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RESEARCH ARTICLE

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Epidemiologic transition of lung cancer mortality in Italy by sex, province of residence and birth cohort (1920-1929 to 1960-1969)

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Abstract

Space-time analysis of mortality risk is useful to evaluate the epidemiologic transitions at the subnational level. In our study, we analysed the death certificate records for lung cancer in Italy in 1995-2016, obtained from the Italian National Institute of Statistics. Our objective was to investigate the spatial-temporal evolution of lung cancer mortality by sex and province of residence (n = 107) using the birth cohort as relevant time axis. We built Bayesian space-time models with space-time interactions. Among males (n = 554 829), mortality peaked in the 1920-1929 cohort, followed by a generalised decline. Among females (n = 158 619), we found novel original evidence for a peak in the 1955-1964 cohort, equivalent to a 35-year delay, with a downward trend being observed thereafter. Over time, the documented north-south decreasing mortality gradient has been replaced by a west-east decreasing gradient. Naples has become the province at highest risk in Italy, both among males and females. This pattern is consistent with an epidemiologic transition of risk factors for lung cancer to the south-west of the country and raises concern, because 5-year age-standardised net survival from the disease in this geographic area is lower than in northern and central Italy. The variability of mortality rates among provinces has changed over time, with an increasing homogeneity for males and an opposite trend for females in the more recent birth cohorts. These unprecedented observations provide evidence for a profound spatio-temporal transition of lung cancer mortality in Italy.

KEYWORDS
birth cohort, epidemiologic surveillance, lung cancer, mortality, space-cohort Bayesian model

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases; ISS, Istituto Superiore di Sanità; ISTAT, Istituto Nazionale di Statistica (Italian National Institute of Statistics); RR, relative risk; SMR, standardised mortality ratio.

What's new?

While trends in lung cancer parallel trends in smoking, substantial geographic variations exist in lung cancer incidence and mortality within and between countries. Here, to better understand epidemiologic transitions at a subnational level, the authors examined lung cancer mortality specifically in Italy over the period 1995-2016. Mortality peaked among males born between 1920 and 1929 and among females born between 1955 and 1964. A decreasing trend north-south through the country shifted to a decreasing west-east gradient, with Naples carrying the highest lung cancer mortality risk, highlighting major spatio-temporal shifts in lung cancer in Italy over the last several decades.

1 | INTRODUCTION

Lung cancer mortality trends in space and time across Europe reflect the geography and evolution of the smoking epidemic.[1] Their knowledge may offer insights into future perspectives for lung cancer control in every single country.[2] At present, in fact, no consistent geographic patterns of lung cancer mortality on a continental scale can be discerned. According to estimates for the year 2020, the highest rates in the male population are seen in eastern Europe (age-standardised [Europe] rate per 100 000, 91.2) followed by southern (82.3), western (76.2) and northern Europe (62.5). With respect to females, northern Europe ranks first (44.7) followed by western (35.9), southern (25.6) and eastern Europe (20.7).[3] Cross-sectional comparisons, however, are unwarranted, because different countries may be in different phases of the smoking/lung cancer epidemic,[4] of their economic trajectory and of their tobacco control programmes.[4-6]

Contrasting country-specific time trends in mortality is more informative of the evolution of the epidemic. Among males, the rates began to decrease in the late 1970s in Sweden, Finland and the United Kingdom and during the 1980s in The Netherlands, Belgium and Switzerland, followed by Spain and Eastern Europe in the 1990s.[6] In Sweden, Finland and the United Kingdom, mortality dropped starting with generations born in the first decade of the past century. In southern Europe, a decrease occurred only for cohorts born in the middle of the century and after.[6]

Regarding females, the spatial-temporal pattern of lung cancer mortality is more complex. During the 1980s, the rates plateaued in the United Kingdom, Ireland and Iceland but not in Finland, Sweden and Norway. In western Europe, mortality remains rising. During the 1990s, the rates stabilised in some, but not all, eastern European countries. In most southern European countries, mortality is lower but still increasing.[6] Importantly, where female mortality has begun to decrease, the downturn has occurred some years or decades later than in the male population.[6,7]

In Italy, the estimated average lung cancer age-standardised (Europe Standard Population) mortality rates in 2020 ranked below the median of 40 European countries in both sexes, but more among males (73.4 per 100 000 vs 81.2 in a range of 37.9-125.0) than among females (26.9 vs 29.0 in a range of 8.3-63.5).[3] The increasing trend declined around 1990 for males, while continuing for the female population.[8] Around 2010, some reports provided early indications that mortality[9,10] as well as incidence[11] were reaching a peak among younger females. So far, however, no analytical evidence has been presented for a stable reduction in recent generations. The only exception consists in the aggregate data made recently available by the International Agency for Research on Cancer's Global Cancer Observatory interactive web-based platform.[12] More importantly, no research whatsoever has addressed whether the evolution of the epidemic differs geographically within Italy. In other countries too, internal geographic differences in lung cancer mortality trends have seldom been explored.[13,14]

The above considerations provided the rationale for conducting an in-depth nationwide analysis of lung cancer mortality trend in Italy between 1995 and 2016, by sex, birth cohort and province of residence. Our general objectives were (a) to update our knowledge of the epidemiologic transition of the disease, (b) to determine, in particular, the current status of the epidemic in the most recent birth cohorts of Italian females and (c) to assess whether the between-sex differences in the epidemiologic evolution of lung cancer are geographically homogeneous across the country.

2 | MATERIALS AND METHODS

2.1 | Rationale and design

The temporal evolution of mortality can be analysed along two different time axes, that is, the birth cohort and the calendar period. Changes in the prevalence of risk factors for lung cancer usually have greater effects on the former.[4,15] However, the most common approach to the analysis of the temporal evolution of lung cancer is the period approach, because the analysis by birth cohort requires the availability of data for a long time span.

Space-time variation in mortality is particularly suited to evaluate the evolution of the mortality gradient across geographic areas and the presence of migration of risk factors. Researchers have generally considered large-scale data collected at a national[16] or international level.[4-6] Two examples of analysis on a small geographic scale are in studies by Dreassi et al[17] and Catelan et al,[18] which dealt with the space-time variation in lung cancer mortality at the municipality

level in the male population of an Italian region. The period and, respectively, the birth cohort were considered relevant time axes. An example of bivariate disease mapping, with disease mortality being studied in the same area in both sexes through Bayesian space-time models, can be found in Biggeri et al.[9]

In the present study, we evaluated the temporal and spatial evolution of lung cancer mortality by sex and province of residence, taking the birth cohort as relevant time axis. The analysis was performed using Bayesian space-time models in which the space-time interaction was allowed. The Bayesian inference has the advantage to borrow strength when considering the set of Lexis diagrams from the whole pool of Italian provinces (n = 107).

2.2 | Mortality data

The Italian National Institute of Statistics (*Istituto Nazionale di Statistica*, ISTAT) and the Italian National Institute of Health (*Istituto Superiore di Sanità*, ISS) made available to us the anonymous records of lung cancer death certificates of all Italian males (n = 554 829) and females (n = 158 619) who died between 1995 and 2016 (more recent data were not yet ready for use at the time of analysis). Records were extracted by the Statistical Service of the ISS from the ISTAT cause-specific mortality database using the codes for lung cancer from the International Classification of Diseases (ICD), that is, 162 (according to the ICD-9)[19] between 1995 and 2002 and C33-C34 (ICD-10)[20] thereafter.

The provinces of residence were defined according to the 2016 criteria from the ISTAT and were identified by grouping the recorded municipalities. For each province, residents and deaths were cross-classified into 18 age groups (0-4, ..., 85+) and five calendar periods (1995-1999, ..., 2015-2016).

For the space-time analysis, we considered nine birth cohorts (1920-1929, ..., 1960-1969) corresponding to people aged 30 to 74 years at the beginning of the study period. We focused on these cohorts because they were followed-up for the whole period and yielded a substantial number of events. Figure S1 shows the correspondence between birth cohorts, age groups and calendar periods.

We fitted age-period-cohort models on the data for the whole of Italy to estimate adjusted mortality rate ratios for calendar periods and birth cohorts. For males, there were large death counts, so that log-linear models with many parameters tended to be well-supported. This is a known phenomenon in the analysis of contingency tables.[21] To be parsimonious, we opted for a forward selection strategy. We started with the simplest model and tested for adding further parameters while adjusting for overdispersion. For females, data counts were on average 4.7 times smaller. However, we did not find any overdispersion and the forward and backward selection strategies gave the same results.

We also computed directly standardised mortality rates using the 2013 revision of the European standard population.[22] On average, the rates standardised in this way were 60% higher than they would be if the 1976 European standard population was used. Standardised mortality ratios (SMRs) were computed using an internal indirect standardisation.[23]

In the analysis by province, the expected number of deaths was calculated using age-specific reference rates derived from the age-cohort model fitted at the national level.[24] In this way, the expected number of deaths was not influenced by cohort effects, which could then be specified as parameters in the Bayesian models. We assumed the multiplicative age-cohort model[25] to be valid. Other studies have shown examples in which the interaction terms or period effects are not relevant.[26,27] Observed and expected deaths were aggregated along the diagonals of the Lexis diagram representing the abovementioned nine birth cohorts, thus collapsing over the age dimension by province.

2.3 | The Bayesian space-cohort model

We described the overall evolution in space and time of lung cancer mortality in Italy through space-time models in which the birth cohort was taken as the relevant time axis. Let us assume that $O_{i,j}$, the number of observed deaths in the ith province ($i = 1, ..., 107$) for the jth birth cohort (j = 1920-1929, ..., 1960-1969), follows a Poisson distribution with mean $E_{i,j}\theta_{i,j}$, where $E_{i,j}$ indicates the expected number of deaths under indirect standardisation and $\theta_{i,j}$ the relative risk (RR). Following the specification of Besag et al,[28] a random effects model is assumed for the logarithm of RR

$$\log(\theta_{ij}) = \alpha + \mu_i + \nu_i + p_j + \xi_{ij}$$

where α represents the intercept, for which an a priori improper uniform is assumed; μ_i a spatially structured random term and ν_i a spatially unstructured random term. The term μ_i, called clustering random term, captures the Poisson overdispersion, which is spatially structured and shrinks the RR toward a local mean. The clustering component μ_i is modelled, conditionally on $\mu_{l\sim i}$ terms ($l \sim i$ denotes the set of adjacent areas to the ith one, index l assumes all integers from *1* to n_i, the number of adjacent areas to the ith one) as Normal($\overline{\mu}_i$, $\lambda_u n_i$) where:

$$\overline{\mu}_i = \sum_{l\sim i} \frac{\mu_l}{n_i}$$

The term ν_i, called the heterogeneity random term, captures the Poisson overdispersion, which is not spatially structured and stabilises the RR toward the global mean. The a priori distribution for the heterogeneity is assumed to be Normal(*0*,λ_v). The hyperprior distributions of the precision parameters λ_v, λ_u are assumed to be Gamma (*0.5*,*0.0005*). The Gamma density is parameterized as shape and rate.[29] The random term p_j represents the effect of the jth cohort whose a priori distribution is assumed to be a first-order random walk with normal independent increments. The term ξ_{ij} represents the space-time interaction, whose prior distribution can be specified in several ways depending on the assumptions about the dependence structure. In our model, we assumed that the interaction terms are

structured both in space and time.[30] The space-time interaction terms are therefore modelled as Normal($\bar{\xi}_i, \lambda_\xi 2n_i$) for the generic jth cohort while the interaction terms are modelled as Normal($\bar{\xi}_i, \lambda_\xi n_i$) for the first and last cohort. The means of this conditional normal distribution are:

$$\begin{cases} \xi_{ij+1} + \sum_{k\sim i} \frac{\xi_{kj}}{n_i} - \sum_{k\sim i} \frac{\xi_{kj+1}}{n_i} & \text{first cohort} \\ \xi_{ij-1} + \sum_{k\sim i} \frac{\xi_{kj}}{n_i} - \sum_{k\sim i} \frac{\xi_{kj-1}}{n_i} & \text{last cohort} \\ \frac{(\xi_{ij-1} + \xi_{ij+1})}{2} + \sum_{k\sim i} \frac{\xi_{kj}}{n_i} - \sum_{k\sim i} \frac{(\xi_{kj-1} + \xi_{kj+1})}{2n_i} & \text{all the others} \end{cases}$$

The prior for the space-time interaction terms is a Markov Random Field, where also second-order neighbours enter in the conditional distributions. In other words, we smoothed the RRs over the temporal neighbours of the spatial neighbours. This is coherent with the epidemiologic knowledge about the spatial-temporal trends. The hyperprior distributions of the precision parameters of the time parameters λ_p and λ_ξ are assumed to be Gamma(0.5,0.0005)[29] (see Dreassi et al for methodological details).[17]

The models used ran on province-level data, which were not sparse and the results were robust to hyperpriors specifications.

The models were fitted with Bayesian approaches. The marginal posterior distributions of the parameters of interest were approximated by Monte Carlo Markov chain (MCMC) methods. For each model, we ran two independent chains. Checks for the achieved convergence of the algorithm were performed according to Gelman and Rubin.[31] We used the WinBUGS software[32] to perform the MCMC analyses and the STATA software version 16 (StataCorp LP, College Station, TX) for the other statistical analyses.

2.4 | Disease mapping

In reporting the continuous risk surface, we chose a continuous grey tones scale. The choropleth maps were plotted using absolute and relative scales (Figures S4-S9). An absolute scale in a choropleth map is obtained defining class cutpoints with limits based on a priori criteria. We chose the following class cutpoints for RRs: 0.00 to 0.60; 0.60 to 0.80; 0.80 to 1.00; 1.00 to 1.20; 1.20 to 1.50; 1.50 to 2.00; 2.00 to 3.00. Absolute scales are useful to show the change of risk among different maps because each map is based on the same class cutpoints.

A relative scale in a choropleth map is obtained defining class limits based on percentiles of a RR distribution. We used sextiles of the distribution. Relative scales are useful to show the change of the geographic pattern of risk among different maps because each map has its own class cutpoints. In this way, we facilitated the reader in exploring the time-varying geographic pattern of lung cancer risk in Italy, which is also present in the maps based on absolute scale but is partially confused by the strong time pattern by birth cohort.

3 | RESULTS

3.1 | Age and sex specific time evolution of lung cancer mortality rates

Between 1995 and 2016, 554 829 deaths were observed among males and 158 619 among females, for an age-standardised mortality rate of 101.7 per 100 000 and 21.5 per 100 000, respectively. Table 1 shows the 5-year age-specific mortality rates and death counts by 5-year calendar period and sex. The rates by column represent the cross-sectional age-specific curve of mortality rates for each calendar period. The rates by diagonal represent the longitudinal age-specific curve of mortality rates of each birth cohort. In Figure S1, the birth cohorts corresponding to the diagonals of the Lexis diagram are shown. Highlighted in grey are the birth cohorts used for the spatial-temporal analysis. In Figure 1, we plotted (panel (A), males; panel (B), females) the rates of Table 1 by column (calendar period) and age class representing the cross-sectional age-specific curve of mortality rates for each calendar period. We also plotted (panel (C), males; panel (D), females) the rates of Table 1 by diagonal (birth cohort) and age class representing the longitudinal age-specific curve of mortality rates of each birth cohort.

With regard to the SMRs by calendar period, the Italian population showed a marked decrease among males, while the risk for females was still increasing (Table 2). To better understand these opposite gradients, the curves of age-specific rates by calendar period and birth cohort should first be considered. The cross-sectional curves of age-specific mortality rates by calendar period appeared to have different shapes (Figure 1). For males, the more recent the calendar period the younger the age group with the highest rate whereas, for females, the more recent the calendar period the older the age group with the highest rate. In other words, the rank of each calendar period depended on which age group we considered, both among males and females. Consequently, the comparison between calendar periods was challenging to summarise and age acted as an effect modifier.

On the contrary, the curves of age-specific mortality rates, if viewed longitudinally, that is, by birth cohort, appeared to be roughly parallel to each other and showed a similar pattern, with higher rates for the same age group in all birth cohorts, that is, age 80 to 84 among males and 85+ among females (Figure 1). Furthermore, the rank of each birth cohort was the same in all age groups for males and females. This behaviour was expected based on the natural history of the disease.[33] The observed data, therefore, supported a modelling approach based on the birth cohort time dimension. To better illustrate the consistency and regularity of these patterns, we plotted in Figure S2 the curves of birth cohort-specific mortality rates by age group in both sexes.

3.2 | Age-period-cohort models of lung cancer mortality rates

Fitting the age-cohort model to the data in Table 1 yielded the birth cohort effects estimates (log rate ratios) shown in Figure 2. We took

TABLE 1 Observed lung cancer mortality rates per 100 000 person-years and number of deaths by sex, calendar period and age group. Italy, 1995-2016.

	Calendar period									
	Males					Females				
Age group	1995-1999	2000-2004	2005-2009	2010-2014	2015-2016	1995-1999	2000-2004	2005-2009	2010-2014	2015-2016
0-4	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	11	1	1	3	0	3	2	2	0	0
5-9	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	7	2	2	1	0	1	2	0	0	0
10-14	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
	6	4	0	0	0	5	3	1	1	1
15-19	0.1	0.1	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0
	9	5	4	2	0	3	6	2	2	1
20-24	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.0
	13	10	9	8	1	14	9	6	8	1
25-29	0.3	0.2	0.2	0.3	0.2	0.3	0.2	0.3	0.2	0.2
	34	24	22	27	7	32	21	25	15	5
30-34	0.8	0.7	0.7	0.5	0.5	0.8	0.6	0.5	0.6	0.4
	98	79	80	50	18	87	64	59	56	13
35-39	3.1	2.4	2.0	1.8	1.6	1.8	1.6	1.4	1.5	1.3
	319	283	237	202	66	186	182	161	169	52
40-44	10.1	8.3	5.7	4.8	4.1	4.3	4.8	4.1	3.6	3.2
	963	861	673	580	197	409	505	483	436	151
45-49	29.3	21.7	16.7	12.9	11.7	7.8	9.2	9.7	8.5	6.9
	2792	2042	1746	1539	570	757	881	1038	1031	342
50-54	67.2	52.5	41.1	32.2	27.1	13.7	15.2	18.4	19.4	16.7
	5827	4904	3844	3356	1268	1224	1465	1786	2113	806
55-59	123.5	109.2	89.6	70.3	58.8	19.1	24.1	27.3	31.1	33.7
	10 573	9181	8214	6482	2342	1730	2125	2623	3045	1423
60-64	217.3	182.0	161.8	137.7	116.6	29.1	31.7	38.5	42.5	48.0
	17 046	14 842	13 146	12 229	4105	2518	2818	3356	4054	1819
65-69	357.2	287.0	246.9	224.2	200.5	47.1	47.0	49.8	59.7	63.9
	25 265	20 814	18 977	17 276	6956	3945	3923	4308	5091	2433
70-74	481.2	439.9	362.5	318.2	305.1	64.6	66.0	65.3	75.6	84.3
	27 816	27 166	23 643	22 301	8235	4963	5195	5192	6244	2635

TABLE 1 (Continued)

Age group	Calendar period					Females				
	Males									
	1995-1999	2000-2004	2005-2009	2010-2014	2015-2016	1995-1999	2000-2004	2005-2009	2010-2014	2015-2016
75-79	535.0	548.9	507.3	432.5	385.6	79.5	86.1	88.8	94.4	96.0
	18 849	25 335	25 977	23 962	9428	4295	5904	6339	6876	2970
80-84	519.3	576.7	593.6	560.9	497.4	88.9	101.0	111.3	115.0	121.5
	11 806	14 016	19 609	21 338	8230	3574	4444	6343	6894	2987
85+	442.0	461.1	530.4	547.5	543.4	86.3	101.5	117.0	122.5	132.6
	6934	8103	10 417	14 569	6840	3146	4206	5517	7435	3622
Average annual number of lung cancer deaths	25 673.6	25 534.4	25 320.2	24 785.0	24 131.5	5378.4	6351.0	7448.2	8694.0	9630.5

Note: For each age group, the first row represents rates and the second row counts.

the 1905-1914 birth cohort as reference category and, to compare the time evolution in males and females, we scaled the effect of the 1930-1939 birth cohort of females to be equal to that of males. In males, the birth cohort at highest risk was the one born between 1920 and 1929, that is, those people who were aged 15 to 24 years at the end of World War II. For the cohorts born after 1940, a decrease in mortality was observed. This decline continued until a plateau for the cohorts born after 1970. As far as females are concerned, the risk of dying increased progressively by birth cohort and peaked among those born between 1955 and 1964, that is, those aged 15 to 24 years at the end of the 70s. Subsequently, a decrease was observed which was less rapid than that occurring among males. Lung cancer mortality peaked among females 35 years later than among males.

We also fitted a series of age-period-cohort models to the whole national data to check for the presence of a non-linear calendar period effect above the birth cohort effect. We did not find evidence for this (males: Likelihood Ratio chi-square test 0.14, P-value = 0.98, comparing the age-period model vs the age-drift model and adjusting for overdispersion; females: Likelihood Ratio chi-square test 4.40, P-value = 0.22, comparing the age-period-cohort model vs the age-cohort model; data not shown).

3.3 | Bayesian space-time modelling of lung cancer mortality rates by Italian provinces

The time evolution of death rates was not homogeneous. We built Bayesian space-time models to study the geographic variability of time patterns. Figure 3 (panel (A), males; panel (B), females) shows the geographic pattern of the RR in males and females in the nine birth cohorts 1920-1929, ..., 1960-1969 predicted by the Bayesian space-time models. Among males, in all Italian provinces, we observed a clear-cut reduction of the risk of dying starting with the earlier birth cohort. The range of the RRs was smaller for the younger cohorts compared to the older ones, which indicates a more homogenous geographic pattern over time. A stronger spatial pattern was evident for the older birth cohorts, with a higher risk in the north and a lower risk in the south. Among females, we observed a rise in RRs peaking for the 1955-1964 birth cohort, but with some variability by province. A north-south gradient and a tendency to decreasing differences among provinces were much less evident than in males. In both sexes, the north-south decreasing mortality gradient has been replaced by a west-east decreasing gradient, which penalises the provinces facing the Tyrrhenian Sea. In Figure S3, multiple boxplots of the logarithm of Bayesian RRs by sex and birth cohort are shown.

Figures S4 and S5 depict the maps of RRs by sex using a scale based on sextiles of the RR distribution for each birth cohort. That is, each map has its own scale. The nine birth cohort-specific Spearman correlation coefficients between the series of provincial RRs observed in males and females ranged between 0.32 and 0.80 (Table S1). Figures S6 and S7 depict the maps of SMRs by sex on an absolute

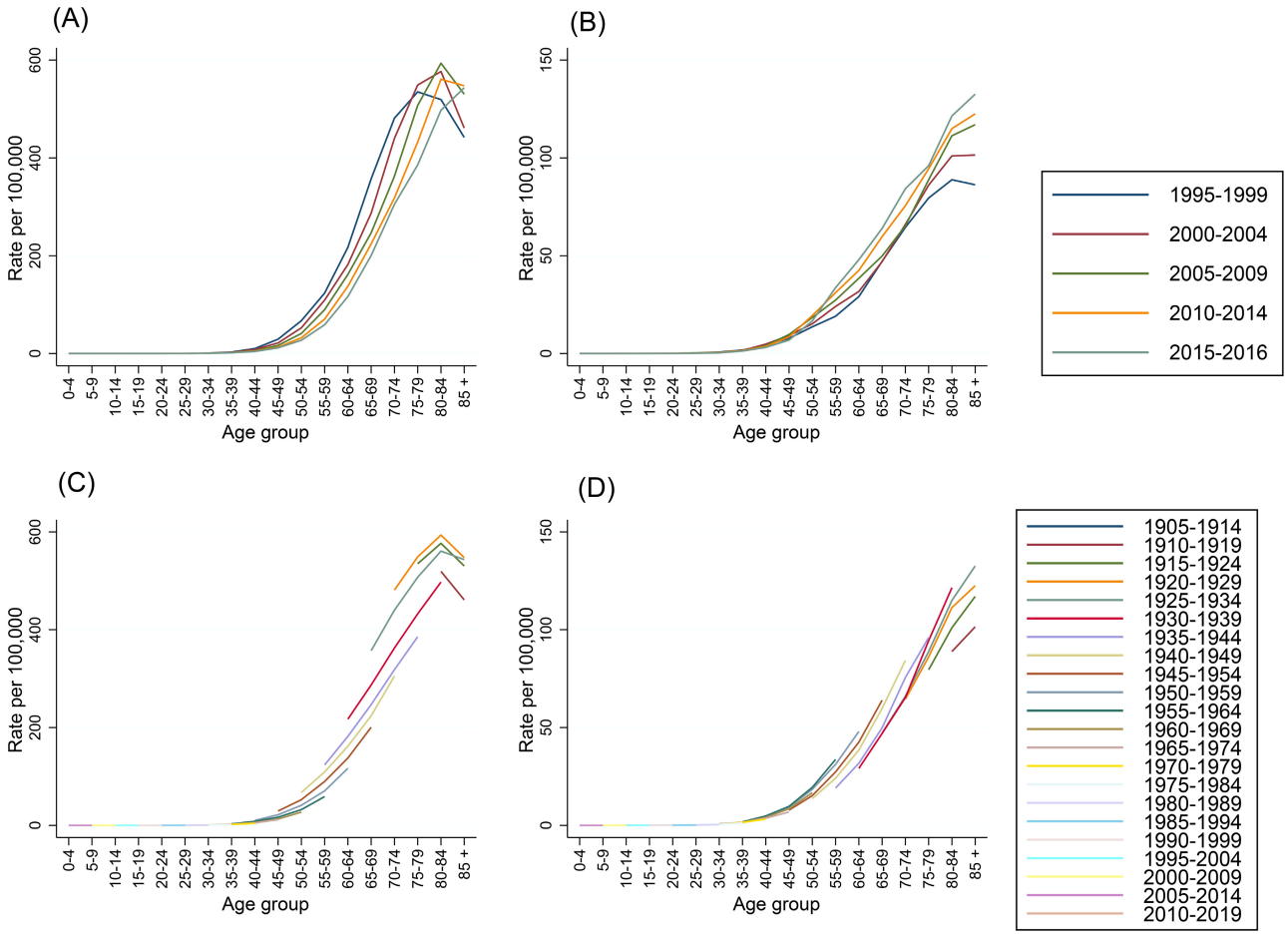

FIGURE 1 Curves of age-specific lung cancer mortality rates by calendar period (panel (A), males; panel (B), females) and birth cohort (panel (C), males; panel (D), females). Graphs for males and females are shown on different scales. Italy, 1995-2016.

TABLE 2 Observed and expected number of lung cancer deaths and age-standardised lung cancer mortality ratios (SMR per 100) and 90% confidence intervals (90% CI), by sex and calendar period. Italy, 1995-2016.

	Males			Females		
Calendar period	Observed	Expected	SMR (90% CI)	Observed	Expected	SMR (90% CI)
1995-1999	128 368	107 149	120 (119-120)	26 892	31 492	85 (84-86)
2000-2004	127 672	117 046	109 (108-110)	31 755	34 034	93 (92-94)
2005-2009	126 601	128 896	98 (98-99)	37 241	36 829	101 (100-102)
2010-2014	123 925	141 288	88 (87-88)	43 470	39 614	110 (109-111)
2015-2016	48 263	60 450	80 (79-81)	19 261	16 652	116 (114-117)

Note: SMR = 100 is the average for the whole period 1995-2016.
Abbreviations: CI, confidence interval; SMR, standardised mortality ratio.

scale. Finally, Figures S8 and S9 depict the maps of SMRs by sex on a relative scale.

In Figure 4, the birth cohort trends by province are shown, and the risk profiles of some selected provinces are highlighted. The reduction in mortality and the tendency to geographic homogeneity are evident in males. However, there was a large difference in the rate of decrease by province. In north-eastern provinces (like, for example, the province of Venice), the drop was very steep and their ranks changed substantially, as they moved from the higher positions for the 1920-1929 birth cohort to the lower positions for the 1960-1969 birth cohort. In southern provinces (like, for example, the province of Palermo in Sicily) the rate of decrease was smoother in the

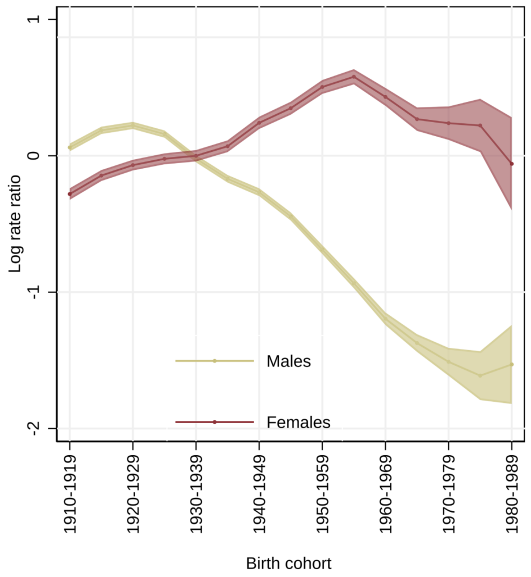

FIGURE 2 Cohort effects estimates from the age-cohort model fitted on lung cancer mortality rates by sex (yellow lines depict males, red lines depict females) and 90% confidence interval. The cohort effects estimates (log rate ratios) were obtained taking the birth cohort 1905-1914 as a reference and scaling the females' cohort effect to be equal to the males' cohort effect for the 1930-1939 birth cohort. Italy, 1995-2016.

older cohorts. The province of Naples was outlying, since it had the highest risk in all birth cohorts, and its gap with the rest of Italy did not show any sign of closing. In Figures S10 to S20, the birth cohort trends by province in the main Italian administrative regions are shown.

For females, the trends in Figure 4 differed widely by province. A tendency toward increasing geographic homogeneity was evident only for the youngest birth cohort (1960-1969). In the province of Venice, the oldest birth cohort ranked around the maximum level of risk while the youngest one ranked in the lowest quartile. The risk reduction started with the 1950-1959 birth cohort, a pattern consistent with all the north-eastern provinces. Moving from the north-east to the south, the birth cohort with the highest rate changed, being the 1955-1964 cohort for north-central Italy and the 1960-1969 cohort for southern Italy. The decrease was more gentle in the southern provinces. Some of them have not reached the peak yet, notably in Campania and Sardinia. The province of Naples was also outlying for females. The risk became the highest at the national level starting with the 1955-1964 birth cohort.

Comparing females with males at the provincial level, the two mortality peaks appeared to be separated by 30 years in Venice, 40 years in Rome and at least 50 in Naples, where no reversal of the trend is discernible yet.

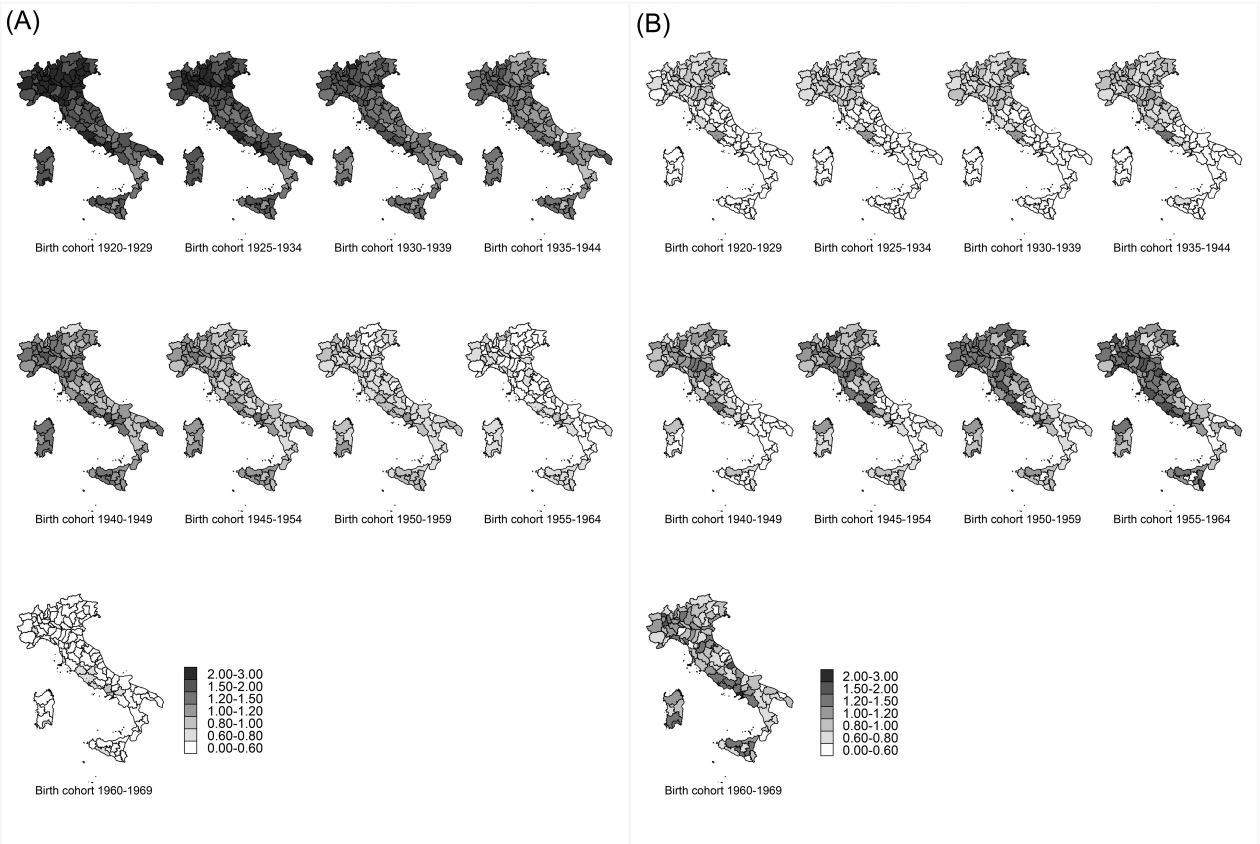

FIGURE 3 Geographic distribution of lung cancer mortality Bayesian relative risks by province (panel (A), males; panel (B), females). Absolute scale. Italy, 1995-2016.

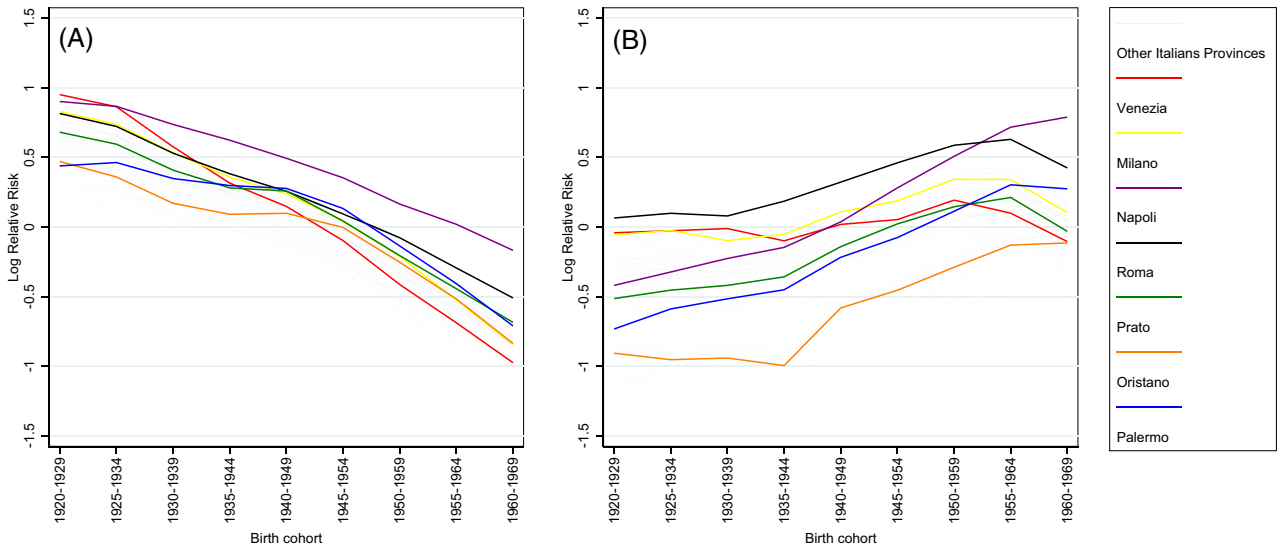

FIGURE 4 Lung cancer mortality Bayesian log relative risks by birth cohort and province (panel (A), males; panel (B), females). Italy, 1995-2016.

4 | DISCUSSION

4.1 | Temporal trends in the context of European data

The above findings can be better interpreted by contextualising them in lung cancer mortality trends reported elsewhere in Europe. Among males, mortality rates started to decrease, for example, in the late 1970s in Sweden, Finland and the United Kingdom, during the 1980s in the Netherlands, Belgium and Switzerland, and in the late 1990s in Spain and several eastern European countries.[6] This suggests a trend toward decreasing mortality that has spread from north-western to south-eastern Europe. Since its inception, the decrease appeared to be a birth-cohort-related phenomenon. In Sweden, Finland and the United Kingdom, for example, the downtrend was first observed in those cohorts born in the first decade of the 20th century, whereas in southern Europe the earliest cohorts involved were those born after World War II. In any case, the decrease extended to all subsequent cohorts, which replaced the previous high-risk ones and led to a reduction in overall mortality.

Among females, lung cancer mortality has reached a plateau or has started to decline in some countries of north-western Europe, particularly in the United Kingdom, Ireland and Iceland. This is due to a downtrend in the cohorts born after 1950. Conversely, total rates are still growing in Finland, Sweden and Norway, although a reversal is expected for the near future. In contrast, but with some exceptions, the rates are increasing in western Europe (especially in France and The Netherlands) and in most southern European countries up to the cohorts born until the 1960s.[4,6] Noteworthy, the generations of European females at maximum risk have been observed from five (as in Hungary) to 50 years (as in The Netherlands) after the equivalent male cohorts.

These differences suggest that, in many countries, males and females are in different phases of the lung cancer epidemic. Our findings show that this is also the case for Italy. For males, our results are in keeping with previous regional-level mortality studies which showed a peak in the 1920-1929 cohort, that is, the generation who were young males after World War II, followed by a uniform decline throughout the country. For females, we can formally confirm the circumstantial findings of previous smaller-scale mortality studies.[9,10] Mortality has peaked in the 1955-1964 cohort, the generation of females who were students during and after the social movements of the late 1960s. Subsequently, a downward trend has begun in many Italian provinces, with more exceptions in southern Italy (Figures S8 and S14-S16). This is an original finding, because previous regional-level data had shown a generalised increase even in the most recent birth cohorts studied.[10,34]

4.2 | Spatial trends

The data reported here also demonstrate that the time trend in lung cancer mortality by sex is interrelated with a geographic transition, that is, a change in the geographic pattern of rates. The long-standing north-south decreasing mortality gradient has been replaced by a west-east decreasing gradient, with a drop of rates in the regions facing the Adriatic Sea and a different situation in those facing the Tyrrhenian Sea, where mortality RR is stagnating or still worsening. Thus, we can confirm the consistency of a previous observation showing, for the first time, a decline in mortality in the high-risk regions of north-eastern Italy paralleled by an opposite change in the Campania Region.[10]

Among males, the provinces along the Tyrrhenian Sea now rank first in mortality, and, in particular, Naples has taken the place of Venice as the province at highest risk. For females, the change in the mortality ranking is consistent with that seen among males, with a decreased risk in northern and north-eastern provinces for the cohorts born in the 1950s and after and in central Italy for the cohorts born since the 1960s. In southern Italy, no cohort-dependent reduction has occurred yet. As for males, the highest risk is in the province of Naples.

The analysis of spatial trends deserves two more comments. First, provincial-level data offer several other pieces of information that are beyond our scope but may be interesting from a local perspective. In general, they result from socio-economic peculiarities. For example, the province of Carbonia-Iglesias showed higher RR among males compared to other Sardinian provinces, which is the result of occupational exposures in the mining industry.[34] In the Lombardy Region, the mortality drop for females occurred earlier in the province of Como, the one with the highest socio-economic standard. In the Veneto Region, among males, mortality remained notably higher in the province of Rovigo, a socio-economically 'frail area'.[35]

Second, mortality trends at the provincial level are influenced by the trends occurring in capital cities and major cities. Therefore, the evolution of RR for rural and sparsely inhabited municipalities could not be well described by our data, especially in southern Italy and particularly so among females.

4.3 | Changing health issues and inequalities

Over the decades, the highest levels of exposure to risk factors for lung cancer have migrated across the country. This changeover poses two problems. The first is that the maximum mortality risk is moving to geographic areas where 5-year age-standardised net survival (males, 13%; females, 18%) is lower than in the rest of the country (north-eastern Italy: males, 16%; females, 20%. North-western and central Italy: males, 15%; females, 19%).[36] The second problem is that the design of smoking prevention and cessation campaigns needs to be reconsidered, to determine whether they should be tailored to a changing target population.[4]

A third correlate of the transition is that the variability of provincial mortality rates has changed in opposite directions for males and females. In the earliest cohort, the heterogeneity of rates was greater for males. In the most recent one, the opposite is seen. In fact, this is mostly accounted for by the huge mortality increase observed among females living in Naples, specifically among those born after World War II. This subset of the Italian female population warrants an in-depth evaluation.

4.4 | Factors involved in temporal and spatial trends

The temporal and spatial patterns by which the upward trend in lung cancer mortality ceased in Europe, including Italy, among males and the different patterns observed among females suggest that different factors were involved. For males, the reversal of the trend has spread from north-western to south-eastern Europe, which suggests that an improving socio-economic status has been the major driver of the change in smoking habits. This would be consistent with the known inverse association between multiple socio-economic status indicators and disease risk.[37] In Italy, the changing direction of the geographic mortality gradient mirrors the fact that the regions facing the Adriatic Sea—more specifically, Marche, Abruzzo and Puglia—have attained a high level of economic development several decades after north-western Italy.[38-40]

As regards females, the socio-economic gradients have certainly had a role in determining the previous north-south and the current west-east mortality gradients. Conversely, the socio-economic factors cannot entirely explain the substantial delay with which the reversal of the mortality trend occurred. We raise two linked hypotheses: Italian females have modified their smoking habits about 35 years after males because they had a much lower baseline risk of disease and, for this reason, the upward mortality trend has caused a sufficient social alarm much later among them than among males. Consequently, despite being exposed to the same smoke-free laws and the same antismoking education campaigns as males, they have responded later. This view is supported by the consideration that the attitudes of Italian females toward another cancer epidemic, that of melanoma, have been definitely different. With a roughly comparable incidence of disease,[41] females have preceded males in adopting sun avoidance and skin self-surveillance practices.[41,42] Socio-economic and cultural gradients have probably cooperated with baseline risk of lung cancer in influencing females' attitudes. This would explain why the delay of the mortality peak for females vs males was 30 years in Venice (north-eastern Italy), 40 years in Rome (central Italy) and at least 50 in Naples (south-western Italy), where the trend for females remains increasing.

4.5 | Strengths and weaknesses

Investigating the birth cohort effects allowed us to anticipate future mortality rates, because these will be related to current mortality trends in the most recent generations. We emphasise that the analysis of trends by birth cohort encompasses a wide time span and enables describing the evolution of mortality in a longer time perspective than the one allowed by cross-sectional analyses.

Our study has a high degree of novelty for three reasons. First, this multifaceted epidemiologic passage, consisting of a temporal and a spatial component, has never been previously reported in Italy with a degree of detail as high as in the present study.

Second, we broke down the analysis into as many as 107 provinces, which is an opportunity so far seldom available to studies of trends by birth cohort in Europe and beyond.[13,14] A province, in Italy, is a small geographic unit. The small geographic basis of the data, coupled with a great statistical power, made it possible to

obtain a high-resolution overview of the multifaceted changes that are ongoing.

And third, data were derived from the national mortality registry. As a result, our study was free of the selection bias potentially affecting incidence studies from those countries where cancer registration covers only part of the national population. This is the case, among others, for Italy, where most of the currently available incidence data are from the northern regions.[41,43]

There are also methodological issues in our study that need to be pointed out. First, the age group and the calendar period did not always have the same dimension due to limitations in data availability. However, this problem was restricted to the last time period and impacted only the last birth cohort studied.

Second, different specifications are possible for the space-time interaction terms. In our models, the interaction terms were structured both in space and time.

Third, we used data cross-classified in 5×5-year cells in the Lexis diagram with age groups spanning from 0-4 to 85+ years. Because of the Italian population's ageing, it is common to find in current literature that the last age group is subdivided into three subgroups (85-89, 90-94, 95+). We did not do so to be consistent with the population structure in the 1990s (the percentage of people of 85 years was among males and females respectively 0.5% and 1.2% in 1995, 0.6% and 1.5% in 2000, 0.6% and 1.4% in 2005, 0.8% and 1.9% in 2010, 1.0% and 2.2% in 2015, 1.2% and 2.4% in 2020). The last calendar period studied was 2015-2016, a 2-year period, but we assumed the mortality estimates for this period to be valid for the whole period 2015-2019. In the birth-cohort dimension, our assumption was similar. For example, the 1960-1969 cohort was observed in the age group 50 to 52, but we assumed the estimates to be valid for the age group 50 to 54. Major biases are unlikely, because the number of deaths in these cells was low.

Finally, our study might be affected by differences or temporal changes in access to effective diagnosis and treatment techniques. However, these cannot necessarily be considered to introduce a bias into results. An increased healthcare expenditure, with improved quality and accessibility of services, is a correlate of economic growth, thus reinforcing the inverse association of socio-economic indicators with lung cancer mortality.

5 | CONCLUSIONS

Our study provides evidence for a profound spatio-temporal transition of lung cancer mortality in Italy. We conclude the following: (a) among males, mortality was confirmed to have reached a peak in the 1920-1929 cohort, followed by a generalised decline; among females, there was novel evidence for a peak in the 1955-1964 cohort, followed by an unevenly distributed downward trend; (b) the north-south decreasing gradient has been replaced by a west-east decreasing gradient, with Naples currently being the province at highest risk for both sexes; (c) the diversity of mortality rates was greater for males in the earliest cohort and for females in the most recent one; (d) for both sexes, an improving socio-economic status has been the major driver of the change in smoking habits, with an average 35-year delay being observed for females; and (e) the delay, in fact, was 30 years in Venice, 40 years in Rome and at least 50 in Naples, where the trend for females remains on the rise.

AUTHOR CONTRIBUTIONS

Dolores Catelan: Conceptualization, Methodology, Validation, Formal Analysis, Writing—Original Draft, Writing—Review & Editing, Supervision. **Annibale Biggeri:** Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Writing—Original Draft, Writing—Review & Editing, Supervision. **Lauro Bucchi:** Investigation, Writing—Original Draft, Writing—Review & Editing, Supervision. **Valerio Manno:** Resources, Data Curation, Writing—Review & Editing. **Marilena Pappagallo:** Resources, Data Curation, Writing—Review & Editing. **Giorgia Stoppa:** Methodology, Software, Validation, Formal Analysis, Data Curation, Writing—Review & Editing, Visualisation. **Francesco Grippo:** Resources, Data Curation, Writing—Review & Editing. **Luisa Frova:** Resources, Data Curation, Writing—Review & Editing, Supervision. **Federica Zamagni:** Software, Validation, Formal Analysis, Writing—Original Draft, Writing—Review & Editing, Visualisation. **Roberta Crialesi:** Resources, Writing—Review & Editing, Supervision. **Giada Minelli:** Resources, Data Curation, Writing—Review & Editing, Supervision. The work reported in the article has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Research data are available from Giada Minelli (contact email: giada.minelli@iss.it) upon reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Committee at the Romagna Cancer Institute (ID: IRST100.37).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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