SPANDIDOS
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Trends in cervical cancer: A decade-long analysis of incidence, survival and demographic disparities in a Northern Italian province

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Abstract. While cervical cancer is relatively uncommon in Western countries, it continues to pose significant concern due to its high mortality rates. Intraepithelial forms [cervical intraepithelial neoplasia (CIN) 2 and CIN 3] are more prevalent in regions with comprehensive screening coverage, particularly in areas that use the Papanicolaou test and HPV detection. The present study aims to characterize the trends of precancerous lesions and infiltrating tumors over a decade, assessing survival rates by age, stage and country of origin. A total of 1,752 CIN 2/3 lesions and 152 infiltrating cancers were recorded in the Reggio Emilia Cancer Registry between January 2008 and December 2018. A clear increase in CIN 2/3 lesions was observed over the years while infiltrating tumors remained rare and the numbers of cancer cases declined. The 5-year survival rate was found to be 67%, with survival closely correlated with stage (88, 82, 74 and 12% for stages I, II, III and IV, respectively) and age (84, 80 and 37% for ages <40, 40-65 and 65+, respectively). Multivariable analysis confirmed an excess risk for advanced stages III (HR 3.1; 95% CI, 1.3-7.3) and IV (HR 19.6; 95% CI, 8.2-46.7), as well as in women 65+ (HR 2.8; 95% CI, 1.0-8.1). Analysis of national origins revealed comparable stage distribution for Italians and non-Italians at stage I (41 vs. 47%), while a notable disparity emerged for stage IV (28 vs. 6%). This difference could be attributed to the average age of Italians compared to non-Italians (59 vs. 49 years). Overall, the present study underscored the importance of continued surveillance and intervention strategies targeting advanced-stage disease, particularly in older populations and among non-Italian patients. Efforts to enhance screening coverage and access to timely interventions remain critical in reducing the burden of cervical cancer and improving survival outcomes.

Introduction

Cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality among women globally, with an estimated 604,000 incident cases and 342,000 deaths worldwide in 2020 (1). Notably, the incidence rates exhibit a significant disproportionality, with low-income countries experiencing higher rates compared to their high-income counterparts (18.8 vs. 11.3 per 100,000), a trend mirrored in mortality rates (12.4 vs. 5.2 per 100,000) (1). In the context of Italy, the annual calculation of cervical cancer cases stands at 2,400, representing 1.3% of all female tumors, with mortality figures below 500 cases. Encouragingly, the 5-year survival rate is recorded at 67% (2). Human papillomavirus (HPV) stands as the primary risk factor for cervical cancer (3). Supplementary factors contributing to susceptibility include inadequate sanitation, sexually transmitted infections such as HIV and Chlamydia trachomatis, tobacco use, higher parity, and prolonged use of oral contraceptives (4). Notably, significant reductions in cervical cancer incidence and mortality have been observed across many countries, a trend attributed not solely to socioeconomic conditions but also to the decline in persistent HPV infection (5). Cervical screening has also played a pivotal role in reducing cancer incidence rates, by facilitating the detection of precancerous conditions such as cervical intraepithelial neoplasia (CIN 2) and CIN 3 (6). Cervical cancer is widely acknowledged as being nearly completely preventable owing to the remarkably efficacious primary prevention provided by the HPV vaccine and the secondary prevention afforded by screening programs. Regrettably, the implementation of these preventive

measures has not been uniformly applied across countries or even within them. As of May 2020, less than 30% of low- and middle-income countries (LMICs) had instituted national HPV vaccination programs, in stark contrast with over 80% of high-income countries (HICs) (7). According to the World Health Organization (WHO), screening is advised for women aged between 30 and 49, using either a Papanicolaou test (cervical cytology) every 3-5 years or an HPV test every 5 years. This screening regimen aims to detect precancerous forms and must be complemented by prompt and efficient treatment (8,9). In 2018, acknowledging the substantial global burden of cervical cancer and the growing disparities, the WHO Director-General issued a call for worldwide efforts toward the elimination of cervical cancer, defined as achieving an incidence rate of ≤4 per 100,000 women worldwide. This ambitious goal is to be pursued through a triple-intervention strategy, encompassing: 1) vaccinating 90% of all girls by age 15 years, 2) screening 70% of women twice in the age range of 35 to 45 years, and 3) ensuring the treatment of at least 90% of all precancerous lesions detected during screening (10). Despite concerted efforts to facilitate early diagnosis of lesions, the presence of invasive tumors continues to pose a significant public health challenge, frequently being identified at an advanced stage and carrying a poor prognosis.

This study aims to delineate the pattern of precancerous lesions and invasive cervical cancer in relation to age, stage, and country of origin.

Materials and methods

Patients. Data from this population-based cohort study were obtained from the Reggio Emilia Cancer Registry (RE-CR), approved by the provincial Ethics Committee of Reggio Emilia (Protocol no. 2014/0019740 of 04/08/2014). The leading information sources of the RE-CR comprise anatomic pathology reports, hospital discharge records, and mortality data, integrated with laboratory tests, diagnostic reports, and information sourced from general practitioners or by directly consulting medical records. Encompassing a population of 532,000 inhabitants, the RE-CR is considered a high-quality CR distinguished by its contemporaneous data (extending to the end of 2021), a high percentage of microscopic confirmation (100% for cervical cancer cases), and the absence of death certificate only (DCO) cases (11).

Clinicopathological data. Cervical cancer cases were identified and classified according to the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) (12), specifically under the topography code C53. The study included all cases of cervical infiltrating cancer diagnosed between 2008 and 2018. Data on the cancer stage, as per the TNM 7th edition (13), were obtained by reviewing medical records from hospital archives.

Statistical analysis. Descriptive analyses were conducted to examine patients' characteristics, age at diagnosis, and tumor morphology, stratified by tumor behavior: non infiltrating tumors (CIN 2/3) and infiltrating tumors. For cases of invasive malignancy, additional descriptive statistics were computed for tumor stage and T classification. In addition,

specific incidence rates were calculated for each tumor behavior category using the population of the Province of Reggio Emilia (recorded on January 1st of each year) as denominators. To allow for meaningful comparisons, incidence rates were standardized using the direct method, with the 2013 European Standard Population as a reference. The reported rates are presented on an annual basis: trends of incidence were performed for the years 2000-2020. The 5-year relative survival rate of cancers diagnosed between 2008 and 2018 was determined. Relative survival estimates overall survival adjusted for contributing causes of death and is defined as the ratio of the observed survival proportion in a cohort of cancer patients to the expected survival proportion in a comparable group of cancer-free individuals. Relative survival was estimated using the Pohar Perme method, wherein net survival for a cohort is assessed by weighting with the inverse of the individual-specific expected survival probabilities. Additionally, a multivariable Cox proportional hazard regression model was developed to investigate the relationship between stage, age, and overall survival, with time expressed in years. Kaplan-Meier methods were employed to ascertain time-to-event outcomes, specifically overall survival by age, stage, and age-adjusted stage. The 95% confidence intervals were also provided. Finally, trends over time were analyzed by calculating the annual percent change (APC) in age-standardized rates using Joinpoint Regression analysis. All analyses were performed using Stata 16.1 software.

Results

Between 2008 and 2018, a total of 1,752 cases of CIN 2/3 and 152 cases of invasive malignancy of the uterine cervix were registered (Table I). The mean age at diagnosis for CIN 2/3 cases was 37.8 years, while for invasive malignancy it was 56.7 years. Analysis of the distribution by age group revealed that 64.5% of CIN cases occurred in women under the age of 40, whereas 82.2% of the infiltrating forms were diagnosed in women aged 40 and above (Table I, Fig. 1). Among CIN 2/3 lesions, a striking 98.2% of cases exhibited squamous morphology, underscoring its predominant nature. In contrast, among the infiltrating forms, squamous morphology remained prominent, accounting for over 76.4%, while 16.4% showed adenocarcinoma morphology, and the remaining 7.2% represented other morphologies. Regarding stage distribution, the findings indicated that 42.1% of cases were diagnosed at stage I, followed by 12.5% at stage II, 20.4% at stage III, and 23% at stage IV (Table I). Analysis of T classification distribution revealed that 46.7% of cases were categorized as T1, followed by 16.5% as T2, 11.2% as T3, and 15.1% as T4 (Table I). Over the years, the incidence of infiltrating forms showed a declining trend, decreasing from 6.4 to 4.7 per 100,000 individuals, with an APC of -3.1% (Fig. 2A). Conversely, there has been a notable increase in the incidence of CIN 2/3 lesions, with an APC of 36.6% in the period 2015-2018, after decreasing in the following period 2018-2020 (Fig. 2B). In terms of stage distribution, among women under 40 years old, the majority of tumors (55.6%) were diagnosed in stage I, a pattern that remains consistent among women aged 40-64 (53.9%). On the other

Table I. Distribution of CIN2/3 and infiltrating cervical tumors by age, morphology and stage in the Province of Reggio Emilia, January 2008-December 2018.

| Parameter	CIN 2/3 (n=1752)		Infiltrating (n=152)	
	Mean, n	SD (%)	Mean, n	SD (%)
Age at diagnosis, years	37.8	10.5	56.7	16.6
Age at diagnosis (group), years				
<40	1130	64.5	27	17.8
40-64	602	34.4	76	50.0
≥65	20	1.1	49	32.2
Morphology				
Squamous cell neoplasms[a]	1721	98.2	116	76.4
Adenocarcinoma[a]	26	1.5	25	16.4
Carcinoma[a]	5	0.3	-	-
Others	-	-	11	7.2
Stage				
I	-	-	64	42.1
II	-	-	19	12.5
III	-	-	31	20.4
IV	-	-	35	23.0
Unknown	-	-	3	2.0
T				
T1	-	-	71	46.7
T2	-	-	25	16.5
T3	-	-	17	11.2
T4	-	-	23	15.1
Unknown	-	-	16	10.5

[a]*in situ* for CIN 2/3.
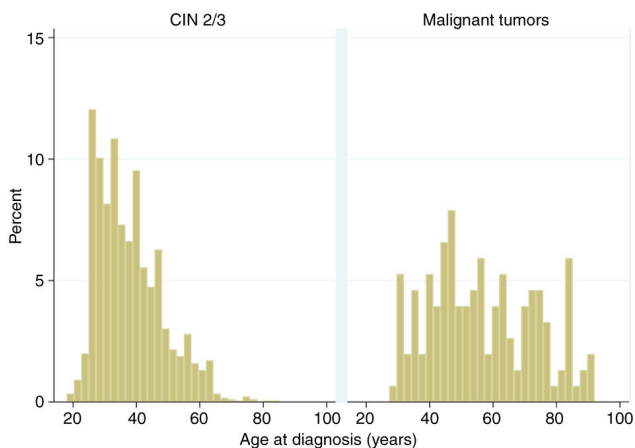
Figure 1. Distribution of CIN2/3 (non infiltrating) and infiltrating cervical tumors by age in Province of Reggio Emilia from January 2008-December 2018 (CIN, cervical intraepithelial neoplasia).

hand, stages III and IV prevail among elderly women, collectively constituting 86.1% of the entire case series (Table II). The overall 5-year survival rate stands at 66.6%, exhibiting a robust gradient correlated with the tumor stage. Specifically, survival rates were 88.2, 82.1, 74.1, and 12.1% for stages I, II, III, and IV, respectively (Table III). Additionally, age demonstrated a significant gradient, with survival rates of 84.3, 79.7, and 36.9%, for women under 40 years old, those aged 40-64, and 65+, respectively. The univariable analysis (Table IV) confirmed an increased risk associated with stages III (HR 3.3; 95% CI 1.4-7.7) and IV (HR 28.3; 95% CI 12.7-62.7), as well as for women aged 40-64 (HR 6.0; 95% CI 2.9-12.7) and those aged 65+ (HR 119.7; 95% CI 30.1-126.3). In the multivariable analysis, the excess risk persisted independently from other confounders for stages III (HR 3.1; 95% CI 1.3-7.3) and IV (HR 19.6; 95% CI 8.2-46.7), as well as exclusively in women aged 65+ (HR 2.8; 95% CI 1.0-8.1). Furthermore, the impact associated with stage and age is evident in the Kaplan-Meier survival estimates by stage (Fig. 3A) and age (Fig. 3B). However, upon adjusting for age, only stages III and IV exhibited a worse prognosis (Fig. 3C). Among the registered precancerous lesions, 19.9% of women were of foreign origin. However, the percentage increased to 22.4% among the infiltrating malignant lesions. While there are minor disparities in the distribution by stage between the early and locally advanced forms, notable differences emerged for stage III (17.8 vs. 29.4%) and IV (27.9 vs. 5.9%) (Table V).
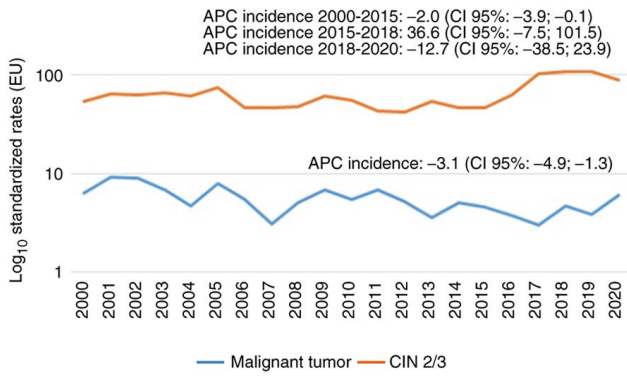
Figure 2. Log₁₀ age-standardized incidence rates of CIN 2/3 and infiltrating cervical tumors per 100,000 person-years in the Province of Reggio Emilia in the period January 2000-December 2020 (CIN, cervical intraepithelial neoplasia).

Discussion

This study aimed to provide a comprehensive overview of cervical lesions over a ten-year period, examining their incidence in relation to age, stage, and country of origin. One significant finding is the remarkably low incidence of infiltrating forms observed in our series, constituting only 0.8% of all female tumors. This incidence rate contrasts with the 1.3% reported in Italy nationally, according to the AIOM report (2), and the 2.5 % reported in Europe (14). In our study, incidence trends indicate a decline, with the Age-Standardized Incidence Rate (ASIR) decreasing from 6.4 to 4.7 per 100,000 individuals (APC -3.1%). Accordingly, findings from the literature spanning from 1990 to 2019 suggest a general decline in both incidence and mortality rates, except in East Asia and South Africa, where there has been a notable increase in the APC among women aged 15-49 (15). For instance, in China, there has been an observed increase in incidence, with the TSD rising from 11.1 to 16.4 (APC 3.7%), accompanied by a corresponding increase in mortality from 3.2 to 4.8 (APC 3.6%) (16). Furthermore, this increase appears more pronounced among women residing in rural areas (17). In Canada, a notable decline in cervical cancer incidence has been documented, with rates decreasing from 19 to 7 per 100,000 individuals. However, it is noteworthy that the highest incidence rates are recorded in advanced stages and among women over 55 years old (HR 1.34) (18). Similarly, in Taiwan, a significant drop in incidence rates has been noted with an APC of -7.2% (19). Our study, concomitant with the decline in infiltrating forms, showed a distinct increase in precancerous lesions, which have risen from 120 to 260 cases per year. This increase can be attributed to the introduction of HPV research, which has enhanced the detection rate by 40% (20). Notably, this increase predominantly affects younger women, with 65% of diagnoses occurring in those under 40 years old. HPV plays a key role in the development of cervical cancer. The persistence of high-risk (HR)-HPV infection following conization is widely recognized as a significant risk factor for CIN 3 recurrence (21), particularly in cases with positive endocervical margins (22). Indeed, HR-HPV-negative high-grade

cervical dysplasia is associated with more favorable outcomes compared to patients with documented HR-HPV infection (23). In Switzerland, the age-standardized incidence of cervical cancer and CIN 3 has shown an increase from 2.4 to 3.3/100,000 and from 11.6 to 26.9/100,000, respectively (24). The average age at diagnosis is 56.7 years, slightly higher than findings from an Indian study which reported an average age of 52.9 years (25). Additionally, an increase in diagnoses has been seen among young women aged 43 to 49, with no significant differences noted for those aged 65 and above (26,27). In developed countries, well-organized cervical cancer screening programs have been instrumental in achieving a significant reduction in invasive cancer incidence and mortality rates. These programs, which typically involve cytological screening combined with colposcopy and HPV triage, have led to a dramatic decline in the burden of invasive cancer incidence and mortality (28). However, there persists a glaring disparity in the cervical cancer burden between high-income countries (HICs) and low- and middle-income countries (LMICs), with the highest incidence and mortality rates observed in regions such as Africa, South Asia, and Latin America (29). While population-based screening programs have effectively decreased cervical cancer incidence and mortality in HICs, the same success has not been replicated in LMICs due to lack of effective organized screening programs. Data from the Norwegian CR show a clear reduction in mortality, with an 80% drop noted in women aged 26-69 who undergo screening (30). Finally, our study shows that 42% of infiltrating tumors are diagnosed in stage I. However, the incidence of metastatic tumors remains significantly high, accounting for 23% of the entire case series and escalating to 66% among women aged 65 and above. In our study, the 5-year survival rate was 66%, with survival rates for the first three stages hovering around 80% but sharply dropping to 12% for stage IV. Age exhibits similar trends, with survival rates overlapping for younger individuals and adults, exceeding 80%, but halving to 44% for those over 65 years old. After adjusting for age and stage, the multivariable analysis revealed an excess of risk for elderly women, and a significant risk persists for both stage III and particularly stage IV. From the literature we understand that advanced age is consistently recognized as a prognostic factor for survival (31), and in the presence of an advanced stage, the risk can be amplified up to 8 times (32). Data from the Surveillance, Epidemiology, and End Results (SEER) program confirm poorer survival outcomes for women 70 and above, attributed partially to receiving fewer treatments, with a 2.8 times increased risk of dying (33), a finding further corroborated by other studies (34). Regarding the relationship between Italians and non-Italians, among women with CINs, 80% are Italian and 20% are non-Italian. However, for infiltrating forms, the proportion of non-Italians rises to 22.4%. Interestingly, there are no differences observed in the distribution by stage for the early stages, whereas metastatic forms are more frequently recorded among Italians compared to non-Italians (28 vs 6%). This discrepancy is not surprising considering the fact that the average age of non-Italian patients with infiltrating cancer is 49 years, while among Italians it is 59 years. A wealth of information exists concerning cervical cancer screening and its implications. In 206 European countries, the availability of Pap tests stands at 78%, while HPV screening is accessible

Table II. Distribution of infiltrating cervical tumors by stage and age in the Province of Reggio Emilia, January 2008-December 2018.

Stage	<40 years n	<40 years %	40-64 years n	40-64 years %	65+ years n	65+ years %
I	15	55.6	41	53.9	8	16.3
II	3	11.1	5	6.6	11	22.5
III	6	22.2	16	21.1	9	18.4
IV	3	11.1	12	15.8	20	40.8
Unknown	0	0.0	2	2.6	1	2.0

Table III. Province of Reggio Emilia, January 2008-December 2018: 5-year relative survival overall of infiltrating cervical tumors, by stage and age.

Parameter	%	95% Confidence intervals
Overall	66.6	58.1-73.7
Stage		
I	88.2	76.6-94.2
II	82.1	53.7-93.9
III	74.1	53.1-86.8
IV	12.1	3.7-25.6
Age, years		
<40	84.3	63.3-93.8
40-64	79.7	68.6-87.3
65+	36.9	23.0-50.9

Table IV. Cox regression analysis of infiltrating cervical tumors adjusted for age and stage in the Province of Reggio Emilia, 2008-2018.

Parameter	Univariable analysis HR	Univariable analysis 95% CI	Multivariable analysis HR	Multivariable analysis 95% CI
Stage				
I	1.0	Ref.	1.0	Ref.
II	2.1	0.7-6.1	1.6	0.5-5.1
III	3.3	1.4-7.7	3.1	1.3-7.3
IV	28.3	12.7-62.7	19.6	8.2-46.7
Age group, years				
<40	1.0	Ref.	1.0	Ref.
40-64	6.0	2.9-12.7	1.6	0.6-5.1
65+	119.7	30.1-126.3	2.8	1.0-8.1

Ref. Cox (44).

in 35% of these nations. Compliance with screening among women aged 30-49 varies significantly, ranging from 84% in HICs to 48% in LMICs, and dropping to 11% in countries with very low income (35). SEER data reveal a higher prevalence of squamous cell carcinoma in Black Hispanic women, with elevated mortality rates and lower 5-year survival rates across all subtypes and stages (36). A Swedish study showed that immigrants had lower incidence rates of cervical cancer compared to those residing in their countries of origin but higher than native Swedes (Relative Risk 1.13) (37). Unfavorable factors associated with survival include receiving care in low-volume hospitals (38), socioeconomic deprivation (39), and being followed in non-university or non- (40). Additionally, black ethnicity, being displaced (41), and low level of education are risk factors associated with poor survival (25), as treatment also plays a crucial role in influencing outcomes (42). Among the strengths of this work, we highlight the fact that it is population-based data and therefore there is no selection bias, and it is recent and of good quality. Unfortunately, the work involves only one center, so in the future it would be important to repeat the analyses involving other Italian centers. Another limitation of the study is the lack of data on HPV vaccination and on the socio-economic status of the patients, which could have a strong impact on the incidence of these tumors.

In conclusion, with high adherence to screening and the availability of HPV vaccination programs, cervical cancer has become increasingly rare in Western countries. The reduction of cervical cancer incidence hinges on the widespread dissemination of the HPV vaccine among the entire at-risk population, coupled with ensuring screening for timely detection and treatment of high-grade dysplasia. Healthcare providers should focus on minimizing the occurrence of advanced-stage cancers by diligently attending to symptoms, especially in elderly women. It is imperative to conduct targeted investigations in this age group, which may not be included in routine screening and vaccination campaigns. By adopting a comprehensive approach that includes vaccination, screening, and symptom awareness, we can continue to make strides in the prevention and early detection of cervical cancer, ultimately saving lives and improving public health outcomes.

Acknowledgements

Availability of data and materials

The data generated in the present study are not publicly available due to ethical and privacy issues to but may be requested from the corresponding author. Requests for data must be approved by the Ethics Committee after the presentation of a study protocol.

Authors' contributions

LM conceptualized the study, performed the experiments, wrote the original draft, visualized the data and supervised the

Table V. Number and percentage of women with CIN2/3 and infiltrating cervical tumors in the Province of Reggio Emilia, January 2008-December 2018.

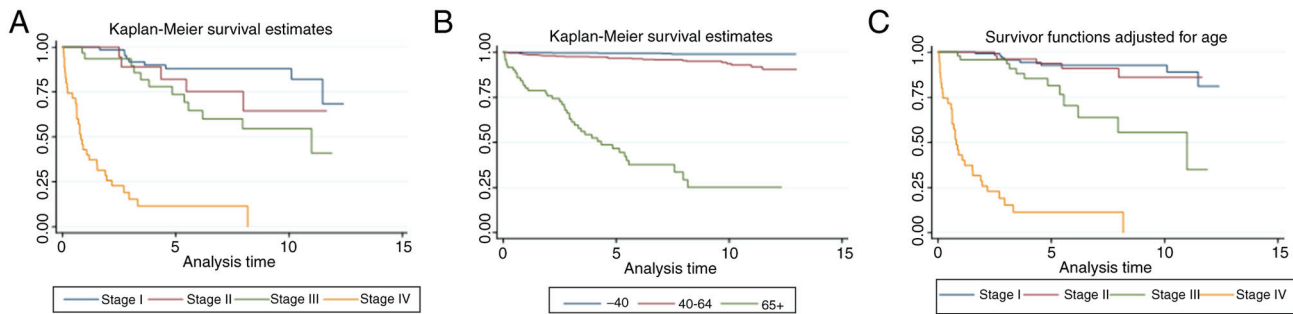| Population	CIN 2/3		Infiltrating		Total	
	n	%	n	%	n	%
Italians	1,403	80.1	118	77.6	1,521	79.9
Non-Italians	349	19.9	34	22.4	383	20.1
Total	1,752	100	152	100	1,904	100

Figure 3. Kaplan-Meier survival estimates by (A) stage, (B) age and (C) stage adjusted for age of infiltrating cervical tumors in the Province of Reggio Emilia January 2008-December 2018.

study. FMa analyzed the data. IB acquired the data, reviewed and edited the manuscript, and visualized the data and supervised the study. FR and VM performed the experiments and supervised the study. FMo, AN and LA analyzed and interpretated the data, and supervised the study. VDM conceptualized the study, wrote the original draft, performed the experiments and managed the study. All authors have read and agreed to the final version of the manuscript. LM and FMa confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This population-based cohort study used data from the Reggio Emilia Cancer Registry, approved by the Provincial Ethics Committee of Reggio Emilia (approval no. 2014/0019740 of August 2014). The Ethics Committee authorized, even in the absence of consent, the processing of personal data, including those suitable for revealing the state of health of patients who are deceased or untraceable for the execution of the study.

Patient consent for publication

According to Italian legislation, population-based cancer registries collect pseudonymized personal data for surveillance purposes that do not need the collection of explicit individual consent, without any direct or indirect intervention on patients, therefore the approval of a research ethics committee was not required (43).

Competing interests

The authors declare that they have no competing interests.

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