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Cervical cancer screening history among women diagnosed with cervical cancer in Estonia 2017–18

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Background: Despite the national cervical cancer screening programme launched in 2006, Estonia has one of the highest cervical cancer incidence rates in Europe. While the overall coverage of cervical cytology is high, the factors related to cancer screening history prior to cancer diagnosis need to be studied. **Methods:** In this study, we aimed to examine the 10-year screening history of women diagnosed with cervical cancer in Estonia in 2017–18, using data collected from laboratory reports from 2007 to 2018. From each report, we extracted information on the date and result of cytology and on the laboratory where the sample was assessed. We analysed these data across cancer histology, the time interval between the last test result and cancer diagnosis and the laboratory type (local or regional). **Results:** Among 319 women with cervical cancer, 181 (56.7%) did not have any cytology reports available. Among 138 women with at least one cytology, 60% had 1–3, 24% 4–6 and 16% ≥7 tests (mean 3.7) before cancer. In 78% of women, the last test was performed less than 5 years before cancer diagnosis and 62% of these tests did not report any abnormalities. The last cytology results differed significantly between the regional and local laboratories ($P = 0.028$). **Conclusion:** Women received the cervical cancer diagnosis in Estonia despite having several screening tests 10 years prior to the diagnosis. The proportion of cytology tests without any abnormalities less than 5 years before the diagnosis was worryingly high and needs further investigation together with the difference between laboratory types.

Introduction

With a population of 1.3 million and a female population of 700 000, Estonia has one of the highest cervical cancer incidence rates in Europe, which is twice as high as the average incidence rate in the European Union[1]. Each year, around 150 women are diagnosed with cervical cancer and about 60 dies from it. The high incidence has been an issue for many years, and as a recent study confirmed, the incidence has steadily increased among all age groups over the last 40 years[2].

Indeed, efforts have been made to stop and reverse this trend. In 2006, a nationwide organized cervical cancer screening programme was established[3], which offered a free-of-charge cervical cytology (conventional Pap-smear) every 5 years to women with valid health insurance in the age group 30–55 years. In 2021, the programme was further improved to adhere to European guideline recommendations[4]. According to the clinical guideline algorithm, all abnormal screening results will be followed up depending on the abnormal cytology result, the woman's age and pregnancy status[5].

However, the organized screening programme has suffered from a low coverage that has never exceeded 50% in the target group[6]. At the same time, opportunistic screening is extremely prevalent, forming 75% of all annual cytology tests performed in Estonia[7]. A cytology may be taken opportunistically at any time and is fully reimbursed by the Health Insurance Fund (HIF) (health insured women only). In 2018, a routine human papillomavirus (HPV) vaccination programme for 12-year-old girls with a 9-valent HPV vaccine started, but it will take decades to see the vaccine impact on the incidence of cervical cancer and its precancerous lesions.

A recent case–control study showed that half of the Estonian women diagnosed with cervical cancer had not undertaken any cytology tests during a 7-year period before the diagnosis[8]. Still, another half of the women diagnosed with cervical cancer had been screened at least once. Due to unavailable data, no previous studies have addressed the detailed screening history—including test result—among women with cervical cancer in Estonia. As the Estonian Cancer Screening Registry was established only in 2015, data on screening history for earlier periods can only be collected from cytology reports obtained from pathology laboratories performing the tests or from medical histories.

The aim of this study was to examine the 10-year screening history among women diagnosed with cervical cancer in Estonia in 2017–18, including comparing the results across tumour histology and type of laboratory.

Methods

Estonian Cancer Registry

In this population-based study, we included women who were diagnosed with cervical cancer [International Classification of Diseases 10th revision (ICD-10) code C53] or cervical cancer *in situ* (ICD-10 code D06) in 2017–18, according to the Estonian Cancer Registry (ECR). The ECR is a nationwide population-based cancer registry with data available since 1968, and as a result of compulsory cancer case reporting, the registry has high data validity and quality[9].

For each woman, we obtained information on cancer diagnosis (date of diagnosis, age at diagnosis, topography and morphology) and personal identification number (PIN), enabling us to follow the women across various data sources, and collect comprehensive and accurate information. According to the ICD for Oncology third edition (ICD-O-3) morphology codes, cervical cancer cases were divided into squamous cell carcinomas (SCC) (ICD-O-3 morphology codes 80523, 80703, 80713, 80723, 80733, 80763, 80833),

adenocarcinomas (ADC) (ICD-O-3 morphology codes 81403, 82113, 83103, 83803, 83843, 84803, 84823), *in situ* cases (ICD-O-3 morphology codes 80102, 80522, 80702, 80772, 81402) and other, unspecified group (ICD-O-3 morphology codes 80003, 80013, 80103, 80213, 85603, 87203, 91203).

Laboratories

By law, each laboratory operating in Estonia must archive all laboratory reports for 30 years. In February 2021, we contacted all 10 Estonian laboratories that had evaluated cervical cytology tests between 2007 and 2018 and asked them to provide cytology test reports for all women in our study population for previous 10 years before the cervical cancer diagnosis. We used PINs to identify the correct laboratory reports for each woman.

We included all cytology results until 6 months before cancer diagnosis since the tests immediately before the diagnosis may have been related to the diagnostic process of symptomatic cancer.

From each report, we extracted the cytology result according to the Bethesda System (TBS)[10] and the assessment date. Based on the Estonian Gynaecologists' Society recommendation, all cervical cytology results should have been reported in the TBS since 2006. However, it is known that both TBS and Papanicolaou classification systems have been used over time. Diagnoses of PAP I/PAP II, PAP III, PAP IV and PAP V were translated to the TBS as negative for intraepithelial lesions or malignancy (NILM), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and cancer, respectively. Due to several PAP III and PAP IV diagnosis translation possibilities, we chose the most severe corresponding diagnosis in the TBS to avoid underestimations.

For analysis, we merged atypical squamous cells of undetermined significance (ASC-US) and LSIL into one low-grade atypical changes group (ASCUS/LSIL), and HSIL and atypical squamous cells cannot rule out HSIL (ASC-H) into one high-grade changes group (HSIL/ASC-H). Atypical glandular cells (AGC) remained separately due to its glandular origin.

In addition, we asked each laboratory to provide self-reported information on annual number of cytology tests, the number of pathologists and cytotechnologists involved in cytology assessment on a daily basis and whether regular feedback procedures had been established with the service providers. This information was used to classify all laboratories into two groups. Regional laboratories are affiliated with regional hospitals or cover the whole country, perform a higher annual number of cytology tests, have more capacity in terms of human resources, have a higher level of internal quality indicators, have regular continuing professional development courses and usually have regular feedback system in place. They also have usually contracts with multiple health service providers. Local laboratories are affiliated with hospitals or health care service providers in small provincial towns. Their volume is low and the laboratory team usually consists of one pathologist and one or two laboratory technologists. In total, five regional and five local laboratories were identified.

The time between the last cytology test and cancer diagnosis was grouped as (i) <3 years, (ii) 3–5 years and (iii) >5 years.

Statistics

We used cross-tabulations and percentages for descriptive statistics, and Fisher's exact test to distinguish statistically significant differences between the last cytology test result and laboratory type. To compare the differences between the mean ages, we used two-sample *t*-test. Data management and statistical analyses were done using Stata version 17.0 (StataCorp, College Station, TX, USA).

Sensitivity analysis

To estimate whether we were able to capture all reports from the laboratories, the number of cytology reports obtained from laboratories was compared with HIF claims data. HIF has information on all reimbursed in- and outpatient diagnostic and treatment procedures claims, including all the cervical cytology tests, provided for health-insured people in Estonia (ca. 95% of all the population). As the claims do not include information on the test result, we could only use them to evaluate the completeness of our collected dataset. We compared our dataset with HIF data to assess whether there were any differences in mean age at the last cytology tests, time between the last test and cancer, using two-sample *t*-test.

Ethics

The study protocol was approved by the Research Ethics Committee of the National Institute for Health Development (Decision No. 632, date 26 January 2021).

Data availability

The data that used in this project are available from the corresponding author upon reasonable request.

Results

In total, 319 women in Estonia were diagnosed with cervical cancer or cervical cancer *in situ* in 2017–18. The majority of the cancer cases were SCC (65.2%) followed by *in situ* (12.5%), ADC (12.2%) and other types of cancer (10.0%) (Table 1). The mean age at cancer diagnosis was 56.3, 38.1, 55.4 and 62.7 years (Table 2), respectively, and almost two-thirds of women (62.1%) were younger than 60 years of age (Table 1).

We found that over half of the women (56.7%) did not have any cytology test reports available within 10 years before cancer diagnosis (Table 1), whereas among all the SCC and ADC cases 65.4% and 41.0%, respectively, were without a cytology. The mean age at cancer diagnosis among women without a cytology was 60.7 years, which was higher than for women with at least one cytology (46.5 years) ($P < 0.001$, data not shown) (Table 2). For ADC and *in situ* cases, women with at least one cytology were 17 years younger (both $P < 0.001$, data not shown) and for SCC cases, 9 years younger than women without cytology ($P < 0.001$, data not shown) at the time of cancer diagnosis (Table 2).

Among 138 women with at least one cytology, 60.1% had a total of 1–3 tests, 23.9% 4–6 tests and 15.9% ≥7 tests. Among 72 women diagnosed with SCC, one-fifth (19.4%) had ≥7 cytology results (Table 1). On average, women with at least one cytology had 3.7 tests during the 10-year period before cervical cancer diagnosis (Table 2).

Among 138 women with at least one cytology, 44.2% had the last test less than 3 years, 33.3% 3–5 years and 22.5% more than 5 years before the cancer diagnosis (Table 3). For 62.3% of women, the last cytology result was NILM. Among 61 women who had their last cytology less than 3 years before cancer diagnosis, half had a NILM, 29.5% HSIL/ASC-H, 13.1% ASCUS/LSIL and 8.2% AGC result according to TBS.

The distribution of last cytology results differed significantly by the laboratory type ($P = 0.028$) (Table 3). In total, 67.4% of all cytology tests were assessed in regional laboratories, and among these, 57.0% results were NILM. In local laboratories, the proportion of total NILM results was 73.3%. Across all the cytology tests assessed less than 3 years before cancer diagnosis, regional laboratories reported 38.1% cytology tests as NILM, while in local laboratories, the proportion of NILM results was 73.7%.

Sensitivity analysis

According to the HIF data, 149 women had at least one cytology from 2007 until 6 months before cancer diagnosis. This means that compared with the HIF data, we lacked screening history information on 14 women (9.4%). At the same time, we found laboratory

Table 1 Characteristics of age and screening history among women with cervical cancer diagnosis, Estonia 2017–18

	Total		SCC		ADC		*In situ*		Other	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Total (% row)	319	100	208	65.2	39	12.2	40	12.5	32	10.0
Age group at cancer diagnosis (% column)										
22–29	15	4.7	6	2.9	1	2.6	7	17.5	1	3.2
30–39	49	15.4	24	11.5	6	15.4	18	45.0	1	3.2
40–49	62	19.4	41	19.7	9	23.1	10	25.0	2	6.5
50–59	72	22.6	54	26.0	6	15.4	3	7.5	9	29.0
60–69	60	18.8	40	19.2	8	20.5	1	2.5	11	35.5
70–79	40	12.5	30	14.4	6	15.4	1	2.5	3	9.7
80+	21	6.6	13	6.3	3	7.7	0	0.0	5	16.1
Women without any cervical cytology within 10 years before cancer diagnosis	181	56.7	136	65.4	16	41.0	6	15.0	23	74.2
Women with at least one cervical cytology within 10 years before cancer diagnosis	138	43.3	72	34.6	23	59.0	34	85.0	9	29.0
Number of cervical cytology tests within 10 years before cancer diagnosis (% column)										
1–3	83	60.1	47	65.3	13	56.5	16	47.1	7	77.8
4–6	33	23.9	11	15.3	6	26.1	14	41.2	2	22.2
over 7	22	15.9	14	19.4	4	17.4	4	11.8	0	0.0

Table 2 Mean age at cancer diagnosis and mean number of cervical cytology tests within 10 years before diagnosis among women with cervical cancer, Estonia 2017–18

	Total		SCC		ADC		*In situ*		Other	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mean age										
All included women	54.5	16.2	56.3	15.2	55.4	16.7	38.1	10.9	62.7	14.4
Women without any cervical cytology within 10 years before cancer diagnosis	60.7	13.9	59.5	14.2	64.9	11.4	52.2	7.9	66.5	13.0
Women with at least one cervical cytology within 10 years before cancer diagnosis	46.5	15.4	50.2	15.2	48.7	16.7	35.6	9.3	53.2	14.0
Mean number of cervical cytology tests within 10 years before cancer diagnosis										
Across all the women	1.6	2.6	1.3	2.5	2.2	2.5	3.4	2.9	0.7	1.5
Women with at least one test within 10 years before cancer diagnosis	3.7	2.8	3.7	3.0	3.7	2.2	4	2.8	2.6	1.8

reports for three women (2.2%), whose data were missing from the HIF database, possibly because the cytology tests were taken at a private clinic or women paid by themselves for it, which may be due to lack of national health insurance (data not shown). There were no statistically significant differences between our collected and HIF datasets in terms of mean age at the last cytology tests, the time between the last test and cancer diagnosis (data not shown).

Discussion

The current study is the first to investigate the detailed screening history among women with a cervical cancer diagnosis in Estonia. We found that less than half of the women had any screening activity before the cancers. Nearly 78% of women with at last one cytology within 10 years before cervical cancer diagnosis had their last test less than 5 years before the cancer diagnosis, and 59% of these results were reported as NILM. Also, we noted differences in cytology results by the type of laboratory where the last tests were assessed.

The proportion of women who had their last cytology reported as NILM briefly before the cancer diagnosis is unsettlingly high. Due to cervical cancer natural history, NILM results in less than 3 years before the cancer diagnosis are considered false-negative results[11]. Indeed, it can be argued that some types of cancers, such as ADC or micro-invasive cancers, are hard to detect with conventional cytology[12]. However, our results showed that almost half of NILM results within less than 3 years before the diagnosis resulted in SCC type of cancer, which should be well preventable with a conventional cytology test[13].

Furthermore, we found a high screening activity among women with at least one cytology. On average, each screened woman had 3.7 cytology tests 10 years before cancer diagnosis and 20% of women with SCC were tested seven or more times. While it is known that there are subgroups of cervical cancers that are difficult to prevent with a conventional cytology[12,14], it is unlikely that all women in our study population suffered from them.

This raises the question of why cervical cancer still occurs despite the high number of tests. Indeed, several possible factors need to be discussed. Firstly, we found a significant difference between regional and local laboratories. For this study, 10 laboratories were contacted that analysed cytology tests between 2007 and 2018. Considering that the annual number of cytology tests in Estonia is around 120 000[7], the number of laboratories providing a cytology reading service is unreasonably high, since it is known that the tests are not distributed equally between the laboratories. Unfortunately, it is also known that despite a strong recommendation from the European guidelines[4], neither quality indicators nor quality assurance for laboratories providing this type of service have been put in place by the stakeholders. An in-depth analysis is currently ongoing to better understand the quality of laboratory results.

Secondly, we found that for 38% of women, the last cytology result before cancer diagnosis was abnormal. Our current data do not allow us to assess whether the unsuccessful follow-up was due to the woman's unwillingness to cooperate or poor adherence to clinical guidelines by clinicians. To answer this question, a further study is currently ongoing addressing adherence to follow-up guidelines based on medical records.

Table 3 The result of the cervical cytology before cancer diagnosis by time interval between the last test and cancer diagnosis among women with cervical cancer in Estonia 2017–18

	Overall		Cancer histology								Laboratory type				
			SCC		ADC		*In situ*		Other		Regional		Local		
	N	%	*N*	%	*N*	%	*N*	%	*n*	%	*N*	%	*N*	%	*P*-value
Cervical cytology within 10 years before cancer diagnosis															
NILM	86	62.3	45	62.5	20	87.0	14	41.2	7	77.8	53	57.0	33	73.3	0.028
ASCUS/LSIL	18	13.0	8	11.1	0	0.0	9	26.5	1	11.1	12	12.9	6	13.3	
HSIL/ASC-H	27	19.6	17	23.6	2	8.7	7	20.6	1	11.1	23	24.7	4	8.9	
AGC	7	5.1	2	2.8	1	4.3	4	11.8	0	0.0	5	5.4	2	4.4	
Total	138	100.0	72	100.0	23	100.0	34	100.0	9	100.0	93	100.0	45	100.0	
Cervical cytology less than 3 years before cancer diagnosis															
NILM	30	49.2	13	43.3	10	100.0	5	27.8	2	66.7	16	38.1	14	73.7	0.057
ASCUS/LSIL	8	13.1	4	13.3	0	0.0	4	22.2	0	0.0	6	14.3	2	10.5	
HSIL/ASC-H	18	29.5	12	40.0	0	0.0	5	27.8	1	33.3	16	38.1	2	10.5	
AGC	5	8.2	1	3.3	0	0.0	4	22.2	0	0.0	4	9.5	1	5.3	
Total	61	100.0	30	100.0	10	100.0	18	100.0	3	100.0	42	100.0	19	100.0	
Cervical cytology 3–5 years before cancer diagnosis															
NILM	33	71.7	16	76.2	6	66.7	7	58.3	4	100.0	24	75.0	9	64.3	0.562
ASCUS/LSIL	5	10.9	1	4.8	0	0.0	4	33.3	0	0.0	3	9.4	2	14.3	
HSIL/ASC-H	7	15.2	4	19.0	2	22.2	1	8.3	0	0.0	5	15.6	2	14.3	
AGC	1	2.2	0	0.0	1	11.1	0	0.0	0	0.0	0	0.0	1	7.1	
Total	46	100.0	21	100.0	9	100.0	12	100.0	4	100.0	32	100.0	14	100.0	
Cervical cytology more than 5 years before cancer diagnosis															
NILM	23	74.2	16	76.2	4	100.0	2	50.0	1	50.0	13	68.4	10	83.3	0.884
ASCUS/LSIL	5	16.1	3	14.3	0	0.0	1	25.0	1	50.0	3	15.8	2	16.7	
HSIL/ASC-H	2	6.5	1	4.8	0	0.0	1	25.0	0	0.0	2	10.5	0	0.0	
AGC	1	3.2	1	4.8	0	0.0	0	0.0	0	0.0	1	5.3	0	0.0	
Total	31	100.0	21	100.0	4	100.0	4	100.0	2	100.0	19	100.0	12	100.0	

However, we need to keep in mind that no screening programme is flawless, and even in state-of-art screening programmes such as the Kaiser Permanente Northern California programme in the USA, cancer cases are occurring[15]. In their study, they found that the majority (57.8%) of cases were diagnosed at a localized stage within 1 year or regional/distant stage within 2 years of the first co-test, 7.7% of cases were due to algorithm delays, 9.0% of cases were due to non-compliance with recommended screening and management and 24.5% of cases were due to false-negative co-tests/sampling errors[15]. However, it must be emphasized that the proportion of cancer cases from the total screened population was marginal, and most of the cancer cases detected were in the early stage, demonstrating the protective effect of screening.

Having said that we need to accept a small proportion of cancer cases among screened women are inevitable. Canadian cervical cancer screening programme reported, similarly to our results, a high rate of NILM results just a few years before the cancer diagnosis[16]. Their conclusion that this was most likely due to the low sensitivity of the screening test (conventional Pap-test) is in line with a recent large Polish study[11], which found that laboratories with less than 9000 slides processed per year have significantly more false-negative results than laboratories with a higher number of slides. Results from our study support this finding. Cytology reading and reporting is heavily subjective and related to appropriate knowledge, skill and experience, gained only by sufficient workload[17].

In 2021, the Estonian cervical cancer screening programme was upgraded[18]: the more sensitive high-risk HPV-test replaced conventional Pap-smears as the primary screening test, followed by liquid-based cytology as recommended by the European guideline[4]. HPV-test is known to be more sensitive[19] and prevents the reader-caused experience and subjectivity bias. However, it is known that the prevalence of high-risk HPV subtypes in Estonia is high[20], which may cause a high volume of cytology triage tests that still need to be evaluated by laboratory staff.

Our finding that less than half of the women with a cervical cancer diagnosis had a cervical cytology 10 years prior to a cancer diagnosis is in line with a recently published case–control study[8]. Several studies in Estonia have been undertaken to better understand why women choose not to attend the clinic and give a non-invasive, painless free-of-charge test[21,22]. In agreement with several international studies[23,24], women's education, place of residence and general health-related attitude play a significant role also in Estonia. Within the 2021 screening programme upgrade, the screening age range was extended to 30–65 years and women without health insurance are now included in the programme. Also, after a randomized intervention study, which showed that HPV self-sampling was well accepted among long-term screening non-attenders in Estonia[25], HPV self-sampling is now offered as an option for women who receive a reminder letter.

The current study demonstrates the unsatisfactory situation with the internationally approved quality assurance indicators not in place and not (routinely) measured due to lack of good quality data. According to the sensitivity analyses, we missed laboratory reports on 14 women (9%), highlighting the need for a high-quality nationwide cervical cancer screening registry, which could be used for programme monitoring and evaluation. Our currently used proxy—the laboratory reports—is a reasonably good way to get the needed data. However, this is extremely labourious, time costly and not a sustainable way for routine programme evaluation. Countries that still have not established a screening registry (or similar) or the screening registry data is suboptimal should invest the resources to implement a high-quality data collection system[26].

This article is setting a basis for further studies. There is an urgent need to analyse different quality aspects of Estonian cervical cancer screening programme since the continuously high cervical cancer incidence is unlikely to be attributed only to the low screening coverage. Both stakeholder and provider level analyses are necessary to distinguish the causes that have attributed to this steadily high cervical cancer incidence.

The strength of this study is the uniqueness of the collected data. While screening history data is routinely collected and analysed in many countries, this is the first study of this kind in Estonia. We used

high-quality cancer registry data to define the study population, followed by a profound and systematic search for laboratory reports from all laboratories working at during the study period. Our data collection resulted in a solid data source, which will help to further understand the possible shortcomings in cervical cancer prevention in Estonia.

As a limitation, we missed information on some women. However, to the results of the sensitivity analyses do not suggest that the missed information would have impacted our results. If anything, our current results are underestimating the differences found by laboratory type. Also, it is important to mention that without the women's medical history, including information on follow-up test results, conclusions on cervical cancer screening programme quality in Estonia are limited.

Conclusion

In conclusion, we found that a large proportion of last cytology tests shortly before cancer diagnosis did not detect any abnormalities and this proportion was particularly high if the last test was assessed at a local laboratory. These findings suggest severe laboratory quality issues and emphasize the need for implementing quality assurance mechanisms for pathology laboratories both on national level and internally. In addition, women with abnormal cytology results should have been treated to avoid progression to cancer. Both the quality of laboratory assessment and the quality of further clinical management need to be studied further.

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Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

The data underlying this article cannot be shared publicly due to privacy of individuals that participated in the study. The aggregated data will be shared on reasonable request to the corresponding author.

Key points

- Cervical cancer incidence in Estonia is unacceptably high.
- We used laboratory reports to describe screening history of women with cancer.
- We found a high rate of normal test results just before cancer diagnoses.
- Differences found by laboratory type indicate possible quality issues.
- Further steps are needed to improve laboratory quality control.

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