Reasons for low cervical cancer survival in new-accession European Union countries. A EUROCARE-5 study.

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ABSTRACT

Purpose

With better access to early diagnosis and appropriate treatment, cervical cancer (CC) burden decreased in several European countries. In Eastern European (EE) countries, which accessed European Union in 2004, CC survival was worse than in the rest of Europe. The present study investigates CC survival differences across five European regions, considering stage at diagnosis (local, regional, metastatic), morphology (mainly squamous versus glandular tumours) and patients' age.

Methods

We analysed 101,714 CC women diagnosed in 2000-2007 and followed-up to December 2008. Age-standardised 5-year relative survival (RS) and the excess risks of cancer death in the 5 years after diagnosis were computed.

Results

EE women were older and less commonly diagnosed with glandular tumours. Proportions of local stage cancers were similar across Europe, while morphology- and stage-specific RS (especially for non-metastatic disease) were lower in Eastern Europe. Adjusting for age and morphology, excess risk of local stage CC death for EE patients remained higher than that for other European women.

Conclusion

Stage, age and morphology alone do not explain worse survival in Eastern Europe: less effective care may play a role, probably partly due to fewer or inadequate resources being allocated to health care in this area, compared to the rest of Europe.

Keywords

Europe, Cervical cancer, Morphology, Population-based study, Stage at diagnosis, Survival

Background

With better access to early diagnosis through population screening, increasingly implemented in Europe, and wealth and lifestyle changes, cervical cancer (CC) burden is decreasing in several European Union (EU) countries [1,2].

Since the early 2000s, following a proposal by the US National Cancer Institute, the concomitant use of chemo-radiotherapy (vs. radiotherapy alone) led to significant improvements in survival: this important advancement in CC treatment was adopted by many European countries. This impacted CC prognosis, mainly for those patients diagnosed with advanced disease [3].

Latest results of the EUROCARE-5 study (population-based investigation of European cancer survival), showed an increase in 5-year relative survival (RS) from 61% in 1999–2001 to 65% in 2005–2007 overall [4]. However, substantial differences in RS persisted in the EU to a disadvantage of Eastern European countries [4]. During 1999-2007, Eastern European countries have undergone strong political and economic changes (transformation), that have influenced the health system [5,6]. Most of these countries joined the EU from 2004 onwards.

Inadequacies in treatment and sub-optimal screening may influence poor outcome. However, differences in stage at diagnosis, morphological diagnoses, or age at diagnosis, i.e. the main prognostic factors affecting CC survival [4,7], may also play a role [8-10].

The aim of our retrospective observational study was to investigate survival differences for women diagnosed with CC across Europe, by morphology, age, and stage at diagnosis, also distinguishing between countries that joined the EU more recently, and those that did so earlier and other European countries.

Materials and Methods

We analysed 103,465 adult (≥15 years) women archived in the EUROCARE-5 database, diagnosed with primary malignant CC (C53, according to the third edition of the International Classification of Diseases for Oncology (ICDO-3; [11]) in 2000-2007, and followed-up to the end of 2008 [12]. After excluding major errors (missing, invalid or inconsistent information; 0.2%), cases known by death certificate only (1.0%) or diagnosed incidentally at autopsy (0.2%), and alive cases with unknown survival time (0.2%), the dataset included 101,714 CC cases.

Data were provided by 85 population-based cancer registries (CRs), with either regional or national coverage, from 28 European countries (including the four UK regions), grouped into five European regions (Supplementary Table 1 [Table S1]): Ireland and United Kingdom (UK/Ireland), and Northern, Central, Southern, and Eastern Europe.

Countries were additionally divided into two groups: *New Member States* (*New MS*; Bulgaria, Croatia, Czech Republic, Estonia, Latvia, Lithuania, Malta, Poland, Slovakia, Slovenia), EU members from 2004, and *Other countries*, the remaining 18 European countries and UK regions.

Squamous and glandular tumours defined according to ICDO-3 morphology codes (Table S2, [10]), were separated from other epithelial, mesenchymal, germ cell type, melanocytic tumours and those with mixed structures [*Other malignancies*]. Microinvasive squamous cell carcinomas (MSCC; ICDO-3 code: 8076) were also analysed.

Age at diagnosis was categorised into six groups (15-29, 30-44, 45-54, 55-64, 65-74, and ≥75 years). As regards stage, this information was not uniformly collected and regularly provided by all CRs. The EUROCARE-5 protocol required the collection of stage according to at least one of three staging systems: TNM (the most detailed), condensed TNM or extend of diseases (EoD, the least detailed). Condensed T, condensed N, and condensed M categories are local (TL, NL and ML) or advanced (TA, NA and MA); EoD categories are mainly local, regional, metastatic and unknown, and are used by CRs to summarise stage by indicating how far a cancer has spread from its point of origin, using all available information [13]. The EUROCARE-5 protocol did not specify clinical versus pathological stage, but if both were available, registries were asked to send pathological stage for non-metastatic cases, as information on metastasis is usually available from clinical stage. The categories of the three staging systems were reduced to mutually compatible ones, thus producing a new variable, reconstructed stage (i.e., stage here after), categorised into local, regional, metastatic, and unknown, thereby minimising the amount of missing information. [13]. For CCs, only 8 CRs, with either national (Austria, Norway, Slovakia and Slovenia) or regional (Parma (Italy), Navarra (Spain), Lower Silesia (Poland), and Grisons (Switzerland)) cancer registration (Table S1), provided good quality stage information, thus consenting stage-specific analyses for 13,937 women with CC, according to European Region, age at diagnosis, and morphology.

Statistical methods

Data collection, quality control and statistical methods are described elsewhere [12]. Further quality control procedures, i.e., analysis of the quality, comparability and completeness of cancer stage at diagnosis data, were developed to determine which stage data were reliable and which should be discarded [13].

RS, i.e. the ratio of observed survival in the patient group to expected survival (computed by Ederer II method) in a comparable group of the general population assumed to be free of the cancer of interest, was estimated using the complete approach and age-standardised (to take into account the different age structure of European populations [12]). Generalised linear models [15] were used to estimate the relative excess risk of death (RER) during the 5 years after diagnosis for local stage CCs, by European region, age at diagnosis, and morphology.

The analyses were performed using SEER*Stat and Stata softwares [16,17].

Results

Among the 101,714 CC cases included in the analyses, the most common morphology group was squamous tumours (73%), followed by glandular tumours (14%), and the group of *Other malignancies* (13%; Table 1).

Compared to *Other countries*, *new MS* were characterised by higher proportions of squamous tumours (77% versus 71%) and lower proportions of glandular tumours (8% versus 16%). MSCC was 8% of squamous tumours, varying from 6% in *new MS* to 10% in *Other countries*. Glandular tumours varied from 5% (Estonia) to 9% (Czech Republic and Slovakia) in Eastern Europe, and from 11-12% (Slovenia, Croatia, and Austria) to 21-22% (Iceland, UK-Northern Ireland, and Sweden) in the rest of the EU, reaching 29% in Finland. Low MSCC proportions were found in Eastern Europe (6% of squamous tumours, range: <1% in Poland; 9% in Czech Republic), whereas high proportions of *Other malignancies* were found in Austria, Belgium (Flanders), Croatia, and Poland (18-37%).

Age-standardised 5-year RS was 58% for *New MS* and 63% for *Other countries*. RS varied from 63% for squamous and glandular tumours to 51% for *Other malignancies*, with higher figures (for all three analysed morphology groups) in *Other countries* compared to *new MS* (squamous tumour: 65% versus 60%; glandular tumours 64% versus 57% and *Other malignancies*: 52% versus 50%; Table 2).

Morphology-specific RS estimates were high for Northern Europeans, and reached the lowest figures for women diagnosed in UK/Ireland and Eastern Europe (mainly Bulgaria, Latvia and Poland).

Overall, 5% (4% in *New MS*; 6% in *Other countries*) of women aged 15-29 years at diagnosis, 69% (74%; 67%) 30-64; 13% (14%; 12%) 65-74, and 13% (9%; 15%) ≥75 years (Table 3).

Northern Europe and UK/Ireland showed similar age distributions compared to Central, Southern, and Eastern Europe, with proportions of young (15-29 years) women about twice that of those in the remaining European regions (6-10% versus 3-4%). Northern Europe was also characterised by the highest proportion of elderly (≥75 years) women (17% versus 9-14%), and UK/Ireland of 30-44-year-olds (37% versus 28-34%). Eastern Europe had the lowest proportion of elderly women (9%).

Survival decreased with advancing age at diagnosis, varying from 85% for 15-29-years-olds to 34% for elderly women. Considering ages <65 years, women diagnosed in *New MS* and in Eastern Europe had a worse prognosis than those diagnosed in *Other countries* and in the rest of Europe, respectively. By contrast, no survival differences were evident for women aged ≥65 years.

Similar age distributions and age-specific RS estimates were found after considering squamous tumours only (Table 3). However, women aged ≥65 years and diagnosed with squamous tumours had a slightly better prognosis than their coetaneous overall.

The MSCC proportion decreased with advancing age, ranging from 22% in 15-29-year-olds to 1% in elderly women (Table S3). This ranking persisted regardless of European region. However, differences in MSCC age distribution across Europe were evident mainly for women aged <65 years.

The subset of 13,937 women with good stage data quality had similar age (Table S4) and morphology (Table 4) distributions, and morphology-specific RS (Table 4) to the whole CC cases diagnosed across the 28 countries, both overall and according to European region. Exceptions were higher proportions of 30-44-year-olds (36% versus 28%) and women aged ≥65 years (11% versus 15%) in Southern Europe (Tables 3 and S4).

Local stage predominated (53%; Table 4), followed by regional (25%) and metastatic (7%) disease stages. Of note, 45% of local stage CCs were diagnosed in women aged <45 years (Table S4).

Southern Europe had the highest proportion of local stage CCs (61% versus 48-56%) and the lowest proportion of metastatic disease (4% versus 7-9%). By contrast, the lowest proportion of local stage CCs and the highest proportion of metastatic cases were found in Northern Europe. The proportion of local stage CCs in Eastern Europe was similar to the average (50% versus 53%).

Five-year RS decreased with advancing stage: from 81% (local) to 46% (regional) and 16% (metastatic), and varied with morphology: similar survival figures were found for local squamous and glandular tumours (80-84%), but RS for regional squamous tumours was around 10% higher than that estimated for regional glandular tumours (48% versus 37%).

Eastern European women had the worst prognosis compared to women in the rest of Europe, irrespective of stage at diagnosis. RS for women diagnosed with local stage CCs in Northern and Southern Europe was the highest, both overall (87-88% versus 75-84%) and among squamous tumours only (MSCC included: 88-91% versus 80-83%; MSCC excluded: 86-88% versus 79-83%).

Even after adjusting for age and morphology, and excluding MSCCs, Central (RER=2 [95% confidence interval 1.3-2.4]) and Eastern (3 [2.0-3.7]) European patients had higher risk of local stage CC death than Northern European patients (Table 5). No differences in the risk of death were evident between squamous and glandular local tumours, also after excluding MSCCs.

Discussion

We found that, compared to CC women diagnosed in *Other countries*, those diagnosed in *New MS* (mainly Eastern European countries) were older, less often diagnosed with a MSCC or glandular tumours, but with similar proportions of local stage tumours. For Eastern Europeans, RS was lower than for other Europeans, both overall and according to age (except for women ≥75 years), stage (especially for non-metastatic disease) and morphology.

These results combined suggest different effectiveness of CC screening programmes (SPs) across Europe. Early CC detection effect is the younger age, the high proportion of local stage CC and the high proportion of MSCCs, glandular tumours and *Other malignancies*, but the low proportion of squamous tumours overall [18-20]. In 2016, 26 out of the 28 EU countries had a SP rolled out or planned [21]. Only in Bulgaria and Cyprus, no SP was available in 2016. SPs have been in place since the 90's in Northern European countries, in UK, The Netherlands, and part of Italy [22,23], but their

uptake increased after the publication of the Council Recommendation on Cancer Screening in 2003, and of The European guidelines for quality assurance in cervical cancer screening (EuG) in 2005 [24,25].

The well-known political, financial and social EU differences are the main reasons for inequalities in the provision and uptake of screening services in Europe.

In Italy, the well organised SP gradually increased in coverage overtime. In Parma, a SP was fully-activated in 2001 [26]. In Spain, the opportunistic screening on national and regional level was introduced following the Council Recommendation in 2003 [27]. In Slovenia, in 2003, the inefficient opportunistic screening from the '60s was transformed into a very well-performed national organised SP, completing its rollout in 2007 [6,28]. In Austria, Belgium, France, Germany, and Switzerland (Grisons) a cytological test in frame of opportunistic screenings has been offered since the '70s: in these countries, this was only slightly modified with the introduction of a few new regional organised SPs [23,29]. By contrast, during the study period, organised SPs had not been fully launched yet in Eastern Europe (Slovakia and Poland (Lower Silesia)) [23], and in the majority of *New MS* they were being planned or piloted. In Estonia and Poland, the first rollout of the nationwide SP only started in 2006 [6].

However, very little is known about SP compliance with the EuG implemented in Eastern Europe. Screening coverage and quality in Poland followed the EuG only partially, and screening had no impact on the CC burden in the country [30]. SPs inadequacy in Eastern Europe is also supported by the fact that, compared to those diagnosed in *Other countries*, women diagnosed in *New MS* were older, with low MSCC proportion and lower RS (for most age groups). The MSCC proportion is an indicator of screening coverage and intensity in the population: several studies found a direct positive association between high MSCC proportion and better CC prognosis, irrespective of the type of screening [18,26,31-32]. However, regardless of the diversity of screening quality, the proportion of local stage CCs in Eastern Europe was similar to the EU average, but RS was lower compared to the rest of Europe. Additionally, the excess risk of local stage CCs death remained higher than that found in Northern Europe, even after adjusting for age and morphology, or excluding MSCCs. These results suggest sub-optimal diagnostic examinations (probably due to partial adherence to evidence-based EuG) and, consequently, less effective treatment for local stages.

In Eastern Europe, a RS lower than elsewhere for the other stage categories suggests that also women with advanced disease probably received less effective treatment. It is known that in 1999 the concomitant use of chemo-radiotherapy (instead of radiotherapy alone) became the standard treatment mainly for advanced diseases [3]. In Germany, significant improvements in RS were found for regional and metastatic stage CC women diagnosed in 2002-2006 at 55-64 and 65-74 years, while SPs did not change for decades, indicating that the new treatment approach expanded at the population level may play a role [8].

We found that RS was similar across Europe for elderly women. Recent studies demonstrated that these patients are at risk of being treated inadequately but their outcome might be better due to the choice of a more appropriate treatment based on their general condition [33-35]. The extension of SPs was proposed for elderly women due to demographic changes and increasing life expectancy, mainly due to the availability of more effective treatments. Additionally, taking into consideration that screen-detected CCs have better prognosis compared to symptomatic CCs [19,36], the HPV self-test was also proposed in order to increase compliance with SP in long-term not-attendant women [37].

To our knowledge, this is the first European population-based study comparing patients and tumours characteristics, and RS among *New MS* and *Other countries* in relation to mass CC screenings, thus constituting the adequate basis for further assessment of trends of CC burden in Europe.

Although this study focused on CCs diagnosed in 2000-2007, results found for Eastern Europeans are still valid in subsequent years, with survival for 2010-2014 persisting lower than EU average in six of the Eastern European countries included in this study, regardless of the slight improvement in some of them [38]. By contrast, survival in Estonia, Slovenia and Croatia was higher or similar to the EU average [39].

One further study limitation concerns the difference in how CRs record stage at diagnosis and the fact that stage-specific analysis were performed on the subset of 13,937 cases (14% of EUROCARE-5 CC cases).

On the subject of registration and comparability of stage across countries, as largely discussed elsewhere [13], it is possible that CRs automatically received information on cancer cases, mainly from cancer hospitals and pathology laboratories. These cases may not contain complete stage information. In fact, it is possible that clinical notes do not state explicitly that a patient lacked nodal or distant metastases, or, similarly, negative results of examinations may not always be included. However, it is often possible to infer stage (mainly EoD) from the clinical notes. Otherwise, some CRs send personnel to hospitals to extract information from primary sources to complement the information that was sent passively. This practice, however, is resource-intensive and its efficacy depends on CR staff availability and competence. In order to reduce the amount of Mx and Nx (unknown), these stages were sometimes classified as M0 or N0. However, a previous sensitivity analysis [13], performed to estimate the error in assuming Mx as M0 revealed that in some CRs this assumption lead to stage misclassification, thus they were not adopted in our stage reconstruction. Furthermore, we found that overall 53% of CC cases were local at diagnosis, and a further 7% were metastatic, with corresponding 5-year RS estimates equal to 81% and 16%. These results are compatible to those found for white US women (local stage: 57%, and 5-year RS around 85%; metastatic stage: 11%, 5-year RS around 8%; [40]), suggesting that the stage reconstruction method we adopted is as valid as the stage information collected by European CRs.

As regards the fact that stage-specific survival analyses were carried out on a subset of CC cases under study, thanks to the similarity in age and morphology distribution and morphology-specific RS between this subset and the whole cases,

we are confident that results on this subset can be transferred to the entire EUROCARE-5 cohort, thus allowing to interpret the impact of the main prognostic factors in the entire EUROCARE-5 cohort.

Finally, high proportions of *Other malignancies* found in some countries suggested problems in quality of morphological codes, this is because the analyses were limited to only well-defined squamous and glandular tumours [11]. Lack of information on individual screening history, diagnostic procedures and treatment constituted additional study limitations.

Conclusions

It was estimated that there are currently 7,192 new CC cases and 3,788 female deaths in *New MS*, 19,976 cases and 7,797 deaths in *Other countries* [2]. Although, the burden of CC is not as severe in Europe, it is still significant, and it is a challenge to public health. The poorer age-, morphology-, and local stage survival estimates, the lower RS for regional stages, together with the high risk of local stage CC death in Eastern Europe suggest both inadequate organised SPs and inadequate treatment. The fact that multivariable modelling showed a persisting high risk of death in Eastern Europe, after considering stage, age and morphology, suggests that all these factors only partially explain the differences in outcomes. Hence, other factors must have contributed. A possibility includes less effective treatment were administered in these countries compared to the rest of Europe. Further studies are needed on treatment across Europe, and above all in Eastern European countries. The current joint European Network of Cancer Registries/EUROCARE round, which is collecting data on cases diagnosed up to 2012 [9], -emphasises the importance of collecting information on treatment, so forthcoming studies will be able to focus on treatment, allowing evaluation of treatment effectiveness and quality of care.

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Authors' contributions

MBL and PM designed the study, drafted the report

MBL, MK defined morphology grouping and literature searching

PM, SR carried out statistical analysis and helped to write the manuscript

MBL, PM, AH revised critically the manuscript and contributed to data interpretation

All authors contributed to the writing of the paper. They reviewed and approved the final version.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest

Ethical approval

The study protocol was approved by the Ethical Committees of the Fondazione IRCCS Istituto Nazionale dei Tumori (Milan) and of the Italian National Institute of Health (Istituto Superiore di Sanità-Rome). Data sending was considered to imply ethics approval of partecipating cancer registries.

Data availability

Further information regarding survival data are available on the web-site of the EUROCARE study (www.eurocare.it) at the following page: https://w3.iss.it/site/EU5Results/forms/SA0007.aspx

Informed consent

Not applicable

References

1. von Karsa L, Anttila A, Ronco G, Ponti A, Malila N, Arbyn M et al (2008) Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening, 1st edn. European Communities, Brussels

2. IARC (2018) The Global Cancer Observatory. http://gco.iarc.fr. Accessed ~~4 July 2019~~ 14 November 2019

3. National Cancer Institute (1999) NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival. http://www3.scienceblog.com/community/older/archives/B/nih478.html. Accessed ~~4 July 2019~~ 14 November 2019

4. Sant M, Chirlaque Lopez MD, Agresti R, Sánchez Pérez MJ, Holleczek B, Bielska-Lasota M et al (2015) Survival of women with cancers of breast and genital organs in Europe 1999–2007: Results of the EUROCARE-5 study. Eur J Cancer 51:2191–2205

5. Romaniuk P, Szromek AR (2016) The evolution of the health system outcomes in Central and Eastern Europe and their association with social, economic and political factors: an analysis of 25 years of transition. BMC Health Serv Res 16:95

6. Maver PJ, Seme K, Korać T, Dimitrov G, Döbrőssy L, Engele L et al (2013) Cervical cancer screening practices in central and eastern Europe in 2012. Acta Dermatovenerol Alp Pannonica Adriat 22:7–19

7. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D et al (2014) Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5 – a population-based study. Lancet Oncol 15:23-34

8. Chen T, Jansen L, Gondos A, Emrich K, Holleczek B, Luttmann S et al (2012) Survival of cervical cancer patients in Germany in the early 21st century: a period analysis by age, histology, and stage. Acta Oncologica 51:915-921

9. Haelens A, Roche L, Bastos J, Woronoff AS, Zorzi M, Francart J et al (2017) Trends in net survival from cervical cancer in six European Latin countries: results from the SUDCAN population-based study. Eur J Cancer Prev 26 Trends in cancer net survival in six European Latin Countries: the SUDCAN study:S92-S99

10. Vaccarella S, Franceschi S, Zaridze D, Poljak M, Veerus P, Plummer M et al (2016) Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017–40: a population-based study. Lancet Oncol 17:1445-1452

11. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM et al (2013). International classification of diseases for oncology (ICD-O), 3rd edn. World Health Organisation, Geneva

12. Rossi S, Baili P, Capocaccia R, Caldora M, Carrani E, Minicozzi P et al (2015) The EUROCARE-5 study on cancer survival in Europe 1999-2007: database, quality checks and statistical analysis methods. Eur J Cancer 51:2104-2119

13. Minicozzi P, Innos K, Sánchez M-J, Trama A, Walsh PM, Marcos-Gragera R et al (2017) Quality analysis of population-based information on cancer stage at diagnosis across Europe, with presentation of stage-specific cancer survival estimates: A EUROCARE-5 study. Eur J Cancer 84:335-353

14. Corazziari I, Quinn MJ, Capocaccia R (2004) Standard cancer patient population for age standardising survival ratios. Eur J Cancer 40:2307–2316

15. Dickman PW, Sloggett A, Hills, Hakulinen T (2004) Regression models for relative survival. Stat Med 23: 51-64

16. Surveillance Research Program (2013) SEER*Stat software: release 8.0.4. National Cancer Institute, Bethesda

17. StataCorp (2011) Stata statistical software: release 12: StataCorp LP. College Station, Texas

18. Kirschner B, Poll S, Rygaard C, Wåhlin A, Junge J (2011) Screening history in women with cervical cancer in a Danish population-based screening program. Gynecol Oncol 120:68-72

19. Andrae B, Andersson TM-L, Lambert PC, Kemetli L, Silfverdal L, Strander B et al (2012) Screening and cervical cancer cure: population based cohort study. BMJ 344:e900

20. Pettersson BF, Hellman K, Vaziri R, Andersson S, Hellström AC (2011) Cervical cancer in the screening era: who fell victim in spite of successful screening programs? J Gynecol Oncol 22:76-82

21. Espina C, Soerjomataram I, Forman D, Martín-Moreno JM (2018) Cancer prevention policy in the EU: Best practices are now well recognised; no reason for countries to lag behind. J Cancer Policy 18:40-51

22. Anttila A, von Karsa L, Aasmaa A, Fender M, Patnick J, Rebolj M et al (2009) Cervical cancer screening policies and coverage in Europe. Eur J Cancer 45:2649-2658

23. Anttila A, Ronco G; Working Group on the Registration and Monitoring of Cervical Cancer Screening Programmes in the European Union; within the European Network for Information on Cancer (EUNICE) (2009) Description of the national situation of cervical cancer screening in the member states of the European Union. Eur J Cancer 45:2685-2708

24. The Council of the European Union (2003) Council Recommendation of 2 December 2003 on cancer screening. Off J Eur Union 878:34-38

25. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N et al (2008) European guidelines for quality assurance in cervical cancer screening, 2nd edn. Office for Official Publications on the European Communities, Luxembourg

26. Serraino D, Gini A, Taborelli M, Ronco G, Giorgi-Rossi P, Zappa M et al (2015) Changes in cervical cancer incidence following the introduction of organized screening in Italy. Prev Med 75:56–63

27. Puig-Tintoré LM, Castellsagué X, Torné A, de Sanjosé S, Cortés J, Roura E et al (2008) Coverage and factors associated with cervical cancer screening: results from the AFRODITA study: a population-based survey in Spain. J Low Genit Tract Dis 12:82-89

28. Zadnik V, Primic Zakelj M, Lokar K, Jarm K, Ivanus U, Zagar T (2017) Cancer burden in Slovenia with the time trends analysis. Radiol Oncol 51:47–55

29. Burton-Jeangros C, Cullati S, Manor O, Courvoisier DS, Bouchardy C, Guessous I (2017) Cervical cancer screening in Switzerland: cross-sectional trends (1992–2012) in social inequalities. Eur J Public Health 27:167-173

30. Nowakowski A, Cybulski M, Śliwczyński A, Chil A, Teter Z, Seroczyński P et al (2015) The implementation of an organised cervical screening programme in Poland: an analysis of the adherence to European guidelines. BMC Cancer 15:279

31. Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W et al (2008) Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. J Natl Cancer Inst 100: 622-629

32. Zucchetto A, Franceschi S, Clagnan E, Serraino D, Zanier L, Franzo A et al (2010) Screening history of women with invasive cervical cancer in north-east Italy. Eur J Obstet Gynecol Reprod Biol 152: 200-204

33. Quinn BA, Deng X, Colton A, Bandyopadhyay D, Carter JS, Fields EC (2019) Increasing age predicts poor cervical cancer prognosis with subsequent effect on treatment and overall survival. Brachytherapy 18:29-37

34. Shimamoto K, Saito T, Kitade S, Tomita Y, Nagayama R, Yamaguchi S et al (2018) A study of treatments and outcomes in elderly women with cervical cancer. Eur J Obstet Gynecol Reprod Biol 228:174-179

35. Albert A, Lee A, Allbright R, Vijayakumar S (2019) Impact of age on receipt of curative treatment for cervical cancer: an analysis of patterns of care and survival in a large, national cohort. J Geriatr Oncol 10:465-474

36. Darlin L, Borgfeldt C, Widén E, Kannisto P (2014) Elderly women above screening age diagnosed with cervical cancer have a worse prognosis. Anticancer Res 34:5147–5151

37. Darlin L, Borgfeldt C, Forslund O, Hénic E, Hortlund M, Dillner J et al (2013) Comparison of use of vaginal HPV self-sampling and offering flexible appointments as strategies to reach long-term non-attending women in organized cervical screening. J Clin Virol 58:155-160

38. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M et al (2018) Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 391:1023-1075

39. OECD/EU (2008) Health at a Glance: Europe 2018: State of Health in the EU Cycle. OECD Publishing, Paris

40. Wright JD, Chen L, Tergas AI, Burke WM, Hou JY, Neugut AI et al (2015) Population-level trends in relative survival for cervical cancer. Am J Obstet Gynecol 213:670.e1-670.e7

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