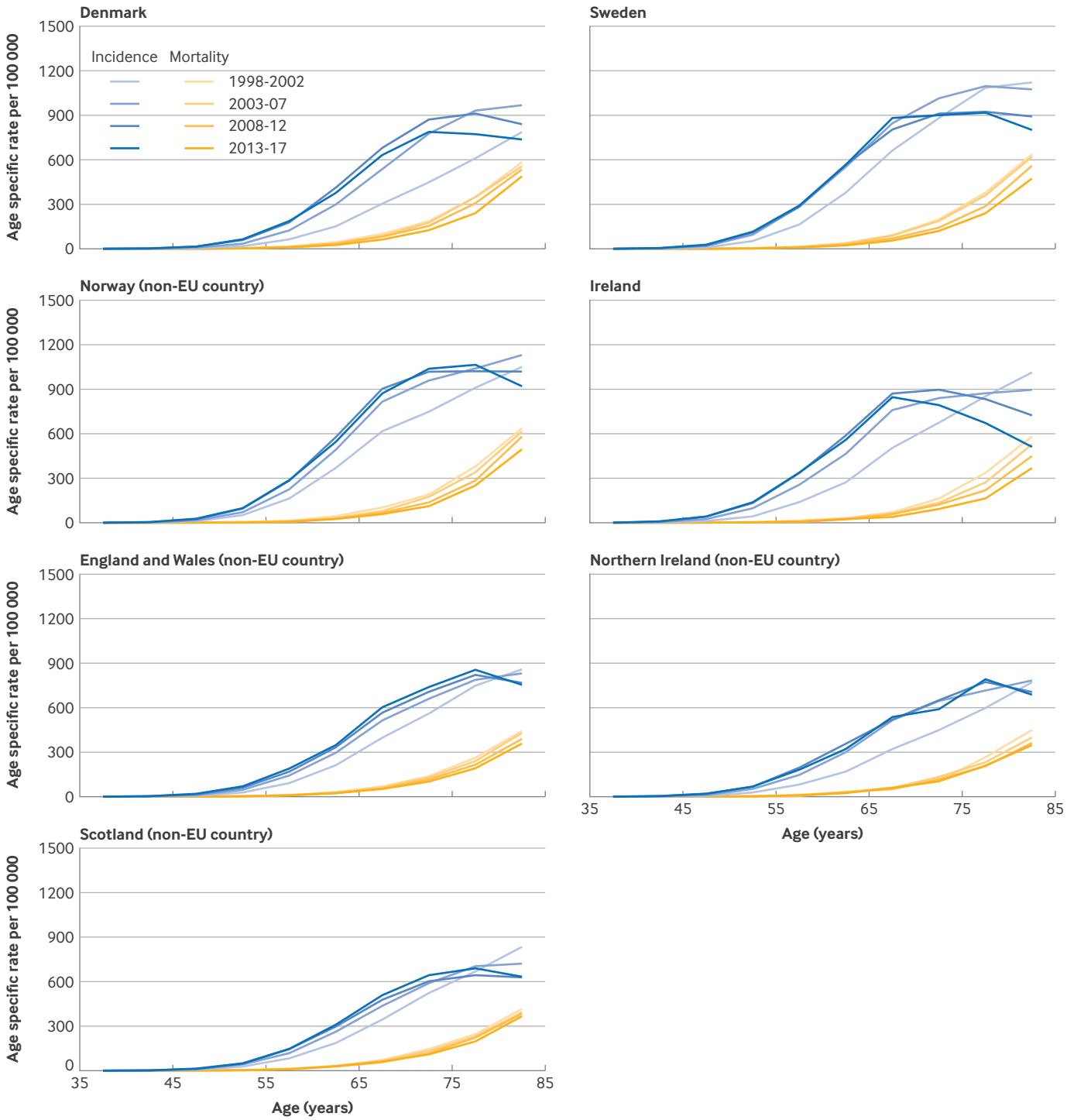

Fig 6 | Age specific incidence and mortality rates of prostate cancer per 100 000 men during 1998-2002, 2003-07, 2008-12, and 2013-17 in northern Europe

earlier observations in the US. This suggests the same mechanism and implicates the potential contributions of both PSA testing and improved treatment outcomes.

In this respect, this comparative assessment should help to improve the understanding of the effect of PSA testing on incidence and mortality in Europe by highlighting consistent patterns across countries. Specifically, our results suggest that the intensity and coverage of PSA testing has been a critical driver for the increasing trends in prostate cancer incidence in Europe. Nevertheless, the possible benefits in terms of reduced mortality appeared to be relatively consistent everywhere, regardless of the extent of the increase in incidence as an indicator of PSA testing.[25] In addition, the magnitude of prostate cancer incidence showed

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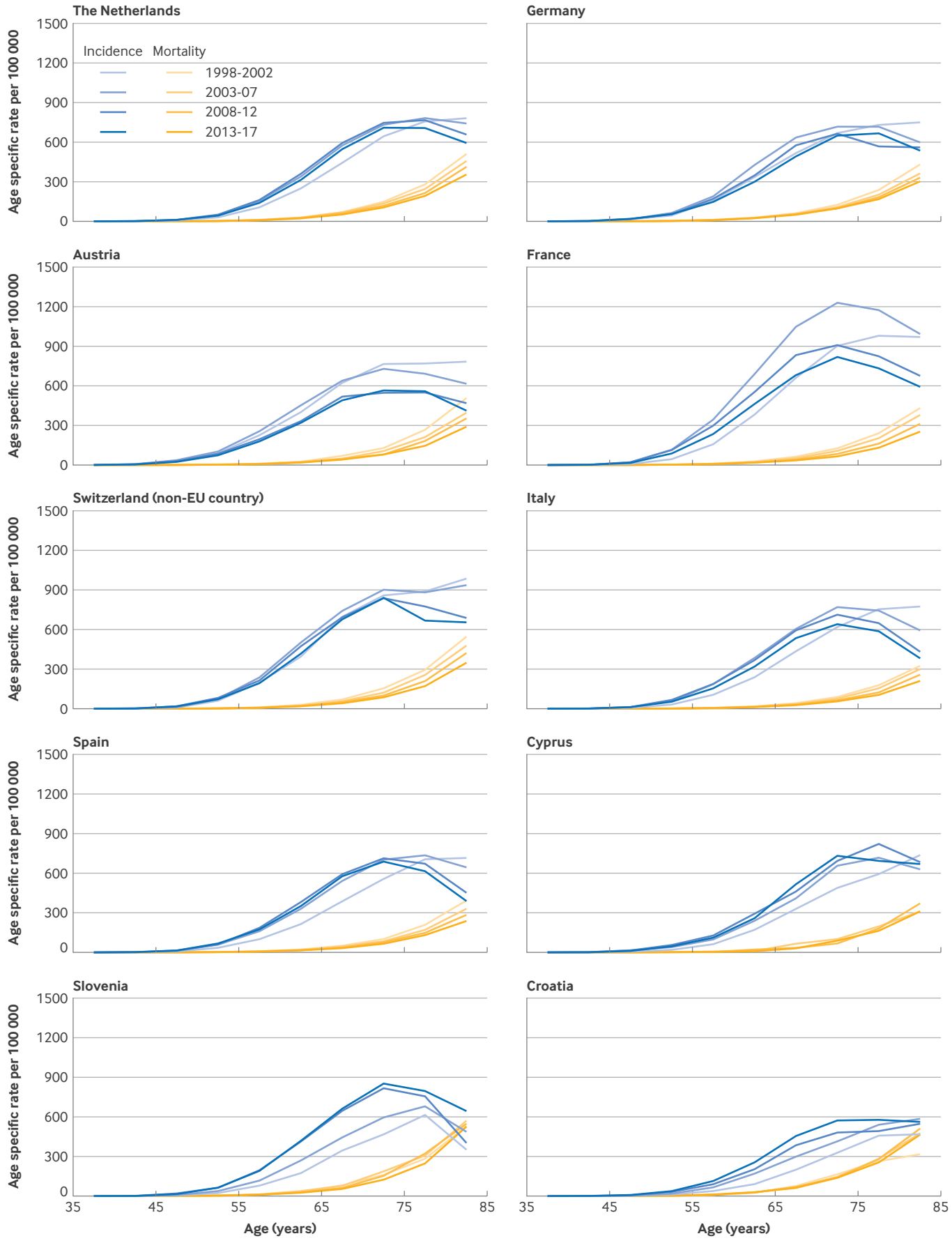

Fig 7 | Age specific incidence and mortality rates of prostate cancer per 100 000 men during 1998-2002, 2003-07, 2008-12, and 2013-17 in central and southern Europe

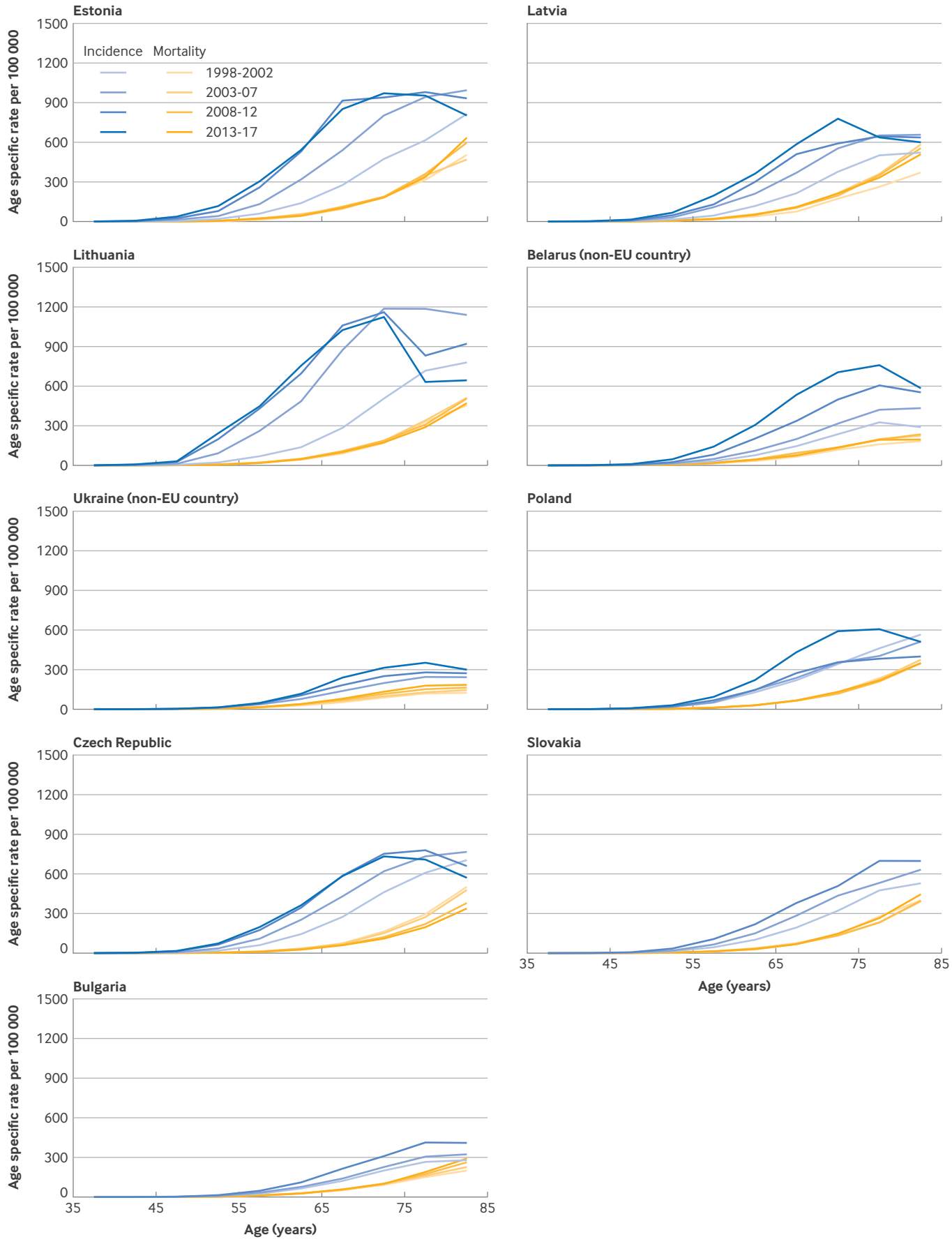

Fig 8 | Age specific incidence and mortality rates of prostate cancer per 100 000 men during 1998-2002, 2003-07, 2008-12, and 2013-17 in the Baltic countries and eastern Europe

doi: 10.1136/bmj-2023-077738 | *BMJ* 2024;386:e077738 | the bmj

little interdependence with mortality at the national level.

The changes in the age specific incidence curves showed a progressively younger age at peak incidence and increasing resemblance to an inverted U-shape. Older data from the 1960s and 1970s suggest that before the initiation of PSA testing, the incidence of prostate cancer increased strongly with age.[1] In contrast, in our study the age specific mortality curves did not substantially change over time and increased steadily with age. The decline in mortality rates affected all age groups proportionally, and the trend towards earlier diagnosis in younger men seemed to have only a negligible impact on subsequent mortality in older age groups.

In most Baltic and eastern European countries, mortality rates were relatively stable, in contrast with the declines elsewhere. Explanations may include the limited extent of PSA testing, as well as a slower adoption of therapeutic advances (compared with more affluent areas on the continent). Lithuania was an exception, with minor declines in mortality in the most recent period, possibly because it is the only country in Europe offering population screening using the PSA test (since 2006).[26] As the national programme has been accompanied by a substantial amount of opportunistic testing, prostate cancer incidence in Lithuania has increased rapidly, reaching the highest levels ever recorded in Europe.

Overall, our findings imply that unregulated and opportunistic PSA testing has had a differential effect at the population level in Europe compared with the results of the randomised screening trials and appear consistent with overdiagnosis. The PSA based screening trials reported a 1.4-fold or smaller increase in incidence,[3 5 27] whereas national incidence rates in most European countries more than doubled from 1990 to 2017 (and in some countries increased up to eightfold, as in Lithuania). The epidemiological features observed in our study, specifically the rapid inconsistent increase in incidence but not mortality and the progressive change in age specific incidence curves, are difficult to explain for factors other than PSA testing. Our findings have commonalities with what has been previously reported for thyroid cancer, where overdiagnosis is an established driver of rapid increases in incidence.[28] Opportunistic examinations of the thyroid (often with ultrasound) have spread rapidly in many countries,[29 30] despite the lack of evidence for a mortality benefit from thyroid screening (in contrast with prostate cancer screening) and of current guidelines, which recommend against population screening for thyroid cancer.[31]

The value of early detection of prostate cancer has been debated extensively, and most of the recent guidelines recommend that asymptomatic men should be offered an informed decision making process about the potential benefits and harms of prostate cancer screening. However, it is still not clear how shared decision making should be implemented, or its possible effect on patient outcomes.[32-34] In countries where such policies have been introduced, the prevalence of PSA testing is disproportionally higher among older men[11] and among men with a higher socioeconomic position.[35] This limits the benefits, increases the risk of overdiagnosis, and increases social inequalities.

Overtreatment may be a consequence of overdiagnosis, with harms of overdiagnosis exacerbated by aggressive management. Recent improvements in the de-escalation of treatment for low risk men with prostate cancer are observed in some countries. In Norway, for instance, the proportion of low risk men managed primarily by active surveillance instead of immediate treatment increased from 20% to 80% during 2008-21, with only 7% of such men treated radically in 2021 (eg, with surgery or radiotherapy).[36] In England, treatment of low risk men was estimated to be 4% in 2018.[37] Heterogeneity in the management and treatment of low risk and high risk localised prostate cancer is substantial, however, even across high income countries.[37] International society based treatment guidelines should be enforced to minimise overtreatment. In addition, many men initially treated with active surveillance decided to switch to active treatment within a few years. The process of reducing unnecessary treatment for prostate cancer is multifaceted and involves various aspects of health systems and the attitude of decision makers, medical practitioners, and patients and their families.[38] It is important to monitor whether opportunistic use of PSA testing, with the consequent cascade of biopsies, aggressive management, and treatment, will continue in the future, especially in settings where the provision of healthcare services is particularly unregulated.

The European Commission has recently recommended that "countries should take a stepwise approach, including piloting and further research to evaluate the feasibility of implementation of organised programmes aimed at assuring appropriate management and quality on the basis of prostate specific antigen (PSA) testing for men up to 70, in combination with additional magnetic resonance imaging (MRI) scanning as a follow-up test."[39] The use of pre-biopsy MRI and of targeted prostate biopsies compared with systematic biopsies alone, should reduce the number of men who will receive an unnecessary diagnosis of prostate cancer, and although changes in clinical practice are already occurring in some settings, they are too recent for any potential effect to be observable in our study. To this extent, some proposals have been advanced, including the implementation of systematically designed, risk based national prostate cancer detection programmes aimed at reducing overdiagnosis and overtreatment and increasing equity.[11 40]

Limitations of this study

The present analysis may refer to different age groups, periods in time, and indicators of PSA testing, and therefore the results should be interpreted with caution. The limitations of this study include the lack of data on cancer stage (due to problems with comparability

across cancer registries) and on treatment modalities. This is of importance as increases in prostate cancer incidence and mortality at more advanced stages have been observed in the US following the USPSTF recommendations against PSA based screening in 2008 and 2012.[41 42] However, the data used in this analysis include IARC's GLOBOCAN and CI5, for which the underlying sources are commonly robust and internationally comparable. Although data for Cyprus and Slovakia have been available only since the early 2000s and early 1990s, respectively, for all other countries under study, cancer incidence trends could be analysed up until the relatively recent period of 2017. In some countries, mortality data are missing for a few years, but those are generally scattered throughout the study period, their impact on the trends and on the general conclusions of the study are negligible. Ecological studies in multiple settings, such as the present one, are an appropriate approach for quantifying and monitoring overdiagnosis.[43] The current review on PSA testing, as noted, does have several limitations. In addition, although we could retrieve data from the literature on the frequency of PSA testing for 12 out of the 26 countries, the information available could not be synthesised or enable quantitative assessments given the lack of comparability of the measures used. A visual inspection of the trend variations in PSA testing showed a strong parallelism with prostate cancer incidence in countries where both indicators were available, but these findings should also be interpreted with caution. In addition to PSA testing, other factors may have affected incidence and mortality rates. The descriptive nature of the data used in the present study, the incompleteness of the data both geographically and temporally, and the lack of information on confounding factors, mean that causality cannot be assumed. The established risk factors for prostate cancer include age (adjusted for in our analysis) as well as family history and genetic predisposition, but these cannot change rapidly within a population. Putative factors include diet, specific drugs, and occupational factors,[44 45] but overall, the cause remains poorly understood. It is, however, unlikely that changes in the prevalence of one or more risk factors could have caused such a surge in incidence, given the variability internationally, and the contrasting mortality trend.

Conclusions

Overall, our results suggest that several of the epidemiological characteristics of prostate cancer in the Europe countries included, particularly the contrast between large heterogeneity in trends for incidence with the more uniform reduction in mortality, are compatible with the highly variable patterns of PSA testing across Europe. The current high incidence of prostate cancer in many countries may be inflated by unregulated and opportunistic PSA testing that serves to mask any variations due to causal factors and may be indicative of overdiagnosis. The importance of these results is further emphasised by the proposed EU guidelines endorsing prostate cancer screening, assuming that resources are available, and that prostate cancer is a public health priority. Careful monitoring and assessment of the benefits and harms, including overdiagnosis, will be essential for the potential implementation of the guidelines and the prospective introduction of population-wide prostate cancer screening.

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We thank Frédéric Lam and Murielle Colombet for technical and data support and the cancer registries and staff for sharing data needed for this study. Where authors are identified as staff of the International Agency for Research on Cancer or the World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer or WHO.

Contributors: SV and ML are joint first authors. SV, ML, and LDM conceived and designed the study. ML contributed to data collection, analyses, and interpretation of the results. SV wrote the first draft of the manuscript. FB, RV, DS, VL, and AA critically discussed and interpreted the results and contributed to the final version of the paper. SV is the guarantor of the study and had final responsibility for the decision to submit the manuscript. All authors read and approved the final version of the paper. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: The Italian Association for Cancer Research supported the work of DS and LDM (grant No 28893).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: DS and LDM were supported by the Italian Association for Cancer Research; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required as the study used publicly available aggregated data.

Data sharing: All data used for analyses are available from the International Agency for Research on Cancer at http://ci5.iarc.fr and the World Health Organization at https://www.who.int/data/data-collection-tools/who-mortality-database.

Transparency: The lead author (SV) affirms that the 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 (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Study results will be disseminated to the public, health professionals, and policy makers through a press release written using layman's terms on the International Agency for Research on Cancer's website. Findings will be shared through mass media communications and social media postings. We will also present findings at national and international conferences oriented towards researchers and clinicians in the specialty of cancer prevention and control. Since the study is based on deidentified and aggregated registration data, we have no plans to disseminate results to individual study participants beyond the usual channels of publication.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: Additional tables S1-S4 and figures S1-S5