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Estimating the impact of an organised screening programme on cervical cancer incidence: a 26-year study from northern Italy

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Abbreviations: APC: age-period-cohort; CC: cervical cancer; CI: confidence interval; CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; IRR: incidence rate ratio; NA, not applicable.

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Abstract

The impact of the organised cervical cancer (CC) screening programmes implemented in Europe since the 1990s has been insufficiently evaluated. We investigated the changes in CC incidence following the introduction of a screening programme in the Emilia-Romagna Region (northern Italy). The study period was 1988-2013. The programme, targeting women aged 25-64 years (1,219,000 in 2018), started in 1998. The annual incidence rates that would be expected in 1998-2013 in the absence of screening were estimated, first, by analysing the annual rates in 1988-1997 with a log-linear model and, second, by analysing the annual rates in 1988-2013 with an age-period model in which the period effect was enforced to be linear. Cervical adenocarcinoma incidence trend over the entire period was used to validate both estimates. Observed annual rates were compared with the two series of expected ones with the incidence rate ratio (IRR). Incidence remained stable during 1988-1997, peaked in 1998 and then decreased until 2007, when it stabilised. The two series of expected rates were virtually coincident and their trends roughly paralleled the stable adenocarcinoma incidence trend. After 2007, the median IRR was 0.60 (95% confidence interval, 0.45-0.81) based on the log-linear model and 0.58 (95% confidence interval, 0.34-0.97) based on the age-period model. Thirty-six to 75 CC cases were prevented annually for an average annual frequency of 6.5 per 100,000 women in the target population. In summary, consistent circumstantial evidences were obtained that the organised screening programme brought about a 40% reduction in annual CC incidence after 10 years.

What's new?

The impact of the European organised cervical cancer (CC) screening programmes has been insufficiently evaluated. This study from Italy documents a 40% decrease in annual CC incidence following the introduction of a regional screening programme. Its strengths are in the robustness of the estimate of the annual CC incidence rates that would be expected in the absence of screening, that is based on two different methods with virtually coincident results, in the many consistent circumstantial evidences for a temporal correlation between the introduction of screening and the incidence decrease, and in the calculation of the screening-attributable frequency of prevented CC cases.

Introduction

In Europe, the introduction of organised screening programmes was recommended in 1993 by the first edition of the European guidelines for quality assurance in cervical cancer (CC) screening[1] and, ten years later, by the Council of the European Union.[2,3]

In actual fact, the implementation of screening programmes is still in progress[3] and, where they exist, major inadequacies remain in key issues including – among others – quality assurance, monitoring, and evaluation.[4] Problems affecting the evaluation of effectiveness are especially worthy of note. Apart from the Nordic Countries, where organised screening activities began in the 1960s and their effects on CC incidence and mortality have been thoroughly investigated since the 1970s,[5-8] the United Kingdom is the only European country where an adequate amount of epidemiologic work has been directed toward evaluating the results of the more recent reorganisation of the screening services.[9-13] In the greater part of Europe, evaluation systems are insufficient and non-standard. This makes it difficult to determine and compare the effectiveness and cost-effectiveness of the different national and regional screening models.[14] Unfortunately, behind a poor level of monitoring and evaluation often lies the inadequacy of the system of management and coordination of the programmes.[15]

These problems must be viewed from the perspective that screening strategies develop and new technologies are increasingly adopted. This will require a higher level of organisation and quality of the screening process and an improved monitoring of targets, outcomes and results.[14,16]

In order to deal with the gap between these needs and the current situation, the second edition of the European guidelines has placed a renewed emphasis on the necessity that screening be organised in a way that allows the quality of the process to be assured and monitored and the effectiveness over time to be demonstrated.[15-17] These efforts should be especially directed to coverage, technical quality, adverse effects, and target outcome, that is, the impact on the burden of CC.[15-17]

We have complied with this suggestion. In this study, covering the years 1988-2013, we have evaluated the changes in CC incidence following the introduction of an organised screening programme in the Emilia-Romagna Region, a large administrative region of northern Italy.

Material and Methods

Setting

The Emilia-Romagna Region organised CC screening programme started in the second half of 1997. According to administrative information, the volume of invitations was initially modest but rose in the subsequent two years. The target population (women aged 25-64 years, n = 1,219,000 on 1 January 2018) was saturated within 2000, after which the annual frequency of invitations stabilised. Up until 2014, the programme was based on the Pap smear. In 2015, the transition to human papillomavirus (HPV)-based screening of women aged 30-64 years was initiated in accordance with national guidelines.[18] Previously, in 2008, a regional HPV vaccination campaign had been implemented starting from girls in the 1996 and 1997 birth cohorts.[19] These have currently not yet entered the target population of the screening programme, which allows to exclude any bias in the results of this study.

The general characteristics of the cytology screening programme are described in detail elsewhere.[20-22] In brief, every three years, resident women in the target age range were invited by a personal letter to attend the district screening centres for a free Pap smear. The samples were taken by trained midwives. Abnormal screening results were notified to women by telephone. Colposcopy assessment was carried out by gynaecologists and gynaecologist-oncologists at selected clinics. The programme was supported by innovative quality assurance schemes for local cytology, pathology and colposcopy services[23,24] and was subjected to epidemiological surveillance.[25,26]

Between 2000, when the annual frequency of invitations stabilised, and 2013, the average annual proportion of resident women aged 25-64 years undergoing screening has been 17.8%, corresponding to 53.4% on a triennial basis. An evaluation of the performance of the screening process is beyond the scope of this study, but data from all Italian regional screening programmes are regularly collected in a standard fashion by the Italian Group for Cervical Cancer Screening and published by the Italian National Centre for Screening Monitoring.[27] The complete series of statistical reports for the years 2002-2015 is available for free down-load on the website of the Centre.[28] The performance

indicators of the Emilia-Romagna Region screening programme have always been acceptable according to the criteria set forth by both agencies.

Objectives

The study had the following objectives: (1) to identify significant changes in CC incidence trend and to assess their temporal correlation with the implementation of the screening programme; (2) to estimate the annual incidence rates that would be expected in the absence of screening; (3) to compare the observed annual incidence rates with those expected; (4) to estimate the annual and cumulative screening-attributable number of prevented CC cases; and (5) to estimate the annual screening-attributable frequency of prevented CRCs per 100,000 women in the target population.

Rationale

A temporal correlation study is an ecological study where the exposure to a protective (or risk) factor and the occurrence of disease are measured at the population level rather than at the individual level.[29] As a consequence, a temporal correlation does not formally demonstrate a causal relationship between two events. On account of this, and in keeping with the literature on impact assessment,[30] our strategy was to perform a sensitivity analysis according to different scenarios. We used two different published methods, which rely on different assumptions, to estimate the expected annual incidence rates in the absence of screening.[31,32] In order to assess the robustness of results, we validated both series of estimated rates by comparing them with the trend in cervical adenocarcinoma incidence rates over the entire period.[33]

Data and study years

Invasive CC (International Classification of Diseases-10th Revision code C53) incidence data for the years 1986-2013 were made available by the seven general and specialised cervical cancer registries that cover the Emilia-Romagna Region. The process of data collection and transmission is under the supervision of the Department of Health of the regional Administration. As shown in the Supporting

Information Table S1, cancer registration was introduced in the area in a phased manner. Data for the years 1986-1987, which were available only for three out the 11 health care districts in the area, were excluded from analysis. The study covered the years 1988 to 2013 and, since the shift to HPV-based screening began in 2015, it was specifically aimed at evaluating the effectiveness of the cytology screening programme.

Given the low frequency of screening invitations sent out in 1997 and the marked increase occurring in 1998 and 1999, we considered 1998 to be the first year of operation of the programme. The finding that incidence was stable up to 1997 while peaking in 1998 (see Results section) provided circumstantial, *post hoc* support for this assumption.

Statistical methods

All observed and expected annual CC incidence rates in the age range 25-64 years were age-standardised by 5-year age groups using the European standard population.

The two approaches with which the expected rates in the absence of screening were estimated have been proposed by previous works on disease incidence predictions,[31,32] one of which specifically addressing the impact of CC screening on the incidence of the target disease.[32] Under the first approach, the annual incidence rates in the years 1988-1997 were included in a log-linear model which was used to calculate the expected rates in the subsequent period, 1998-2013.[31]

Under the second approach, an age-period-cohort (APC) modelling approach [34,35] was used to examine the trend in CC incidence in the years 1988-2013 by age group, time period, and birth cohort, and to disentangle the effect of each of these factors.[32] The analysis was performed on a Lexis diagram based on 4-year time periods and 4-year age groups. In the Supporting Information Figure S1, details of the APC modelling are shown. The best fitting model was found to be an age-period model. This allowed us to identify net calendar time changes in CC incidence that occurred around the time of introduction of the screening programme, assuming that a non-linear change in the period effect could be attributed to this. From this model, the no-screening scenario was obtained using the estimated age

and cohort effects and assuming a linear period effect. In other words, the projected CC incidence rates were extrapolated assuming that the period effect was constant over time.

We validated the two estimates of expected rates using cervical adenocarcinoma incidence rates, according to recent studies.[33,36,37] In doing this, we made two assumptions: first, that the screening programme did not affect to an appreciable extent the incidence of adenocarcinoma due to the very low sensitivity of Pap smear for pre-invasive glandular lesions;[26,36] and, second, that adenocarcinoma has the same etiology as the other CC subtypes.[33] Consequently, according to Lonnberg et al.,[33] we expected that the time trends in the two estimates of expected rates in the absence of screening paralleled the trend in adenocarcinoma incidence rate. We analysed the adenocarcinoma trend over the entire study period with a log-linear model and we compared the regression slope on time with the estimated slopes from the two models used to obtain the expected rates of CC in the absence of screening.

Observed annual CC incidence rates were compared with those expected based on each of the two methods of estimate described above by means of their ratio (incidence rate ratio, IRR) with bootstrap-estimated 95% confidence interval (CI).

The annual age-standardised screening-attributable frequency of prevented CC cases, an absolute measure of the impact of the screening programme on CC incidence,[38] was defined as the difference between the expected number and the observed number per 100,000 women in the target population. As above, the 95% CI of the attributable frequency was estimated with a bootstrapping procedure.

Results

Table 1 shows the observed total CC incidence data (annual numbers and rates) over the 26-year study period (1988-2013) among women aged 25-64 years living in the Emilia-Romagna Region, and the annual incidence rates that would be expected from 1998 to 2013, based on the two methods of estimate, in the absence of screening.

Fig. 1 shows the time trends in observed total CC rates and the expected rates in the absence of screening. In each of the two sections of Fig. 1, the bold line represents the curve of observed total CC rates. In descriptive terms, the rate was stable for 10 years (1988-1997) prior to the implementation of the screening programme. A peak was observed in 1998, the first year of the programme, followed by a decrease. By 2013, aside from random fluctuations, the curve stabilised.

Fig. 1*a* shows the trend in expected incidence rates from the log-linear model (first approach, see Methods section). There was slight increase over time, with a projected value of 15.3 (95% CI, 9.9-20.8) per 100,000 women in 2013. The estimated rate ratio per 1-year increase was 1.003 (95% CI, 0.983-1.024). Fig. 1*b* shows the trend in expected incidence rates from the age-period model (second approach, see Methods section). The incidence rates derived from this model (Fig. 1*b*) virtually coincided with those obtained with the log-linear model, with a projected value of 15.8 (95% CI, 7.4-24.3) in 2013. The estimated rate ratio per 1-year increase was 1.005 (95% CI, 0.980-1.031).

In Fig. 2, the curve of observed total CC incidence rates is plotted together with the curves of observed rates for the two subtypes of CC. It appears that the decreasing trend in observed total CC rates was entirely accounted for by squamous carcinoma, since adenocarcinoma incidence was stable over the entire time period. In addition, the adenocarcinoma incidence trend in 1988-2013 (estimated rate ratio per 1-year increase, 1.005; 95% CI, 0.993-1.016) corresponded to the estimated trend in total annual incidence rates for the years 1988-1997 (estimated rate ratio per 1-year increase, 1.003; 95% CI, 0.983-1.024), as reported in Fig. 1*a*.

In Table 2, observed total incidence rates are formally compared with the two series of expected rates in the absence of screening using the IRR. Due to the high similarity of estimates, the two series of IRRs were virtually coincident. The observed annual incidence became significantly less than expected as early as 2000. The lowest level was reached approximately around 2007, the 10th year of screening, after which only random fluctuations were observed. The incidence decrease stabilised at approximately 40% (median of the annual decreases in the years 2007-2013 under the two approaches; interquartile range, 35%-45%). After a transient excess incidence in 1998, the cumulative number of prevented CC cases became positive in 2000, the 3rd year of screening. When the observed incidence stabilised, the

annual number of prevented CC cases was generally between 36 and 75. In 2013, the 13th of screening, the cumulative number was around 700.

Table 3 shows the annual age-standardised screening-attributable frequency of prevented CC cases per 100,000 women in the target population. From 2007 onward, when the observed incidence reached the lowest level and roughly stabilised, the average annual figure was 6.5 (95% CI, -0.1-18.8) per 100,000 women (data not shown). The expected number of CC cases was derived from the age-period model (for matter of simplicity, we choose a conservative strategy, i.e. the estimate most favouring the null).

Discussion

Soon after the introduction of the screening programme in the Emilia-Romagna Region, CC incidence began to decrease. A simple temporal correlation does not formally demonstrate a cause-effect link. However, we found many consistent circumstantial evidences that the association between the screening programme and the incidence drop was genuine, namely: (1) when the programme was introduced, total incidence was stable; (2) this stable trend was not due to chance, as it perfectly overlapped the national incidence trend during the same years;[39] (3) while most cancer screening programmes are implemented in a geographically gradual manner,[40] the target population of the Emilia-Romagna Region was saturated very rapidly, which strengthens the validity of the observed temporal correlation,[41] (4) the time lag between the introduction of the programme and the incidence decrease was very short; (5) the two series of expected incidence rates in the absence of screening, calculated with two qualitatively different methods, were almost coincident to each other; (6) the drop in total CC incidence was entirely accounted for by the squamous carcinoma subtype and, thus, for by a protective factor acting in a selective manner and independent of the carcinogenetic processes; (7) the validity of both estimated trend lines of CC was corroborated by the finding that their trajectory virtually paralleled the stable trend line of adenocarcinoma, which has the same etiology and is virtually not prevented by screening;[26,33,36,37] and (8) the APC modelling technique provided a specific confirmation that the incidence decrease was the result of an exogenous event and not of a birth-cohort-dependent change in

exposure to risk factors.[32] It clearly appears that all of these facts are not compatible with any comprehensive explanation other than the introduction of the screening programme.

The downward incidence trend, however, ceased somewhat earlier than expected based on literature data. The incidence rate stabilised around 2007, after 10 years of decrease, when it was 40% below the expected level. As suggested by studies of the effect of mammography screening on advanced breast cancer rates,[41-43] the range of time over which CC incidence decreases after the introduction of screening is an approximate measure of the lead time of CC cases averted by the detection and treatment of CIN 2-3. Assuming that CIN2-3 and the preclinical phase of invasive CC have a mean duration of, respectively, 13 years and four years for a total of 17 years,[44] a lead time of 10 years is less than theoretically expected.

In Finland and Sweden, organised screening was introduced between early 1960s and early 1970s for women aged 30-54 years and 30-49 years, respectively.[45] According to data accessible from the NORDCAN (Cancer statistics for the Nordic countries) window of the International Agency for Research on Cancer website ,[46] an incidence peak was observed in the target populations in 1965, supposedly due the most intense phase of the implementation of the programme (Fig. 3). Immediately after, the incidence began to drop rapidly. Around 1980, approximately 15 years later, the decrease ceased in Sweden and slowed down markedly in Finland. In the Emilia-Romagna Region, the duration of decrease was about five years shorter (Fig. 1), which is compatible with a lower sensitivity of the screening procedure for the detection of precursors of invasive CC.

Another finding at variance with studies from north European populations is that we did not observe a non-linear birth cohort effect on CC incidence in the calendar span covered by the study. In the Nordic Countries, a strong linear U-shaped birth cohort effect was observed. Women born after 1940, the calendar period with the lowest risk, experienced a marked increase in CC risk.[32] This upward cohort effect, resulting from changes in sexual behaviour with consequent increase in the prevalence of high-risk HPV infection,[37] enlarged the number of CC cases averted by screening. In Italy, the age at first intercourse – an inverse predictor of the probability of a behaviour at risk in the adult life – has remained almost unchanged in the cohorts born between 1950 and late 1970s.[47] Sexual habits have

appreciably changed only among more recent birth cohorts, who were not covered by this study. In addition, during the second half of past century, women born after World War II have increasingly used the Pap smear on a spontaneous basis, which may have further mitigated the effects of small increases in the prevalence of HPV infection.

Our results should also be compared with those of a previous multiregional Italian study of changes in CC incidence following the introduction of organized screening, authored by Serraino et al., that covered part of the Emilia-Romagna Region.[48] The reported incidence reduction was 25%, considerably less than the one resulting from our estimate. It may be hypothesised that the degree of effectiveness varies across local screening programmes. The temporal pattern of incidence reduction observed in our data, however, suggests a second –and more objective– explanation: the study of Serraino et al. was generally based on as few as 6-8 years of observation after full activation of local screening programmes, when the impact on CC incidence had not been completely achieved yet. Conversely, the study had the merit of providing early evidence that the reorganisation of the screening services in Italy was meeting its objective.

The average annual screening-attributable frequency of prevented CC cases currently observed, 6.5 per 100,000 women, raises the question of cost-effectiveness of the screening programme. A key issue to consider is that its implementation was accompanied by a substantial decrease in spontaneous screening activities, that are known to be more expensive and less effective.[49] In the first half of the 1990s, based on national estimates, the proportion of women aged ≥25 years who had ever undergone a Pap smear spontaneously was certainly above 50%.[48] Currently, the proportion of women aged 25-64 years who spontaneously undergo a Pap smear every three years is 23%.[50] Also, the screening programme has raised the total coverage to 90%.[50]

Three methodological aspects of the rationale and design of this study need to be pointed out. In the first place, evaluating the impact of the screening programme on the whole invited population conforms to the intention-to-screen principle. This approach, however, has limitations that have been noted in the literature.[40] The most severe is that, in the absence of a control population, the incidence

that would be expected in the absence of screening can only be estimated. In this study, we used reference methods proposed in the relevant literature.[31-33,37]

The second aspect to be considered is that cancer registration was introduced in the study area in a geographically gradual manner. This might theoretically affect the observed time trends in CC incidence rates. The Emilia-Romagna Region, however, is extremely homogeneous from a socio-economic perspective. The income and education levels are fairly evenly distributed throughout the area, and a comprehensive welfare state system reduces the potential influence of different social backgrounds on women's behaviour and lifestyle. This means that significant geographical differences in exposure, and in exposure trend, to risk factors for CC are unlikely.

Third, the effects of immigration of high-risk women on CC incidence in Italy are still poorly understood. Based on our data, we can exclude a non-linear birth cohort effect but not a non-linear period effect. If this was present, our estimate of the impact of screening on incidence could be biased in a conservative direction. However, although immigrant women undergoing cervical screening in Italy have a 2.7-fold increased prevalence of CC, they account for less than 15% of the target population.[51] It is nonetheless important that future CC incidence predictions studies explore these issues.

In conclusion, this study confirmed that, with appropriate methods, it is possible to demonstrate the effectiveness of the organised CC screening programmes that have been implemented in Europe since the 1990s. We found many consistent circumstantial evidences for a causal relationship between the introduction of the screening programme in the Emilia-Romagna Region and a significant decrease in CC incidence in the target population. The decrease reached 40% after approximately 10 years and stabilised thereafter. The level of quality of the screening programme was suggested to be sufficient to sustain the ongoing transition to HPV-based screening. The monitoring and evaluation system will continue to operate in order to determine whether the new technology will further reduce the burden of CC in the target population.

Ethical considerations

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

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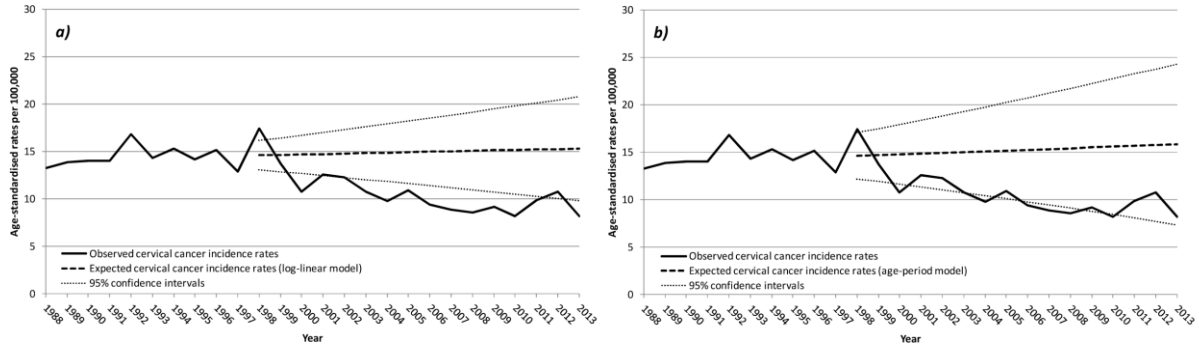
Figure legends

Figure 1. Curve of observed total annual cervical cancer incidence rates per 100,000 women aged 25-64 years in 1988-2013 and curve of total annual rates that would be expected in 1998-2013 in the absence of screening. In the two panels of the Figure, the bold line represents the curve of observed total annual cervical cancer incidence rates. The dashed lines represent the curve of expected total annual rates in the absence of screening derived from (*a*) a log-linear model and (*b*) an age-period model (see text). The dotted lines represent the 95% confidence bands around the expected rates. All rates were age-standardised using the European standard population. Emilia-Romagna Region cancer registries and health care district cervical cancer screening programmes, Italy, 1988-2013.

Figure 2. Curve of observed annual incidence rates of cervical cancer (total), squamous cervical carcinoma, and cervical adenocarcinoma per 100,000 women aged 25-64 years. The bold line represents the curve of observed total annual cervical cancer incidence rates (the same curve as in Figure 1a and Figure 1b). The lower section of the Figure shows the calendar time trends in observed annual rates of the two subtypes of cervical cancer, squamous carcinoma (dashed line) and adenocarcinoma (dotted line). The decreasing trend in observed total annual rates was entirely accounted for by squamous carcinoma. Adenocarcinoma incidence was stable over the entire time period (log-linear model exponential slope 1988-2013, 1.005; 95% CI, 0.993 to 1.016) and corresponded to the estimated trend in total annual rates for the years 1988-1997 (log-linear model exponential slope, 1.003; 95% CI, 0.983 to 1.024). The latter is also the estimated trend for the years 1998-2013 in Figure 1a, which is thus validated by the adenocarcinoma incidence trend. All rates were age-standardised using the European standard population. Emilia-Romagna Region cancer registries and health care district cervical cancer screening programmes, Italy, 1988-2013.

Figure 3. Curve of total annual cervical cancer incidence rates per 100,000 women in the original target populations of the Finnish and Swedish national cervical cancer screening programmes between 1960

and 2015. The data were accessed from the NORDCAN (Cancer statistics for the Nordic countries) window of the International Agency for Research on Cancer website.[46] All rates were age-standardised using the European standard population.



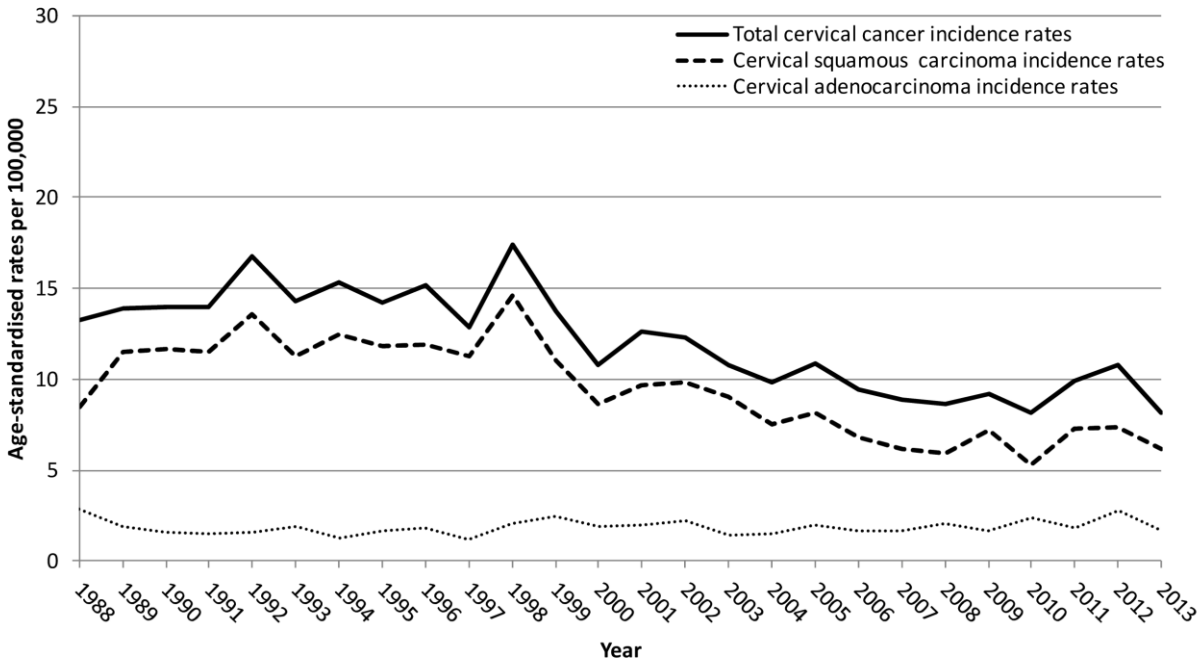


Table 1. Observed total annual cervical cancer incidence (numbers and rates per 100,000 women aged 25-64 years) in 1988-2013, and total annual rates that would be expected in 1998-2013, based on two methods of

estimate, in the absence of screening. Emilia-Romagna Region cancer registries and health care district cervical cancer screening programmes, Italy, 1988-2013.

Year	Observed number	Observed rate	Expected rate (95% confidence interval)	
			From a log-linear model	From an age-period model
1988	53	13.3	NA	NA
1989	62	13.9	NA	NA
1990	65	14.0	NA	NA
1991	80	14.0	NA	NA
1992	93	16.8	NA	NA
1993	89	14.3	NA	NA
1994	96	15.3	NA	NA
1995	111	14.2	NA	NA
1996	105	15.2	NA	NA
1997	136	12.9	NA	NA
1998	181	17.4	14.6 (13.0-16.2)	14.6 (12.2-17.1)
1999	145	13.7	14.7 (12.9-16.4)	14.7 (11.9-17.5)
2000	115	10.8	14.7 (12.7-16.7)	14.8 (11.6-17.9)
2001	134	12.6	14.7 (12.5-17.0)	14.9 (11.4-18.4)
2002	133	12.3	14.8 (12.3-17.3)	14.9 (11.1-18.8)
2003	125	10.8	14.8 (12.1-17.6)	15.0 (10.7-19.3)
2004	114	9.8	14.9 (11.9-17.9)	15.1 (10.4-19.8)
2005	128	10.9	14.9 (11.6-18.2)	15.2 (10.1-20.3)
2006	114	9.4	15.0 (11.4-18.5)	15.3 (9.8-20.7)
2007	107	8.9	15.0 (11.2-18.9)	15.3 (9.5-21.2)
2008	87	8.6	15.1 (11.0-19.2)	15.4 (9.1-21.7)
2009	93	9.2	15.1 (10.8-19.5)	15.5 (8.8-22.2)
2010	84	8.2	15.2 (10.5-19.8)	15.6 (8.4-22.7)
2011	103	9.9	15.2 (10.3-20.1)	15.7 (8.1-23.3)
2012	102	10.8	15.3 (10.1-20.5)	15.8 (7.7-23.8)
2013	77	8.2	15.3 (9.9-20.8)	15.8 (7.4-24.3)

1998 was the year of introduction of the screening programme. The total annual incidence rates that would be expected in 1998-2013 in the absence of screening were estimated by analysing the observed annual rates in 1988-1997 with a log-linear model and the observed annual rates in 1988-2013 with an age-period model in which the period effect was enforced to be linear (in an age-period-cohort modelling analysis, the best fit to the observed rates was obtained with the age-period model). All rates were age-standardised using the European standard population. The ninety-five percent confidence intervals were bootstrap-estimated.

Table 2. Ratio between the observed total annual cervical cancer incidence rates per 100,000 women aged 25-64 years in 1998-2013 and the total annual rates that would be expected, based on two methods of estimate, in the absence of screening, and annual and cumulative number of prevented cervical cancer cases. Emilia-Romagna Region cancer registries and health care district cervical cancer screening programmes, Italy, 1988-2013.

	Method of estimate of expected rate					
	From a log-linear model			From an age-period model		
Year	Incidence rate ratio (95% confidence interval)	Annual number prevented	Cumulative number prevented	Incidence rate ratio (95% confidence interval)	Annual number prevented	Cumulative number prevented
1998	1.18 (1.03-1.30)	-28	-28	1.19 (0.98-1.43)	-27	-27
1999	0.94 (0.80-1.05)	10	-18	0.94 (0.76-1.17)	10	-17
2000	0.74 (0.62-0.83)	41	23	0.74 (0.57-0.94)	42	25
2001	0.85 (0.70-0.98)	24	47	0.85 (0.64-1.12)	25	50
2002	0.83 (0.68-0.98)	26	73	0.83 (0.60-1.12)	28	78
2003	0.73 (0.58-0.87)	46	119	0.72 (0.51-1.00)	49	127
2004	0.66 (0.52-0.80)	60	179	0.64 (0.44-0.93)	62	189
2005	0.73 (0.56-0.90)	48	227	0.71 (0.47-1.05)	50	239
2006	0.65 (0.49-0.82)	63	290	0.62 (0.40-0.96)	66	305
2007	0.60 (0.45-0.77)	71	361	0.58 (0.35-0.91)	75	380
2008	0.60 (0.44-0.79)	58	419	0.57 (0.34-0.93)	61	441
2009	0.63 (0.45-0.84)	55	474	0.59 (0.34-1.00)	58	499
2010	0.56 (0.40-0.76)	66	540	0.52 (0.29-0.91)	70	569
2011	0.67 (0.47-0.94)	50	590	0.63 (0.34-1.12)	54	623
2012	0.74 (0.51-1.05)	36	626	0.69 (0.36-1.26)	40	663
2013	0.56 (0.38-0.81)	61	687	0.51 (0.26-0.97)	65	728

1998 was the year of introduction of the screening programme. The total annual incidence rates that would be expected in 1998-2013 in the absence of screening were estimated by analysing the observed annual rates in 1988-1997 with a log-linear model and the observed annual rates in 1988-2013 with an age-period model in which the period effect was enforced to be linear (in an age-period-cohort modelling analysis, the best fit to the observed rates was obtained with the age-period model). All rates were age-standardised using the European standard population. The ninety-five percent confidence intervals were bootstrap-estimated.

Table 3. Annual screening-attributable frequency of prevented cervical cancer cases in 1998-2013 defined as the difference between the expected number and the observed number per 100,000 women aged 25-64 years. Emilia-Romagna Region cancer registries and health care district cervical cancer screening programmes, Italy, 1988-2013.

Year	Annual screening-attributable frequency (95% confidence interval) of prevented cervical cancer cases
1998	-2.7 (-5.3-0.2)
1999	1.0 (-1.9-4.5)
2000	3.9 (0.7-8.1)
2001	2.3 (-1.3-7.1)
2002	2.7 (-1.2-8.2)
2003	4.2 (-0.1-10.5)
2004	5.3 (0.7-12.3)
2005	4.4 (-0.5-12.3)
2006	5.9 (0.6-14.6)
2007	6.4 (0.8-16.0)
2008	6.8 (0.8-17.2)
2009	6.3 (0.0-17.7)
2010	7.3 (0.7-19.7)
2011	5.8 (-1.1-19.3)
2012	4.9 (-2.3-19.4)
2013	7.7 (0.2-23.4)

1998 was the year of implementation of the screening programme. The number of incident cervical cancers that would be expected in the absence of screening was estimated by analysing the observed annual rates in 1988-2013 with an age-period model in which the period effect was enforced to be linear (in an age-period-cohort modelling analysis, the best fit to the observed rates was obtained with the age-period model). All frequencies were age-standardised using the European standard population. The ninety-five percent confidence intervals were bootstrap-estimated.