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Mendes, D; Mesher, D; Pista, A; Baguelin, M; Jit, M; (2017) Understanding differences in cervical cancer incidence in Western Europe: comparing Portugal and England. European journal of public health. ISSN 1101-1262 DOI: <https://doi.org/10.1093/eurpub/ckx176>

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Understanding differences in cervical cancer incidence in Western Europe: comparing Portugal and England

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Background: Cervical cancer incidence has decreased over time in England particularly after the introduction of organized screening. In Portugal, where opportunistic screening has been widely available with only slightly lower coverage than that of the organized programme in England, rates of cervical cancer have been higher than in England. We compared the burden of cervical cancer, risk factors and preventive interventions over time in both countries, to identify elements hindering the further decline in incidence and mortality in Portugal. **Methods:** We used joinpoint regression to identify significant changes in rate time-trends. We also analyzed individual-level Portuguese data on sexual behaviour and human papillomavirus prevalence, and recent aggregate data on organized and opportunistic screening coverage. We compared published estimates of survival, risk factors and historical screening coverage for both countries. **Results:** Despite stable incidence, cervical cancer mortality has declined in both countries in the last decade. The burden has been 4 cases and 1 death per 100 000 women annually higher in Portugal than in England. Differences in human papillomavirus prevalence and risk factors for infection and disease progression do not explain the difference found in cervical cancer incidence. Significant mortality declines in both countries followed the introduction of different screening policies, although England showed a greater decline than Portugal over nearly 2 decades after centralizing organized screening. **Conclusion:** The higher rates of cervical cancer in Portugal compared to England can be explained by differences in screening quality and coverage.

Introduction

Portugal has had higher burden of cervical cancer than England. Several multi-country comparisons have shown that European countries with poor cervical screening coverage have a higher cervical cancer burden.^{1–4} Reasons for the difference are not obvious because cervical cancer development is multi-factorial and depends on infection with high-risk human papillomavirus (HPV), the rate of progression of pre-cancerous lesions and the existence of preventive interventions such as screening and vaccination.⁵

Opportunistic screening has reduced cervical cancer mortality in some countries; however, it is characterized by unnecessarily frequent screening, heterogeneous quality and poor coverage of underserved women who may be at highest risk. Well organized programmes enable high coverage of the target population, adequate follow-up and equity of access with more efficient resource use but has yet to be implemented in many European countries.⁶

Like most western European countries, England has seen a decline in the burden of cervical cancer following the introduction of cytological screening in 1964, particularly since screening was centrally organized in 1988.⁶

In Portugal, cervical screening was introduced in 1978 but only on an opportunistic basis, although more recently regional organized programmes with varying coverage have been initiated. Each mainland regional health administration (RHA) and the regional health systems of Azores and Madeira are autonomously responsible for the provision of any programme. Partially-organized screening was introduced in 1990 in the Centre region. Fully-organized programmes have been introduced post-2008 with varied regional

coverage in Alentejo, Algarve, Azores and the North. Lisbon and Tagus Valley and the Autonomous Region of Madeira have not implemented such a programme yet.⁷

Here, we investigate the extent to which screening and other factors may have driven differences in cervical cancer incidence between Portugal and England by analyzing estimates and time-trends in multiple data sets including HPV prevalence, cervical cancer incidence and mortality, screening coverage, sexual behaviour and other potential risk factors. We then explore the implications of our results for policy making across Europe.

Methods

Cervical cancer incidence and mortality

European age-standardized rates (EASR) were estimated using the 1976 European Standard Population. Age-standardized incidence was estimated from individual case data provided for 1998–2010 by all four Portuguese population-based regional registries (Azores, Centre, North and South), covering 100% of the population. National estimates were pooled by weighting the regional age-specific number of cases by the respective proportion of the population. For the UK, we used estimates from EUREG and national statistics databases.^{8,9}

Cervical (and other uterine) cancer mortality and female population sizes for both countries were obtained from the WHO mortality database¹⁰ and Statistics Portugal.¹¹ Inaccuracies in death certification were adjusted by reallocating deaths from non-otherwise specified uterine cancers to cervical cancer.¹

We performed segmented regression to analyze rate trends and identify trend joinpoints (i.e. calendar years where the slopes of two linear trends changed). The annual percentage change (APC) was estimated for each segment fitting a log-linear model with the Joinpoint software.¹²

Case-fatality risk

Annual case-fatality risk (CFR) was calculated from incidence and mortality estimates, as its complement (1-Mortality/Incidence) has been considered a valid approximation of the 5-year relative survival for most cancers.¹³ The two-proportion z-test was used to test whether these populations' risks differ significantly.

Cervical cancer survival

We used published 5-year survival estimates from the CONCORD-2¹⁴ and the EUROCORE¹⁵ studies based on cancer registries data.

HPV prevalence

We estimated age-standardized prevalence of 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) from the CLEOPATRE Portugal study which recruited 2165 unvaccinated women aged 18–64 attending National Health Service (NHS) gynaecology, obstetrics and sexually transmitted disease services in 2008/9.¹⁶ Age-specific and overall crude prevalence estimates of high-risk HPV in women attending cervical screening in England were sourced from a systematic review and meta-analysis of the main pre-vaccination studies.¹⁷

Sexual behaviour

Behavioural risk indicators for HPV infection were estimated from individual-level data of the 2007 survey on sexual behaviour and HIV/AIDS in mainland Portugal¹⁸ (1860 valid questionnaires from sexually active women aged 16–65 years). We compared these estimates with those published from the British National Surveys of Sexual Attitudes and Lifestyles (Natsal-2 in 1999–2000 16–44 years old, and Natsal-3 in 2010–12, 16–74 years old).¹⁹ Definitions were standardized across the two surveys (additional information is available on request).

Other risk factors

Published estimates were obtained for risk factors for HPV infection acquisition, persistence and cervical cancer progression: smoking,²⁰ contraception use,²¹ fertility,²² male circumcision²³ and other sexually transmitted infections (STIs).^{24,25} We compared outcomes from European Union surveillance of human immunodeficiency virus (HIV), chlamydia, syphilis and gonorrhoea in both countries. Data on these risk factors were only found for the UK.

Cervical screening

Cervical screening coverage in Portugal prior to the introduction of organized programmes (2008) was obtained from the literature.^{26,27} Coverage post-2008 was estimated from aggregate data provided by RHAs in mainland Portugal. Coverage of opportunistic screening was derived from the number of conventional cytology tests reimbursed to contracted laboratories in 2010–14. For England, we used published screening coverage estimates.²⁸

Results

Cervical cancer incidence

Annual incidence of cervical cancer in Portugal in 1998–2010 ranged from 11.6 (10.8–12.5)–14.3 (13.4–15.3) per 100 000 women; the negative linear trend over that time period was not significant

(Supplementary table S1 and figure 1). In England over the same period, incidence varied between 8.0 (7.7–8.3) and 9.7 (9.4–10.1) and was similarly stable in the 2000s. We estimated a positive APC in 1977–88 followed by a negative APC in 1988–98, but no evidence of a change in incidence in 1999–2011.

In England, the peak age of cervical cancer incidence has shifted from after 45 years in the early 1980s to around 30–45 years in the late 1990s. In Portugal, it peaked at 40–49 year olds in 1998–2010 (Supplementary figure S1).

Cervical cancer mortality

For Portugal (1955–2013), we estimated 2 joinpoints in cancer mortality at 1970 and 1982. There was no evidence of a change in mortality until 1970, with a decline thereafter (figure 1 and Supplementary table S1). Three trend periods were estimated for England with joinpoints in 1964, 1988 and 2006. The APC has declined since 1950, with the steepest decline in 1988–2006.

In 1998–2010, average cervical cancer incidence in Portugal exceeded that in England by 4 cases per 100 000 women. However, cervical cancer mortality was similar between countries (on average 1 more death per 100 000 women annually in Portugal than in England). Both countries show a period-specific effect as age-specific rates declined similarly in consecutive periods and birth cohorts across all age groups apart from the youngest (20–29 and 30–39 years old) (Supplementary figures S2 and S3).

Case-fatality risk and survival

Cervical cancer CFR was higher in England (mean 0.33, range 0.24–0.40, 1998–2010) compared to Portugal (mean 0.30, range 0.25–0.34, 1998–2010) but the difference was not statistically significant ($P > 0.5$ every year) (Supplementary figure S4). Also, CFR declined in England throughout 1996–2011 but not in Portugal (Supplementary table S1).

Allemani and colleagues¹⁴ found that 5-year net survival improved from 54% (50–58%) to 62% (60–63%) in Portugal (1998–2009) and from 58% (57–59%) to 60% (59–62%) in England (1995–2009) (Supplementary table S2). Similarly, the EUROCORE database shows a greater improvement of 5-year relative survival in Portugal [from 58% (56–50%) to 64% (62–66%)] than in England [from 65% (65–66%) to 67% (66–68%)] between 1995–99 and 2000–07.¹⁵

Although similar estimates were found for both countries, slightly greater survival improvement was reported for Portugal in both EUROCORE and CONCORD-2 studies, while we found a steeper decline in CFR for England (Supplementary table S1). Given that population-based survival estimates from high data quality are available, our CFR estimates must be considered cautiously and their complement should not be used instead of 5-year relative survival estimates.

Human papillomavirus prevalence

High-risk HPV prevalence among unvaccinated women with normal cytology was 5.5% (95% CI: 3.6–8.9%) in Portugal and 10.4% (4.5–18.7%) in the UK. The age distribution was similar in both countries, with peak prevalence at 20–24 years of age, followed by a decline until age 40 (Supplementary figure S5). The overall crude high-risk HPV prevalence was similar in England and the UK.

Sexual behaviour

Women's median age of first heterosexual intercourse was higher in Portugal (19 years) than in Great Britain (17 years) (Supplementary table S3). The age difference between partners at start of the relationship was smaller in Portugal compared with that in Great Britain, with 76% and 63% being ≤ 5 years, respectively.

Portuguese women had fewer lifetime partners than British women, but the number of partners over the last year and the proportion of women with ≥ 1 new partner last year were similar

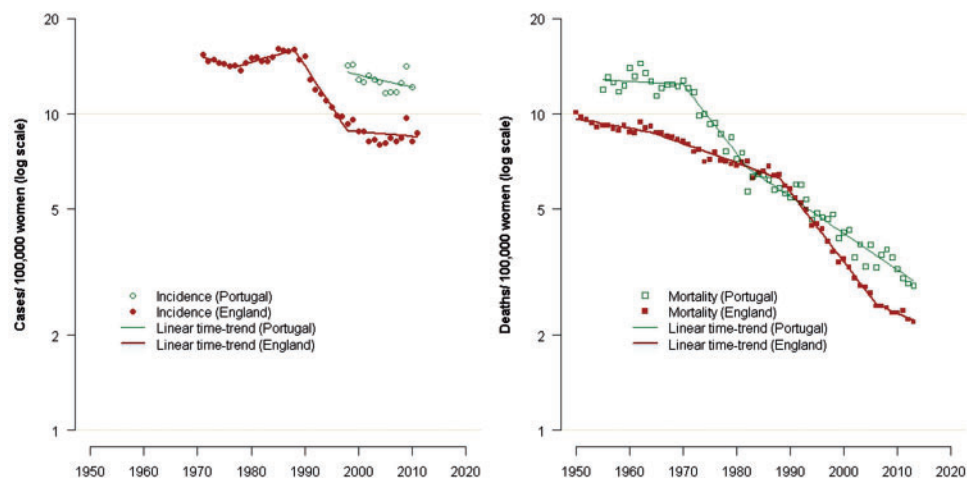


Figure 1 Age-standardized Cervical Cancer Incidence and Mortality by calendar period, EASR. EASR, European age-standardized rate using the 1976 European Standard Population; dots represent annual incidence estimates; squares represent annual mortality estimates; solid lines represent linear time-trends obtained by joinpoint regression; dashed lines represent 95% confidence intervals; *Incidence data pertain to England and mortality data pertain to England and Wales

in both countries. Portuguese women reported 8% of relationships lasting less than 1 month, whereas in Great Britain these account for 51% of the relationships. In both countries, over 30% of reported relationships overlapped.

Overall, Portuguese women were at lower behavioural risk of acquiring HPV from their partners given their later sexual debut, fewer lifetime partners per year and fewer short-term relationships.

Other risk factors

Smoking, the number of full-term pregnancies, the use of oral hormonal contraceptives, and exposure to other STIs have been associated with cervical cancer. Conversely, there is robust evidence of inverse association between male circumcision and HPV acquisition and consequent development of cervical cancer.⁵

Both Portugal and the UK have shown a decreasing trend in tobacco use over the last decade,²⁰ with the prevalence of smoking lower in Portugal than in the UK (Supplementary table S4). The Portuguese fertility rate was lower in the early 2000s than in the UK.²² However, Portugal has higher hormonal contraceptive use, lower condom use and lower prevalence of male circumcision compared to the UK.^{21,23}

The UK has higher gonorrhoea and syphilis incidence, whilst Portugal has higher HIV incidence.^{24,25} Portugal has no organized Chlamydia surveillance system so Chlamydia prevalence cannot be compared with the UK.²⁵

Cervical screening

Cervical screening in Portugal and England differ both in quality and coverage. There is a 20-year lag between countries in the introduction of fully-organized programmes (figure 2).

In Portugal, cervical screening remains mainly opportunistic with lower coverage than in England (figure 3). The proportion of eligible women aged 25–64 screened between 2012 and 2014 in Portugal was lower than in England between 1995 and 2015 (average 3-year coverage 60% vs. 69%, respectively). Despite the introduction of organized screening post-2008 in Portugal, 3-year coverage of resident women in 2012–14 (55%) was lower than in 2002–03 (58%). In England, 5-year coverage also decreased over time.

Organized programmes in Portugal 2012–14 covered at most for 40% of resident women aged 25–64; however, the proportion of eligible women invited for screening via a call/recall system varied from 6% (the North) to 60% (Alentejo), assuming 10% of resident

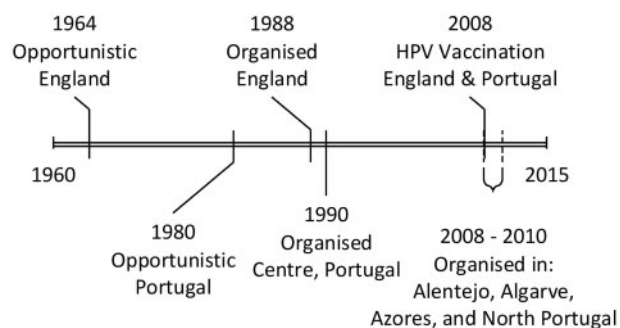


Figure 2 Timeline of main cervical cancer preventive interventions in Portugal and England. Opportunistic and Organised refer to screening programmes

women are excluded for clinical reasons⁷ (Supplementary table S5). Over the same period, the English NHS Cervical Screening Programme was available to all resident women aged 25–64, all eligible women (94% of resident) were invited to participate, and 91% of these were adequately screened.²⁸

Prior to 2008, in both countries, younger women had the lowest participation rates among women eligible for cervical screening (aged from 20/25–60/64, depending on the country) (Supplementary figure S6).

Discussion

Since 1998, cervical cancer incidence and mortality has declined in both Portugal and England, but has been consistently higher in Portugal^{1,29} despite higher prevalence for high-risk HPV and risk factors for cervical cancer (such as sexual activity, smoking and other STIs besides HIV) in Portugal. Indeed, HPV prevalence in England exceeds that in Portugal, with the age distributions of HPV prevalence in the two countries resembling those for Southern and Northern Europe in 1995–2009.³⁰ HPV vaccination was introduced in both countries too recently to have had an effect on cervical cancer incidence as the first vaccinated cohorts reached the screening age of 25 in 2015. Hence, the higher incidence in Portugal can only be explained by differences in screening.

Cervical cancer survival in England is similar to that in Portugal, despite lower incidence. This may be due to screening selectively preventing the less invasive cancers and to differences in access and effectiveness of cancer treatment between countries.³¹

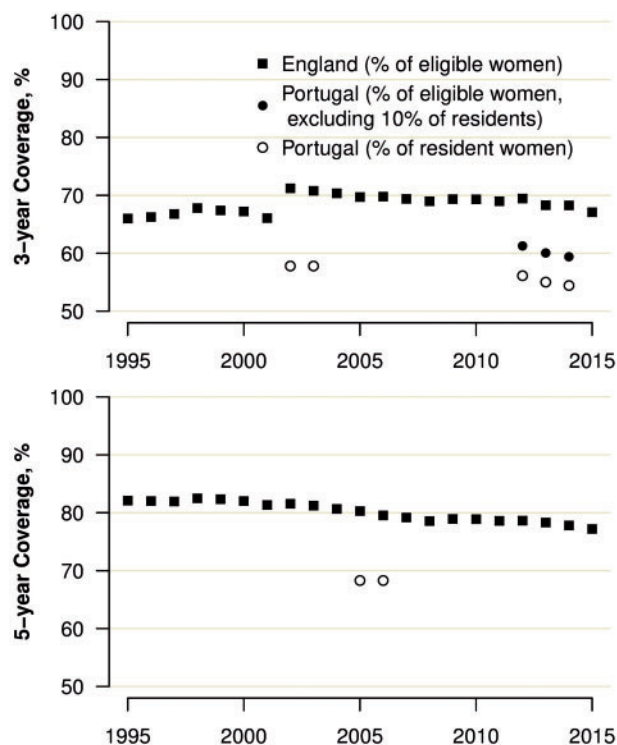


Figure 3 Screening coverage in women aged 25–64 in Portugal^{26,27} and England.²⁸ For England, coverage is defined as the proportion of eligible women aged 25–64 who were screened adequately within the previous 3.5 or 5 years. For Portugal, white dots represent coverage as the proportion of resident women aged 25–64 screened within the previous 3 or 5 years, and black dots represent coverage as the proportion of eligible women aged 25–64 screened within the previous 3 years (assuming 10% of resident women are excluded for clinical reasons⁷)

Registration inaccuracies have hindered trend analyses of cervical cancer.²⁹ More recently, Allemani and colleagues¹⁴ used individual patient data from all four Portuguese regional cancer registries (1998–2009) who reported 100% coverage of the national population and higher overall quality compared to the European average. We assumed similar quality for the data available to us (1998–2010). We corrected for inaccuracies in deaths certification following Arbyn and colleagues' approach.¹ We reproduced their results for Portugal, the Netherlands, and the UK, and extended the analysis to 2013. The reliability of these adjustments is debatable, particularly for Portugal where the Netherlands have been used as reference country, and further methodological research is needed. Consequently, our mortality (and CFR) estimates for Portugal may be underestimates, and the gap between countries could be even greater. These data limitations highlight the importance of high-quality registry data (which may reduce the number of deaths classified as being from uterine cancer not otherwise specified) and effective collaboration between cancer and screening registries to enable monitoring and evaluating the effectiveness of preventive interventions.

Our findings support existing recommendations for investment in well-organized cervical screening programmes.⁶ Opportunistic screening may have somewhat reduced cervical cancer mortality in Portugal but not to the extent seen in England. Time-trends suggest cervical cancer rates in Portugal would have declined more sharply had screening been organized. In the UK, incidence and mortality only declined post-central organization of screening. England (in contrast to Portugal) has seen reductions in the peak age of cervical cancer incidence.³²

These findings are likely generalizable to other European countries—most of which have or are implementing organized

programmes, as previous studies showed that the increasing cohort-specific risk of cervical cancer in Europe (after the 1930–40s) was overridden earlier and more pronouncedly in Northern Europe by the decreasing period-specific risk due to effective screening.² Encouraging trends are seen in the Baltic countries where organized screening has been initiated and incidence is stabilizing, whilst in Bulgaria and Romania (where screening is fairly opportunistic) incidence trends are still increasing.³³

Widespread opportunistic screening might also be hindering the extension of coverage of the recently implemented programmes in Portugal.^{6,7} Other European countries also in transition to organized screening (including Belgium, France, Greece, Italy, Spain and many Eastern European countries) may face similar challenges. Hence, countries with no screening yet (e.g. Albania, Azerbaijan) may benefit from thorough planning and implementation of organized programmes.

Acknowledgements

We thank the help of Pedro Moura Ferreira at the Social Sciences Institute Portugal; Nuno Miranda and Cristina Portugal at the National Programme for Oncological Disease, General-Directorate for Health, Portugal; Tereza Lopes, Filomena Horta Correia, Fernanda Loureiro, Ana Dinis, and Fernando Tavares at the regional health administrations of Alentejo, Algarve, Centre, Lisbon and Tagus Valley, and North; Gonçalo Forjaz, Joana Bastos, Ana Filipa Gonçalves, and Alexandra Mayer-da-Silva at the cancer registries of Azores, Centre, North, and South.

Funding

DM was funded by the Foundation for Science and Technology (individual PhD studentship SFRH/BD/84974/2012) on behalf of the Portuguese Ministry of Education and Science and the Human Potential Operational Programme of the National Strategic Reference Framework, within the European Social Fund of the European Commission's 7th Framework Programme. MJ was part funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Immunization at the London School of Hygiene and Tropical Medicine in partnership with Public Health England (PHE) (grant HPRU-2012-10096). The views expressed are those of the authors and not necessarily those of the NHS (England), the NIHR, the Department of Health (England), Public Health England or NIH Portugal.

Supplementary data

Supplementary data are available at *EURPUB* online.

Conflicts of interest: None declared.

Key points

- Cervical cancer incidence and mortality have been higher in Portugal than in England.
- High-risk HPV prevalence, sexual behavioural risk, and the prevalence of other risk factors for cervical cancer, such as smoking and other STIs (apart from HIV), have been lower in Portugal than in England.
- Differences in cervical screening are likely to explain the higher burden of cervical cancer in Portugal compared to England.
- Cervical cancer rates in Portugal are likely to have declined more rapidly had cervical screening been organized earlier.

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