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Incidence trends of vulvar squamous cell carcinoma in Italy from 1990 to 2015

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HIGHLIGHTS

- In southern Europe, the trends in the incidence of vulvar squamous cell carcinoma have been insufficiently studied.
- In Italy, 38 local cancer registries covering 15 millions women provided incidence data for the period 1990–2015.
- An unexpected decreasing incidence trend among women aged ≥60 years resulted in a decrease in total rate.
- The risk dropped in all cohorts of women born between 1905 and 1940 while rising in the cohorts born since 1945.

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ABSTRACT

Objective. The incidence of vulvar squamous cell carcinoma has increased for decades in most Western countries – a trend virtually restricted to women aged <50 or 60 years. In southern Europe, conversely, the trends have been insufficiently studied. This article reports a study from Italy.

Method. Thirty-eight local cancer registries, currently covering 15,274,070 women, equivalent to 49.2% of the Italian national female population, participated. Invasive cancers registered between 1990 and 2015 with an International Classification of Diseases for Oncology, 3rd revision, topography code C51 and morphology codes compatible with vulvar squamous cell carcinoma (n = 6294) were eligible. Incidence trends were analysed using joinpoint regression models, with calculation of the estimated annual percent change (EAPC), and age-period-cohort models.

Results. Total incidence showed a regular and significant decreasing trend (EAPC, −0.96; 95% confidence interval (CI), −1.43 to −0.48). This was entirely accounted for by women aged ≥60 years (EAPC, −1.34; 95% CI, −1.86 to −0.81). For younger women, the EAPC between 1990 and 2012 was 1.20 (95% CI, 0.34 to 2.06) with a non-significant acceleration thereafter. This pattern did not vary substantially in a sensitivity analysis for the effect of geographic area and duration of the registry. The age-period-cohort analysis revealed a risk decrease in cohorts born between 1905 and 1940 and a new increase in cohorts born since 1945.

Conclusions. The decreasing trend observed among older women and the resulting decrease in total rate are at variance with reports from most Western countries. Age-period-cohort analysis confirmed a decreasing trend for earliest birth cohorts and an opposite one for recent ones.

1. Introduction

The incidence of vulvar squamous cell carcinoma (VSCC) has increased for decades in numerous Western countries [1–7]. Only in a few populations have the rates shown a stable or non-significantly increasing trend [8]. In most studies, the incidence increase has been restricted to women below the age of 50–60 years [1,2,4,5,9,10]. Among older women, apart from exceptions [1], incidence has not [4,10] or not significantly increased [5] or it has only recently increased [2]. There is a general consensus that this observation is consistent with changing sexual behaviours and increasing levels of exposure to the human papillomavirus (HPV) infection in recent birth cohorts.

This view is based on the largely agreed-upon notion that VSCC is made of two broad entities. In general, the warty/basaloid type is related to the HPV infection, is preceded by usual vulvar intraepithelial neoplasia (VIN), and affects primarily younger women, whereas the more common keratinizing type is mostly not related to the HPV infection and occurs in elderly women, often in a background of lichen sclerosus and/or differentiated VIN [11,12].

The epidemiologic knowledge of VSCC, however, is limited by two partly interrelated factors. The first is that there are differences across populations in the level of exposure to the HPV infection and in the epoch when this level began to increase. Critical changes in sexual behaviour have occurred among women born after the 1940s [7,13] or after the 1950s [4] or during the 1960s and 1970s [6], depending on the continent and country investigated. Because of these differences [10], there is geographical variation in the prevalence of HPV in VSCC [10,14], and there are populations that differ in the incidence of VSCC despite an equal prevalence of high-risk HPV infection [13].

The second knowledge gap concerns the limited available information on VSCC trends in several regions of the world, including the western world. This is the case, among others, for southern European countries, where the descriptive epidemiology of the disease has never been investigated in a formal fashion and in detail. For this reason, we conducted a nation-wide study of incidence trends of VSCC in Italy during the last three decades.

2. Methods

2.1. Source of data

The source of data was the database of the Italian Association of Cancer Registries (AIRTUM) [15], which includes anonymous individual records of all newly diagnosed cancer cases. In Italy, cancer registration has been introduced in a phased manner with a marked north-south temporal gradient. When the study was undertaken (April 2019), the years of registration of the associated registries varied between 1976 and 2016.

After approval by the Ethics Committee at the Romagna Cancer Institute (ID: IRST100.37), the study protocol was submitted by the proposing registry to all of the other registries. Of these, 38 (all certified by the AIRTUM) authorized the use of their data. Based on the data made available, the study period was 1990–2015. During this time span, the participating registries supplied data for three to 26 years of registration (median, 20 years). In December 2017, they covered a female population of 15,274,070, equivalent to 49.2% of Italian women. Their main characteristics are shown in Supplementary Table 1.

The records of invasive cancers (n = 6294) with topography code C51 and morphology code 8051-8084 according to the International Classification of Diseases for Oncology, third revision, were selected. The percentage of cases verified by histology (primary tumour or metastases) was 99.7%, the remaining being cases registered based on clinical, instrumental, cytological, and post-mortem histological reports.

2.2. Statistical methods

For descriptive purposes, the trends in age-standardised (2013 European standard population) incidence rate 1990–2015 by age group (<60 years, ≥60 years) were analysed using the joinpoint regression, which enables to detect the point(s) in time when a change in direction or magnitude of a trend occurs. For each time segment, the estimated annual percentage change (EAPC) was calculated with generalized linear models assuming a Poisson distribution.

For sensitivity analysis purposes, all joinpoint regression models were run again after exclusion of one of the three geographical areas (Supplementary Table 1) at a time and, then, of those registries ($n = 15$) that contributed data for <13 years, that is, <50% of the 26-year study period.

Subsequently, an age-period-cohort approach [16,17] was used to analyse the trends in incidence rate by age group, time period, and birth cohort, and to disentangle the effect of each of these factors. We excluded women aged <35 years because of the instability of rates (random fluctuations caused by the low number of VSCC cases and the small size of the population aged under 35 years), and all data for 2015 in order to have homogeneous 5-year periods. This left a subset of 6187 patients available for analysis.

The data were tabulated into eleven 5-year age groups (35–39 to ≥85 years), five 5-year periods (1990–1994 to 2010–2014), and fifteen 9-year birth cohorts. The cohorts are referred to in this article with their mid-year of birth (1905 to 1975). Rates were smoothed using median smoothing splines in order to facilitate the interpretation of trends. The incidence trends were illustrated in detail by plotting the age-specific rates against the cohort and the period.

As a last step in the age-period-cohort analysis, five Poisson regression models were fitted according to the model-building approach [17]. The model goodness-of-fit was evaluated based on residual deviance statistics. Model comparison was conducted using conditional likelihood ratio tests between hierarchically nested models. To avoid overfitting, we also compared the models using the Akaike information criterion (the smaller the better) which penalizes models with large number of parameters [18]. Further details of model fitting are provided in Table 1. In all models, each parameter estimate is interpretable as the natural logarithm of an incidence rate ratio (IRR).

Data analysis was performed using STATA version 15.1 (Stata Corporation, College Station, TX).

3. Results

3.1. Joinpoint regression analysis

The case series included 659 (10.5%) registered patients aged <60 years and 5635 (89.5%) aged ≥60 years. Fig. 1 shows the curves of annual incidence rates for these age groups. The results of the joinpoint regression analysis of trends are shown in the upper row of Table 2. Total incidence (Fig. 1c) showed a regular and significant downward trend, with an EAPC of −0.96. This decline was entirely due to a strong decrease occurring among women aged ≥60 years (Fig. 1b). Conversely, younger women (Fig. 1a) experienced a significant incidence increase between 1990 and 2012, with a rapid but non-significant acceleration in the last few years of observation. These opposite age trends suggested that recent birth cohorts are experiencing an increase in the risk of VSCC.

This pattern of incidence was substantially confirmed by sensitivity analysis (Table 2). For total female population and for women aged ≥60 years, the magnitude of the decreasing trends was only marginally modified when any of the three geographic areas was removed from the models and when analysis was restricted to long-duration registries. With respect to women aged <60 years, both magnitude and downward direction of the trend observed between 1990 and 2012 were roughly confirmed, but the acceleration observed in 2012–2015 became significant after removing the registries of central Italy.

3.2. Age-period-cohort analysis

Table 3 shows the 5-year age-specific incidence rate (y axis) by 9-year birth cohort (x axis) tabulated on a Lexis diagram. The rates were consistently higher with increasing age. The cohort effect was a non-linear one. A small decrease in age-specific incidence rates was observed among the cohorts born between 1905 and 1940. On the contrary, the age-specific incidence increased with each successive cohort born in 1945 or later.

Fig. 2a depicts the plot of incidence rates by age class against the mid-year of birth. This presentation enables the graphical assessment of the effects of age and cohort. Fig. 2b shows the same rates after smoothing by median splines. The non-linear cohort effect is indicated by the fact that cohort trends by age class had different slopes. The most recent cohorts showed the highest increase in incidence rates.

The age-period-cohort analyses found a non-linear effect of the calendar period. The incidence rate grew up to the second half of the 1990s and then declined. In fact, this pattern was weaker than that associated to the cohort effect, as the IRR comparing the highest predicted rate for a birth cohort versus the lowest one was 2.28, almost twice as high as the IRR from the same comparison between calendar periods (IRR, 1.24). The age-period-cohort model provided the best fit to the data (column at right in Table 1). Fitting this model, however, resulted in some overfitting, as indicated by a residual deviance of 21.76 and a number of degrees of freedom of 27. Thus, we preferred a simpler smoothed model with restricted cubic spline with 4 knots on the birth cohort dimension. This strategy used only three degrees of freedom – instead of 14 – for the cohort in the full age-period-cohort model without changes in the goodness of fit (residual deviance, 32.1; degrees of freedom, 38), but with improvement in the Akaike information criterion (7.154 vs 7.366).

The curve of incidence rates by cohort, estimated from the smoothed model, is shown in Fig. 3. The curve is adjusted for the age and period effects. The gross U shape of the plot indicates a slight decline for

Table 1
Age-period-cohort models for trends in incidence of vulvar squamous cell carcinoma in Italy from 1990 to 2015.

Submodel[a]	Goodness of fit			Model comparison			
	Residual DF	Residual deviance	Interpretation	Comparison	Change in DF	Change in deviance	*P* value[b]
1. Age	44	80.67					
2. Age-drift	43	60.11	Trend (drift)	2 versus 1	1	20.56	0.000
3. Age-cohort	30	32.39	Nonlinear cohort effect	3 versus 2	13	27.71	0.010
4. Age-period	40	49.77	Nonlinear period effect	4 versus 2	3	10.34	0.016
5. Age-period-cohort	27	21.76	Period effect adjusted for cohort	5 versus 3	4	10.63	0.014
			Cohort effect adjusted for period	5 versus 4	13	28.01	0.009

DF indicates degrees of freedom.
[a] Five submodels were derived using the factors involved in the age-period-cohort modelling, namely: age, age-drift, age-cohort, age-period and the full age-period-cohort model. The drift term is a linear temporal variation of rates that cannot be attributed to either the period effect or the cohort effect. The model goodness-of-fit was evaluated based on residual deviance statistics. Age, period, and birth cohort effects were derived from pairwise comparisons of the appropriate sub-models. Significance of the pairwise comparisons was examined by comparing the difference in residual deviance and degrees of freedom using the likelihood ratio test. Note that the models 3 and 4 cannot be compared directly in this way and it is not possible to construct a formal test of whether the age-cohort model is significantly better than the age-period model.
[b] Likelihood ratio test.

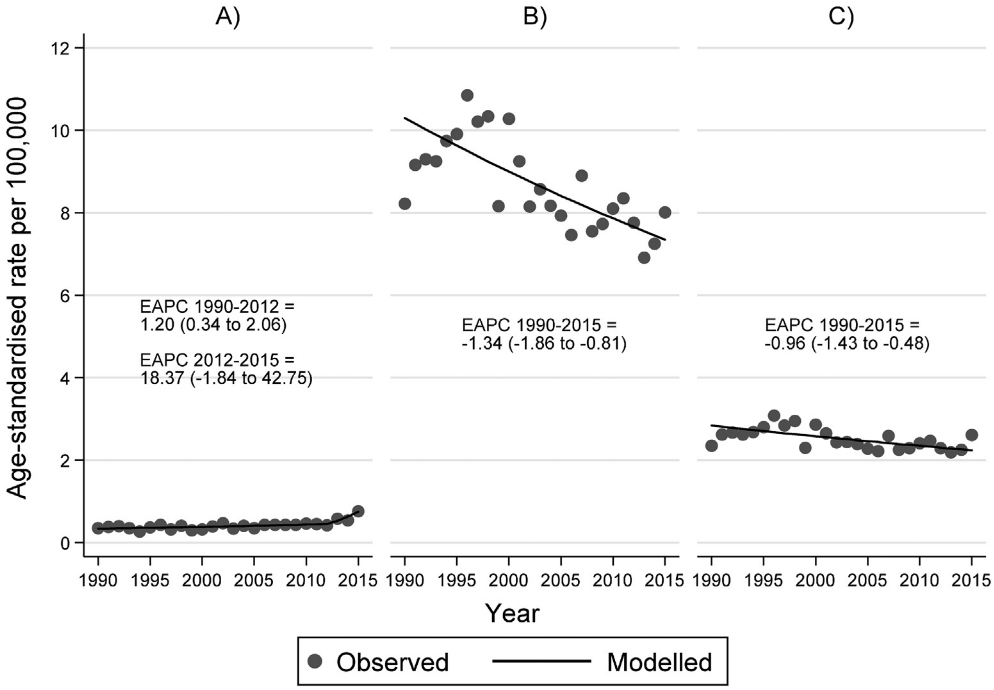

Fig. 1. Curve of observed and joinpoint-modelled annual incidence rates (per 100,000 women) of vulvar squamous cell carcinoma in Italy from 1990 to 2015. The three panels of the figure show the curve for (A) the women aged <60 years, (B) the women aged ≥60 years, and (C) the whole female population. The trends in incidence rates were analysed using the joinpoint regression, which enabled to detect the point in time when a change in direction or magnitude of the trend occurred (if any). The numbers indicate the estimated annual percentage change (EAPC) in incidence rate for each time segment. Total incidence showed a regular and significant decreasing trend, which was entirely accounted for by women aged ≥60 years. For younger women, a significant opposite trend was observed between 1990 and 2012, with a non-significant acceleration in the last few years of observation. All incidence rates were age-standardised using the 2013 European standard population.

generations born between 1905 and 1940, a modest increase for those born approximately between 1945 and 1960, and a pronounced acceleration for those born thereafter.

4. Discussion

4.1. Principal findings

In Italy, the total annual age-standardised incidence rate of VSCC between 1990 and 2015 followed a decreasing trend. This was entirely due to an unexpected decrease among women aged ≥60 years. The upward trend observed among younger women was roughly in accordance with the data generally reported from the other Western populations [1,2,4,5,9,10].

The age-period-cohort modelling analysis provided evidence that these trends resulted from a birth-cohort-dependent change in the risk of VSCC, with a progressive decrease in the earlier cohorts (women born between 1905 and 1940), followed by an increase with each successive cohort born after World War II. In this type of analysis, the cohort effect usually results from changes in lifestyle habits leading to differences in the prevalence of risk factors between different generations.

4.2. Interpretation of results

A decreasing incidence trend among older women has never been observed elsewhere. The rates reported from other Western countries have generally been stable [4,5,10]. The hypothesis of a decrease in the prevalence of lichen sclerosus is not supported by data (incidentally, an opposite trend between 1991 and 2011 has been described in northern Europe [19]). We believe that our finding reflects three other concomitant factors. The first is the long-term decline in the prevalence of the HPV infection in the earliest generations, due to great improvements in the socio-economic status of Italian women in the past century. It must be noted that the HPV infection retains a role (albeit not a major one) in vulvar carcinogenesis even among middle-aged and elderly women. The HPV infection explains approximately 15–25% of all VSCC cases diagnosed among these women [14].

Table 2
Sensitivity analysis of the estimated average percent change in incidence rates of vulvar squamous cell carcinoma in Italy from 1990 to 2015.

Cancer registries removed from the joinpoint regression models	Age < 60 years		Age ≥ 60 years		Total	
	Time segment	EAPC (95% CI)	Time segment	EAPC (95% CI)	Time segment	EAPC (95% CI)
None	1990–2012	1.20 (0.34 to 2.06)	1990–2015	−1.34 (−1.86 to −0.81)	1990–2015	−0.96 (−1.43 to −0.48)
	2012–2015	18.37 (−1.84 to 42.75)				
Registries of southern Italy	1990–2015	1.66 (0.39 to 2.96)	1990–2015	−1.38 (−1.92 to −0.83)	1990–2015	−1.01 (−1.52 to −0.51)
Registries of central Italy	1990–2012	1.42 (0.55 to 2.31)	1990–2015	−1.41 (−1.98 to −0.83)	1990–2015	−0.99 (−1.52 to −0.47)
	2012–2015	26.66 (6.98 to 49.96)				
Registries of northern Italy	1990–2015	1.05 (−0.75 to 2.89)	1990–2015	−1.15 (−2.10 to −0.19)	1990–2015	−0.85 (−1.66 to −0.02)
Registries with short registration period[a]	1990–2015	1.51 (0.30 to 2.73)	1990–2015	−1.28 (−1.85 to −0.72)	1990–2015	−0.97 (−1.48 to −0.47)

EAPC indicates estimated annual percent change; CI, confidence interval.
[a] Registries that contributed data for <13 years, that is, <50% of the 26-year study period.

Table 3
Age-specific incidence rates of vulvar squamous cell carcinoma by birth cohort in Italy from 1990 to 2015.

Age (years)	Birth cohort[a]														
	1905	1910	1915	1920	1925	1930	1935	1940	1945	1950	1955	1960	1965	1970	1975
35–39											0.3	0.2	0.3	0.3	0.1
40–44										0.5	0.4	0.3	0.5	0.5	
45–49									0.3	0.6	0.8	0.8	0.8		
50–54								0.8	0.9	1.2	1.3	1.5			
55–59							1.7	1.6	1.4	1.5	2.1				
60–64						2.7	3.5	3.7	3.2	3.1					
65–69					5.4	5.7	5.7	4.9	4.9						
70–74				10.5	9.7	8.3	8.1	7.4							
75–79			12.0	13.9	12.0	11.6	10.7								
80–84		17.2	19.0	16.7	13.4	15.8									
85–90	17.2	18.5	16.1	13.6	13.7										

[a] The midpoint of the 9-year period of birth is indicated.

The second factor is that the prevalence of obesity, an established risk factor for VSCC irrespective of age [20], has remained relatively low in the earliest generations of Italian women and lower than in women living in the greater part of Western countries [21]. Obesity is an independent risk factor for VSCC [20,22] and, in addition, is positively associated with the risk of lichen sclerosus [23].

The third factor is the low prevalence of smoking in those generations [24]. Currency of smoking is associated with VSCC only in women younger than 70 years, but it may influence the risk of disease through an enhancement of the effect of HPV [20]. The earliest birth cohorts in this study have certainly experienced very low levels of exposure to oral contraceptives and menopausal hormones, too. At present, however, these are considered risk factors only for high-grade VIN [20].

The complex web of causation involved in vulvar carcinogenesis is also essential to explain the increase in VSCC incidence for each subsequent cohort of Italian women born in 1945 or later. There are no clear data indicating such an early change in exposure to HPV infection in Italy. In particular, the incidence of cervical carcinoma, after decades of reduction, has stabilised in the 1990s [25] and current estimates of the rate that would be observed in the absence of screening confirm a stable trend [26]. With respect to head and neck cancers, a nationwide study covering the years 1988–2012 has shown that the incidence of the subset of cases arising from the HPV-related sub-site (i.e., the oropharynx) remained stable among men [27]. An increasing trend was observed among women, but the largest increment was noted in those aged above 60 years. The authors concluded that the role of HPV infection in the epidemiology of head and neck cancer in Italy is increasing, but to a lesser extent and with a different pattern from that observed in other Western countries. Thus, we believe that the trend in VSCC incidence for women born after World War II – especially for those born in the first two decades after World War II, who experienced a modest risk increase (Fig. 3) – has been probably driven by the trends toward

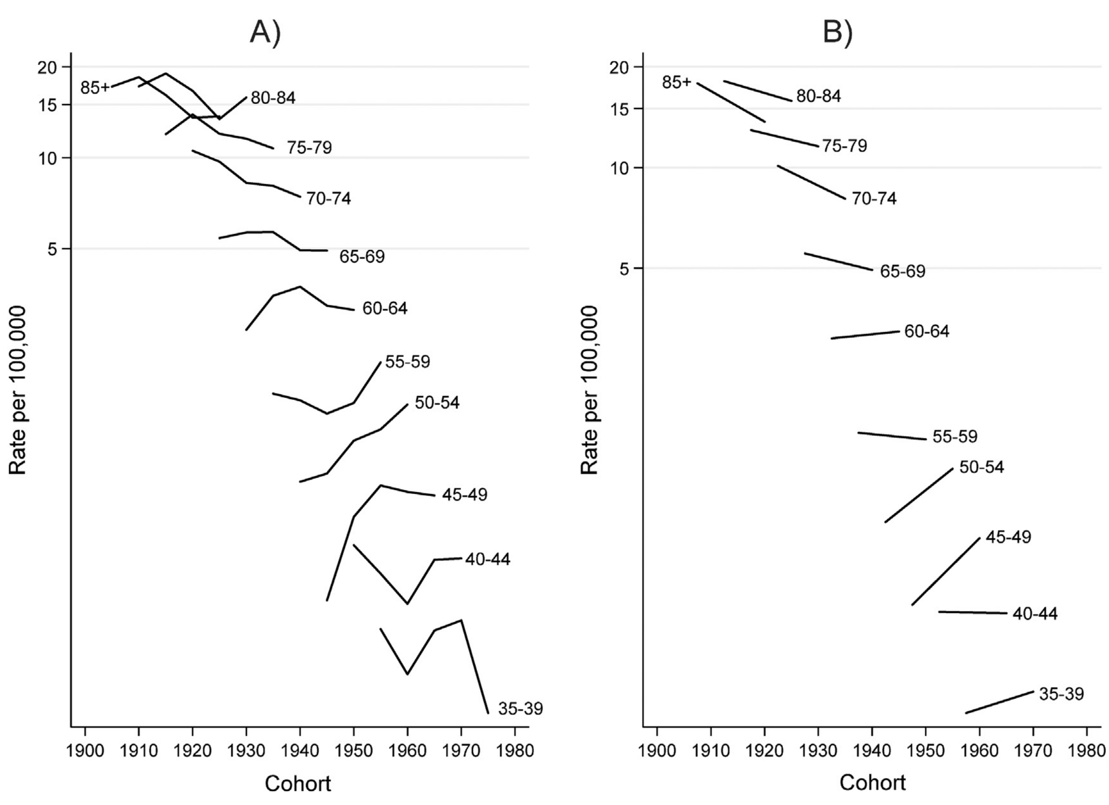

Fig. 2. Trend in incidence rates of vulvar squamous cell carcinoma on a logarithmic scale (per 100,000 women) in Italy from 1990 to 2015, by 5-year age-class and 9-year birth cohort. The rates for each age group are joined by lines and are plotted against the mid-year of birth. The two panels of the figure depicts the rates (A) before and (B) after smoothing by median splines. The non-linear cohort effect is indicated by the fact that the age-specific trends by birth cohort had different slopes. The most recent cohorts showed the highest increase in incidence rates.

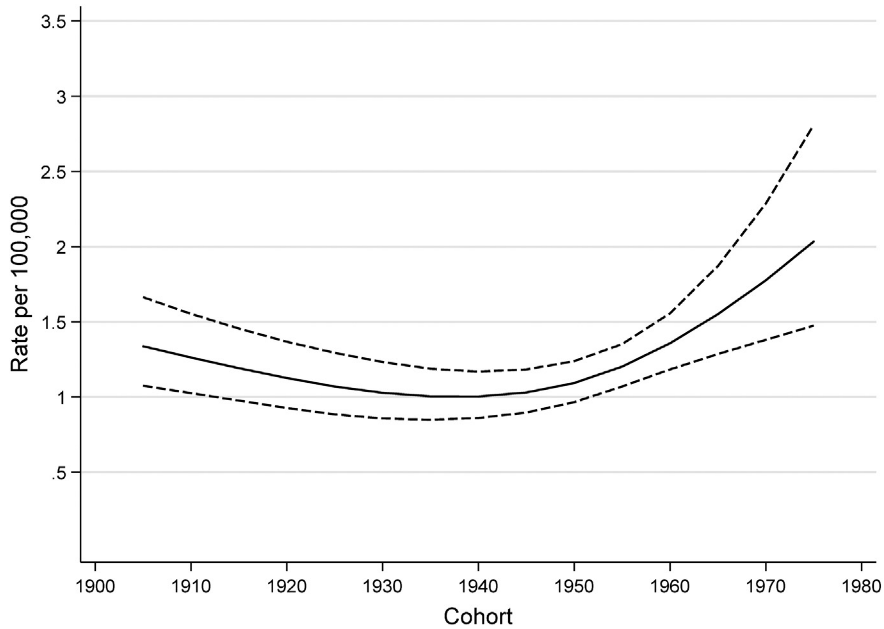

Fig. 3. Curve of incidence rates (per 100,000 women) of vulvar squamous cell carcinoma in Italy from 1990 to 2015, by birth cohort, estimated from the smoothed age-period-cohort model. The curve is adjusted for the age and period effects. The U-shape indicates a slight decline for generations born between 1905 and 1940 followed by a pronounced increase for subsequent generations.

increasing prevalence of obesity and smoking. In the Mediterranean countries, where children have currently the highest rates of childhood overweight and obesity in Europe, the traditional Mediterranean diet has gradually been abandoned by the cohorts born in the second half of the 20th century [28]. This trend has been paralleled by a massive spread of the smoking habit among younger women [24], which has been ongoing approximately until the end of 1990s [29]. For women born in the last few decades of the 20th century, the growing prevalence of the HPV infection began to play a central role, and their risk of disease grew more steeply (Fig. 3).

For cancer types relating to a well-established and dominant risk factor, an increased risk experienced by recent cohorts is likely to persist as these cohorts age, potentially resulting in increasing rates in successively older age groups. The epidemiology of VSCC, conversely, is a multifactorial one and changes partially with woman's age. Consequently, the risk increase currently observed in recent cohorts will not necessarily persist unchanged when these cohorts will grow old. Probably, it will be partly eroded. It must be noted that an uncertainty similar to this surrounds the consequences of the increase in the risk of breast cancer that has occurred in the last decades among European women aged <40 years [30], one of the key facts in current epidemiology of female cancer.

4.3. Strengths and limitations

The main strength of this study lies in its originality, which stems from the geographic target area, and in the use of the age-period-cohort modelling analysis. VSCC incidence trends in southern European countries have never been studied in depth. As regards the statistical methods used in previous studies, they have varied from Poisson regression analysis [1,31] to joinpoint regression analysis [2,6,8,13] to more descriptive approaches [5,7,9]. The age-period-cohort modelling enhances the understanding of incidence trends. This approach allowed us to demonstrate, for the first time in Italy, the multifaceted role of birth cohort in incidence trends of VSCC.

It is important to note that, conversely, we did not observe major period effects. This was expected. In the age-period-cohort modelling of cancer incidence, a period effect is generally interpreted as the result of changes in screening and diagnosis practices. This cannot be the case for VSCC, in which virtually no advances have been made for decades [2,32,33].

Our analysis also has limitations that should be addressed. First, Italian cancer registries do not routinely collect data for detection and treatment nor for tumour size, lymph node status, and tumour stage. If an increase in the rate of early VSCC and an opposite trend for advanced VSCC were observed over time, this might suggest a heightened awareness by the latest generations with increased and earlier detection of the disease in addition to an increased exposure to risk factors. It was also impossible to assess the presence of a trend in incidence by tumour grade, because the information was missing for 59% of cases.

Second, Italian cancer registries have been established very gradually and, in the early years, they were concentrated in northern Italy. In addition, the national coverage is still incomplete (about 50% in this study). In order to control for the potential adverse implications of the changing composition of the pool of registries, Italian researchers often limit their analyses to a small group of historical long-standing registries [27] or to relatively short time periods with higher numbers of active institutions [34]. Both designs have pros and cons. We approached the problem by performing a sensitivity analysis. The robustness of the estimated trends was substantially confirmed. Their direction and magnitude were largely independent of the geographic area and the duration of the registry. Interestingly, an acceleration of the increasing trend among younger women became apparent after the exclusion of the small registries of central Italy. This finding might well be due to an outlier rate but is worthy of monitoring.

A mention should be made of the potential – but remote – possibility that the quality of data in this study suffers from two further biases. First, the fact that VSCC is prone to recurrence increases the possibility that a single patient be registered twice or more. All registries participating in the study, however, follow the rules for multiple primary cancers set forth by the International Agency for Research on Cancer and the International Association of Cancer Registries [35]. These rules have been successfully implemented in a previous nationwide study on multiple malignancies [36].

Second, it can be safely excluded that HPV vaccination has modified the incidence of VSCC. In Italy, HPV vaccination has been actively offered free of charge to 12-year-old girls since 2007, with a coverage of 70% for a complete cycle [37]. In 2015, the last year of this study, the oldest cohort of girls offered the vaccine was aged 20 years. This is an age threshold below which the risk of disease is virtually zero (only one case in our dataset).

5. Conclusions

This study offered a detailed epidemiologic picture of VSCC incidence in Italy. In summary, there was a decreasing trend for earliest birth cohorts and an opposite one for recent cohorts. The former caused total incidence to decrease but the latter requires careful prospective surveillance, given its potential to reverse the current favourable situation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2020.03.013.

Ethical approval

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

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Declaration of competing interest

The authors have no competing interest.

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