Time-Trends in Cervical Cancer Mortality in Portugal

Evolução Temporal da Mortalidade por Cancro do Colo do Útero em Portugal

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ABSTRACT

Introduction: The mortality rate due to cervical cancer is higher in Portugal compared to other European countries. This study aimed to evaluate the time-trends in cervical cancer mortality rates observed in Portugal over the last six decades.

Material and Methods: Age-standardized cervical cancer mortality rates reported in Portugal between 1955 and 2014, were collected from the International Agency for Research on Cancer (IARC). Joinpoint regression analysis was used to identify significant changes in mortality rates by assessing the percentage of annual variation (%AV) of the rate and respective 95% confidence interval (95%CI) according to the age groups.

Results: Among women with 30–39 years, cervical cancer mortality decreased 1.9% per year (95%CI: –2.3; –1.4) throughout the time-period, reaching 0.5/100 000 in 2014. Among women aged 40–49 years, CC mortality decreased between 1971 and 1981 (%AV = –11.6; IC 95%: –14.6; –8.6). Rates then increased by 2.4% per year (95%CI: 1.0; 3.8) until 2001 and such trend reverted from 2001 onwards (%AV = –5.2; IC 95%: –7.7; –2.6), reaching 3.0/100 000 in 2014. In women aged 50–64, 65–74 and 75 years or older, cervical cancer mortality rates decreased from 29.2 to 6.7/100 000, from 34.3 to 7.7/100 000 and from 24.7 to 9.2/100 000. The decline in mortality rates in these three age groups occurred mainly between 1970 and 1980, and there have been no significant changes in the last three decades.

Discussion: In Portugal, the most impressive decline in cervical cancer mortality rates occurred in the 1970s concurrently with changes in the National Healthcare System. The most important changes were the increased access to early diagnosis and the improvement in therapeutic approaches. The plateau that we observed among older women over the last three decades can be partially explained by factors with negative impact on adherence to cervical screening.

Conclusion: There was a marked decrease in mortality due to CC among all age groups. However, we observed a plateau of this indicator in more advanced age groups over the last three decades. These findings suggest the need of promoting adherence to cervical screening in Portugal.

Keywords: Mortality/trends; Portugal; Uterine Cervical Neoplasms/mortality

RESUMO

Introdução: A mortalidade por cancro do colo do útero em Portugal apresenta valores mais elevados em relação a outros países europeus. O objetivo deste estudo é avaliar a variação da mortalidade por cancro do colo do útero, observada em Portugal nas últimas seis décadas.

Material e Métodos: Obtivemos taxas de mortalidade por cancro do colo do útero (padronizadas para a idade) reportadas em Portugal (1955–2014), através da International Agency for Research on Cancer. Utilizando análise de regressão linear *joinpoint*, obtivemos a percentagem de variação anual da taxa (%VA) e respetivo intervalo de confiança a 95% (IC 95%) de acordo com a idade (30–39; 40–49, 50–64; 65–74 e ≥ 75 anos)

Resultados: No grupo com 30–39 anos, a mortalidade por CCU diminuiu 1,9% ao ano, durante todo o período (IC 95%: –2,3; –1,4), atingindo 0,5/100 000 em 2014. Nas mulheres com 40–49 anos houve decréscimo acentuado entre 1971 e 1981 (%VA = –11,6; IC 95%: –14,6; –8,6), com subsequente aumento de 2,4% ao ano (IC 95%: 1,0; 3,8) até 2001, mas que reverteu a partir desse ano (%VA = –5,2; IC 95%: –7,7; –2,6), atingindo 3,0/100 000 em 2014. A mortalidade por cancro do colo do útero diminuiu de 29,2 para 6,7/100 000, de 34,3 para 7,7/100 000, e de 24,7 a 9,2/100 000, respetivamente, nas mulheres com 50–64, 65–74 e com 75 ou mais anos. Nestes três grupos o decréscimo ocorreu principalmente nas décadas de 70 e 80, não havendo variação significativa da taxa nas últimas três décadas.

Discussão: O maior decréscimo da mortalidade por cancro do colo do útero observada em Portugal ocorreu na década de 70 em paralelo com profundas alterações no Sistema Nacional de Saúde caracterizadas pelo aumento do acesso ao diagnóstico precoce e da qualidade do tratamento. Nas últimas três décadas, a mortalidade por cancro do colo do útero estabilizou em idades mais avançadas, o que pode ser explicado parcialmente por fatores com impacto na adesão aos programas de rastreio.

Conclusão: Houve marcado declínio da mortalidade por cancro do colo do útero em todos os grupos etários, embora com estagnação deste indicador desde meados da década de 80 para grupos etários mais avançados. Os resultados sugerem a necessidade de incrementar a adesão a programas de rastreio em Portugal.

Palavras-chave: Neoplasias do Colo do Útero/mortalidade; Mortalidade/tendências; Portugal

INTRODUCTION

Cervical cancer (CC) is the eighth leading cause of cancer in European women, corresponding to an estimated 3% of all the new cases of cancer in 2018. Even though

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a great regional disparity has been found, it represents an important cause of cancer-related death in the female population from some European countries.[1] Two from each 100 cancer-related deaths affecting the Portuguese female population in 2014 were related to CC and almost one quarter of these regarded patients under the age of 55.[2]

CC development is due to a combination of different factors including smoking, long-term oral contraceptive use, multiparity and immunosuppression, namely related to human immunodeficiency virus (HIV) infection.[3] However, sexually transmitted human papillomavirus (HPV) infection is the determining factor for the development of this type of cancer.[3,4]

Sexually transmitted HPV infection leads to low-grade squamous intra-epithelial lesions usually showing spontaneous regression and persistent for a long time in approximately 10% of the patients and to the development of CIN-2 (cervical intraepithelial neoplasia) or higher.[3,4] The transition between squamous and columnar epithelium is the zone of the uterine cervix with the highest risk of malignant transformation following HPV infection.[4] Squamous cell carcinomas have accounted for 75% of the cases, even though different histological subtypes have also been found.[3,5]

Early detection of CIN-2 or 3 allows for a timely approach with excision and more frequent monitoring, which is determinant for the prevention of an invasive carcinoma[3,6] reducing the chance of the development of invasive cancer. Cervical cytology is the reference approach to CC primary screening.[7,8] However, current molecular biology based techniques for HPV detection allow for the identification of high-risk groups[3,9] and increasing screening sensitivity.[10]

Large-scale vaccination for HPV infection is currently in use in different countries,[3,11] even though its introduction is still too recent in order to allow for an assessment of its impact on CC incidence and mortality. The introduction of well-organised screening programs, available to the whole population, including HPV detection tests, are important public health strategies with a clear impact on the reduction of CC mortality.[7,11,12]

Monitoring of CC mortality trends over time is a particularly relevant public health measure, allowing for the identification of less favourable trends or even the search for new preventive strategies, considering that reinforced prevention will have an effect on the reduction of mortality.

This study was aimed at assessing CC mortality trend in Portugal, 1955-2014.

MATERIAL AND METHODS

This was a descriptive study of CC mortality trend in Portugal throughout the past six decades. Data were obtained from the International Agency of Research on Cancer (IARC) database[13] for all the years except information on the years 2004-2006 and 2014 (unavailable from the IARC) which was obtained from the Portuguese *Instituto Nacional de Estatística* (INE).[2] CC mortality rate for the Portuguese population between 1955 and 2014 referred to sequential five-year age groups. Mortality pattern trends for these age groups were visually assessed in order to regroup subsequent age groups with similar patterns of variation. Patients under the age of 30 were excluded from the analysis, due to the small mortality rate in these patients. Age groups were defined by the following classes: 30–39, 40–49, 50–64, 65–74 and 75 or older. Age-adjusted CC mortality rate was obtained for each study year and each age group by use of the direct method of standardisation and the 1976 European population was used as standard.[14]

Joinpoint regression models applied to each age group were used to assess CC mortality trend over time. Line segments separated by joinpoints corresponding to the years in which a significant change in mortality trend over time has occurred were generated by this statistical approach.[15] The annual percent change (APC) of the rate was based on the slope of each line. Therefore, time-trends represented as negative APC were obtained (whenever a reduction was found over a certain time) or as positive APC (when an increase was found) with the corresponding 95% confidence intervals (95% CI). The Joinpoint version 4.3.1.0 software was used for this analysis.[16] The mortality rates that were found and estimated by the regression model are presented as the number of deaths per 100.000 female population of the same age group, while a 0.05 significance level was considered.

Ethics committee approval was not required because the data used in this study is publicly available from the IARC and INE databases.

RESULTS

Age-adjusted cervical cancer mortality rate in Portuguese female population aged 30 or older (1976 European population considered as standard) has decreased from 19.4 in 1955 to 4.4/100,000 in 2014. This decrease was significantly found in all ages, even though a different variation standard of this indicator has been used, according to each age group. The estimated and observed mortality rate variation (according to the results obtained by the regression model) is shown in Fig. 1. The APC in the rate is shown in Table 1, with 95% CI and inflection points, showing a significant change in trends over time for each age group.

Age-adjusted mortality rate has decreased from 3.7 to 0.5/100,000 in the youngest group of female patients (Fig. 1), which has constantly (with no inflection points) and significantly decreased over the study period, with a –1.9 APC

(95% CI –2.3 - –1.4), as shown in Table 1.

Age-adjusted mortality rate has decreased from 17.4 to 3.0/100,000 (Fig. 1) in female patients aged 40-49, with points of inflection at 1971, 1981 and 2001 (Table 1). This trend was only reversed between 1981 and 2001, showing a significant annual 2.4% increase (95% IC range – 1.0-3.8) as shown in Table 1.

CC mortality rate has changed between 1955 and 2014

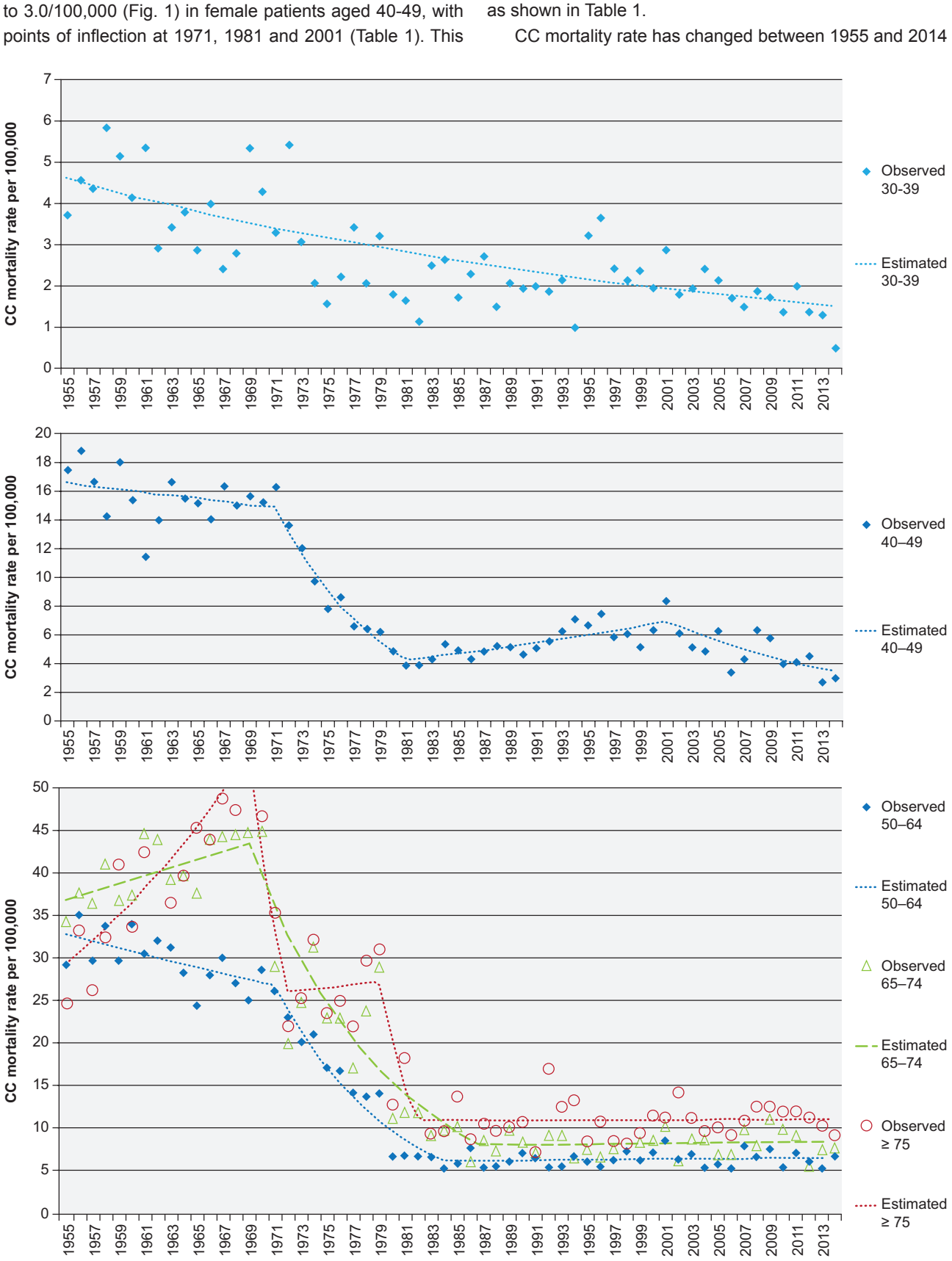

Figure 1 – Age-adjusted CC mortality; Portugal, 1955-2014

from 29.2 to 6.7/100,000, 34.3 to 7.7/100,000 and 24.7 to 9.3/100,000 in women aged 50–64, 65–74 and ≥75, respectively (Fig. 1). A significant decrease in CC mortality rate in women aged 50-64 has been found between 1955 and 1984, while this was found between 1969 and 1987 in women aged 65-74, with a significant increase in the oldest patients between 1955 and 1969 and decreasing trends between 1969 and 1982. A similar pattern of variation in CC mortality rate has been found in the three oldest groups of patients, with no significant changes from 1984, 1987 and 1982, respectively, in the 50-64, 65-74 and ≥75 groups, as shown in Table 1.

DISCUSSION

A significant reduction in CC mortality rate has been found in the Portuguese population between 1955 and 2014. Even though a decreasing mortality rate has been found within all the age groups over the study period, a steady decline in younger patients and a stagnation in the oldest groups have been found over the last years of the study period.

Portugal is one of the Western European countries with the highest CC mortality rates, which has been particularly significant before the 70s, a time in which a significant decline in this indicator has been found in Portugal, closing the gap with other European countries. However, the stagnation of the rates that was found from 1982 onwards made Portugal one of the countries with the highest CC mortality rates.[1] This worrying situation has been already described by other authors[17,18] and is worth mentioning.

Data collected throughout six decades was involved in this study. Changes over time in the diagnostic approach to CC and in the record of the cause of death could have an impact on mortality rate trends over time.[19] Changes in the international classification of diseases (ICD) have occurred over the study period, including three updates since 1970 (ICD-10 update is the most recent).[20–22] There was a significant change in mortality rate trends over time during the seventies, according to the results of the study and it seems unlikely that such significant rate variation could only have been related to these changes in ICD. In addition, this rate variation was not uniform within the five age groups analysed.

In line with other European countries, the first oncological centre has emerged in Lisbon through the first quarter of the twentieth century.[23] The oncological healthcare services provided by this centre were developed with a sustained logistic and technological update over the subsequent years.[24] By the end of the fifties and during the sixties and the seventies these were expanded and decentralised with the opening of new centres in Coimbra and later in Porto. Meanwhile, there was a significant technological improvement and as regards therapeutic approach to cancer, as well as the implementation of screenings aimed at early diagnosis of suspicious pre-invasive lesions.[23,24] During the seventies, the Portuguese healthcare system was significantly updated, particularly regarding the access to healthcare. The reform of the healthcare system was legislated in 1971 with the development of the *Centros de Saúde* (Healthcare

Table 1 – Annual percent change (APC) in cervical cancer mortality rate

Age group (years)	Points of inflection	Period of time	APC [95% CI]	*p*-value
30–39		1955 – 2014	–1.9 [–2.3; –1.4]	< 0.001
40–49		1955 – 1971	–0.6 [–1.6; 0.4]	0.208
	1971	1971 – 1981	–11.6 [–14.6; –8.6]	< 0.001
	1981	1981 – 2001	2.4 [1.0; 3.8]	0.001
	2001	2001 – 2014	–5.2 [–7.7; –2.6]	< 0.001
50–64		1955 – 1971	–1.2 [–2.1; –0.4]	0.004
	1971	1971 – 1984	–10.7 [–12.5; –8.8]	< 0.001
	1984	1984 – 2014	0.2 [–0.5; 0.9]	0.534
65–74		1955 – 1969	1.2 [–0.4; 2.8]	0.148
	1969	1969 – 1987	–9.0 [–10.6; –7.3]	< 0.001
	1987	1987 – 2014	0.2 [–1.1; 0.5]	0.787
≥75		1955 – 1969	4.5 [2.9; 6.1]	< 0.001
	1969	1969 – 1972	–21.7 [–42.8; 7.0]	0.121
	1972	1972 – 1979	0.7 [–5.5; 7.4]	0.819
	1979	1979 – 1982	–26.2 [–55.7; 23.1]	0.238
	1982	1982 – 2014	–0.0 [–0.8; 0.9]	0.935

Centres) as a draft of the future *Serviço Nacional de Saúde* (SNS), which was implemented in 1979. Despite its limited implementation, the first healthcare centres had a role mainly in prevention, associated with health promotion and monitoring.[25,26] The combination of these factors could have contributed to CC decreasing mortality that was found in the seventies, a greater access to early diagnosis, to treatment and to improved treatment quality, leading to improved survival, in line with what was described in another European population, although almost two decades earlier when compared to Portugal.[27]

A decreasing trend in CC incidence has been found in Portugal by a study describing the first years of this millennium, even though no decreasing trend in age-adjusted mortality rate has been found between 1980 and 2005.[17] According to our findings, the stagnation in CC mortality has remained over the past 30 years in the oldest patients, in line with the results described in Spain.[28]

Mortality was significantly reduced by cervical cytology (Pap test) aimed at CC screening.[3,7,8] This diagnostic test was first available in Portugal in the sixties,[29] although only used in opportunistic screening during most of the study time. Although planned CC screening strategies have emerged in the sixties, these were restricted to some areas in Lisbon.[23] The implementation of population based planned screenings was only started in 1990 within the central region of Portugal and was only widespread to other regions from 2008 onwards.[30] In addition, a screening geographical coverage of less than 50% has been found, with different compliance rates according to regions and showing a decreasing trend over the past four years, reaching a value close to 50% in 2014.[30] This situation could only reflect the use of an opportunistic screening, within the search for gynaecological healthcare or following the consultations of family planning, diverting patients from population-based screenings. However, this situation could be explained by non-compliance with any sort of screening. In Portugal,[31,32] in line with what has been found in Spain,[28] a lower screening compliance rate has been found in older *vs.* younger patients, which could explain for the stagnation of CC mortality rates in the oldest age groups.

According to Wang *et al.*, CC development in older patients depends on the level of screening compliance by the age of 50 to 60, with a higher prevalence in patients who were not adequately screened.[33] Epithelial atrophy in addition to regression of the transformation zone found in postmenopausal women have also shown a lower effectiveness for CC screening with advancing years.[34] In addition, HPV infection presents with a latency status, under immunological control within the epithelial basal layer, with reactivation from latency later in life.[35] Considering that post-CC survival decreases with age,[36] both circumstances combined could explain for the stagnation of the mortality rates amongst older patients. Therefore, CC prevention strategies aimed at elderly patients are crucial.

Patients under age 40, in whom a pregnancy is more likely, with an increased contact with healthcare professionals during perinatal period, will more likely undergo CC screening. This could explain for the decreasing trend in CC mortality over the whole study period which was found in the youngest age group. The pattern of variation in CC mortality rate that was found in the Portuguese population seems to show that the reduction found in younger patients is due to CC screening and to timely therapeutic approaches.

The highest incidence of CC has been found in Portuguese patients aged 40 to 49.[1] According to our findings, an increased mortality rate has been found in this age group in the eighties and in the nineties, even though this was reverted over the last years of this time series. This suboptimal trend has been described by other authors and was explained by the migration flow coming from the former Portuguese African colonies, from 1975 onwards.[18] Higher prevalence of HPV and HIV infection has been found in populations with an African origin, when compared to the remaining Portuguese population.[18,37] Concomitant HPV and HIV infection is related to an increased risk of CC mortality[7] in these populations.

A decreasing incidence of squamous cell and increasing incidence of adenocarcinoma (associated with a poorer outcome)[5] has been found,[38] which could be explained by a more difficult identification of this subtype in cytology.[3,5] The database that was used for this analysis did not allow for the study of the contribution of each histological subtype of CC in mortality, which is a limitation of this study. Further studies are needed for the evaluation of the incidence of adenocarcinoma and its contribution to CC mortality in the Portuguese population.

A decreasing incidence of cervical lesions has been found in geographical areas in which HPV vaccine has been introduced.[39] This vaccination was introduced in Portugal ten years ago[29] and studies on this subject are expected to understand its long-term effect on CC mortality in Portugal. Meanwhile, screening participation should be encouraged, leading to recommendations and promotion of screening compliance of the whole female population.

CONCLUSION

A significant decline in cervical cancer mortality has been found in Portugal, in all the age groups that were analysed. However, the relevance of this indicator remains almost unchanged since the middle eighties, for all the age groups except the youngest. The disclosure of information regarding the Portuguese population is crucial, according

to these findings, aimed at increasing the participation in cervical cancer screening programs.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data. Informed consents were obtained.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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