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Brain cancer cluster investigation around a factory emitting dichloromethane

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Background: The health risks associated with dichloromethane (DCM) for the general population living near industrial activities have not yet been quantified, primarily due to lack of epidemiological datasets. In the absence of such human data, we undertook a cancer cluster investigation in Cyprus around a historically using DCM plant producing shoe soles that were globally exported. We designed the methodology to investigate the possible existence of a cancer cluster in the area around the factory (point zero) and within a radius of 500 meters. **Methods:** A retrospective comparative population study was designed using a group of cancer patients living or working in the chosen geographical area around the factory. **Results:** Mean stack emissions of DCM of 88 mg/Nm^3 and flow rates of 850 g/h exceeded the permissible DCM limits established for industrial zones. Brain and central nervous system (CNS) cancer incidence rates showed significant ($P < 0.001$) increase in the study area around the plant when compared with those observed in other areas of Cyprus. Calculated standardized incidence ratios for brain/CNS after adjusting for the age at diagnosis ranged from 11.3–25.7 [mean 6.5 (3.02 : 12.3)] for the study area. **Conclusions:** We showed the association between chronic, unintentional DCM exposures and brain/CNS cancer cases for the general population located in a residential area being in close proximity with a plant historically emitting DCM.

Introduction

Dichloromethane (DCM) or methylene chloride (CASRN, Chemical Abstract Services Registry Number, 75-09-2) is a chlorinated organic solvent that has been widely used in the industry.[1] DCM finds use as paint stripper, in sprays/aerosols as propellant/solvent, in chemical processing, metal cleaning and degreasing, printer ink removal.[1] It is ubiquitous in the

environment, because of its high usage and volatility though a series of anthropogenic/industrial activities. As such, the IARC has published a few monographs for its carcinogenic potential and recently classified DCM as probable carcinogen, based on scientific evidence from occupational health studies;[1] no such general population health studies exist for DCM.

Unintentional exposures to chemical(s) and their mixtures for the general population residing around industrial activities in urban areas is an upcoming environmental health issue for the European Commission.[2] The chemical-based health risks for the general population living near industrial activities have not yet been quantified, primarily due to lack of such epidemiological datasets. A causal hypothesis was *a priori* formulated using occupational health evidence linking DCM with carcinogenesis.[1] In the absence of human data for DCM exposures in the general population, we undertook a cancer cluster investigation around a plant in Cyprus, using historically DCM in its activities producing shoe soles that were globally exported.

Methods

Study location and methodology

In 2012, we set out to investigate the possible existence of a cancer cluster around a shoe sole-producing factory in Latsia municipality, Nicosia, Cyprus. The factory initiated the shoe sole production around 1983 and stopped its activity in 2009 after intense pressure by residents whose households were located in close proximity to the factory. We designed the methodology to investigate the possible existence of a cancer cluster in the area around the suspected factory (point zero) and within a radius of 500 meters (figure 1).

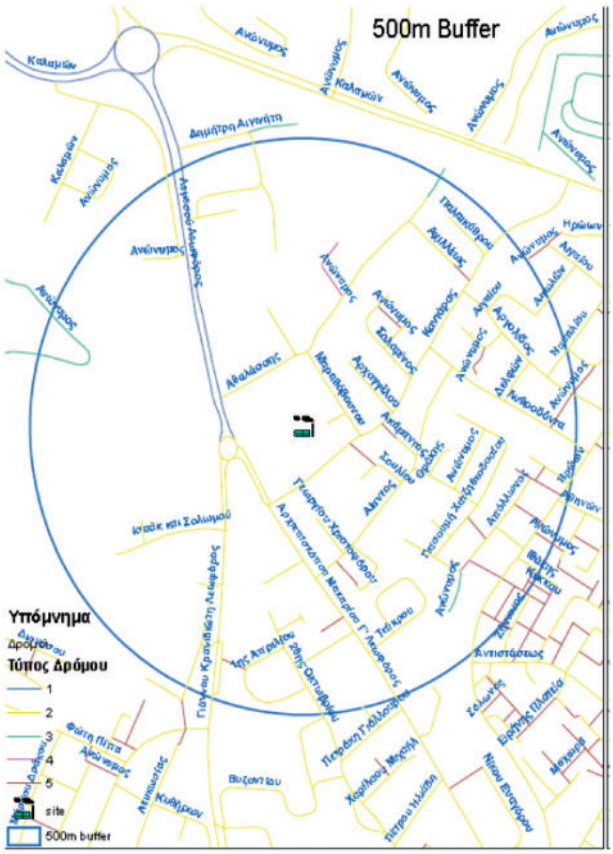

Figure 1 Map of the area showing the location of the factory and the geographical area under investigation of a possible cancer cluster in Nicosia, Cyprus. The radius of the study area around the factory was 500 meters

The 500-meters radius-based distance was *a priori* set for the study. A retrospective comparative population study was designed using a group of cancer patients living or working in the chosen geographical area around the factory that gave their written consent to participate in this study. All data used was fully anonymized. The study was approved by the National Bioethics Committee (EEBK/OP2013/01/28).

Given the radius of 500 meters around the factory and based on a cancer list received from the committee of cancer patients in the vicinity of the area around the plant (municipality of Latsia), we approached cancer patients or their immediate relatives (for those who had already died) in 2013 and asked for their written consent to include them in our study, by giving us access to their medical records, including diagnosis characteristics and pertinent dates. All brain cancer cases were histologically confirmed, but details of histology, such as subtypes of brain cancer were not available. We also geocoded the participants' home or work address by visiting each home of the participants, and confirmed using an official geographical map created by the Cyprus Department of Lands and Surveys in 2008. The population data used, both for the study area around the factory and other areas of Nicosia for comparison were based on CENSUS data (2011) and obtained in hard copies after acquiring proper approvals from the Population Registry of the Statistical Service of Cyprus in May 2012. Population CENSUS data showed similar age distribution of the population in the area around the factory when compared with other geographical areas of Cyprus (Supplementary figure S1). Eligible volunteers for this study were those that satisfied the following inclusion criteria: lived or worked in the selected study area ± 5 meters away from the borders of the selected zip codes, and diagnosed with any cancer between the years 1998–2008 (years for which cancer registry data existed). We recorded a total of 82 cancer cases who accepted to participate in our study, out of >90 cancer initially recorded cases. Drop-outs were observed due to the voluntary nature and the sensitivity of the subject. We had to exclude 32 cancer cases, because they did not meet the set inclusion criteria.

Statistical analysis

Observed cancer incidence rates in the study area were compared against those from specific geographical areas, namely, other municipalities of the Nicosia city (Latsia, Aglantzia and Agios Dometios), the whole Nicosia District and the whole population of Cyprus, as calculated using incident cancer data between the years of 1998 and 2008 that was obtained by the Cancer Registry of the Cyprus Ministry of Health. A reliable comparison of new incident cancer cases by the different geographical areas of Cyprus, including the study area was made possible by accounting for the calculated annual incident rates of each cancer site per 100 000 population for different areas of Cyprus (study area, Latsia, Aglantzia, Agios Dometios, Nicosia District). This calculation took place for each one of the 11 years (1998–2008) for which cancer incident rates data existed. The cancer sites that were considered in the study area were only those for which incident rates data was made available by the Ministry of Health for the period 1998–2008 (pancreas, brain-CNS, leukemia, lung, lymphoma, breast, uterine, esophageal, prostate and colon).

Standardized incidence ratios (SIR) were calculated using indirect age standardization of the mean brain cancer incidence rates data as available by the Cyprus Ministry of Health cancer registry database for the whole Cyprus population (1998–2000). Age at diagnosis was used to classify the observed cancer cases to the appropriate age group for comparison purposes. Continuous variable data were presented as mean $\pm$ standard deviation, unless stated otherwise. Statistical analyses were conducted with R (version 3.3.15). Tests were two-tailed. The level of a nominal significance was set at $P<0.05$.

Table 1 New annual crude cancer incidence rates (per 100 000 of population) for different geographical areas of Cyprus, including the study area

Year	Cyprus	Nicosia district	Municipality Ag. Dometios	Municipality Aglantzia	Municipality Latsia	Study area
1998	243	256	349	305	238	127
1999	248	259	232	243	218	187
2000	255	287	463	327	298	243
2001	276	288	371	280	377	238
2002	295	308	403	329	256	58
2003	308	327	386	320	398	114
2004	334	338	393	286	243	446
2005	323	316	514	410	212	381
2006	333	311	480	340	216	105
2007	365	337	479	327	270	199
2008	370	332	461	416	251	284
Annual Mean	304,5	305,4	412	325,8	270,6	216,6

Notes: Cancer sites included were: pancreas, brain/CNS, leukemia, lung, lymphoma, breast, uterine, esophageal, prostate and colon.

Table 2 New annual brain/CNS cancer incidence rates (per 100 000 of population) for different geographical areas of Cyprus, including the study area

Year	Cyprus	Nicosia District	Municipality Ag. Dometios	Municipality Aglantzia	Municipality Latsia	Study area
1998	6	9	16,5	0	8,5	64
1999	5	7	16,5	11	17	62
2000	6	8	16,5	5	16,5	0
2001	5,5	5	0	0	0	0
2002	5	6,5	8	10,5	0	59,5
2003	5,5	5	8	0	8	0
2004	6	7	8	10	0	56
2005	4	4	0	0	14,5	163
2006	7	5,5	0	5	0	0
2007	7	7	8	5	20	0
2008	6,5	5	8	5	6	47,5
Annual Mean	6	6	8	5	8	41

Results

Cancer cluster population characteristics

Out of a total of >90 cases that initially agreed to participate but either declined later or did not meet the inclusion criteria, a total of 82 cancer cases were included in the study and their cancer diagnosis was validated with their official medical records obtained after patient's written consent. The actual year of cancer diagnosis for those 82 cases ranged between from 1985–2011. Thirty-two cancer cases were excluded from further analysis, because they occurred outside the test period (1998–2008). Another set of 12 cancer cases were excluded, because their household geographic coordinates did not fall within the selected zip codes of the study area. Thus, we eventually included 37 out of the 82 registered cancer cases that met all of our inclusion criteria. About 40% of the selected cancer cases were males and the median age of the participants was 63 years old (range 03–91 years old).

Crude mean annual cancer incidence rate (1998–2008) for the study area was 216.6/100 000 population, being the lowest of all the regions under comparison (table 1); it showed an increase in 2004, reaching 446/100 000, but this trend did not continue. Also, the Latsia Municipality, where the study area belongs to, had an all cancer mean incidence rate slightly below the average for the District of Nicosia, i.e. 270.6/100 000 compared to 305.4/100 000.

Dichloromethane exposure assessment

A report by the Department of Labour Inspection of the Ministry of Labour and Social Insurance (unpublished data) and data from the Registrar of Companies in Cyprus showed evidence (hard copies) that the plant systematically used DCM in its operations starting around 1983 until 2009 (closure of the plant). Based on our team's personal visit to the factory site and the area around it, we observed literally adjacent houses on two sides of the plant. The area also looked residential with numerous homes around the plant. DCM measurements at the stack of the plant were taken in 2005 and 2006 by the Department of Labour Inspection (based on the Atmospheric Pollution Control Law of 2002 and the Waste Gas Emissions Permit no. 106/2004). Data showed that in almost all stack exhaust samples, mean DCM emissions of 88 mg/Nm^3 and flows of 850 g/h exceeded the permissible DCM limits established for industrial zones (20 mg/Nm^3 and 100 g/h, EU Directive 1999/13). Our personal contacts with officers and official records from the Department of Labour Inspection revealed that there was no gas emission permit for other industries in the 500-m area around the plant, except for a gasoline refilling station. Thus, it appeared that the plant was the only factory in the area with a waste gas emission permit, indicative of its substantial annual DCM emissions. Based on the annual number of plant operating hours reported by the company and the calculated mean DCM emissions rate, we calculated that the mean plant's annual total DCM emission rate was ~6.9 tonnes per year.

Meaningful (significant) cancer cluster

The prerequisites for the definition of a meaningful cancer cluster require the statistically significant increase in observed cancer cases for a specific area and period of time, and often involving a high cancer risk for a particular (sub)population group. The high risk could be associated with a common exposure agent for this population group, which could have significantly increased the risk of developing cancer. At the same time, the definition of a

Table 3 Standardized incidence ratios of brain/CNS cancer site applying indirect age standardization from the official Cyprus cancer registry data

Age groups	Area population	Age-adjusted SIR	Expected cases	Observed/Validated	SIR (95% CI)
0–4	134	4,93	0,07	1	13,8
5–9	182	1,80	0,04	0	0,0
10–14	224	4,20	0,10	0	0,0
15–19	208	1,70	0,04	1	25,7
20–24	141	0,00	0,00	0	0,0
25–29	165	2,10	0,04	0	0,0
30–34	122	1,00	0,01	0	0,0
35–39	198	3,77	0,08	0	0,0
40–44	217	2,00	0,05	0	0,0
45–49	166	3,90	0,07	0	0,0
50–54	146	10,73	0,17	1	5,8
55–59	109	13,10	0,16	0	0,0
60–64	89	9,00	0,09	1	11,3
65–69	70	21,00	0,16	2	12,4
70–74	44	11,00	0,05	0	0,0
75+	75	11,00	0,09	2	22,0
Total	2290		1,23	8	6,5(3,02 : 12,3)

meaningful (significant) cancer cluster could be satisfied with one or both of the following conditions, namely, (i) the cancer cluster referring to a rare cancer site, and/or (ii) the existence of a possible causal risk factor associated with the said cancer site.

Our estimates showed the significant ($P < 0.001$) increase in the incidence of new cases of brain cancer and central nervous system (CNS) in the study area around the plant when compared with those observed in other areas of Cyprus (table 2); a distance-response gradient could be observed showing how the average distance from the main study area (plant, point zero) could be reflected upon the new annual brain cancer incident rates (distance, annual mean brain/CNS incidence rates per 100 K population), i.e. study area (0.5 km, 41/100 K), Latsia (2 km, 8/100 K), Aglantzia (8 km, 5/100 K), Agios Dometios (13 km, 8/100 K), district of Nicosia that includes all of the aforementioned areas (>100 km, 6/100 K), and the whole Cyprus. The calculated SIR for brain/CNS after adjusting estimates for the age at diagnosis ranged from 11.3–25.7 with a mean estimate of 6.5 (3.02 : 12.3), showing the statistically significant ($P < 0.005$) increase in SIR of brain/CNS for those observed in the study area (table 3). Our calculations were conservative, since we excluded a few brain cancer cases for the following reasons: one case of brain cancer was excluded despite fulfilling our inclusion criteria, since this person eventually declined to consent despite her/his initial agreement to participate; two cases of brain cancer residing in the adjacent zip code to those included in our study area; and one brain cancer incident residing in the study area, but cancer-diagnosed in 1985, a year not included in the study period. Incidence rates for other cancer sites were also elevated in the study area, albeit not statistically significant ($P > 0.05$), such as, breast, leukemia and prostate. The combination of the facts, namely, (a) the rarity of the brain cancer site and (b) a statistically significant ($P < 0.001$) increase in the observed new cases against expected in the 500-meters radius area suggested the presence of a meaningful (significant) brain/CNS cancer cluster around the plant (point source DCM pollution).

Discussion

This is the first human study reporting the association between chronic exposures to DCM and age-adjusted incident brain/CNS cancer cases for the general population residing around a plant that was producing shoe soles for >25 years in Cyprus.

Is DCM responsible for carcinogenesis in the area around the factory? With >100 K chemicals marketed worldwide, evidence for carcinogenicity for most of environmental chemicals is scarce, since only 110 of them have been classified as known carcinogens and < 80 classified as probable carcinogens (category 2 A), including DCM, and <300 agents classified in category 2B (IARC volumes 1-117, item 5 http://monographs.iarc.fr/ENG/Classification/latest_classif.php). Historically, the IARC review panel on DCM carcinogenicity had earlier classified DCM to category 2B back in 1999,[3] because of insufficient potential of carcinogenicity in humans and sufficient evidence of carcinogenicity in animal studies. Since then, a number of human studies was published by looking into the possible association of occupational DCM exposures with carcinogenesis; this allowed the reassessment of updated scientific evidence during the latest (2014) IARC panel review on DCM carcinogenicity where DCM was classified as a probable carcinogen (category 2 A),[1] based on sufficient evidence for carcinogenicity in experimental animals and limited evidence of carcinogenicity in humans. The term limited evidence of carcinogenicity in human studies refers to evidence for positive association between exposure to the risk factor (DCM) and cancer for which there was a causal interpretation, but luck, uncertainty and confounding factors cannot be ruled out with almost complete certainty.[1]

The publicly available DCM epidemiological studies have all been conducted in occupational settings. Heineman et al.[4] reported the association between brain cancer and occupational exposure to DCM (300 men with brain cancer and 300 controls). A similar study design of brain cancer patients and matched controls but of a much larger sample collected from the whole of the United States (12 980 women who died by brain cancer) showed a statistically significant increase in the odds of brain cancer by 20% due to exposure to DCM.[5] There were two other studies in adults[6,7] and a study in children[8] that did not show a statistically significant increase in brain cancers due to DCM exposures. Other human studies have observed associations between occupational exposure to DCM and an increased risk for other types of cancer, including liver cancer and biliary tract cancer, Non-Hodgkin's lymphoma and multiple myeloma.[9]

A geographical resolution down to the kilometer range or less was not available using data from the Cyprus' official cancer registry. Because the plant was a known point source of historic DCM pollution, using and emitting DCM for more than 20 years, and because the carcinogenic potential of DCM was already known since the earlier IARC classification (1999), we *a priori* set the 500-meter range in 2012 as a scientifically sound distance away from the source (the plant) that our search for cancer cases could be focused upon. Actually, it has been commonly observed that an area of about 500-meter (or 500 x 500 area pixels) away from a suspected point source of exposure to carcinogen(s) may be used in cancer cluster

studies.[10,11] However, the extent of buffer zone around a point source of pollution, especially for volatile compounds, like the DCM may be also dependent upon the physicochemical properties of the pollutant and the local meteorological conditions. In fact, a distance-response gradient was observed extending beyond our study area (distance, annual mean brain/CNS incidence rates per 100 K population), supporting the choice of the selected buffer zone range, i.e. this study area (0.5 km, 41/100 K), Latsia municipality (2 km, 8/100 K), Aglantzia municipality (8 km, 5/100 K), Agios Dometios municipality (13 km, 8/100 K), including the district of Nicosia that includes all of the aforementioned areas (>100 km, 6/100 K).

It was found that the registry-based expected brain cancer incidence rates (extrapolated from the registry-based municipality incidence rates) were not nearly close to the observed cancer cases (8x times difference). Additionally, all cases were confirmed by house visits to confirm their residency there during the last years. Two out of the eight observed brain cancer cases were workers in the point source (out of a total of ~20 workers employed by the factory); when these two cancer cases were excluded part of a sensitivity analysis, the statistical ($P < 0.001$) significance of the calculated SIRs did not change. Additionally, two eligible brain cancer cases that we initially thought being within the 500-meter range were eventually confirmed being outside the 500-meter and within the 500–1000 meter radius, and thus, were excluded from incidence rate calculations.

A few limitations were observed in this study; one of them was the relatively small sample size. Despite the small sample size, we were able to observe a statistically significant increase in SIR of brain/CNS cancer cases for the study area; this statistical significance did not change even after exclusion of two brain cancer cases (plant workers). This was a retrospective study and as such the lack of a comprehensive DCM exposure assessment was an unavoidable limitation. A dispersion model to define a toxic threat zone of DCM hazards could be part of a future epidemiological study, while a human biomonitoring could indeed help in better integrating all possible sources and routes of DCM exposure but this was not possible due to the retrospective nature of the study. The lack of relevant confounder variables such as socioeconomic status and occupational history or other chemical exposures was also another limitation, but information was only available for age/sex of participants. Typical confounders that have been used in the statistical analysis of brain cancer epidemiological studies are: ionizing radiation, occupational history, various environmental or industrial chemicals, age, gender, demographics and residence location. Lifestyle/behavior risk factors, such as diet, alcohol and smoking are not yet considered as exposures that relate to brain cancer development, albeit commonly used in epidemiological studies focused upon other cancer sites (thyroid, lung, breast etc.).

The possible socioeconomic status confounding may not be relevant for this study area, because it represents a relatively homogeneous population with respect to its socioeconomic (SES) status. The city of Nicosia in Cyprus (where the study area was located) is neither characteristic for its wide urban social disparities, nor for its socioeconomically disadvantaged populations, particularly when compared with the magnitude of spatial differences in SES status typically observed in other European cities. Cyprus is a small country with a relatively homogeneous population and wide socioeconomic disparities are not to be found in large scale. The pixel area of 500-meters radius around the point source of the plant is not anticipated having large socioeconomic indicator differences with the rest of the municipality it belongs to (Latsia municipality) for which brain cancer incidence rates were available.

Conclusions

Here, we showed for the first time the chronic, unintentional exposures to DCM for the general population residing around a plant that was historically emitting DCM and the exposure DCM effects on the incident cases of brain/CNS cancer. To the best of our knowledge, there are no published studies on the health effects of DCM for the general population.[12] This dataset will further enrich the global literature on the health effects of DCM for the general population, calling for improved public health surveillance and awareness protocols regarding unintentional exposures to populations surrounding industrial activities.

Acknowledgements

We would like to thank all the residents of the affected area (Latsia) who gave written consent in participating. All data used was fully anonymized. The study was approved by the National Bioethics Committee (EEBK/OP2013/01/28). The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. KCM conceived, coordinated the study and collected/managed the data. MV and KCM did the statistical analyses and interpretations. Both KCM and MV wrote the manuscript.

Supplementary data

Supplementary data are available at *EURPUB* online.

Conflicts of interest: None declared.

Key points

- Dichloromethane exposure associated with elevated brain cancer incidences rates around a factory
- A meaningful cancer cluster around a point source was observed in Cyprus
- First ever human dataset linking dichloromethane exposures to brain cancer for general population

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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.