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Invasive Cervical Cancer Detection After Transition to Primary Human Papillomavirus Screening: Population-Based Linkage Study in Portugal

Deteção do Cancro do Colo do Útero Após Transição para o Rastreio Primário com Teste do Papilomavírus Humano: Estudo de Ligação de Dados de Base Populacional em Portugal

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ABSTRACT

Introduction: Invasive cervical cancer (ICC) is a key outcome for evaluating cervical cancer screening (CCS) programs. Monitoring ICC trends and distinguishing cancers detected within and outside the organized screening program are essential for assessing program impact, particularly during transitions such as the introduction of human papillomavirus (HPV) based primary screening.

Methods: We conducted a retrospective population-based study in Portugal's Central Region (2014 - 2023). Deterministic linkage was performed between the organized CCS database and hospital morbidity records. Invasive cervical cancer cases were classified as screen-detected or non-screen-detected based on prior screening history. Incidence rates were calculated using population denominators. Poisson regression models with log link and log-transformed population offsets were fitted to estimate incidence rate ratios (IRR) comparing cytology-based (2014 - 2019) and HPV-based (2020 - 2023) periods, adjusting for temporal trends.

Results: A total of 654 ICC cases were included. Screening participation remained broadly stable over time. The HPV-based period was associated with a significantly higher rate of screen-detected ICC (IRR = 1.94; 95% CI 1.11 - 3.40) compared with the cytology period. In contrast, ICC incidence outside the organized screening program did not differ significantly between periods (IRR = 0.94; 95% CI 0.65 - 1.35).

Conclusion: The transition to HPV-based primary screening was associated with a shift in ICC detection towards the organized screening program, without evidence of a corresponding increase in incidence among women diagnosed outside the organized screening program. These findings should, however, be interpreted with caution in light of the early phase of implementation and potential external factors influencing access to diagnosis. Overall, the results support a shift in detection within the screening pathway rather than changes in underlying disease occurrence. Strengthening integration between screening, hospital, and cancer registry data remains essential for robust evaluation of cervical cancer screening policies.

Keywords: Early Detection of Cancer; Medical Record Linkage; Papillomaviridae; Papillomavirus Infections/diagnosis; Uterine Cervical Dysplasia/diagnosis; Uterine Cervical Neoplasms/diagnosis

RESUMO

Introdução: O cancro do colo do útero (CCU) é um indicador-chave na avaliação dos programas organizados de rastreio. A monitorização de tendências e a distinção entre casos detetados no âmbito do rastreio e casos diagnosticados fora do programa são essenciais para avaliar o impacto do rastreio, sobretudo durante transições programáticas, como a introdução do rastreio primário com teste do papilomavírus humano (HPV).

Métodos: Foi realizado um estudo retrospetivo de base populacional na Região Centro de Portugal (2014 - 2023). Foi efetuado um cruzamento determinístico entre a base de dados do programa organizado de rastreio e a base de dados de morbilidade hospitalar. Os casos de CCU foram classificados como detetados no rastreio ou fora do rastreio com base na história prévia de participação. As taxas foram calculadas com os respetivos denominadores populacionais. Foram ajustados modelos de regressão de Poisson (função de ligação *log*) com *offset* logarítmico da população em risco para estimar razões de taxas (IRR) entre os dois períodos de rastreio (citologia, 2014 - 2019, e teste HPV, 2020 - 2023), com ajustamento temporal.

Resultados: Foram incluídos 654 casos de CCU. A participação no rastreio manteve-se globalmente estável ao longo do período do estudo. O período de rastreio com teste HPV associou-se a uma taxa significativamente superior de CCU detetados no âmbito do rastreio (IRR = 1,94; IC 95% 1,11 - 3,40), não se tendo observado diferenças significativas na incidência de CCU diagnosticados fora do programa (IRR = 0,94; IC 95% 0,65 - 1,35).

Conclusão: A transição para o rastreio primário com teste HPV associou-se a uma redistribuição da deteção de CCU para o âmbito do programa organizado, sem evidência de aumento concomitante da incidência entre mulheres diagnosticadas fora do rastreio. Estes resultados devem, no entanto,

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ser interpretados com cautela, no contexto da fase inicial de implementação e de fatores externos que possam ter influenciado o acesso ao diagnóstico. Globalmente, os achados são consistentes com maior deteção no percurso do rastreio e reforçam a importância da integração de sistemas de informação para avaliação das políticas de rastreio.
Palavras-chave: Detecção Precoce de Cancro; Displasia do Colo do Útero/diagnóstico; Infecções por Papillomavirus/diagnóstico; Neoplasias do Colo do Útero/diagnóstico; Papillomaviridae; Registo Médico Coordenado

KEY MESSAGES

- Human papillomavirus-based primary screening was associated with higher rates of invasive cervical cancer detected within the organized screening program.
- Invasive cervical cancer incidence among women diagnosed outside the organized screening program did not increase across periods.
- Findings support a shift in detection within the screening pathway rather than changes in underlying disease occurrence.
- Early-stage disease was more frequent among screen-detected cancers, reinforcing the role of organized screening in early diagnosis.
- Deterministic linkage between screening and hospital data enables pathway-specific evaluation and highlights the need for integrated data systems to support evidence-based policies.

INTRODUCTION

The incidence of invasive cervical cancer (ICC) remains the most robust indicator of the effectiveness of cervical cancer screening (CCS) programs, reflecting their capacity to prevent invasive disease through early detection and treatment of precursor lesions.[1,2] Over the past decade, many high-income countries have transitioned from cytology-based screening to primary human papillomavirus (HPV) testing, a shift supported by extensive evidence demonstrating superior sensitivity for detection of high-grade cervical lesions and reductions in ICC incidence.[3-5]

In Portugal, organized CCS has been progressively implemented since the 1990s, with the Central Region pioneering the establishment of a population-based program initially based on cytology.[6,7] The transition to HPV-based primary screening was introduced in 2019,[8] accompanied by an extension of the recommended screening interval from three to five years, reflecting the higher sensitivity and negative predictive value of HPV testing.[2] This transition aligned national policy with the European Beating Cancer Plan and the World Health Organization's global strategy for cervical cancer elimination by 2030.[9,10]

The effectiveness of CCS programs is ultimately reflected in long-term reductions in ICC incidence and mortality. However, during periods of program transition, early evaluation necessarily relies on intermediate indicators, such as changes in cancer detection within screening and patterns of diagnosis outside the program.[11,12] Distinguishing cancers detected within and outside the screening program provides critical insight into real-world program performance and equity, particularly in the early phases following the implementation of HPV-based screening.[11,12] Accurate classification of cancers according to screening exposure depends on the availability of individual-level data and robust linkage between screening and clinical data sources. In this context, the examination of basic demographic patterns, including age distribution, is important to ensure comparability of cases over time and to exclude major shifts in the underlying population at risk. Recent studies have demonstrated the value of linking population-based data sources, including screening registries, hospital discharge data, and cancer registries, for comprehensive and accurate cancer surveillance.[12-14] Countries with integrated information systems, such as Finland, Sweden, the Netherlands, and Australia, have provided detailed analyses of cervical cancer trends, enabling timely program adjustments and assessment of the combined effects of screening and vaccination.[14-17]

In this context, data linkage has become a cornerstone of cancer surveillance and screening program evaluation, enabling accurate estimation of incidence and differentiation between screen-detected and non-screen-detected cancers.[18,19] In Portugal, however, integration between screening, hospital, and cancer registry data remains limited, posing challenges to comprehensive outcome assessment. Consequently, evaluations of CCS performance must rely on the pragmatic use of available linked administrative and clinical data sources, within existing governance and data protection frameworks.[18,19] Additionally, external factors affecting healthcare delivery, such as the COVID-19 pandemic, may have impacted access to care, screening activities, and cancer diagnosis during the study period.[8,20-22]

Against this background, this study aimed to evaluate trends in ICC incidence in Portugal's Central Region between 2014 and 2023, distinguishing cases detected within and outside the organized screening program and

examining changes following the transition to HPV-based primary screening. Specifically, the study had the following aims: 1) describe annual numbers and rates of screen-detected and non-screen-detected ICC, including age distribution; and 2) evaluate the association between the transition to HPV-based screening and ICC detection patterns.

METHODS

Study design and setting

A retrospective population-based study was conducted in Portugal's Central Region between January 2014 and December 2023. The region covers an area of 22 635 km^2 and has approximately 1.66 million inhabitants.[23] The organized CCS program is delivered through 86 primary care units and supported by eight referral public hospitals, including a dedicated cancer center.

During the cytology-based screening period, women were invited to participate in screening at three-year intervals. Following the introduction of HPV-based primary screening (implemented in 2019, with program roll-out described here from 2020 onwards), the recommended screening interval was extended to five years. Between 2019 and 2022, an overlap between cytology- and HPV-based invitation cycles temporarily affected the eligible population and the denominators used for participation indicators. As this study captures the first screening round under the HPV-based program, these transitional dynamics should be considered when interpreting screening participation and absolute screening volumes.

Study population and data sources

The study population comprised all women diagnosed with ICC in the public hospitals of the Central Region between 2014 and 2023, as well as all women who participated in the organized CCS program within the same period. Population estimates were obtained from Statistics Portugal.[23]

Data were obtained from two primary sources that were subsequently linked at the individual level:

1) *SiiMA Rastreios,* the national screening information system,[24] which contains individual-level records of participation in the organized CCS in primary care, including screening test type (cytology or HPV), test results, triage procedures, and follow-up pathways;

2) Hospital morbidity databases (GDH), a national administrative database of hospital admissions and day cases, which includes diagnostic information coded using the International Classification of Diseases, 10th Revision (ICD-10),[25] as well as basic demographic characteristics.

The screening database was used to identify women participating in the organized CCS program and to characterize prior screening history, while GDH data were used to identify ICC diagnoses occurring in the public hospital system of the Central Region. The combination of these data sources, through individual-level linkage, enabled the classification of ICC cases as *screen-detected* or *non-screen-detected* based on prior screening history, and supported the analysis of cancer detection patterns in relation to screening exposure.

Invasive cervical cancer case identification and data abstraction

Invasive cervical cancer cases were identified from GDH databases of the eight public hospitals in Portugal's Central Region, following institutional and ethics committee approvals. For each case, additional clinical information (date of diagnosis, age at diagnosis, and tumor stage at presentation) was obtained from hospital clinical registries.

In each participating hospital, data abstraction was performed by a designated co-investigator using a standardized data collection template to ensure consistency across centers. Extracted data were subsequently harmonized and consolidated into a single analytical dataset.

Annual aggregates of ICC cases were generated to support the calculation of study indicators, including the total number of ICC diagnoses and their distribution according to screening detection status. Definitions of study indicators, data sources, and calculation methods are summarized in Appendix 1, Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24709/15995).

Linkage procedure

A deterministic linkage was performed between the organized CCS database and hospital morbidity records using a unique national health user identifier derived from the national health system number. Record linkage was conducted using identifiable data under restricted access conditions. Following successful linkage, all personal identifiers were pseudonymized prior to analysis; subsequent analyses were performed on aggregated data.

Hospital morbidity records from the eight public hospitals in the Central Region were first harmonized and merged into a single consolidated dataset. Duplicate records corresponding to the same ICC case across different hospitals were identified using the unique identifier and removed, ensuring that each cancer diagnosis was counted only once.

The consolidated hospital dataset was then deterministically linked to individual-level screening records from the CCS database. Screening histories were used to classify ICC cases according to screening detection status. Invasive cervical cancer cases were classified as screen-detected when an abnormal screening test or referral recorded within the organized CCS program was identified before

diagnosis, within the recommended program-specific interval (36 months for cytology-based screening and 60 months for HPV-based screening). During the transition period, classification was based on screening modality and corresponding interval applicable to the most recent screening episode recorded before diagnosis. Cases were classified as non-screen-detected when no prior screening record meeting these criteria was identified.

Owing to data protection and governance requirements, linkage with the National Cancer Registry using a common personal identifier was not feasible. Consequently, ICC case identification relied exclusively on hospital-based data sources, which allowed the capture of all ICC cases diagnosed and treated in the public hospital system of Portugal's Central Region during the study period.

Statistical analysis

Annual counts and rates of ICC were summarized using medians and quartiles (Q1 - Q3) to describe temporal patterns and account for the skewed distribution of annual indicators.

To compare screening periods (cytology-based: 2014 - 2019 *versus* HPV-based: 2020 - 2023), generalized linear models (GLM) with a Poisson distribution and log link were fitted to estimate incidence rate ratios (IRR) and corresponding 95% confidence intervals (CI). Screening period was included as the main independent variable. To account for differences in the population at risk, the natural logarithm of the relevant population denominator was incorporated as an offset term (number of screened women for screen-detected ICC, number of unscreened women for ICC diagnosed outside the organized screening program, and total female population for overall ICC rates). To account for underlying temporal trends, a time variable was additionally included as a continuous term coded from 1 to 10 (2014 - 2023). Given the limited number of time points and the potential correlation between time and screening period, sensitivity analyses were performed [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24709/15995)].

Differences in age group distribution and stage at diagnosis between screening periods were assessed using Pearson's chi-square tests. Age groups were defined a priori based on epidemiological[26] and programmatic[8] considerations (< 45 years, 45 - 64 years and ≥ 65 years). Stage distribution analyses were conducted separately for screen-detected and non-screen-detected cancers, with missing stage information retained and analyzed as a distinct category.

All statistical analyses were conducted using IBM® SPSS Statistics version 30.0.0.0.

Ethical considerations

Ethical approval for this study was obtained from the ethics committee of the Central Region Health Administration, as well as the ethics committees of the Portuguese Institute of Oncology of Coimbra Francisco Gentil (IPOFG), Coimbra Hospital and University Centre (CHUC), Baixo-Vouga Hospital Centre (CHBV), Tondela-Viseu Hospital Centre (CHTV), Figueira da Foz Hospital (HFF), Leiria Hospital Centre (CHL), Cova da Beira Hospital Centre (CHCB), Local Health Unit of Guarda (ULS-Guarda), and the Portuguese Institute of Oncology of Porto Francisco Gentil acting on behalf of National Cancer Registry.

As this was a retrospective study based on anonymized hospital registry data, the requirement for individual informed consent was waived by all participating ethics committees. The study was conducted in accordance with the ethical standards of the institutional and national research committees and the Declaration of Helsinki and its later amendments or comparable ethical standards.

RESULTS

The analysis included all ICC cases diagnosed in the public hospitals of Portugal's Central Region between 2014 and 2023, as well as all women participating in the organized CCS program during the same period. Over the study period, 720 ICC diagnoses were identified, and 594 074 screening episodes corresponding to 334 828 screened women were recorded. After exclusion of duplicate hospital records (n = 66) and cases without a valid personal identifier (n = 14), a total of 654 ICC cases were included in the final analysis.

Screening participation remained broadly stable across the study period, although the absolute number of screened women decreased during the early HPV-based period, reflecting the extension of screening intervals from three to five years (Table 1).

Following the transition to HPV-based screening, descriptive analyses showed an increase in the annual number and rate of ICC cases detected within the organized screening program, while ICC cases diagnosed outside the organized screening program remained relatively stable (Fig. 1). Median annual screen-detected ICC increased from 17.5 (12.0 - 19.3) in the cytology-based period to 29.0 (21.5 - 30.5) in the HPV-based period, corresponding to an increase in the detection rate from 0.26 to 0.58 per 1000 screened women (Table 1, Fig. 2). In contrast, median annual ICC diagnosed outside the organized screening program changed from 44.5 (41.0 - 50.8) to 40.0 (40.0 - 49.0), with incidence rates of 7.01 and 6.25 per 100 000 unscreened women, respectively. The coincidence between the median and the lower quartile can be attributed to limited variability in annual counts during this period (Table 1, Fig. 2).

Table 1 – Annual descriptive indicators of ICC detection by screening period

Indicator	Cytology-based (2014 - 2019) Median (Q1 - Q3)	HPV-based (2020 - 2023) Median (Q1 - Q3)
Screened population (n)	32 546 (29 320 - 37 069)	27 193 (19 528 - 29 469)
Screening participation (%)	41.9 (39.4 - 51.2)	45.0 (34.7 - 51.3)
ICC screen-detected (n)	17.5 (12.0 - 19.3)	29.0 (21.5 - 30.5)
ICC outside screening (n)	44.5 (41.0 - 50.8)	40.0 (40.0 - 49.0)
Proportion of screen-detected ICC (%)	25.1 (21.6 - 31.2)	37.6 (32.3 - 41.3)
Screen-detected ICC rate (per 1000 screened women)	0.26 (0.20 - 0.29)	0.58 (0.38 - 0.72)
ICC outside screening rate (per 100 000 unscreened women)	7.01 (6.50 - 7.90)	6.25 (6.13 - 7.43)

Q1: first quartile; Q3: third quartile

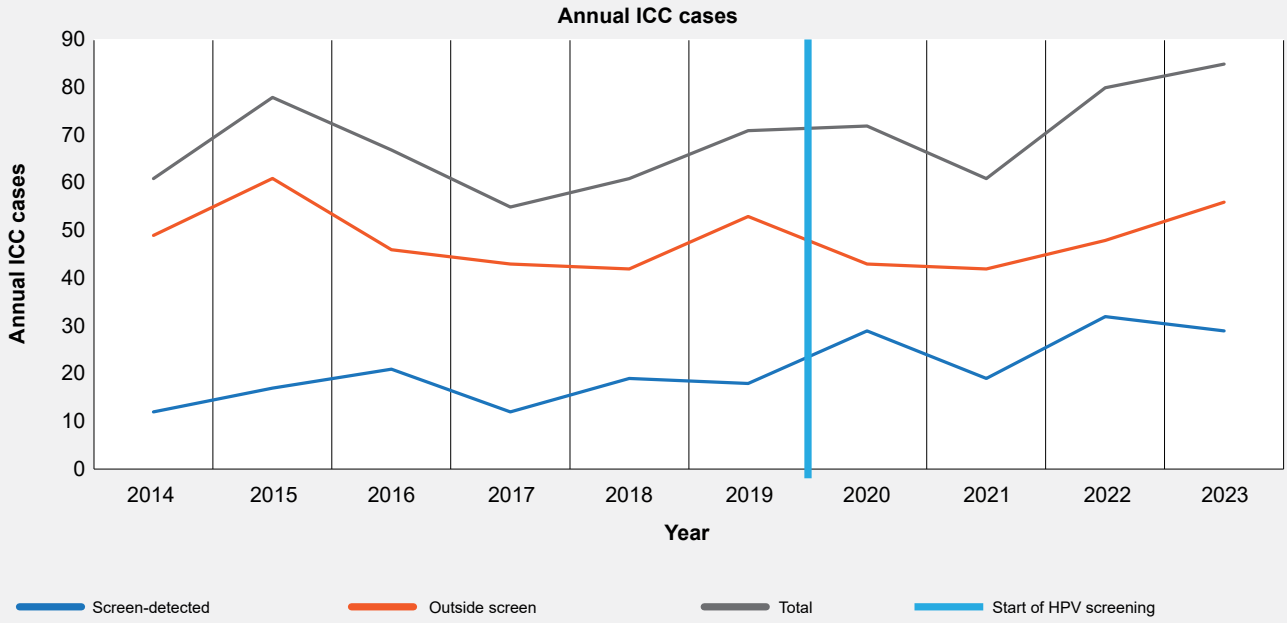

Figure 1 – Annual number of ICC cases by detection status (total, screen-detected, outside screening), Portugal's Central Region, 2014 - 2023. The vertical line indicates the introduction of HPV-based primary screening

Human papillomavirus-based screening was associated with a significantly higher rate of screen-detected ICC compared with cytology-based screening (IRR = 1.94; 95% CI 1.11 - 3.40, p = 0.020) after adjustment for temporal trends. Time was not independently associated with screen-detected ICC (IRR per year = 1.02; 95% CI 0.93 - 1.13, p = 0.687) (Table 2). Sensitivity analyses using models without temporal adjustment yielded consistent results, with a similar magnitude of association (IRR = 2.15; 95% CI 1.63 - 2.82) [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24709/15995)].

For ICC diagnosed outside the organized screening program, no significant difference was observed between screening periods (IRR = 0.94; 95% CI 0.65 - 1.35, p = 0.734) (Table 2) and no significant temporal trend was detected (IRR per year = 0.99; 95% CI 0.94 - 1.06, p = 0.836) (Table 2). Sensitivity analyses showed consistent

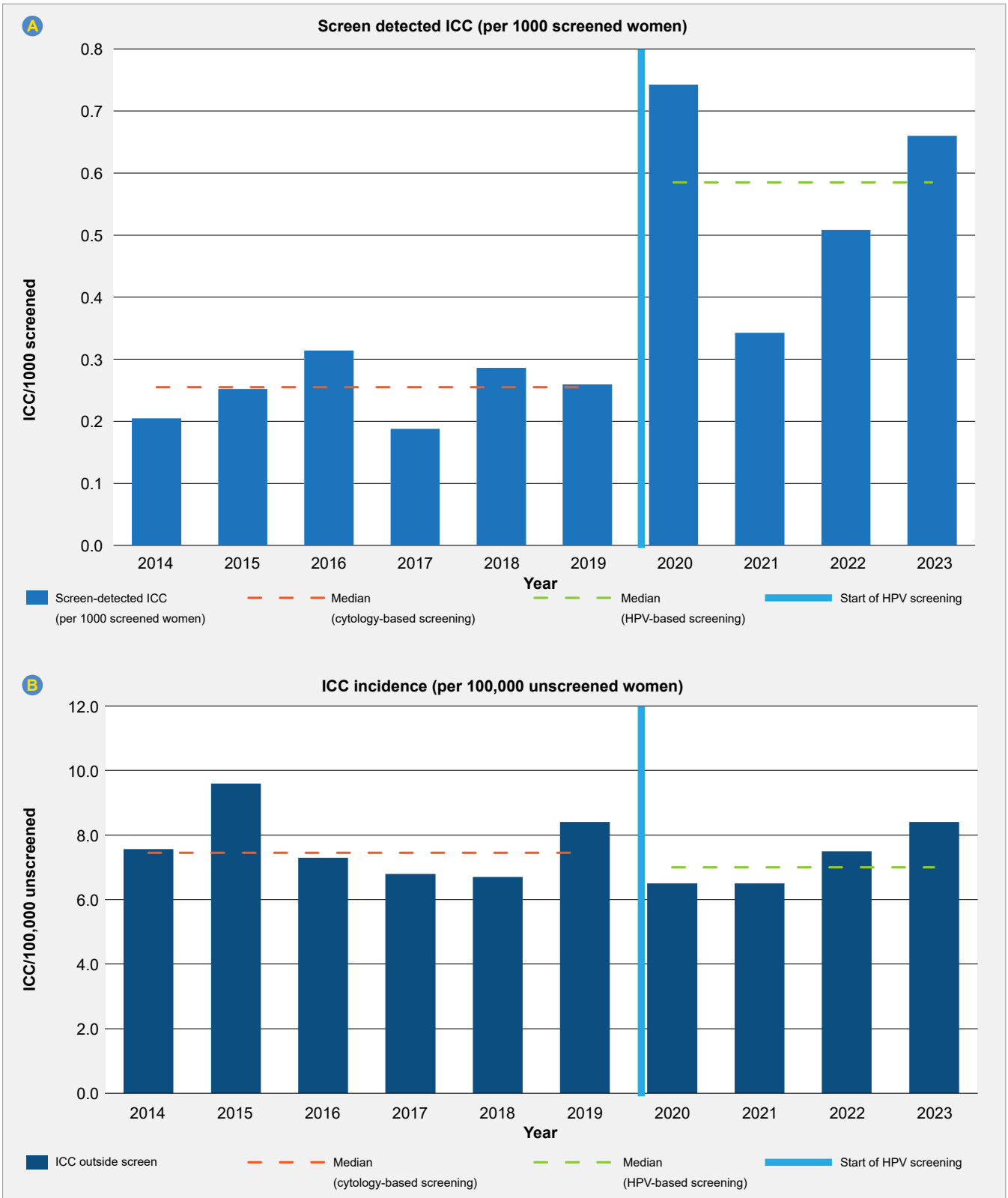

Figure 2 – Annual rates of ICC detected within and outside the organized screening program, Portugal's Central Region, 2014–2023. (A) Screen-detected ICC rate (per 1000 screened women). (B) ICC incidence outside the organized screening program (per 100 000 unscreened women). Horizontal dashed lines represent the median values for each screening period (cytology-based: 2014 - 2019; HPV-based: 2020 - 2023). The vertical line indicates the introduction of HPV-based primary screening.

findings [Appendix 1, Table 2 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24709/15995)]. Age-group distribution did not differ between screening periods. Stage at diagnosis was primarily associated with screening detection status, with early-stage disease being more frequent among screen-detected cancers in both periods. Among screen-detected cases, differences in stage distribution between periods were not statistically significant. Among non-screen-detected cases, stage distribution differed significantly between periods, with a higher proportion of late-stage disease in the HPV period and a lower proportion of cases with unavailable stage information (Table 3).

DISCUSSION

This population-based study evaluated ICC detection patterns in Portugal's Central Region between 2014 and 2023, distinguishing cancers detected within and outside the organized CCS program and examining changes following the transition from cytology-based to HPV-based primary screening.

Two main findings emerged. First, after the introduction of HPV-based screening, the rate of ICC identified within the organized CCS program increased, while screening participation remained broadly stable. In Poisson regression models including screening period and time, the HPV-based period was independently associated with a higher rate of screen-detected ICC compared with the cytology-based period and no independent temporal trend was observed. Overall, these findings suggest a shift in ICC detection towards the organized screening pathway following HPV implementation, without evidence of a corresponding increase in incidence outside the program.

Second, ICC incidence among women diagnosed

Table 2 – Multivariable Poisson regression analysis of invasive cervical cancer rates by screening period (Portugal's Central Region, 2014 - 2023)

Outcome	Screening period IRR	95% CI	*p*-value	Time IRR per year	95% CI	*p*-value
Screen-detected ICC	**1.94**	1.11 - 3.40	0.02	1.02	0.93 - 1.13	0.69
ICC outside screening	**0.94**	0.65 - 1.35	0.73	0.99	0.94 - 1.06	0.84
Total ICC	**1.05**	0.78 - 1.41	0.09	1.01	0.96 - 1.07	0.60

Models fitted using Poisson regression with log link and log-transformed population offsets

Table 3 – Age distribution and stage at diagnosis of ICC cases by screening period and detection status (Portugal's Central Region, 2014 - 2023)

A. Age group distribution of ICC cases by screening period			
Age group (years)	**Cytology-based (2014 - 2019)** n (%)	**HPV-based (2020 - 2023)** n (%)	***p*-value**[a]
< 45	97 (25.9)	74 (26.4)	
45 - 64	155 (41.4)	122 (43.6)	
65+	122 (32.6)	84 (30.0)	
Total	**374 (100)**	**280 (100)**	**0.765**
B. Stage at diagnosis among screen detected ICC cases			
Stage at diagnosis	**Cytology-based** n (%)	**HPV-based** n (%)	
Early-stage	53 (54.1%)	49 (45.4%)	
Late-stage	26 (26.5%)	44 (40.7%)	
Unavailable	19 (19.4%)	15 (13.9%)	
Total	**98 (100)**	**108 (100)**	**0.092**
C. Stage at diagnosis among non-screen detected ICC cases			
Stage at diagnosis	**Cytology-based** n (%)	**HPV-based** n (%)	
Early-stage	59 (21.4%)	35 (20.4%)	
Late-stage	131 (47.5%)	112(65.1%)	
Unavailable	86 (31.1%)	25 (14.5%)	
Total	**276 (100)**	**172 (100)**	**< 0.001**

a: Pearson's χ^2 test comparing distributions between screening periods within each subgroup. Stage information was unavailable for some cases and is presented as a separate category

outside the organized screening program did not differ significantly between screening periods and showed no significant temporal trend. This stability suggests that the observed increase in screen-detected ICC reflects changes within the screening pathway rather than a concurrent increase in population-level incidence.

These findings are consistent with international experience following HPV implementation, where early increases in cancers detected within screening were not accompanied by parallel increases in overall ICC incidence.[15,17,27] The increase in screen-detected ICC observed after HPV implementation is consistent with the higher sensitivity of HPV testing compared with cytology, particularly during the first screening round, when previously undiagnosed prevalent disease may be identified.[3,5,27,28] Population-based studies from the Netherlands, Nordic countries, and Australia have described early increases in cancer detection following HPV implementation, followed by stabilization or declines as programs mature.[14,15,17,28] These observations underscore the importance of sustained monitoring over longer time horizons to distinguish transient detection effects from long-term reductions in ICC incidence.

The inclusion of the 2020 – 2021 period within the HPV-based period represents an important source of potential bias, as the COVID-19 pandemic disrupted cancer screening and diagnostic pathways globally.[20,21,29] In addition to affecting screening participation, the pandemic may also have influenced access to diagnostic services and the timing of cancer diagnosis. These factors should therefore be considered when interpreting comparisons between screening periods.

A higher proportion of late-stage disease was observed during the HPV-based period among non-screen-detected cases, while differences among screen-detected cancers were not statistically significant. However, these findings should be interpreted in light of the substantial proportion of cases with missing stage information, particularly in the earlier period, which may reflect improvements in data completeness over time rather than true changes in disease stage at diagnosis. In addition, these patterns may reflect a combination of factors associated with the transition to HPV-based screening. An important organizational change was the extension of screening intervals from three years to five years, and the present study captures the first screening round of the HPV-based program, during which detection of prevalent cancers across a range of stages may occur. In this context, increased detection within the organized program likely reflects identification of previously undiagnosed disease rather than immediate changes in underlying disease occurrence.[2,17,28] Potential delays in diagnosis during the COVID-19 pandemic may also have contributed to the observed patterns.

Distinguishing cancers detected within and outside organized screening provides important insight into screening performance and equity. In this study, early-stage disease was more frequent among screen-detected cancers, whereas late-stage disease predominated among cancers diagnosed outside the organized program in both screening periods. Differences in stage distribution between screening periods were not statistically significant among screen-detected cancers but were observed among non-screen-detected cases. This suggests that stage at diagnosis may be more strongly associated with screening exposure than with the screening modality, although these findings should be interpreted cautiously given the limitations described above.[11,12]

Effective differentiation between screen-detected cancers and cancers detected outside the screening program depends critically on linkage between screening and cancer outcome data.[11] International experience shows that countries with integrated screening and cancer registry systems are better positioned to conduct continuous program evaluation, systematic cancer audits, and timely policy adjustments.[12–14,17] However, legal and governance constraints remain major barriers to data linkage in many countries, often outweighing technical limitations. Despite existing legal frameworks allowing the processing of health data for public health and quality assurance purposes, implementation remains heterogeneous across Europe.[30]

In Portugal, linkage between screening data and population-based cancer registry records remains restricted. In this study, deterministic linkage between screening records and hospital morbidity data enabled differentiation between screen-detected and non-screen-detected ICC. Compared with fully integrated registry systems, this approach does not allow systematic cancer audit, complete capture of cancers diagnosed outside the public hospital system, or standardized follow-up outcomes such as treatment and survival. While informative for regional program monitoring, it limits comprehensive national surveillance and detailed evaluation of long-term screening effectiveness.

From a public health perspective, these findings illustrate the importance of integrated data systems to interpret early effects of major screening transitions. Data interoperability should therefore be considered a structural component of effective cancer control, alongside screening technology and program design.

Strengths and limitations

This study has several methodological strengths. It is based on population-level data covering a ten-year period and includes all ICC diagnoses recorded in public hospitals within the study region, together with screening data from the organized CCS program. Deterministic individual-level

linkage between screening and hospital data enabled classification of ICC cases according to screening detection status using objective administrative records.

Several limitations should be acknowledged. First, linkage with population-based cancer registry records was not feasible, and ICC case identification relied on hospital morbidity data. Although all major public referral centers were included, cases diagnosed or treated exclusively in the private sector may not have been captured, potentially leading to under-ascertainment. Second, the relatively small number of annual time points may have limited statistical precision and restricted the ability to fully disentangle temporal trends from period effects in regression models, despite the use of sensitivity analyses. Third, stage at diagnosis was unavailable for a proportion of cases, particularly in earlier years, which may have limited the interpretation of temporal changes in stage distribution and reduced statistical power for stage-specific comparisons.

Finally, the study reflects the early phase of HPV-based screening implementation, including the first screening round under the new protocol and a period overlapping with the COVID-19 pandemic. Therefore, conclusions regarding long-term impact on population-level ICC incidence should be interpreted with caution.

CONCLUSION

The transition to HPV-based primary screening in Portugal's Central Region was associated with a significant increase in the rate of ICC detected within the organized screening program, without evidence of a corresponding increase in incidence among women diagnosed outside the organized screening program. These findings support the interpretation that early effects of HPV-based screening are reflected primarily in changes in detection within the screening pathway rather than shifts in underlying disease occurrence.

Given the early phase of implementation and concurrent external disruptions, these findings should be interpreted cautiously and require confirmation with longer follow-up.

Beyond the screening modality itself, the study highlights the importance of individual-level data linkage for monitoring screening performance during major programmatic transitions. Strengthening interoperability between screening systems, hospital databases, and cancer registries is essential to support robust evaluation of CCS policies and timely interpretation of early program effects.

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The authors declare that no AI tools were used during the preparation of this work.

AUTHOR CONTRIBUTIONS

RS: Conceptualization, methodology, validation, formal analysis, investigation, writing – original draft, writing – review and editing, visualization, project administration.

JAFM, ARG, PS: Conceptualization, methodology, validation, writing – review and editing, project administration.

FG: Conceptualization, validation, writing – review and editing.

FL: Conceptualization, writing – review and editing.

HN, HS, IS, MP, MB, SP, TR, VC: Investigation, writing – review and editing.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

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RS is the treasurer of the Portuguese Society of Senology.

All other authors have no conflicts of interest to declare.

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