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Age-related incidence of cervical cancer supports two aetiological components: a population-based register study

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Objective To assess whether age-related incidence of cervical cancer supports two aetiological components and to assess trends in these components due to risk factors and to organised screening in Finland.

Design Population-based register study.

Setting Finnish Cancer Registry.

Population Cervical cancer cases and female population in Finland in 1953–2012.

Methods Cervical cancer incidence was estimated using Poisson regression where age-specific incidence consists of two (early-age and late-age) normally distributed components.

Main outcome measures Accumulated net risks (incidences) and numbers of cancer cases attributed to each age-related component by calendar time.

Results The accumulated cervical cancer incidence in 2008–2012 was only 30% of that in 1953–1962, before the screening started. The fit of the observed age-specific rates and the rates based on the two-component model was good. In 1953–62, the accumulated net risk ratio (RR; early-age versus late-age) was 0.42 (95% CI 0.29–0.61). The early-age component disappeared in 1973–77 (RR 0.00; 95% CI 0.00–0.08). Thereafter, the risk for the early-age component increased, whereas the risk for the late-age component decreased, and in 2008–2012 the RR was 0.55 (95% CI 0.24–0.89).

Conclusions In Finland, cervical cancer incidence has two age-related components which are likely to indicate differences in risk factors of each component. The trend in risk of both components followed the effects of organised screening. Furthermore, the risk related to the early-age component followed changes in risk factors, such as oncogenic HPV infections and other sexually transmitted diseases and smoking habits.

Keywords Age-related components, cervical cancer, incidence, time series 1953–2012.

Tweetable abstract Cervical cancer incidence has two age-related components which are likely to have differencies in their aetiology.

Linked article This article is commented on by P Sasieni, p. 779 in this issue. To view this mini commentary visit http://dx.doi.org/10.1111/1471-0528.13757.

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Introduction

Age-specific incidence of cervical cancer increases rapidly, usually reaching a peak at 40–50 years of age, followed by a plateau and a variable decline thereafter.[1] This kind of age-related incidence pattern with an early peak or plateau in risk is rare for an epithelial cancer. It is proposed that it reflects the natural history of infections with human papillomavirus (HPV) and the related carcinogenic mechanisms.[1,2] The natural age profile in the incidence is confounded by screening.

Ashley[3,4] suggested already in the 1960s that the age-related incidence pattern of cervical cancer corresponds to two components with different natural histories. One form of cervical cancer, occurring at young ages, is slow-growing and responds to treatment; the other occurs at older ages and is less responsive to treatment.[3,4] The natural history differences and age incidence patterns are consistent with differences in causes of a multi-aetiology disease, such as cervical cancer.[4–6] An oncogenic HPV infection is considered the necessary cause of cervical cancer;[7] other causes[8–10] are considered cofactors.[2]

In Finland, the organised cervical cancer screening programme was phased in from 1963 onwards. Since the early 1970s, practically all women aged 40–50 years have been invited to participate in the programme. From the mid-1970s, the coverage of organised screening was practically 100% in 35-year-old women and about 55 and 20%, respectively, in 30- and 55-year-old women.[11] According to a bylaw on public health, passed in 1992, the municipalities must provide cervical cancer screening for 30- to 60-year-old women. All the time, the screening interval has been 5 years and the attendance of those invited has been somewhat above 70%.[11,12] However, the organised programme does not entirely explain the early decrease in cervical cancer incidence. In the early years of the programme, spontaneous testing was relatively more common than organised screening. In fact, the highest detection rates of carcinoma *in situ* were observed from 1965 to 1974 (about 10 per 100 000 woman-years).[13] This represents the period when most women had their first smear test (organised or spontaneous), resulting in high numbers of CIN lesions being found at the first-ever screen.

From the beginning of 1990s, the incidence of cervical cancer started to increase in women below 40 years of age, whereas in women older than 55 years, the incidence has been constantly decreasing. The increased incidence in these younger women has been interpreted as a result of changes in risk factors, such as exposure to oncogenic HPV infections and other sexually transmitted diseases (STD) related to changes in sexual behaviour and changes in the smoking habits in women.[11,14,15] In addition, the effectiveness of the screening programme was proposed to have decreased because the abrupt increase in incidence by calendar time coincided with major changes in the organisation of screening. These changes increased variation in the quality of the laboratory performance.[11,16,17]

The objective of this study is to assess whether the age-related incidence of cervical cancer during the last 60 years supports the existence of two aetiological components. We also assess how changes in risk factors (oncogenic HPV infections and cofactors) and screening of cervical cancer affected these aetiological components in Finland.

Methods

Data

The numbers of invasive cervical cancer cases diagnosed in Finland in 1953–2012 in women aged 20–84 years were obtained from the Finnish Cancer Registry. The cases were defined by the ICD-O-3 topography code C53 (excluding cases with lymphoma, leukaemia or multiple myeloma, and cases with CIN III, carcinoma *in situ* or dysplasia gravis of cervix uteri). The female population counts in Finland for the same period were obtained from Statistics Finland in 1-year groups of age and calendar time.

Incidence model with two age-related components

The age-specific numbers of cervical cancer cases were modelled using the Poisson regression where the age-specific incidence curve $u(a)$ is a mixture of two scaled normal densities:[18]

$$u(a) = u_1(a) + u_2(a) = \sum_{i=1}^{2} \alpha_i \exp\left[-\frac{1}{2}\left(\frac{a-\mu_i}{\sigma_i}\right)^2\right], \quad (1)$$

where α_i is a scale factor that specifies the level of incidence rate, μ_i is the mean and σ_i is the standard deviation of the age-related component i ($i = 1, 2$; for early- and late-age component, respectively).

Twelve, 5-year calendar periods from 1953–57 to 2008–2012 were used in the analysis. Dependences in the mean and the standard deviation over the 12 calendar periods were described by normally distributed random effects to improve identifiability of the two age-related components. This hierarchical model was fitted in a Bayesian framework using OPENBUGS software.[19] A similar model but with one aetiological component only was also fitted and compared with the two-component model using the deviance information criterion (DIC).[20] Posterior medians and 95% equal tail posterior intervals (CI) were calculated from the simulated joint posterior distribution using the R program.[21] The incidence model and the joint posterior distribution are described in more detail in the Appendix S1.

Estimates of accumulated net risk and numbers of cancers

The accumulated net risk U_i of age-related component i was estimated as an integral of the incidence rate of the component i ($i = 1, 2$) over age:

$$U_i = \int_{-\infty}^{\infty} u_i(a)\mathrm{d}a = \sum_{a=-\infty}^{\infty} u_i(a). \quad (2)$$

This approximates the probability of contracting the cancer due to age-related component i, if there is zero risk of death and a proportion of population who would remain free of cervical cancer.[6] Therefore, U_i is an estimate of the aetiological impact of component i.

The number N_i of cervical cancer cases that were attributed to component i and diagnosed at 20–84 years of age,

$$N_i = \sum_{a=20}^{84} u_i(a) y_a, \quad (3)$$

is related to the actual population experience and can be considered a real life indicator of the age-related component i in an observed population with the actual observed

risk of death in Finnish women. Here y_a denotes the number of person-years in the Finnish female population in a given year of age a. The numbers depend on the age structure of the population in a given calendar period. Therefore, the age-standardised (to the female population in 1953–2012) risk ratio (RR) between the early- and late-age component in the number of cervical cancer cases was estimated (see Appendix S1 for more details).

Results

Figure 1 shows the age-specific incidence rates and the fitted curves of the two-component model (1) for cervical cancer by 5-year calendar periods in Finland in 1953–2012. The parameter estimates of the age-related components are shown in Table 1. The overall fit of the model with the observed rates was very good, and the two-component model was clearly better than the model with one component only (DIC 4459 versus 5168).

In Finland in 1953–62, the accumulated net risk of cervical cancer ($U_1 + U_2$) was 1.8%, with 361 incident cases ($N_1 + N_2$) per year, before the screening programme was gradually introduced (Table 2). The risk was 0.5% for the early-age and 1.3% for the late-age component RR, early- versus late-age, 0.42, 95% CI 0.29–0.61], with an average number of 153 and 208 new cases per year, respectively. The early-age component disappeared temporarily in the 1970s (Figure 2). Since then, the risk of the early-age component has increased to 0.2%; the risk of the late-age component was 0.4% (RR 0.55; 95% CI 0.24–0.89) in 2008–2012. The average numbers of cancers attributed to early- and to late-age component were 76 and 64 new cases per year, respectively, in 2008–2012. In 2008–2012, the accumulated net risk of cervical cancer and the annual number of incident cases were only 30 and 25% of those in 1953–1962, respectively (Table 2).

Discussion

Main findings

In 1953–62, before the organised screening programme was phased in, the incidence of cervical cancer in Finland was

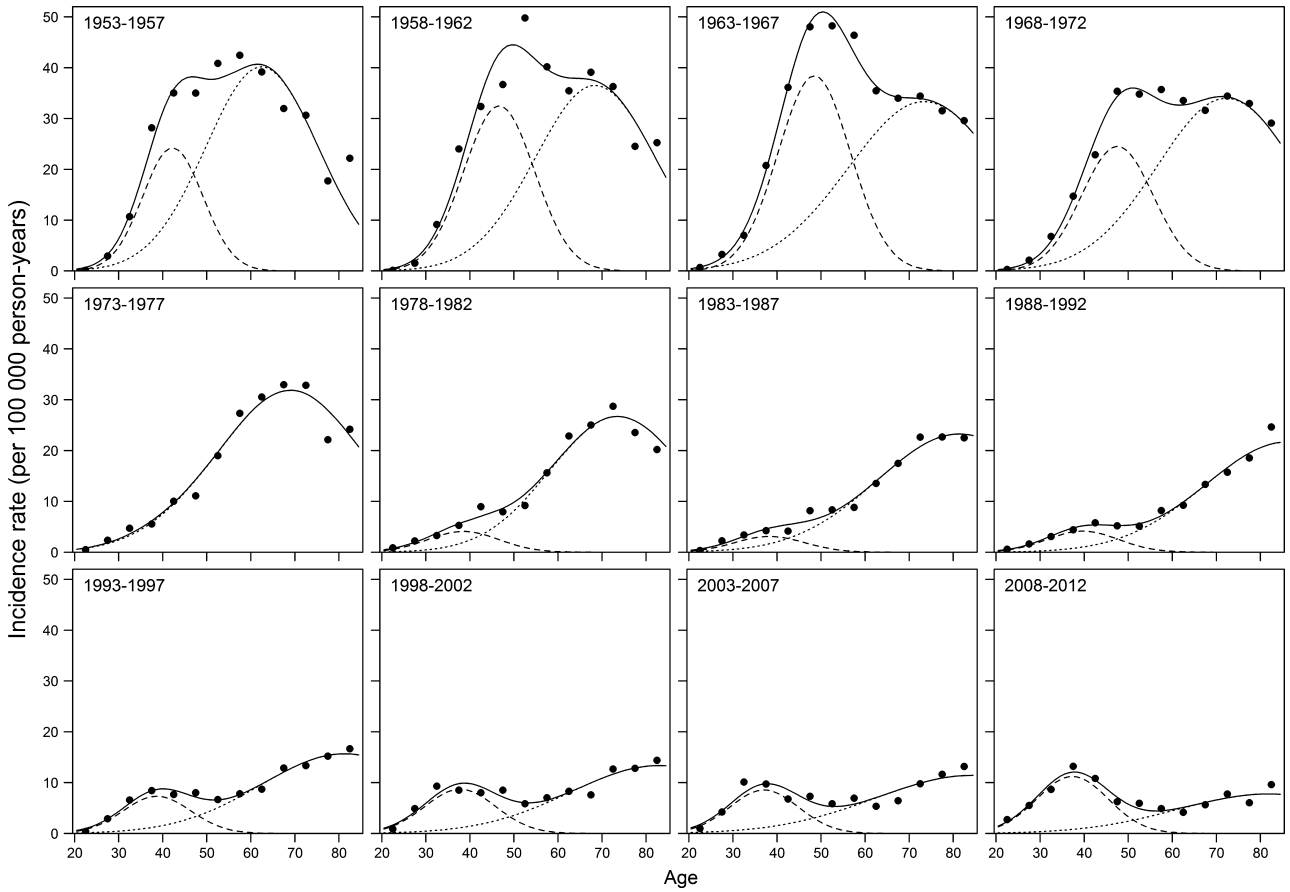

Figure 1. Observed incidence rates (dots) of cervical cancer in Finland in 5-year periods from 1953–57 to 2008–2012 for 5-year age groups from 20–24 to 80–84 years. Fitted values of the incidence rates (solid lines) and of the two age-related components of incidence (dashed and dotted lines) based on the model (1) are also shown.

Table 1. Parameter estimates and 95% CIs of the two components (1: early-age; 2: late-age component) of age-specific incidence rates for cervical cancer diagnosed at 20–84 years of age in Finland in 1953–2012

Calendar period	Scale factor		Mean		Standard deviation	
	α_1	α_2	μ_1	μ_2	σ_1	σ_2
1953–1957	25 (19, 32)	40 (34, 45)	42 (40, 45)	63 (60, 66)	7 (5, 8)	13 (11, 14)
1958–1962	33 (26, 40)	37 (32, 41)	47 (45, 48)	69 (65, 73)	8 (7, 9)	14 (11, 16)
1963–1967	38 (32, 47)	34 (30, 38)	48 (47, 50)	74 (68, 82)	8 (7, 9)	17 (13, 21)
1968–1972	25 (19, 31)	34 (31, 38)	48 (46, 50)	72 (68, 78)	8 (7, 9)	16 (13, 18)
1973–1977	0 (0, 5)	32 (30, 35)	39 (32, 53)	69 (67, 72)	8 (6, 10)	17 (13, 19)
1978–1982	4 (0, 7)	27 (24, 30)	39 (34, 46)	74 (71, 82)	8 (7, 10)	15 (12, 24)
1983–1987	3 (0, 5)	24 (20, 30)	39 (35, 43)	81 (76, 95)	8 (6, 10)	19 (14, 27)
1988–1992	4 (3, 6)	22 (18, 34)	40 (37, 43)	86 (79, 105)	8 (7, 10)	19 (14, 28)
1993–1997	7 (6, 9)	16 (14, 20)	39 (37, 41)	81 (76, 94)	8 (6, 9)	19 (15, 27)
1998–2002	9 (7, 9)	14 (11, 19)	38 (36, 40)	83 (76, 99)	8 (7, 10)	20 (15, 30)
2003–2007	9 (7, 10)	12 (10, 17)	37 (35, 39)	84 (77, 104)	8 (6, 9)	22 (16, 33)
2008–2012	11 (9, 13)	8 (6, 11)	37 (36, 39)	82 (75, 101)	8 (7, 9)	21 (15, 34)

Table 2. Accumulated net risk of cervical cancer (U_i, per 100 000 person-years) and numbers of cervical cancer cases (N_i, per year) diagnosed at 20–84 years of age for each component (i = 1: early-age; 2: late-age) and for their sum (Total)

Calendar period	Net risk			Number of cases		
	U_1	U_2	Total	N_1	N_2	Total*
1953–1957	417	1291	1708	121	225	346
1958–1962	655	1268	1923	185	190	374
1963–1967	791	1464	2255	222	192	414
1968–1972	500	1353	1853	141	201	342
1973–1977	0	1347	1347	0	241	241
1978–1982	85	1029	1114	28	169	196
1983–1987	63	1099	1162	22	136	158
1988–1992	85	1029	1114	31	105	136
1993–1997	142	761	903	53	103	156
1998–2002	178	687	865	63	91	155
2003–2007	168	642	810	57	87	144
2008–2012	230	415	644	76	64	140

*The same as the average observed number of cases per year.

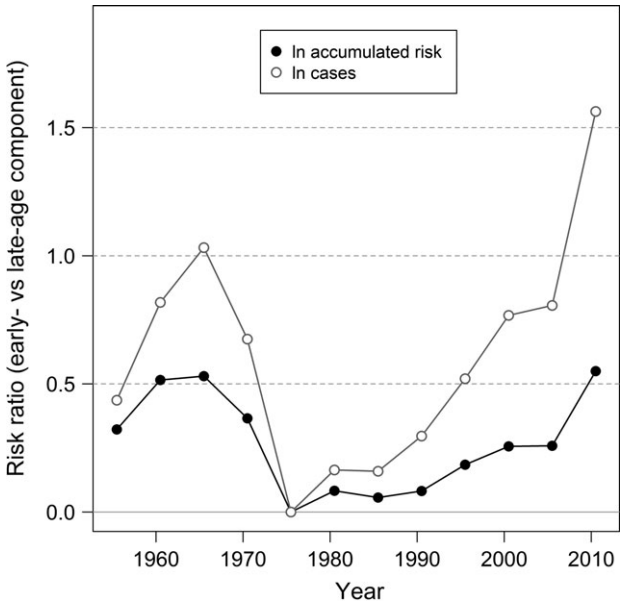

Figure 2. Risk ratio between early- and late-age component in the accumulated net risk of cervical cancer (black dots and lines) and in the number of cervical cancer cases (grey open circles and lines).

consistent with the hypothesis of two aetiological components. The fit of the two-component model with the observations was good in all the time periods considered in spite of substantial changes in the incidence rates, with the exception of 1973–77. We discuss the extent to which the changes in accumulated incidence of the two age-related components reflect the effects of the organised screening programme and changes in the causes of cervical cancer.

There was an increase in the risk of cervical cancer in the early-age component during the first 10 years in 1953–62 and a decrease in 1968–72. Thereafter, this component disappeared temporarily. All these changes could be interpreted as an effect of screening. Since the 1990s, the risk due to the early-age component has increased. The youngest women, those below 30 years of age, had in 2008–2012 a higher risk of cervical cancer than ever before. However, the accumulated risk due to the early-age component in 2008–2012 was still only half of that in the 1950s. The late-age component dominated the overall cervical cancer risk in the 1950s. Thereafter, the risk due to the late-age component decreased

with calendar time, and in 2008–2012 it was only one-third of the risk in the 1950s and the 1960s. The average number of cervical cancers decreased by 61%, from 361 (in 1953–1962) to 140 cases (in 2008–2012) per year.

Strengths and limitations

The shape of the age-incidence curve in cervical cancer is atypical.[1] Our study gives a possible explanation for this anomaly using two age-related and overlapping components.

A long time period of 60 years, which includes more than 40 years of organised cervical cancer screening, provides a firm basis to explore the age-specific incidence rates and to assess the existence of two aetiological components and their changes over time. The current study provides a substantial extension (from 1975 to 2012) of the previous study by Hakama and Penttinen,[18] which covered calendar years 1953–1974.

The cervical cancer incidence rates of the two aetiological components overlap substantially. The assumption of two normally distributed components is convenient and theoretically credible[6] but is not necessarily the only option. Any model of this complexity offers credible interpretation on several other hypotheses as well. Identifying the fixed-effect parameters of the two latent components by calendar time is difficult, especially in the 1970s, when the early-age component was the smallest. Therefore, we used a hierarchical model, which improved identifiability by reducing random variation in the period-specific estimates via hierarchical estimates of the means and standard deviations of the aetiological components. This avoids the decrease in the number of degrees of freedom compared with the method of the earlier study by Hakama and Penttinen[18].

We do not have individual-level data on different background factors (e.g. screening history, prevalence of HPV infections and smoking habits) which may have changed simultaneously over time. Therefore, the separate effects of changes in screening and in risk factors on the two aetiological components of cervical cancer incidence cannot be explicitly quantified.

Because screening has a smaller effect on the incidence of adenocarcinoma than on the incidence of squamous cell carcinoma, it would have been useful to measure the changes in the aetiological components separately in these cell types. However, the two components could not be identified in adenocarcinomas. This is likely due to a small number of cases, or the two components may not even exist in adenocarcinoma, because the two cell types are likely to have partly different aetiologies.[22]

Interpretation

We propose that the most likely explanation for the long-term existence of the two age-related components is that the components have partly different risk factors. Ashley[3,4] suggested that the bimodality in the incidence of cervical cancer corresponds to different natural histories. One form, occurring at young ages, is slow-growing and responds to treatment; the other occurs at older ages and is less responsive to treatment. Similar bimodality was also found for cancers in other primary sites.[23–26] Cancer is a disease of multiple aetiology, with many causes. De Waard[27] hypothesised that Clemmesen's hook[23] in the incidence of breast cancer was caused by two aetiologically different entities, the first related to ovarian oestrogens and the second to adrenocortical oestrogens as a result of Western lifestyle. In eye cancers the retinoblastomas with inherited cause(s) occur in childhood, whereas eye melanomas in adults are probably related to environmental exposures.[24] Oncogenic HPV infection is considered the necessary cause of cervical cancer[7] and other causes[8–10] are called cofactors.[2] Our results do not contradict the role of necessary cause of the oncogenic HPV infection. It is sufficient for the two components that the cofactors are not identical. If all the other causes are the same, then there are more causes of the late-age component than the early-age component.

The effectiveness of screening depends on how a programme is organised.[2] In UK the change of the programme resulted in a major decrease in the incidence of invasive cervical cancer.[28] There was a major change in the organisation of the screening programme in Finland, as the responsibility was moved from central to local authorities during the 1990s. The laboratories owned by the third sector were simultaneously replaced by new private ones, and the screening path was disrupted due to these changes.[16,17] Consequently, there was variation in the quality of the laboratory performance in the 1990s and in the invitational system because of the decentralisation. Participation in the organised screening programme decreased among women under 50 years of age in the 2000s.[12]

In Finland, there was a steady increase in HPV-16 prevalence among pregnant Finnish women from the 1980s to the 1990s.[14,15] A series of detailed questionnaire studies have shown that the sexual behaviour of 18- to 34-year-old Finnish women changed considerably from 1971 to 1999.[29] The average number of lifetime sexual partners grew from 2.6 to 7.7 and the mean age of sexual debut decreased from 18.9 to 16.6 years.[29] Therefore, the STD cofactors became more prevalent.

The proportion of 14- to 18-year-old girls who smoked cigarettes daily increased by 5 percentage points during the 1980s and 1990s.[30] Among women aged 45–64 years, the prevalence increased even more than among teenagers in the same period. Any of these changes in screening and in risk factors since the 1990s may have contributed to the increase in the early-age component.

The late-age component dominated the overall cervical cancer risk in the pre-screening period. The proportion of women over 60 years old who had previously participated in the organised screening programme, increased with calendar time. In 2010, for example, a vast majority of women between 60 and 90 years of age had been invited for screening at least once in their life.[11,12] Consequently, the late-age component decreased, particularly from the 1980s onwards. Also the increasing trend in the mean and the variance of the late-age component is consistent with the effect of screening that gradually appeared by increasing age. The most recent accumulated risk of cervical cancer due to the late-age component was only one-third of the risk in the 1950s and the 1960s; the annual numbers have gone down from over 200 to less than 70. The correlation of the risk factors with the late-age component is poor or non-existent. However, the data are insufficient because the evidence on STD infection prevalence covers relative young (fertile) women. It remains to be seen whether the decrease in effectiveness of screening and changes in risk factors will also affect women who stem from the cohorts with changes in the screening organisation and in sexual mores, when the same women become older.

Conclusions

Our results support the hypothesis that there are two aetiological components in age-related cervical cancer risk: first, a decreasing and, subsequently, an increasing trend in risk of the early-age component which followed both the effects of organised screening and the trends in the prevalence of oncogenic HPV infections and other STDs, and smoking habits in Finland. The continuous decrease in the risk of cervical cancer in the late-age component is consistent with the long-term effect of screening.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MH planned the design. MH, JP and KS planned the method. KS analysed the data and wrote the first draft of the article. KS, JP, NM and MH contributed to the interpretations of the analyses and revision of the article, and approved the final version for submission.

Details of ethics approval

Register-based observational studies do not require ethical approval in Finland. The researchers used anonymised data from the Finnish Cancer Registry in the analyses. Data protection laws and regulations on privacy were strictly obeyed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Incidence model with two age-related components and age standardisation of risk ratio in cancer cases. ■

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