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Screening histories of women with CIN 2/3 compared with women diagnosed with invasive cervical cancer: a retrospective analysis of the Norwegian Coordinated Cervical Cancer Screening Program

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Abstract

Objective: This study compares the screening history for women with cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma in situ (ACIS) with women with different stages and subtypes of cervical carcinoma.
Methods: An analysis of the Norwegian Coordinated Cervical Screening Program comparing all cases with a CIN 2/3/ACIS ($N = 8586$) with all ICC ($N = 777$) in the period 2000–2002. All Pap smears since 1992 were used to characterise detection mode and screening history. Multinominal regression models estimated the risk associated with detection mode and adequate Pap smear history.
Results: A wide range of age at diagnosis, from 16 to 92 years of age was observed regardless of the stage of the disease. Fifty five percentage of the women diagnosed with CIN 2/3/ACIS had an adequate screening history. Of women diagnosed with SCC, 45.1% in stage I, and 10.5% in stage IV had an adequate history. The median age of women with CIN 2/3 (34 years) and squamous cervical carcinoma (SCC) stage I (37 years) given an adequate Pap smear history was not significantly different. For women with ACC, the proportion with adequate screening history was roughly 50% for all stages. After adjustment for detection mode and age, the OR for being diagnosed with ICC stage I compared to CIN 2/3 was 1.2 (95% CI: 1.0–1.5), while the OR of being diagnosed with ICC stage II–IV was 3.4 (95% CI: 2.3–4.8).
Conclusions: Women with CIN 2/3 and ICC stage I were similar with respect to screening histories, i.e. detection mode and age at diagnosis, while women with ICC stage II–IV seldom had an adequate screening history and were diagnosed at a significantly higher age.

Introduction

Cervical carcinoma is considered a progressive disease that develops through a series of pre-invasive stages (CIN, grade I, II and III) before invasion occurs. With the advent of the Pap smear in the 1940s, detection of asymptomatic CIN became possible, paving the way for screening. The intention of screening is to achieve an early diagnosis, i.e. in the case of cervical carcinoma; to detect and treat CIN 2/3, which prevent development of invasive cervical carcinoma (ICC). The introduction of organized cervical cancer screening programs has had a major impact on the incidence of ICC [1–3], However, countries with well-organised screening programs have notably different incidence rates of ICC, and in some instances significantly higher than countries without [2, 4]. Furthermore, not all ICC are prevented, even among women who have complied with screening program guidelines [5–12]. Improvements to screening programs have therefore focused on the most appropriate screening interval [13].

Several studies with different methodological approaches [14–17] have tried to estimate the duration of the pre-invasive phase, in order to decide the most appropriate screening interval. However, these estimates vary between 5 and 16 years [13, 18–25]. Recent knowledge on the natural history of HPV infection, which is

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believed to be the initiating causal factor, indicates an even shorter duration of the pre-invasive phase [26–31]. However, several meta-analyses have shown that few lesions progress from CIN 1 thru CIN 2, CIN 3 to ICC [32–34]. Once developed, most CIN lesions spontaneously regress with the highest regression rates for CIN 1.

With the realisation of a dynamic rather than progressive nature of this disease [35], the effectiveness of a cervical screening program depends on ensuring regular access to Pap smears for the female population. This study assessed the effectiveness of the Norwegian cervical cancer screening program by examining whether women diagnosed with CIN 2/3 have had regular Pap smears, and compared their screening history with the screening history of women who were diagnosed with different stages and subtypes of ICC.

Material and methods

The Cancer Registry of Norway (CRN) is responsible for several registers of pre-malignant lesions and cancers as well as the screening program for cervical cancer. In this study, the Cancer Register, the Register of pre-malign cervical lesion treatment, and the Cytology Register have been linked by the use of the Norwegian personal identification number (PIN). This PIN is a unique 11 digit-number given to each Norwegian citizen, and is used in all official registers, including all registers at the CRN. The registers used in this study are described in the following.

The Cancer register

The CRN has collected information on pre-cancerous lesions and cancer patients in Norway since 1953. The database uses a reporting system that is based on pathology, autopsy and cytology reports, clinical records and death certificates. One record is the result of accumulated reports on one person for each disease. The registration is based on a modified version of International Classification of Disease, version 7 or version O (ICD-7/ICD-O). Staging is done according to Fédération Internationale Gynécologie et d'Obstetrique (FIGO). When referring to results from this registry, only histologically verified CIN and ICC are included, and the CIN classifications will be used. The registration of ICC is practically 100% complete in Norway.

The register of pre-malignant cervical lesion treatment

The Register of pre-malignant cervical lesion treatment has registered all treatments of CIN 2/3 and ACIS made in hospitals since 1998. The report form is based on pathology, cytology and surgical treatment reports. When referring to results from this registry, only histologically verified CIN are included, and the CIN classifications will be used. By combining the Register of pre-malignant cervical lesion treatment and the Cancer Register, a near complete registration of CIN 2/3 and ACIS cases in Norway in the period 2000–2002 is achieved.

The Cytology register

The Cytology register has registered all Pap smear collected in Norway since 1992 regardless of age, and opportunistic or invited Pap smears. The basis for registration is Pap smears, i.e. one record in the registry contains information from one Pap smear. Among the information stored are PIN, age of the women at the date of the smear, morphology, and the date when the smear was analysed. All 22 laboratories, including private ones, report on a standardised cytology report to the CNR. Classification of the morphologic diagnosis is done according to a modified version of the SNOMED coding system [36]. In the current study, the cytological diagnoses were translated to the Bethesda classification [37] and when referring to results from this registry, this classification will be used.

Screening guidelines

The Norwegian guidelines recommend that a woman have a Pap smear every three years. For a woman who has an unsatisfactory, atypical squamous cell of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL) Pap smear, the recommendation is a new Pap smear within six months. If a woman has three consecutive smears of these categories within an 18-month period, the recommendation is a colposcopy-guided biopsy. After a high-grade squamous intraepithelial lesion (HSIL) Pap smear, a colposcopy-guided biopsy is recommended.

Study population

Women in Norway with a histology verified CIN 2/3, ACIS or ICC in 2000–2002 ($N = 9370$) were identified in the Cancer Register and the Register of pre-malign cervical lesion treatment. Women with ICC were subdivided into stage and type; Squamous (SCC), Adenocarcinoma (ACC) and other (OCC). The women were checked for all Pap smears, since January 1st 1992. The date of the first histological specimen was used, and

women with a histological verified lesion in the 12 months prior to the first diagnosis in 2000 were excluded.

Definitions

Two different periods in relation to the histological diagnosis of a CIN 2+ were defined; diagnostic and screening period.

Diagnostic period

The first period is termed "diagnostic" period and immediately precedes the diagnosis of CIN 2+, in which the interest lies in the detection mode, i.e. number of Pap smears and their results in relation to the diagnosis of CIN 2+. This maximum duration of two years of this period is chosen in accordance with the screening guidelines that specify that women with equivocal or LSIL Pap smear should be followed up by repeat cytology for up to 18 months before a histological test should be performed. To classify the duration from the first cytological indication to the histological diagnosis of CIN 2+, the first abnormal cytology within the diagnostic period was stratified according to if it was taken shortly before diagnosis, i.e. within six months, or within 6–24 months. The start of the diagnostic period is the date of the first abnormal Pap smear, prior to the diagnosis of CIN 2+. For women without a Pap smear, or those having a normal Pap smear only, the diagnostic period started 24 months prior to the histological diagnosis.

Screening period

The second period is termed "screening period", and extends from the start of the diagnostic period to 1 January 1992. The interest in this period is whether the women have been adequately screened. Women who had been adequately screened were defined in this study as having:

1. A normal Pap smear within the last four years of the screening period
2. At least two normal Pap smears in the entire screening period
3. If the women have an abnormal Pap smear within the screening period, a subsequent normal Pap smear should be registered within the screening period

Statistics

Ninty-five percentage confidence intervals (CI) were calculated by the exact method when describing proportions and by a binominal method for medians. Quantile regression was used to test for differences in median age. Multinominal logistic regression models were used to calculate odds ratios (OR) with 95% CI. Women with CIN 2/3 or ACIS were used as a reference category when estimating OR for detection mode and screening histories when comparing women with CIN 2/3, ICC stage I and stage II–IV in the regression models. All analyses were performed in Stata version 8.2.

Results

In the three-year period 2000–2002, 11 times more women were registered with a histologically verified CIN 2/3 or ACIS ($N = 8586$) than with ICC ($N = 777$) (Table 1). CIN 3 was the dominant diagnosis with 83% of the pre-malignant lesions. Of the invasive cases, 76% were squamous cell carcinomas, while 16% were adenocarcinomas, and the last 7% were other types of cervical malignancies.

Age at diagnosis

The median age for women with CIN 2/3 was 34 years. The youngest being 16 years while the oldest was 92 years. 13.8% of CIN 2 was diagnosed in women below screening age of 25, while 1.3% of the cases were diagnosed in women above screening age. For women diagnosed with CIN 3 the corresponding proportions were 7.0% and 1.3%. For women with ACIS, 3.3% were diagnosed before screening age, and 8.4% of the cases were diagnosed above screening age.

The median age of women with SCC was 48 years, but with considerable differences within stage. Women diagnosed with stage I had a median age of 41 year while women diagnosed in stage IV had a median age of 63, i.e. 22 years older. In stage I, 8.7% of the cases were diagnosed in women above screening age, while the proportions were 30.8% in stage II, 34.5% in stage III, and 41.0% in stage IV.

Figure 1 shows the distribution of age at diagnosis. For CIN 2, CIN 3, and SCC stage I, the distribution is left skewed. CIN 2 and 3 peaks just below 30 years of age, while SCC stage I have a peak at approximately 37 years. A conspicuous feature is the bimodal distribution of SCC stage II and III, peaking at approximately age 50 and late 70s. The SCC stage IV is slightly right skewed with a peak of around 70 years of age.

Women with a previous CIN 2+

Out of the 9363 women with a CIN 2+ lesion, 283 (3%) had a previously CIN 2+ histologically diagnosed

Table 1. Distribution of incident CIN 2+ in 2000–2002, by age and women with previous CIN 2+ lesion

Histological diagnosis	N	%	Age			Women with a previous CIN 2+	
			Median	95% CI	Min/Max	n	%
CIN 2	1353	14.5	34	33–34	16/85	45	3.3
CIN 3	7113	76.0	34	33–34	16/92	203	2.9
ACIS	120	1.3	38	34–40	21/85	15	12.5
SCC	592	6.3	48	47–50	20/93	17	2.9
Stage I	323	54.6	41	40–43	20/90	10	3.1
Stage II	130	22.0	57	53–63	28/92	5	3.9
Stage III	84	14.2	56	53–63	31/88	1	1.2
Stage IV	39	6.6	63	59–71	28/88	1	2.6
Unknown	16	2.7	65	50–86	29/93	0	0.0
ACC	127	1.4	44	42–50	17/95	3	2.4
Stage I	93	73.2	42	39–44	17/95	2	2.2
Stage II	19	15.0	52	44–60	37/78	1	5.3
Stage III	6	4.7	78	42–85	41/86	0	0.0
Stage IV	5	3.9	73	51–81	51/81	0	0.0
Unknown	4	3.2	64	52–78	52/78	0	0.0
OCC	58	0.6	54	44–63	23/94	0	0.0
Stage I	27	46.6	47	39–59	33/83	0	0.0
Stage II	12	20.7	46	31–56	23/80	0	0.0
Stage III	8	13.8	74	42–89	39/94	0	0.0
Stage IV	6	10.3	68	58–87	57/88	0	0.0
Unknown	5	8.6	76	34–83	34/83	0	0.0
Total	9363	100	34		16/95	283	3.0

more than one year prior to the current diagnosis. This proportion was similar for all lesions except for ACIS were 13% of the women had a previously diagnosed CIN 2+ lesion (Table 1). Women with previous CIN 2+ have been excluded from the following analysis.

Detection mode

Table 2 shows the results and timing of abnormal Pap smears, if any, during the diagnostic period. The first indication of an abnormality was detected within six months of the diagnosis for 62% of the women with CIN 2/3, while the proportion was 71% of the women with ICC stage I, and 50% for women with stage I–IV. The majority of these women had a Pap smear with a diagnosis of HSIL, except for women with ICC stage II–IV where the cytological diagnosis of carcinoma prevailed.

Among women with CIN 2/3, 35% had an abnormal Pap smear between six and 24 months prior to the diagnosis, the majority were diagnosed with ASCUS on this first abnormal Pap smear. 13.5% of women with ICC stage I had a Pap between six and 24 prior to the diagnosis; also here ASCUS was the dominant diagnosis. Among women with ICC stage II–IV, 4.0% had an abnormal Pap smear six to 24 months prior to diagnosis.

Altogether 3.4% of women with CIN 2/3 did not have an abnormal Pap smear within 24 months of the diagnosis, while 15.3% of the women diagnosed with ICC stage I did not have an abnormal Pap smear within 24 months of the diagnosis. 46.5% of the women with ICC stage II–IV did not have an abnormal Pap smear within 24 months of diagnosis.

Table 3 shows the most severe cytological diagnosis on Pap smear within 24 months of histological diagnosis. For women with a CIN 2/3/ACIS, 85.6% had a HSIL, 7.3% had a LSIL and 1.2% had no Pap smears two years prior to the diagnosis. Of the women with an ICC stage I, 80.1% had either a HSIL or cancer as their Pap smear diagnosis, while 10.0% percent did not have a Pap smear prior to diagnosis. Women with ICC stage II–IV, 40.9% had no Pap smear within 24 months of diagnosis, while 17 women (5.7%) had a normal Pap smear. Examination of the pathology reports revealed that all of these women had sought medical care due to symptoms (e.g. bleeding), and/or were discovered when treated for another type of cancer.

The most prevalent mode of diagnosis found in Table 3, i.e. a HSIL Pap smear, was used as the reference for the comparison the Pap smear diagnosis and the severity of the histological diagnosis. These

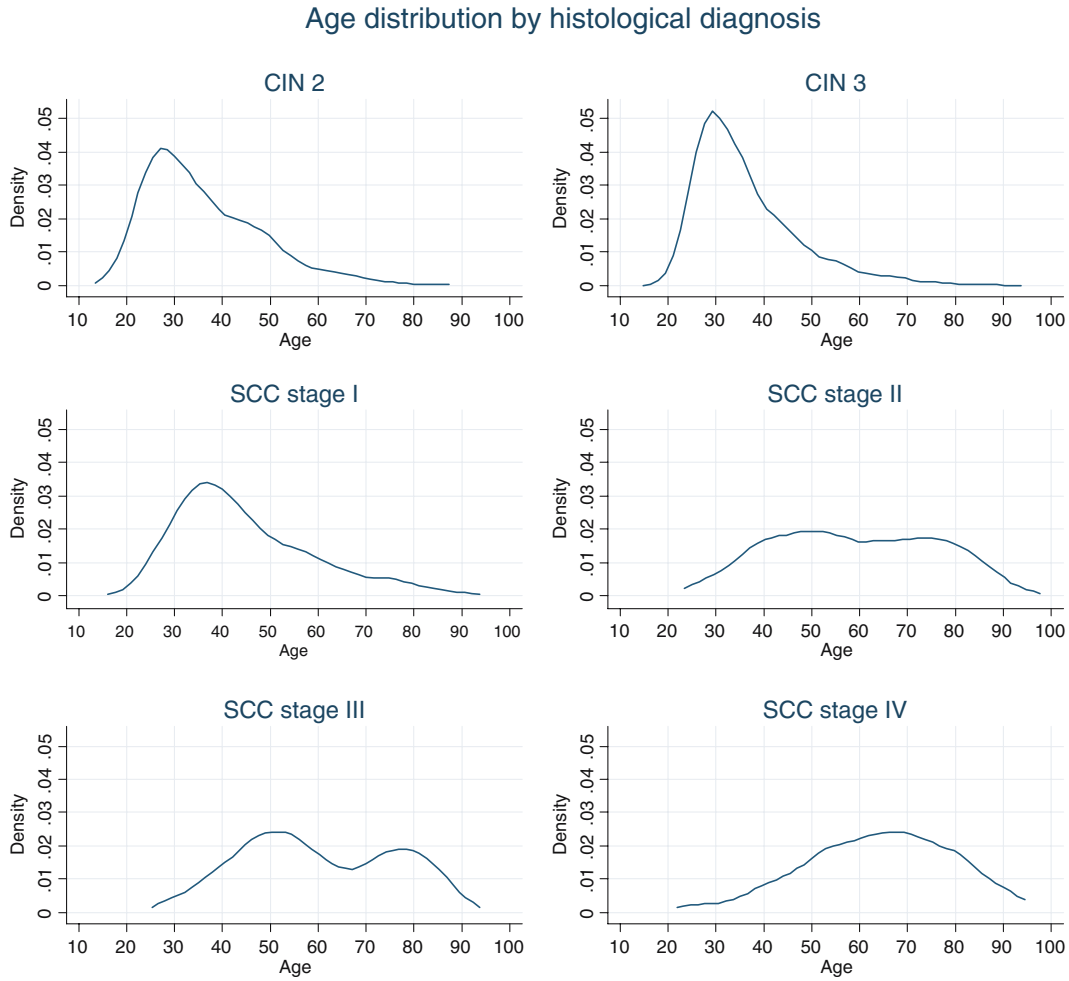

Fig. 1. Age distributions at time of diagnosis.

Table 2. Women with CIN 2+ by previous Pap smears within less than 6 months and 6–24 month in 2000–2002

Cytological diagnosis on first abnormal Pap smear	CIN 2/3/ACIS		ICC stage I		ICC stage II–IV	
	N	%	N	%	N	%
First abnormal Pap smear within 6 months of histological diagnosis	5125	61.6	307	71.2	149	49.5
Unsatisfactory	79	1.5	9	2.9	11	7.4
ASCUS	293	5.7	19	6.2	10	6.7
LSIL	333	6.5	6	2.0	2	1.3
HSIL	4351	84.9	208	67.8	47	31.5
Cancer	69	1.3	65	21.2	79	53.0
First abnormal Pap smear between 6 and 24 months of histological diagnosis	2912	35.0	58	13.5	12	4.0
Unsatisfactory	184	6.3	9	15.5	4	33.3
ASCUS	1195	41.3	32	55.2	4	33.3
LSIL	825	28.3	7	12.1	1	8.3
HSIL	704	24.2	10	17.2	3	25.0
Cancer	4	0.1	0	–	0	–
No abnormal cytology within 24 months of histological diagnosis	286	3.4	66	15.3	140	46.5
Total	8323	100	431	100	301	100

Table 3. Women with CIN 2+ by the most severe Pap smear within 24 month of diagnosis in 2000–2002

Most severe cytological diagnosis on abnormal Pap smear within 24 months of histological diagnosis	CIN 2/3/ ACIS N = 8323	ICC stage I N = 431	ICC stage II–IV N = 301	ICC stage I		ICC stage II–IV	
	%	%	%	OR[a]	95% CI	OR[a]	95% CI
No Pap smear	1.2	10.0	40.9	8.7	5.9–12.9	77.3	50.7–117.9
Normal	2.3	5.3	5.7	2.7	1.7–4.2	7.7	4.2–14.0
Unsatisfactory	0.3	1.4	3.3	5.8	2.4–14.4	49.0	21.2–113.4
ASCUS	2.2	1.9	2.7	1.1	0.5–2.2	4.6	2.1–10.1
LSIL	7.3	1.4	1.0	0.3	0.1–0.7	0.9	0.3–2.8
HSIL	85.6	61.5	16.9	1	Ref	1	Ref
Cancer	1.2	18.6	29.6	15.3	10.9–21.4	57.8	37.8–88.4
Total	100.0	100.0	100.0				

[a] Age-adjusted.

analyses thus give a risk estimate of other Pap smear diagnosis than a HSIL relative to a HSIL diagnosis. When comparing women with CIN 2/3 with women with ICC stage I, it was 8.7 (95% CI: 5.9–12.9) times more likely that women with ICC stage I have had no Pap smear in the 24 months prior to diagnosis. The same figure was 77 (95% CI: 50.7–117.9) when comparing women with CIN 2/3 with women with ICC stage II–IV. Women with ICC stage I were 2.7 (95% CI: 1.7–4.2) more likely to have had a normal Pap smear as their most sever Pap smear than women with CIN 2/3 and similarly, women with ICC were 7.7 times (95% CI: 4.2–14.0) more likely than women with CIN 2/3. It was more likely that a women with ICC stage I had an unsatisfactory Pap smear than a women with CIN 2/3 (OR = 5.8 (95% CI: 2.4–14.4)), while women with ICC stage II–IV were 49.0 (95% CI: 21.2–113.4) times more likely. It was as likely that a women with ICC stage I had had an ASCUS Pap smear as her most sever cytological diagnosis as a women with CIN 2/3 (OR = 1.1 (95% CI: 0.5–2.2)), while it was significantly more likely that a woman with ICC stage II–IV had a unsatisfactory Pap smear than women with CIN 2/3. Women with ICC stage I were less likely to have had an LSIL as their most severe Pap smear compared to women with CIN 2/3 (OR = 0.3 (95% CI: 0.1–0.7)).

An analysis was also performed when restricting the histological diagnosis to CIN 2/3 and SCC, which showed similar results (not in tables).

Screening history

The women diagnosed with CIN 2+ in 2000–2002 were followed-down in the screening period. 83.3 thousand women-years were observed in this time-period with a minimum of six years and a maximum of 11 years for each woman depending on the date of diagnosis and detection mode. A total of 29,292 Pap smears were recorded, a mean number of 3.2 Pap smears per woman, with a maximum of 25 Pap smears for one woman.

Among women diagnosed with a precancerous lesion, less than 10% were without a prior normal Pap smear in the screening period (Table 4). Among women who were diagnosed with SCC stage I, 25.6% had no prior Pap smears, while the proportion was 66.4% in stage II, and 78.9% in women diagnosed with stage IV SCC. This proportion was different in different ages (not in tables). For women aged below 25 years, 28.1% were diagnosed with CIN 2 without a prior Pap smear, while 4.9% in the age group 25–69, and 31.3% of women above 69 years of age. Similarly, for women diagnosed with CIN 3, 20.5% of women diagnosed below 25 years of age had no prior Pap smears, while 8.3% in the age group 25–69, and 50.6% above 69 years. For ICC, no women below 25 years of age were diagnosed without a prior Pap smear. Among women 25–69 years of age diagnosed with SCC, 36.9% had no prior Pap smear, with an increasing proportion with advancing stage, from 21.9% of the women in stage I to 77.3% in stage IV. Similarly, for women with ACC, 17.4% of women 25–69 years who were of age diagnosed with stage I disease had no prior Pap smear, while 50.0% were in stage IV. Women above 69 years diagnosed with ACC stage I 33.3% had no prior Pap smears, while 100% of the women diagnosed at stage IV did not either. More than 70% of women diagnosed with a precancerous lesion had more than two normal Pap smears in the screening period (Table 4). Among women diagnosed with SCC stage I, 57.5% had prior to this two or more normal Pap smears, while 24% in stage II and 10.5% in stage IV. Similar proportions were found for women diagnosed with ACC or OCC.

Table 4. Proportion of women without a normal Pap smear, with two or more normal Pap, with abnormal Pap smear, abnormal Pap smear without subsequent normal

	Proportion without Pap % (95% CI)	Proportion with two or more normal Pap % (95% CI)	Proportion with abnormal Pap smear % (95% CI)	Proportion with abnormal Pap smear without subsequent normal % (95% CI)
CIN 2	8.5 (7.0–10.2)	71.4 (66.9–76.1)	35.5 (32.3–38.9)	9.1 (7.5–10.9)
CIN 3	9.7 (9.0–10.5)	72.9 (70.9–74.9)	31.6 (30.3–33.0)	5.2 (4.7–5.8)
ACIS	7.6 (3.3–15.0)	80.1 (64.7–100)	25.7 (16.9–37.4)	4.8 (1.5–11.1)
SCC	46.4 (41.0–52.4)	39.3 (34.4–44.8)	15.8 (12.7–19.4)	1.4 (0.6–2.7)
Stage I	25.6 (20.3–31.8)	57.5 (49.4–66.6)	23.0 (18.0–29.0)	1.9 (0.7–4.2)
Stage II	66.4 (52.9–82.3)	24.0 (16.2–34.3)	10.4 (5.5–17.8)	0.8 (0.0–4.5)
Stage III	74.7 (57.3–95.8)	13.3 (6.6–23.7)	3.6 (0.7–10.6)	1.2 (0.0–6.7)
Stage IV	78.9 (53.3–100)	10.5 (2.9–27.0)	5.3 (0.6–19.0)	0.0 (0.0–9.7)
ACC	26.6 (18.3–37.4)	55.7 (43.3–70.4)	17.7 (11.1–26.9)	4.0 (1.3–9.4)
Stage I	17.6 (10.0–28.6)	65.9 (50.3–84.9)	23.1 (14.3–35.3)	5.5 (1.8–12.8)
Stage II	44.4 (19.2–87.5)	38.9 (15.6–80.1)	5.6 (0.1–31.0)	0.0 (0.0–20.5)
Stage III	66.7 (18.2–100)	16.7 (0.4–92.8)	0.0 (0–62.0)	0.0 (0–61.5)
Stage IV	80.0 (21.8–100)	20.0 (0.5–100)	0.0 (0.0–73.7)	0.0 (0.0–73.7)
OCC	43.1 (27.9–63.6)	31.1 (18.4–49.0)	8.6 (2.8–20.1)	0.0 (0.0–13.7)
Stage I	25.9 (10.4–53.4)	44.4 (23.0–77.6)	11.1 (2.3–32.5)	0.0 (0.0–30.7)
Stage II	50.0 (18.3–100)	33.3 (9.1–85.3)	16.7 (2.0–60.2)	0.0 (0.0–46.1)
Stage III	62.5 (20.3–100)	12.5 (0.3–69.4)	0.0 (0.0–46.1)	0.0 (0.0–61.5)
Stage IV	66.7 (18.2–100)	0.0 (0.0–61.4)	0.0 (0.0–61.5)	0.0 (0.0–73.8)

For women with CIN 2 or CIN 3, more than 30% had had an abnormal Pap smear, while 25.7% of the women with ACIS had had an abnormal Pap smear. Between 4.8% and 9.1% of these women had had an abnormal Pap smear without a subsequent normal Pap smear. Among women with SCC and ACC, the proportion of women with a prior abnormal Pap smear was 15.8% and 17.7%, respectively. The highest proportion, 23%, was found in women diagnosed at stage I, with a significantly lower proportion in women diagnosed at more advances stages. Few women with ICC had had an abnormal Pap smear without a subsequent normal Pap smear.

The mean number of Pap smears was approximately 3.8 Pap smears for women with precancerous lesions. A somewhat smaller mean number of 3.4 were found for women with SCC and ACC, while women with OCC had a lower mean number of 2.6. The mean number of prior Pap smears was not different in different stage for SCC, while for ACC the mean number of Pap smears was higher in stage I compared to stage II–IV (not in table).

Characterization of screening behaviour

Following the definition of women adequately screened in the screening period, as defined in the method section, 54.7% of the women diagnosed with CIN 2, 56.6% of the women with CIN 3, and 60.0% of the women with ACIS had an adequate screening history (Table 5). The median age was equal for all pre-cancerous lesions, 34 years, regardless of adequacy of Pap smear screening history (not in table).

For women diagnosed with SCC, 31.0% had an adequate history, with 45.1% in stage I, and 10.5% in stage IV. The median age for women with SCC stage I and an adequate Pap smear screening history was 37 years, while the median age was 45 years if the Pap smear history was not adequate, which was significantly different ($p < 0.00$) (not in table). Comparing median age between women with CIN 2/3 (34 years) and SCC stage I (37 years) given an adequate Pap smear history did not give a significant difference ($p = 0.10$). For women with SCC stage IV the median age was 41 years for women with adequate Pap smear history, while the median age for women without an adequate Pap smear history was 65 years.

Analyses stratified on age and stage showed that very few women below 25 years and above 70 years of age had an adequate screening history. For women with ACC, the proportion with adequate screening history was roughly 50% for all stages.

Table 5. Proportion of women with adequate Pap smear history by age and diagnosis

	Proportion with adequate Pap smear history			
	Adequate Pap smear history % (95% CI)	<25 years[a] % (95% CI)	25–69 years % (95% CI)	>69 years % (95% CI)
CIN 2	54.7 (50.7–58.8)	36.2 (28.1–46.0)	57.6 (53.2–62.3)	62.5 (30.0–100)
CIN 3	56.6 (54.8–58.4)	42.3 (36.8–48.5)	58.2 (56.3–60.1)	18.0 (10.3–29.2)
ACIS	60.0 (46.1–76.8)	50.0 (6.1–1)	64.1 (48.8–82.7)	22.2 (2.7–80.3)
SCC	31.0 (26.6–35.9)	40.0 (4.8–100)	37.3 (31.9–43.4)	6.0 (2.4–12.3)
Stage I	45.1 (37.9–53.1)	40.0 (4.8–100)	48.1 (40.3–56.8)	12.0 (2.5–35.1)
Stage II	20.0 (12.9–29.5)	0 (–)	25.9 (16.2–39.2)	7.5 (1.5–21.9)
Stage III	8.4 (3.4–17.4)	0 (–)	13.0 (5.2–26.7)	0.0 (0.0–12.7)
Stage IV	10.5 (2.9–27.0)	0 (–)	13.6 (2.8–39.9)	6.3 (0.2–34.8)
ACC	43.6 (32.7–56.8)	50.0 (1.3–100)	46.7 (34.7–61.6)	20.0 (4.1–58.4)
Stage I	52.8 (38.9–69.9)	50.0 (1.3–100)	52.3 (38.2–70.0)	66.7 (8.1–100)
Stage II	22.2 (6.1–56.9)	0 (–)	21.4 (4.4–62.6)	25.0 (0.1–100)
Stage III	16.7 (0.4–92.9)	0 (–)	50.0 (1.3–1.0)	0.0 (0.0–92.2)
Stage IV	20.0 (0.5–1.0)	0 (–)	50.0 (1.2–1.0)	0.0 (0.0–100)
OCC	27.6 (15.8–44.8)	50.0 (2.5–100)	34.9 (19.5–57.5)	0.0 (0.0–100)
Stage I	37.1 (17.8–68.1)	0 (–)	41.7 (20.0–76.6)	0.0 (0.0–100)
Stage II	33.3 (9.1–85.3)	50.0 (2.5–100)	30.0 (6.2–87.7)	0.0 (0.0–100)
Stage III	12.5 (0.3–69.6)	0 (–)	25.0 (0.6–1)	0.0 (0.0–100)
Stage IV	0.0 (0–61.5)	0 (–)	0.0 (0.0–100)	0.0 (0.0–100)

[a] Adequate history not defined by screening program.

Risk of ICC compared to CIN 2/3 conditional on screening and detection mode

A multinominal logistic regression model, comparing women with CIN 2/3 to women with ICC stage I and stage II–IV, gave an increased likelihood of 1.5 (95% CI: 1.2–1.8) and 7.0 (95% CI: 5.0–9.5) of not having an adequate screening history, respectively (Table 6). After adjustment for detection mode and age, the OR for being diagnosed with ICC stage I compared to CIN 2/3 was still significant with an OR of 1.2 (95% CI: 1.0–1.5). Also the OR of being diagnosed with ICC stage II–IV remained significant with an OR of 3.4 (95% CI: 2.3–4.8). The OR for detection modes, adjusted for adequate screening and age did not change significantly from the OR reported in Table 3.

Restricting the analysis to SCC only, did not change the results significantly.

Table 6. Comparison of women with CIN 2/3/ASCI, ICC stage I, or ICC stage II–IV, by adequacy of screening and detection mode. Results from four multinominal regression models

	ICC stage I				ICC stage II–IV			
	Crude		Adjusted		Crude		Adjusted	
Adequately screening								
Yes	1	Ref	1	Ref	1	Ref	1	Ref
No	1.5	1.2–1.8	1.2	1.0–1.5	7.0	5.0–9.5	3.4	2.3–4.8
Detection mode (most severe Pap within 24 months of histological diagnosis)								
No Pap			10.4	7.0–15.5			89.0	58.8–134.8
Normal			3.3	2.1–5.1			10.7	5.9–19.5
Unsatisfactory			6.3	2.6–15.6			64.1	27.9–147.7
ASCUS			1.2	0.6–2.4			6.1	2.8–13.3
LSIL			0.3	0.1–0.6			0.7	0.2–2.4
HSIL (ref)			1	Ref			1	Ref
Cancer			19.4	14.0–27.0			77.1	50.8–117.2
Age								
<25 years			0.2	0.1–0.4	0.1	0.0–0.4	0.1	0.0–0.4
25–69 years			1	Ref	1	Ref	1	Ref
>69 years			2.0	1.2–3.2	21.3	15.5–29.1	5.3	3.5–8.1

Discussion

This study concern women diagnosed at CIN 2/3, ICC stage I, or ICC stage II–IV in the Norwegian co-ordinated cervical cancer screening program and their screening histories. Three main associations were addressed; firstly, age at diagnosis. Secondly, the mode in which the histological diagnosis was achieved, i.e. screening or not. Thirdly, a woman's screening history.

Age at diagnosis

A wide range of age at diagnosis was found in this study. Women at 93 years of age were diagnosed with CIN 3 and SCC stage I, and women with ICC were diagnosed at age 17. However, the median age of pre-invasive lesions were 34 years, while SCC stage I was 41 years, and SCC stage IV was 63 years. Many studies have been published over the last 50 years, trying to explain the wide range of the age of diagnosis, firstly giving rise to a theory of two biologically different types of cervical cancer, a slow growing one in young women and a fast growing type in older women [38] with a mean duration of the pre-invasive phase to be 16 years in women between 25 and 35, and 1 year in women above the age of 65 [21]. Later, studies which showed fast growing tumours in young women accumulated [5, 8, 10, 23, 39–50].

However, these theories were studies of the so-called protective effect of Pap smears, which showed a similar duration of the pre-invasive phase regardless of age [22]. This was collaborated by studies of the natural history of HPV, which showed that a lesion developed within two years of infection, regardless of age [26, 31]. Presently, there is no theory regarding the development of ICC that would explain the observed variation of age at diagnosis.

Duration of the asymptomatic invasive phase of cervical cancer has been much less studied. Most studies assume that this phase is short, usually less than two years. However, the rationale for keeping this assumption seems rather murky, and dates back to Dunn in 1953 who clearly states that it is "arbitrarily chosen and not based on any sound evidence" [18]. The present study found a substantially larger difference in age at diagnosis between stage IV and stage I, than between stage I and CIN 3, with 22 and 7 years, respectively.

Detection mode

There are two modes of being diagnosed without being screened. Firstly, the lesion could be detected without any Pap smear as an accidental finding of another procedure. Secondly, a Pap smear might be taken due to patient complaints at a doctor's visit. However, in this study the most common mode to be diagnosed with CIN 2+ was a HSIL Pap smear within six months of histological diagnosis.

Women with late stage ICC were more likely not to have any Pap smears than women diagnosed with a CIN 2/3 as 1.2% of CIN 2/3 were not screening detected, compared to 40.9% of the ICC stage II–IV. Of the women with CIN 2/3 with a smear within the diagnostic period, a LSIL or HSIL was more common than among women with ICC, while equivocal results or a normal Pap smear was more common among women with an ICC. Similarly, Boyes found that women with a normal Pap smear were found to have significantly more advanced ICC than women with a recent abnormal Pap [42]. Several explanations for this somewhat counter intuitive finding might exist. The resulting normal Pap smear might have been taken incorrectly or falsely read, which has been reported to be the case in 20%–67% when re-reading Pap smears [8, 43, 46, 51] or the changes might have developed rapidly [5, 26, 39, 40, 52]. The tumour might be inaccessible or the Pap smear might be extremely difficult to screen [51], and an equivocal diagnosis is given. Equivocal Pap smears have been shown to be associated with ICC [11, 53, 54]. Failure to diagnose a SIL, given that an underlying lesion exists, is thus indicative of invasion already having occurred.

Screening history

In this study, 10% of women with CIN 3 had no Pap smears during the screening period, while 26% of women with SCC stage I, and 66%–79% of stage II–IV. Similarly, Sasieni found that 45% of women with ICC stage Ib+, and 21% with Stage Ia, in England had no Pap smear more than six months before the diagnosis [23].

Women diagnosed with ICC stage I or CIN 2/3 had more often several previously normal Pap smears, compared to women diagnosed with ICC of stage II–IV. Bertlesen found that half of the women with CIN 3/ICC had a previously normal Pap smear, and argues that CIN 3 may be the result of a rapid progressive lesion rather than one with a protracted build up [39]. Sung in a follow-up study of women in a prepaid health plan in the US found that 53% of the women with ICC had no Pap in the period 6–36 months prior to diagnosis [10]. These women compared to women with a recent Pap smear, present with later stage disease, had symptoms, and were older.

It was women diagnosed with CIN 2/3 and stage I who also had the highest proportion of a prior abnormal

Pap smear. This might seem as another counter intuitive result, however, a prior abnormal Pap smear is associated with having been screened regularly, which again is associated with being diagnosed with an asymptomatic disease. Also, women with a prior abnormality might get Pap smears on a regular basis due to their previous experience.

An adequate screening history was defined as having a normal Pap smear within the last four years of the screening period, and at least two normal Pap smears in the entire screening period; In the case of the woman having an abnormal Pap smear within the screening period, a subsequent normal Pap smear should be registered within the screening period. Fifty eight percentage of women with CIN 2/3, 48% with ICC stage I, and among 13% of women with stage II–IV was found to have an adequate screening history. In the multivariate analysis when adjusting for age and mode of detection, not having an adequate screening history was associated with a 3.4 times higher risk of being diagnosed at stage II–IV compared with CIN 2/3, while stage I was associated with only 1.2 times higher risk. As argued by Sasiene et al., micro invasive cervical cancers (stage Ia) are usually screening detected [13]. ICC stage II–IV are thus detected among women without an adequate Pap smear screening history, and are usually diagnosed because of symptoms.

For women in screening age with ACC, the proportion with adequate screening history was roughly 50% for all stages, indicating that Pap smear screening is not very effective in reducing the incidence of adenocarcinomas as found by several other studies [55–57].

Conclusion

Increasing coverage has been shown to drastically reduce the incidence rates of invasive cervical cancer [2, 3, 58, 59]. However, it is important to remember that a Pap smear in an asymptomatic woman is a screening procedure, not a preventive one. As Dunn pointed out in 1981, ''A population that has been screened has all the future potential for developing new disease that it had before it was screened'' [60]. The results of this study emphasise the importance of having regular Pap smears.

However, a large proportion of the women diagnosed with ICC, was diagnosed with stage I disease and with an adequate screening history. However, these women have excellent prognosis [61], and should probably be considered as a successful outcome of screening, as argued by e.g. Sasieni [13]. This would also explain the anomaly of highly organised screening program with relatively high incidence rates of ICC, as the proportion of stage I disease would be large.

Nevertheless, suggestions that screening should be performed more frequently among younger women (less than three years) while older women could be screened every five years have been put forward [13]. In a recent study by Peto, the prevalence of newly diagnosed CIN 3 increased with time since last normal smear, indicating that most cases persist for several years. CIN 3 prevalence did not increase further for screening intervals exceeding five years, however, suggesting that CIN 3 eventually regress, while the prevalence of lesser abnormality was almost independent of screening interval [62]. Although HPV prevalence and risk taking behaviour is related to age, the growth rate of the lesion might not be age dependent and the value of adding HPV testing in screening programs might be undermined by the short lead time gain by HPV detection as cellular changes occur three months after HPV infection [28, 63]. However, if a woman has not gotten the disease at a particular age, this is predictive of her not developing the disease in the future. This is supported by studies that shows that the relative protection of a normal Pap smear remained high for the first three years, then declined steadily and after six years there were no significant protection left [15, 22, 23, 64].

Current knowledge, supported by the results of the present study, suggests that implementation of differentiated screening interval based on previous screening history and age within the Norwegian cervical cancer screening program, is warranted.

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