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Is it rational to start population-based cervical cancer screening at or soon after age 20? Analysis of time trends in preinvasive and invasive diseases

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ABSTRACT

The effect of starting screening at age 20 in 1988 was assessed by analysing (a) the age-specific incidence and distribution of stage and histology of invasive diseases, and (b) the detection rates of histologic moderate to high-grade intraepithelial neoplasia (CIN 2–3/AIS), and 1st abnormal cytology and repeat low-grade cytology after follow-up observation. Cancer incidence increased significantly at age 25–34 after 1979 due to early stage squamous cell and adenocarcinoma. After an initial increased rate of preinvasive disease, CIN 3 decreased significantly at age 30–34 after 1988, at age 25–29 after 1993, and levelled out after 1998 at age 20–24. The rates of CIN 2 levelled out after 1998. The rates of repeat low-grade smears decreased after observation at age 20–24 by 80%. The study confirms an increasing rate of preinvasive and invasive disease among younger women and indicates the benefit of starting organised screening at 2–3 year intervals soon after age 20.

1. Introduction

In Iceland, organised cervical cancer screening started in 1964 and became nationwide in 1969 with screening at 2–3 year intervals in the 25–69-year-old age group. Younger and older women could also attend of their own accord. Due to an increased cancer incidence the screening organisation and guidelines were intensified after 1979 with successive installation of an improved call–recall system and improved quality assurance, and finally the lower age limit was decreased to 20 years in 1988 with rescreening at 2–3 year intervals.[1,2]

International screening guidelines, however, recommend starting screening at age 25 with 3–5 year intervals[3,4] and the cost effectiveness of screening women under 25 has been criticised due to the high prevalence of low-grade smears at that age, most of which will regress spontaneously. IARCs Working Group for implementation of conventional cytology thus recently concluded that there is minimal benefit and even harm in screening below age 25.[3]

The Human papillomavirus (HPV) is the main aetiological factor in the development of cervical cancer.[5] Two vaccines (Gardasil™ and Cervarix™) which target the most common oncogenic types (HPV 16/18) have been developed[6] and one of these (Gardasil™) has recently been accepted by the US Food and Drug Administration (FDA) for public health use.[7] Although these vaccines will, in time, decrease the prevalence of the disease a combined public health approach with cytological screening will, however, be needed. Cost-effectiveness studies have indicated that the most effective public health approach would be a combined approach starting with

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vaccinating women at or before age 12 followed by cytological screening conducted at 2–3 year intervals from age 24 to 25.[8,9]

The aim of the present study was to evaluate the value of screening in the age group 20–34 by analysing trends in preinvasive and invasive diseases. This was done by analysing in 5-year age classes the age-specific incidence rates of invasive disease since 1955 for those aged 20–69 and the following data for the 20–34 age group: (a) the distribution of stage and histology of invasive disease since 1964, (b) the detection rates of CIN 2–3 (gold standard for definitive therapy) irrespective of visit number since 1979, and (c) the detection rates of high-grade smears (HSIL: high-grade squamous cell lesion; ASC-H: atypical squamous cells, cannot rule out HSIL; AIS: adenocarcinoma *in situ*) and low-grade smears (ASC-US: atypical squamous cells of uncertain significance; AGUS: atypical glandular cells of uncertain significance; LSIL: low-grade squamous cell intraepithelial lesion) and low-grade smears after the follow-up observation of the first low-grade smears (Nordic standard for colposcopic referral) since 1979. Finally, the screening implications of large-scale HPV vaccinations were evaluated.

2. Material and methods

2.1. *The material*

The national screening programme in Iceland takes into account both the smears taken at organised screening and those taken at spontaneous screening (currently about 25% of all smears taken in Iceland). All data on screening attendance (organised and spontaneous) and preinvasive disease are registered at the Cancer Detection Clinic and invasive disease at the Cancer Registry of the Icelandic Cancer Society. The data in this study are therefore based on a nation wide registration.

The average 3-year screening attendance at age 20–24, 25–29 and 30–34 was 23%, 62% and 72%, respectively, in 1979–1988 and increased to 62%, 78% and 82% in the same age groups in 1989–2003 (Fig. 1). In this study, information on preinvasive disease was limited to the period 1979–2003, with follow-up to February 2005. All rates on preinvasive diseases were calculated per 1000 women screened. The incidence of invasive disease, on the other hand, was calculated per 100,000 women in the population per year.

Grouping of the smears was based on the Bethesda system[10] and the histology classification on the CIN classification system.[11] The screening guidelines after 1979 recommended observing the low-grade smears (ASC-US, AGUS, LSIL) for 6–12 months and referring women with a high-grade smears (HSIL, AIS, ASC-H) and repeat low-grade smears for colposcopy. The tradition has been to observe the low-grade histology (CIN 1) and refer women with high-grade histology (CIN 2–3) for cone biopsy.

Invasive cases were classified according to the International Federation of Gynecology and Obstetrics (FIGO) classification[12] and histology in accordance with the World Health Organization (WHO) classification.[13] Stage IA (microinvasive disease) was defined as an invasion of 5 mm or less from the basement membrane of the surface epithelium or gland of origin and treated with conisation, whereas more advanced stages were treated with radical hysterectomy (stage IB) or pelvic radiotherapy (stage IIA and higher).

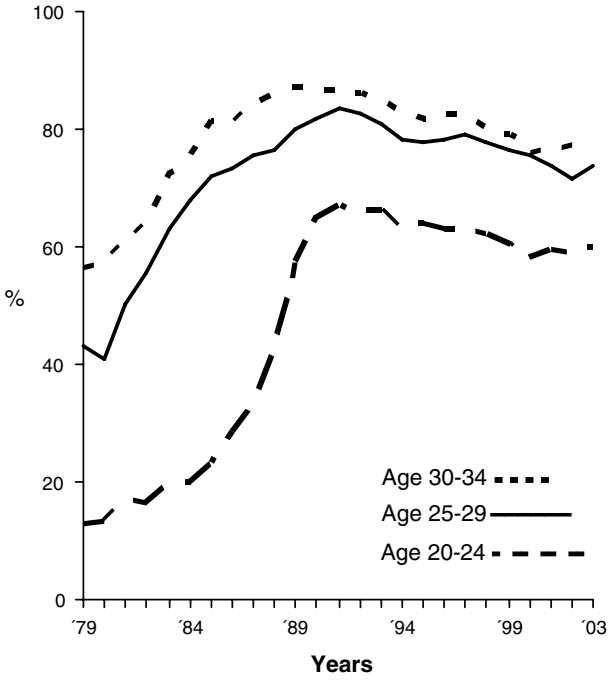

Fig. 1 – Three-year attendance rates at organised and spontaneous screening in the 20–24, 25–29 and 30–34 year age groups, 1979–2003.

2.2. *Age-specific incidence, stage and histology*

The age-specific incidence rate was analysed in 5-year age classes between 20 and 69 and the periods 1955–1978 and 1979–2003. The distribution of stage and histology was obtained for 5-year age classes from age 20 to 34 and in 5-year periods during 1964–2003.

2.3. *Detection rate of CIN 2–3*

Analysis was in 5-year age classes for women 20–34 years and in 5-year periods for the calendar years 1979–2003. Within each time period the detection rate was calculated according to the number of women in each age class diagnosed for the first time with CIN 2–3 divided by the total number of women attending screening in the same age class and time period. The number of women with CIN 3 was then subtracted from the total number of women with CIN 2–3 to give the number with CIN 2. The age of each case was defined according to the age of the women at the respective histological end-points.

2.4. *Detection rate of low- and high-grade smears*

The detection rate of abnormal cytology was calculated in the same way as that of abnormal histology. The number of women with high-grade cytology was subtracted from the total number of women with abnormal cytology to give the number with low-grade cytology. The age of each case was defined

according to the age of the women at the respective cytological end-points.

2.5. Detection rate of repeat low-grade smears

The detection rate of repeat low-grade smears was also analysed in 5-year age classes between ages 20 and 34 and in 5-year periods for 1979–2003. The rate was calculated according to the number of women with two low-grade smears divided by the number of women diagnosed with a low-grade smear for the first time, in the respective age group and time period. When calculating the rate of two low-grade Pap smears, women with a high-grade smear after a first low-grade smear were excluded.

2.6. Statistics

The significance of differences in proportions and rates was tested by using the software package Confidence Interval Analysis.[14] The significance level was set at 0.05 and all tests were two sided.

3. Results

3.1. Age-specific incidence, stage and histology

The age-specific incidence in the 20–24 age group was about the same in 1955–1978 and 1979–2003 (2.6/100,000/year versus 2/100,000/year) but increased during the latter period in the 25–29 (7.4 versus 17.2; $p < 0.001$) and 30–34 (16 versus 24.2; $p = 0.009$) age groups. The incidence decreased significantly after age 40 (Fig. 2).

Table 1 shows that the age-specific incidence was relatively unchanged after 1978 in each of the 5-year age classes from 20 to 34. About 60% (65/108) of all cases diagnosed at age 20–34 were microinvasive cases. The rate of microinvasive cases increased from 2.5 in 1964–1978 to 8.6 in 1979–2003 ($p < 0.001$) and the rate continued to increase ($p < 0.03$) at ages 25–34 after 1988. In 1989–2003 29% (13/44) of these cases were diagnosed at 1st visit, 27% (12/44) within 3 years, 11% (5/44) between 3 and 5 years and 32% (14/44) 5 years or later after the last normal smear.

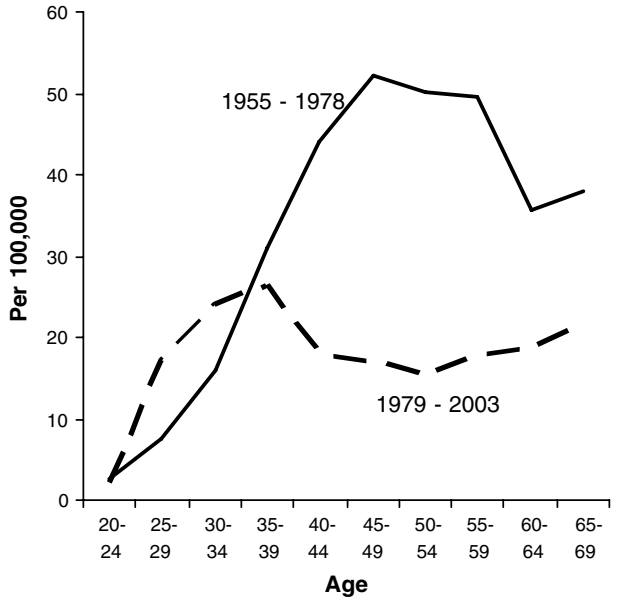

Fig. 2 – Age-specific incidence of cervical cancer during 1955–1978 and 1979–2003 in 5 year age classes between the ages of 20 and 69.

The rate of stage IB increased from 1.9/100,000 in 1964–1978 to 4.7 ($p = 0.009$) in 1979–2003 but the rate of stage IIA and more advanced cases decreased from 2.8 to 0.9 ($p = 0.06$). The rate of squamous cell carcinoma and adenocarcinomas increased significantly between these periods from 5.9 to 11.1 ($p = 0.004$) and 0.3 to 1.6 ($p = 0.02$), respectively, whereas the rate of adenosquamous carcinomas increased non-significantly ($p = 0.36$).

3.2. Detection rate of high-grade cytology

Table 2 shows that the detection rate of high-grade cytology increased in the 20–24 age group up to 1994–1998 ($p < 0.001$) and decreased thereafter ($p = 0.002$). In the 25–29 and 30–34 age groups, the rate increased ($p < 0.001$) up to 1984–1988, was relatively stable during the next two periods, and decreased thereafter ($p < 0.001$). The detection rate of high-grade cytology at age 20–24 in 1989–2003 was lower ($p < 0.001$) than at age 25–29 but higher ($p = 0.001$) than at age 30–34.

3.3. Detection rate of low-grade cytology

Table 2 shows that the detection rate of low-grade cytology increased in the 20–24 age group up to 1994–1998 ($p < 0.001$) and levelled out thereafter ($p = 0.23$). In the 25–29 and 30–34 age groups, the rate increased ($p < 0.001$) up to 1994–1998, and decreased thereafter ($p < 0.001$).

The detection rate of repeat low-grade smears within 18 months after the first low-grade smear increased in the 20–24 age group during the observation period ($p < 0.001$). The rate in the 25–29 age group increased up to 1989–1993 ($p < 0.001$) but decreased thereafter ($p = 0.03$). At age 30–34 the rate increased up to 1989–1993 ($p = 0.10$) but decreased thereafter ($p = 0.01$).

3.4. Detection rate of CIN 2 and CIN 3

As shown in Table 2 the rate of CIN 3 increased at age 20–24 up to 1994–1998 ($p < 0.001$) and levelled out thereafter ($p = 0.41$). The rate increased in the 25–29 age group until 1989–1993 ($p < 0.001$) but then decreased ($p = 0.004$). At age 30–34 the rate increased up to 1984–1988 ($p < 0.001$) and decreased thereafter ($p < 0.001$). At age 25–34 the combined detection rate of CIN 3 decreased ($p < 0.001$) in 1999–2003 compared to the period 1989–1998.

The rate of CIN 2 increased at age 20–24 up to 1994–1998 ($p < 0.001$) and then levelled out ($p = 0.65$). At age 25–29 the rate increased until 1994–1998 ($p < 0.001$) but then levelled out ($p = 0.11$). At age 30–34 the rate increased up to 1994–1998 ($p = 0.002$) and decreased thereafter ($p = 0.47$). At age 25–34 the combined detection rate of CIN 2 decreased ($p = 0.37$) in 1999–2003 compared to the period 1989–1998.

Table 1 – Number of invasive cervical cancer cases (N), annual age-specific incidence rates per 100,000 (r), stage and histology distribution in the 20–24, 25–29 and 30–34 year age groups in 1964–2003

Time periods	Age 20–24					Age 25–29				Age 30–34			
Stage distribution	N	(r)	IA	IB	IIA+	(r)	IA	IB	IIA+	(r)	IA	IB	IIA +
1964–1978	23	(2)	1	1	1	(6)	3	2	1	(15)	4	3	7
1979–1988	43	(2)	0	1	1	(18)	8	8	2	(26)	13	7	3
1989–2003	65	(2)	3	1		(17)	17	8	1	(23)	24	11	
Histology distribution			Sq	Ad	Adsq		Sq	Ad	Adsq		Sq	Ad	Adsq
1964–1978	23	(2)	1	0	2	(6)	6	0	0	(15)	12	1	1
1979–1988	43	(2)		1	1	(18)	16	0	2	(26)	19	2	2
1989–2003	65	(2)	2	1	1	(17)	19	4	3	(23)	28	4	3

Sq: squamous cell; Ad: adenocarcinoma; Adsq: adenosquamous.

Table 2 – Number (N) of women screened, women with abnormal histology (CIN 3; CIN 2), abnormal cytology (1st high-grade: HG; 1st low-grade: LG; repeat low-grade: 2×LG) and detection rate per 1000 women screened (rate) according to age classes and 5-year periods in 1979–2003

Age group	Women screened	CIN 3		CIN 2		HG		LG		2 × LG	
Time periods	N	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Age 20–24											
1979–1983	3822	21	5.5	3	0.8	45	11.8	110	28.8	22	5.8
1984–1988	7836	83	10.6	27	3.4	196	25.0	322	41.1	74	9.4
1989–1993	12,582	170	13.5	60	4.8	326	25.9	828	65.8	157	12.5
1994–1998	11,772	183	15.5	93	7.9	387	32.9	916	77.8	166	14.1
1999–2003	11,870	169	14.2	100	8.4	306	25.8	875	73.7	188	15.8
1979–1988	11,658	94	8.1	30	2.6	241	20.7	432	37.1	96	8.2
1989–2003	36,224	522	14.4	253	7.0	1019	28.1	2619	72.3	511	14.1
Age 25–29											
1979–1983	9083	129	14.2	20	2.2	230	25.3	230	25.3	33	3.6
1984–1988	13,040	301	23.1	44	3.4	491	37.7	453	34.7	90	6.9
1989–1993	14,120	358	25.4	56	4.0	506	35.8	735	52.1	129	9.1
1994–1998	12,511	306	24.5	71	5.7	462	36.9	718	57.4	92	7.4
1999–2003	12,290	264	21.5	52	4.2	350	28.5	542	44.1	84	6.8
1979–1988	22,123	430	19.4	66	2.9	1227	32.6	683	30.9	123	5.6
1989–2003	38,921	928	23.8	179	4.6	1318	33.9	1995	51.3	305	7.8
Age 30–34											
1979–1983	8839	129	14.6	11	1.2	202	22.9	176	19.9	35	4.0
1984–1988	12,238	274	22.4	24	2.0	407	33.3	339	27.7	59	4.8
1989–1993	14,061	263	18.7	37	2.6	372	26.5	510	36.3	77	5.5
1994–1998	13,537	243	18.0	40	3.0	360	26.6	573	42.3	64	4.7
1999–2003	12,464	184	14.8	31	2.5	243	19.5	363	29.1	43	3.4
1979–1988	21,077	403	19.1	35	1.7	609	28.9	515	24.4	94	4.5
1989–2003	40,062	690	17.2	108	2.7	975	24.3	1446	36.1	184	4.6

4. Discussion

Descriptive data on trends in invasive and preinvasive diseases are essential for policy makers to evaluate the effect of screening in different age groups. In Iceland, the decision to start screening at age 20 with 2–3 year intervals was based on the increasing rates of pre-invasive and invasive diseases after 1980 in women under the age of 40.[1] This decision is in line with the recommendations from professional organisations in the USA that recommend the commencement of screening 'approximately 3 years' after the onset of vaginal intercourse and no later than 21 years of age.[15,16] This approach, however, is not in line with international guidelines which recommend starting screening age 25[3,4] and definitely not with earlier assumptions that screening should be conducted every 5 years, preferably beginning at age 30.[17]

The findings of this study are in agreement with other reports[16,18,19] that there have been significantly increased detection rates of preinvasive disease in the younger age groups during recent decades. The findings concur with papers from the United States of America, United Kingdom and the Nordic countries[18–21] reporting a lower median age at the first sexual intercourse and increased number of sexual partners, STD and HPV,[20] as well as unpublished data from

the Cancer Detection Clinic supporting a direct correlation between the number of sexual partners and abnormal cytological results. The results also concur with the established causal role of sexually transmitted HPV infections in cervical cancer[5,15,16,22] a conclusion that is in line with a Finnish population-based survey confirming a significant increased incidence of HPV type 16 preceding a recent increase in the rate of pre-invasive and invasive diseases in Finland.[23]

It has been estimated that 40–50% of sexually active women will become infected with HPV within 2–3 years after sexual debut[22,24,25] with a median 8–14 month duration of a new HPV infection.[15] Only a minority of the infected women, however, will develop subclinical disease (10%) or abnormal cytology (4%),[18] most of which will regress[22,24,25]. Screening among adolescents and younger women has therefore been said to create problems due to the high rate of unnecessary diagnostic and therapeutic procedures.[3,16,17,25]

In this study, the detection rate of low-grade smears during 1989–2003 was 40% higher in the 20–24 age group compared to the 25–29 age group. However, in line with other reports[26] the rate of these abnormal smears decreased markedly during follow-up and thereby diminished the need for unnecessary diagnostic and therapeutic procedures. At the same time, it is internationally common practice to refer women with a high-grade cytology for colposcopy. In 1989–2003, the proportion of women with such smears in the 20–24 age group was intermediate between the other two age groups and was significantly higher than the rate at age 30–34. Both these results support the benefit of starting screening before age 25.

Time trends in preinvasive disease at any age reflect the screening intensity at that and younger ages. In Iceland, the rates of CIN 2–3 increased initially in the 25–34 age groups concurrent with intensified screening after 1979, but thereafter the rates of CIN 3 decreased after 1988 in the 30–34 age group and later also at age 25–29. The findings therefore support the conclusion that the decreasing rates in the 30–34 age group were at first due to the intensified screening in the 25–29 year age group, whereas the decreasing rates after 1993 in both the 25–29 and 30–34 year age groups were associated with a lowering of the age limit in 1988.

Time trends in the 20–24 age group mainly reflected the prevalence of pre-invasive disease. The rates of CIN 3 increased significantly in this age group up to 1998 and then levelled out. At the same time the proportion of CIN 2 was increasing and accounted in 1999–2003 for 37% of the CIN 2–3 lesions. The high rates of CIN 2–3 at age 20–24 thus support starting screening before age 25.

The increasing trend of CIN 2 in this young age group together with the intermediate risk profile and reversibility of these lesions[27] and an increased risk of pregnancy-related morbidity post-excisional treatment,[28] however, points to the need for biomarkers[29] which could allow more conservative follow-up in young and nulliparous women with CIN 2 lesions. Although pregnancy-related morbidity is not a part of this study such complications have been reported to be dependent on the size of the cone, the operation method and the skills of the operator.[28]

The question at what age to start screening, however, should not solely take into consideration trends in high-grade pre-invasive lesions but also trends in the age-specific incidence of invasive disease in relation to analyses of stage distribution and the screening history in these cases. This study shows a significantly increased rate of invasive disease in the 25–29 age group after 1980, which is also in line with data from the UK and the Nordic countries.[17,30,31]

This study also confirms that the increased age-specific incidence rate after 1980 was mainly due to increased rate of squamous cell carcinoma and adenocarcinoma diagnosed at an early stage (microinvasive and stage IB). The results are in agreement with other reports that shorter screening intervals are needed for the younger women[32] but contradict assumptions that these cases are difficult to diagnose at screening.[17] The rate of microinvasive cases increased significantly in the 20–34 age groups and the rate of advanced cases decreased in parallel with intensified screening after 1979. The rate increased further after decreasing the lower age limit in 1988 and intensifying the call for rescreening at 2–3 year intervals. In the period 1989–2003, 68% of all cases in this age group were microinvasive cases and these had already started to accumulate within 3 years after the last normal smear. This can be regarded as a sign of the success of the reformed screening programme, as the diagnosis of microinvasive diseases enables fertility-sparing treatment in these younger women.

The prerequisite for good screening results is organised screening with computerised call- and recall system which takes into account all smears taken at spontaneous as well as at organised screening, with centralised working rules and follow-up of all women with abnormal screening results. The screening system needs to feed information to doctors, nurses and politicians as well as to the targeted women with the intention of preventing overscreening and overtreatment and to decrease anxiety among those women diagnosed with cytological abnormalities. Such a system will continue to have the same significance before and after the introduction of HPV 16/18 vaccinations due to the limitations of the vaccines and the false security they may cause among the vaccinated women and their near relatives and sexual partners.

This study confirms that in well-organised screening overtreatment of young women with low-grade lesions can easily be avoided and the results indicate the benefit of starting organised screening soon after age 20 with a screening interval of 2–3 years.

The introduction of large-scale HPV 16/18 vaccinations will, however, within the next two decades, decrease the prevalence of the disease among younger women and thereby decrease the positive predictive value of cytological screening. The decreased prevalence of abnormal smears may decrease the alertness of the cytoscreeners, thus stimulating the incorporation of more expensive screening techniques. This will decrease the cost effectiveness of the screening and press decision makers to change the age limits and lengthen the screening intervals.

To evaluate the effect of the upcoming large-scale HPV vaccinations researchers therefore need to combine descriptive data on trends in invasive and preinvasive diseases in the prevaccine era with data on the distribution of HPV types in these lesions to assess information about the potential effect of different combinations of type-specific vaccines on ongoing cytological screening programmes.

Conflict of interest statement

None.

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