TALLINN UNIVERSITY OF TECHNOLOGY
School of Information Technologies
Department of Health Care Technology

Evelin Anion 153587YVEM

ANALYSIS OF SELECTED QUALITY INDICATORS IN THE ESTONIAN CERVICAL CANCER SCREENING PROGRAM IN 2016

Master´s thesis

Supervisor: Piret Veerus
MD, PhD
Co-supervisor: Peeter Ross
MD, PhD

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Infotehnoloogia teaduskond
Tervishoiutehnoloogiate instituut

Evelin Anion 153587YVEM

ÜLEVAADE VALITUD EMAKAKAELAVÄHI SÕELUURINGU KVALITEEDINÄITAJATEST EESTIS AASTAL 2016

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Juhendaja: Piret Veerus
MD, PhD
Kaasjuhendaja: Peeter Ross
MD, PhD

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Author’s declaration of originality

I hereby certify that I am the sole author of this thesis. All the used materials, references to the literature and the work of others have been referred to. This thesis has not been presented for examination anywhere else.

Author: Evelin Anion

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Abstract

The aim of the thesis was to analyse five selected quality indicators of the cervical cancer screening program in Estonia to get an evaluation of the screening test performance in 2016 and to observe screening test data quality in the Estonian Cancer Screening Registry (ECSR).

In Estonia, the incidence and mortality rates of cervical cancer are one of the highest in Europe. However, cervical cancer can be prevented by regular screening of women at risk. In Estonia, the population-based screening started in 2006 and the national cancer screening registry was established in 2015 to monitor the effectiveness of cervical cancer screening on a regular basis by using the key performance indicators.

The study was designed as a population-based cross-sectional study based on the data of performed screening tests and colposcopies in ECSR and additionally collected information about unknown Pap test results and/or subsequent histological analyses from healthcare service providers participating in organized cervical screening in 2016. The quality indicators were estimated according to the European Guidelines for Quality Assurance in Cervical Cancer Screening.

Additional information was received from 10 out of 21 institutions for 1054 women and eventually the data completeness of screening tests in ECSR was approximately 50%. The proportion of screened women with abnormal cytology findings was 7.24%. The most prevalent results were ASC-US (3.74% of all known results), followed by LSIL (1.47%) and HSIL (1.18%) lesions. The proportion of women with colposcopy was 2.1% and the positive predictive value (PPV) of colposcopy for CIN2+ was 22.3% and 6% for CIN3+. The estimates for detection rates (DRs) of CIN1, CIN2 and CIN3 were 3.0, 3.7 and 1.4 per 1000 screened women respectively. The overall test specificity was 99.4%.

In conclusion, Estonian cervical cancer screening test performance indicators analysed in this study were comparable with the mean values of the member states of the European Union. However, only half of the results of performed screening tests were known and

the measures might be different when complete data on cytology and histology analyses were obtainable. Therefore, it is clearly needed to improve the centrally collected health data quality and increase data acquisition for the exact evaluation of cervical cancer screening in Estonia.

This thesis is written in English and is 33 pages long, including 7 chapters, 5 figures and 3 tables.

Annotatsioon

Ülevaade valitud emakakaelavähi sõeluuringu kvaliteedinäitajatest Eestis aastal 2016

Käesoleva töö eesmärgiks oli analüüsida viit Eesti emakakaelavähi sõeluuringu programmi kvaliteedi indikaatorit 2016. aastal, et hinnata sõeluuringu testide tulemusi ja vaadelda andmete kvaliteeti vähi sõeluuringute registris.

Eestis on emakakaelavähi esinemissagedus ja suremuse määr Euroopas üks kõrgemaid. Samas on emakakaelavähk üks vähestest vähiliikidest, mida on võimalik vältida riskirühma kuuluvate naiste regulaarse testimisega. Eestis käivitus rahvastikupõhine sõeluuringuprogramm 2006. aastal ja 2015. aastal loodi riiklik vähi sõeluuringute register, et koguda andmeid sõeluuringutes osalejate ja saadud tulemuste kohta ning hinnata regulaarselt programmide tõhusust.

Antud uuringus kasutati vähi sõeluuringute registris olevaid 2016. aastal emakakaelavähi sõeluuringu sihtrühma kuuluvatel naistel teostatud Pap-testide ja kolposkoopiate andmeid. Täiendavalt koguti infot asjakohaste histoloogiliste uuringute (biopsiate) ja ka teadmata tulemusega Pap-testi(de) kohta tervishoiuteenuste osutajatelt, kes 2016. aastal osalesid organiseeritud emakakaelavähi sõeluuringus. Kvaliteedi indikaatorite arvutamine teostati Euroopa emakakaelavähi sõeluuringute kvaliteedi tagamise juhiste kohaselt.

Lisaandmeid saadi 1054 naise kohta 10-lt asutuselt 21-st ning emakakaelavähi sõeluuringu testide andmete täielikkuseks 2016. aastal kujunes ligikaudu 50%. Patoloogiliste Pap-testide osamäär skriinitud naiste hulgas oli 7,24%. Kõige levinum abnormaalne tulemus olid ASC-US (3,74% kõigist teadaolevatest tulemustest), millele järgnesid LSIL (1,47%) ja HSIL (1,18%) leiud. Kolposkoopial käinud naiste osakaal oli 2,1% ja kolposkoopilise uuringu positiivne tõepärasuhe CIN2+ korral oli 22,3% ja CIN3+ korral 6%. CIN1, CIN2 ja CIN3 juhtude avastamismäärad oli vastavalt 3,0, 3,7 ja 1,4/1000 skriinitud naise kohta. Üldine testi spetsiifilisus oli 99,4%.

Kokkuvõtvalt võib öelda, et selles uuringus analüüsitud 2016. aasta Eesti emakakaelavähi sõeluuringu kvaliteedinäitajate tulemused olid võrreldavad Euroopa Liidu riikide keskmiste väärtustega. Arvesse tuleb võtta seda, et kõikide teostatud sõeluuringu testide tulemused ei olnud teada ning antud näitajad võivad olla teistsugused, kui omataks täielikku teavet tsütoloogiste ja histoloogiliste uuringute tulemuste kohta. Seetõttu oleks vaja parandada tsentraalselt kogutavate terviseandmete kvaliteeti ja tõsta andmehõivet, mis võimaldaks emakakaelavähi sõeluuringuprogrammide tõhususe täpsemat hindamist.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 33 leheküljel, 7 peatükki, 5 joonist, 3 tabelit.

List of abbreviations and terms

ASC-US	Atypical Squamous Cells of Undetermined Significance
ASR	Age-standardised Rate
CIN	Cervical Intraepithelial Lesion
DR	Detection Rate
ECSR	Estonian Cancer Screening Registry
EHIF	Estonian Health Insurance Fund
ENHIS	Estonian National Health Information System
EU	European Union
HPV	Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
KPI	Key Performance Indicator
LOINC	Logical Observation Identifiers Names and Codes
LSIL	Low-grade Squamous Intraepithelial Lesion
NIHD	National Institute for Health Development
NILM	Negative for Intraepithelial Lesion of Malignancy
NOMESCO	Nordic Medico Statistical Committee
PPV	Positive Predictive Value
SNOMED CT	Systematized Nomenclature of Medicine – Clinical Terms
TBS	The Bethesda System

Table of contents

List of figures

List of tables

1 Introduction

In Estonia, the incidence and mortality rates of cervical cancer are one of the highest in Europe [1]. Of all cancers, cervical cancer is the one that can be prevented by regular screening of women at risk [2]. Long-term experience in the Nordic countries have demonstrated that the implementation of high-quality cervical cancer screening programs reduces the mortality and incidence of the invasive disease [3].

In 2006 a national population-based cervical cancer screening program was launched in Estonia to reduce the incidence and mortality of cervical cancer. Quality assurance and improvement are essential parts of screening programs and key performance indicators (KPIs) dealing with screening intensity, test performance, diagnostic assessment and treatment are used to monitor the performance of screening programs [4]. These measures also provide the basis for comparison with other European Union countries and set standards.

The Estonian Cancer Screening Registry (ECSR) was established in January 2015 and it collects data digitally from Estonian National Health Information System (ENHIS) about breast, cervical and colorectal cancer screening [5]. The collected data allows the registry to analyse the performance of screening programs in Estonia. So far merely the indicators concerning screening intensity have been investigated and published. To get more information on program activity and its efficiency, screening test performance indicators need to be measured as well.

The aim of the current study is to assess a set of standard KPIs for the year 2016 according to European Guidelines for Quality Assurance in Cervical Cancer Screening. The selected quality indicators include:

- distribution of screened women by the results of cytology
- referral rate for colposcopy
- positive predictive value of colposcopy
- the rate of detection of histologically confirmed CIN+
- the specificity of the screening test

Data about performed cytology tests and colposcopy procedures will be obtained from ECSR. Additional information regarding further histological evaluation of abnormal cytology results necessary for calculating some of these parameters is not collected in registry's database and is intended to inquire in specific Excel tables directly from 21 health service providers that participated in cervical cancer screening program in 2016.

However, the secondary use of screening data is influenced by the completeness of the data in the registry. Therefore, the screening test data quality in the ECSR will also be observed in this analysis.

2 Literature overview

This section provides an overview of the development of cervical cancer, its preventive strategies, and the performance monitoring of cervical cancer screening programs. In addition, cervical screening organization in Estonia and ECSR are introduced as well.

2.1 Cervical cancer epidemiology, pathogenesis and risk factors

Cervical cancer is the fourth most commonly diagnosed cancer among women and the fourth leading cause of cancer deaths worldwide, accounting for 12% (527,600) of the new cancer cases and 8% (265,700) of the cancer deaths among females in 2012 [1]. The incidence, and especially mortality rates, vary significantly within European Union (EU) member states being higher in Eastern and lower in Western and Northern Europe.

The overall age-standardized incidence rate (ASR) of cervical cancer in Europe is 11.4 per 100,000 women [1]. The lowest ASR (European) are observed in Switzerland (4.2/100,000), Malta (4.6/100,000) and Finland (4.9/100,000) [6]. With an estimated ASR of 23.3 per 100 000 and mortality rate of 8.1 per 100 000 women in 2012 [1], Estonia is one of the countries in Europe with the highest incidence and mortality rates for cervical cancer.

The trends in cervical cancer incidence over the past few decades in Europe show no noticeable decline [7]. Although the overall mortality from cervical cancer has decreased by 10% in EU and significantly in the older member states (e.g. UK and Italy) [8], [9], the rates have remained constant at a high rate or have even slightly increased during the last decade in other Eastern European countries including Estonia [1].

The incidence of cervical cancer in Estonia has increased especially in younger age groups mainly due to the influence of several novel behavioural risk factors such as the early onset of sexual life, smoking, oral contraceptive use and multiple sex partners [2], [10]. Consequently, cervical cancer has become the second most common female cancer in women aged 15 to 44 years in Estonia as well as in the EU [11].

The pathogenesis of cervical cancer is initiated by human papillomavirus (HPV) infection of the cervical epithelium during sexual intercourse. Over 200 types of HPV have been identified so far, which are categorized according to their oncogenic potential into high and low-risk groups [11]. Two HPV types, 16 and 18, are the most prevalent as well as perilous causing 70% of cervical cancer and precancerous cervical lesions. HPV is the most common sexually transmitted infection and it has been estimated that 80-90% of all sexually active people get it at some point in their lives [12]. Despite this high prevalence, most HPV infections cause no symptoms and regress spontaneously within 1-2 years. Persistent infection with oncogenic HPV is considered to be the main etiological agent that contributes to the development of cervical cancer precursors and cervical cancer [13]. HPV DNA has been detected in up to 99.7% of invasive cervical cancers worldwide [14], but considering its high frequency, infection alone is not sufficient to cause cervical cancer and several cofactors must play a role in disease progression (e.g. genetic differences, hormonal effects, chronic inflammation etc.) [15].

In general, cervical cancer development (Figure 1) is a continuous process progressing from the HPV infected cervical epithelium through different stages of precursor lesions (called histologically as cervical intraepithelial neoplasias (CIN) or cytologically as squamous intraepithelial lesions (SIL)) and it usually takes 10 to 15 years for the invasive disease to develop [16].

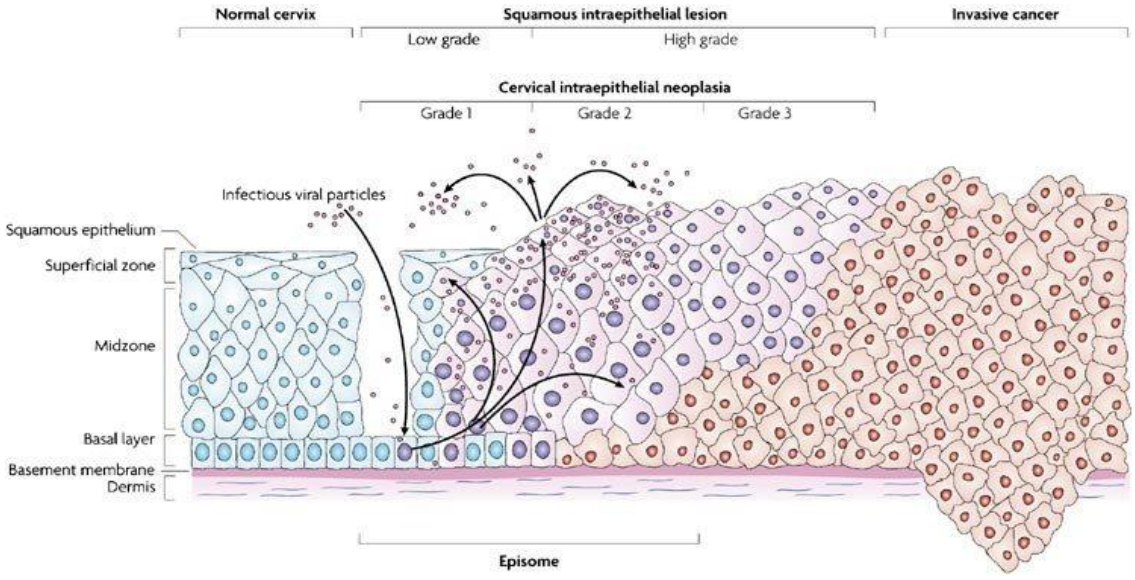

Figure 1. Schematic representation of the development of cervical cancer [17]

2.2 Prevention and early detection

Primary prevention of cervical cancer is the vaccination against HPV among young adolescents before sexual debut. Starting from the year 2018 the HPV vaccination has been incorporated in the national immunization program also in Estonia [18]. However, it has been estimated that HPV vaccination will not have much effect on cervical cancer incidence before the year 2040 [7].

Secondary prevention is screening – it is testing all women at risk for cervical cancer most of whom will be asymptomatic. The purpose of screening is to identify abnormal cells that may evolve into cancer if left untreated or diagnose cervical cancer at an early stage [19]. The main screening test for precancerous lesions and cervical cancer currently used in Estonia is a cytological smear known as Pap test, where the cells from the cervix are collected with a brush and/or a spatula and transferred on to a glass slide, fixed in alcohol, stained according to Papanicolaou staining technique and examined under the microscope by cyto-technologist and/or pathologist. Depending on the severity of an abnormal Pap test result, the woman is further referred to a procedure called colposcopy where the cervix is examined under bigger magnification to detect any malignancy. A sample of a tissue biopsy may also be taken during the colposcopy for histopathological analysis to confirm the abnormal finding.

Some countries in Europe have also started to use HPV testing for primary screening (e.g. Netherlands, Sweden for women 30-64-years old), where cervical screening sample is first tested for the presence of an HPV infection [10].

2.3 Cancer screening programs

According to EU recommendations, the cervical cancer screening should start at the age of 20 to 30 years and be extended up to 60 to 65 years with a 3- or 5-year interval [20]. Cancer screening programs recommended by the EU Council in 2003 [21] are based on scientific evidence of efficacy. The balance between harms and benefits should be clearly demonstrated to be in favour of the benefits and the program should be cost-effective, affordable and acceptable for the population.

There are two types of screening programs – organized and opportunistic. The organized screening involves an explicit policy with specified age categories, method, and interval for screening; a defined target population; a management team responsible for implementation; a health care team for decisions and care; a quality assurance structure; and a method for identifying cancer occurrence in the population [22]. In opportunistic or "unorganized" screening the screening test is taken spontaneously by a healthcare professional and all the supports and quality assurance properties of an organized program might not be included.

Organized screening appears to be more effective and largely more cost-effective than opportunistic activity. It has been shown to reduce cervical cancer incidence and mortality by up to 80% at the population level with the level of mortality reduction related to the screening program coverage [3]. Therefore it is suggested that screening will be offered through organized screening programs that have higher quality assurance and effective evidence-based interventions on screening outcomes [20].

The protective effect of screening on cervical cancer mortality and incidence have been shown in many studies conducted in the nations or regions where organized screening programs are in place or in studies where women periodically participate in opportunistic screening. Some of the longest running effective population-based cervical cancer screening programs in the world are in EU countries e.g. Finland [21], where the organized screening was established already in the 1960s and its incidence and mortality rates from cervical cancer are one the lowest in Europe. The incidence of cervical cancer is higher among women who have not participated in the cervical cancer screening [23]. Even a single lifetime screening test has been shown to reduce the risk of dying from or being diagnosed with advanced cervical cancer [23].

2.3.1 Quality assurance and monitoring of screening programs

The objective of quality assurance and monitoring of cervical cancer screening programs is to increase its effectiveness in reducing cancer incidence and mortality in the population, and to control undesired effects and costs.

Screening is an effective strategy for preventing cancer when the screening program is highly organized, has a quality assurance system in place, and when performance and

evaluation of the outcomes are regularly and continuously monitored [6]. This can mostly be realized by acquiring complete and accurate data on invitations, visits, confirmed diagnosis and treatment with corresponding linkages of the screening data with other registers [20].

Currently, Estonia is collaborating in different projects that contribute reducing the cancer burden and improving the quality of cancer care and early diagnostics. One of these projects is EU-TOPIA (Towards improved screening for breast, cervical and colorectal cancer in all of Europe) that aims to evaluate and quantify the impact (harm and benefit) of screening programs in all European countries. The goal is to enhance existing cancer screening programs and improve cost-effectiveness and equity across Europe [24].

2.3.2 Key performance indicators (KPIs)

The quality and possible impact of a cancer screening program are assessed on the basis of key performance indicators (KPIs). KPIs can provide more direct evaluation of a cervical cancer screening program and give a valuable opportunity to continuously improve the quality and effectiveness of the program.

In the second edition of "European Guidelines for Quality Assurance in Cervical Cancer Screening" experts from 28 EU member states have collaboratively prepared the updated recommendations and standards for monitoring the performance of cervical cancer screening programs. KPIs listed in the EU guidelines are used to monitor the screening process in order to identify and react to potential problems in time [20]. These indicators are divided into three groups and deal with screening intensity, screening test performance, and diagnostic assessment and treatment. The indicators address the measures of population coverage, acceptance of diagnostic tests and treatment, detection rates and the predictive values of the test [21]. The focus of this master´s thesis is on the indicators that address the aspects of screening test performance.

The measurement of quality indicators also allows pan-European comparison of the national programs and the definition of common benchmarks for cancer screening programs [21]. Recently, Estonia has been providing screening performance data for the second report on the implementation of the Council Recommendation on cancer screening [21]. The recommendation was created to evaluate selected indicators in all 28

EU member states for comparison to some of the targets set in the European quality assurance guidelines and other standards. Estonia is also taking part in an online application Nordscreen that presents interim performance and outcome indicators from Nordic population-based cancer screening programs from participating registries in Estonia, Sweden, Iceland, Norway, Finland and Denmark [25]. Nordscreen provides a brief overview of the program organization in addition to yearly updated standardized summary data about the amount of registered screening tests and test coverage [25].

2.4 Cervical cancer screening in Estonia

In Estonia, the population-based cervical cancer screening program was implemented in 2006 under the authority of the Estonian Health Insurance Fund (EHIF) together with National Institute for Health Development (NIHD). It is funded by the EHIF and the Ministry of Social Affairs. The target group is women aged 30-59 years and the invitations to screening are sent by post with a 5 year-interval after a negative test. Women with a previous history of cervical cancer, those without health insurance, and women for whom the Pap test has been reimbursed in the last 12 months are excluded. The results of the screening test are reported to the participants via telephone or email [26]. Abnormal findings are managed according to the national guidelines [26].

The proportion of opportunistic screening in Estonia is extremely high: about 91% of smears are taken outside the organized screening program as part of regular check-ups [27]. Opportunistic screening has a high coverage among younger women but tends to be low in middle-aged and older women, thus missing the population at the greatest risk and have a small effect on morbidity and mortality [28].

It has been demonstrated that the trend in the incidence of cervical cancer reflects the coverage and quality of screening [29]. In Estonia, the coverage of the target population is currently 50% [30], but at least 70% is recommended in order the screening program be effective. Without an effective screening program, the cervical cancer incidence in Estonia is expected to continue to rise compared to effective prevention and screening that should gradually reduce the rate 50-60% by 2040 [7].

2.5 Estonian Cancer Screening Registry (ECSR)

Quality assurance can be performed only with an existing and well-functioning central screening registry that enables the evaluation of screening programs (including planning, conducting and evaluation of results) and to develop measures for improvement.

The ECSR was established in 2015 at the NIHD that operates under the authority of the Ministry of Social Affairs. The ECSR coordinates the execution of cancer screening at a national level. The registry collects data about the results and treatment of breast, cervical and colorectal cancer screening programs [5] to provide an annual status of the national screening programs and to document the screening quality over time. The collected data enables the registry to analyse and evaluate the efficiency and quality of the programs, gives an opportunity to participate in international cancer research, compare Estonian situation with other countries and to perform epidemiological research that could be used as the basis for designing health policy and for allocating financial and human resources [31]. The results of the research help to develop appropriate measures for cancer prevention and treatment for the Estonian population and to fight against cancer.

ECSR is the first registry in Estonia that collects its data digitally. It has an innovative IT solution that retrieves all the necessary information from the ENHIS and makes regular linkages with other relevant databases (e.g. Cancer Registry and Cause of Death Registry). The ECSR includes both a digital database and archived registry data, and its regular tasks include the selection of the target group, sending invitations to participants, data collection and analysis, and composing annual reports [31].

The ECSR collects data about organized screening tests as well as opportunistic screening tests as recommended in the EU guidelines. The annual statistical reports are published and available on the web-page of Health Statistics and Health Research Database (http://pxweb.tai.ee/PXWeb2015/index.html).

2.5.1 Data acquisition and exchange

The functioning of the registry requires cooperation between healthcare providers, different national registries, EHIF and ENHIS. The screening data acquisition process (Figure 2) starts with the formation of a target group by the ECSR according to the selected values (year of birth, the existence of insurance, past medical history of cervical cancer etc.). In addition to the invitations sent by mail, digital screening invitations are also composed for the target group in ENHIS, which can be seen on the patient portal (www.digilugu.ee) for the patient and in ENHIS for health care workers regardless of the visiting institution. During the visit, a healthcare service provider (HCSP) performs the screening test and/or additional investigations or treatments and documents the test results and medical case history. Confirmed epicrisis and/or test reports are sent to the central system. The ECSR then systematically queries the data about the screening results of the individuals belonging to the target group from ENHIS and collects the results in its own database for the purpose of subsequent data processing and statistics [32].

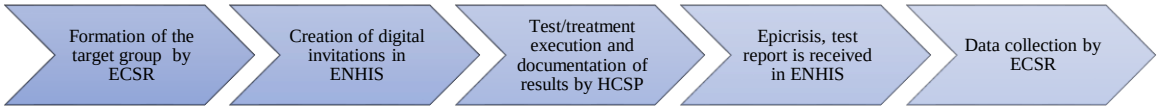

Figure 2. Digital data acquisition process in cancer screening (Source: author´s own creation).

The data exchange services between the ECSR and other national databases are illustrated in Figure 3. The ECSR gets all its data from other national databases via X-Road data exchange layer using automatic data inquiries [33]. ENHIS initially facilitates the sharing of the diagnostic data in the health information system to the screening registry for the formation of a target group and later facilitates the data collection from basic, additional and treatment screening documents. Basic personal data, personal identification codes and contact addresses are retrieved from the Population Registry for the purpose of digital invitations. Data about primarily detected cervical cancer cases are obtained from The Estonian Cancer Registry in order to exclude these women from the target group. Death

events are periodically updated from Estonian Causes of Death Registry and data about reimbursed health care services and the validity of health insurance are obtained from EHIF [34].

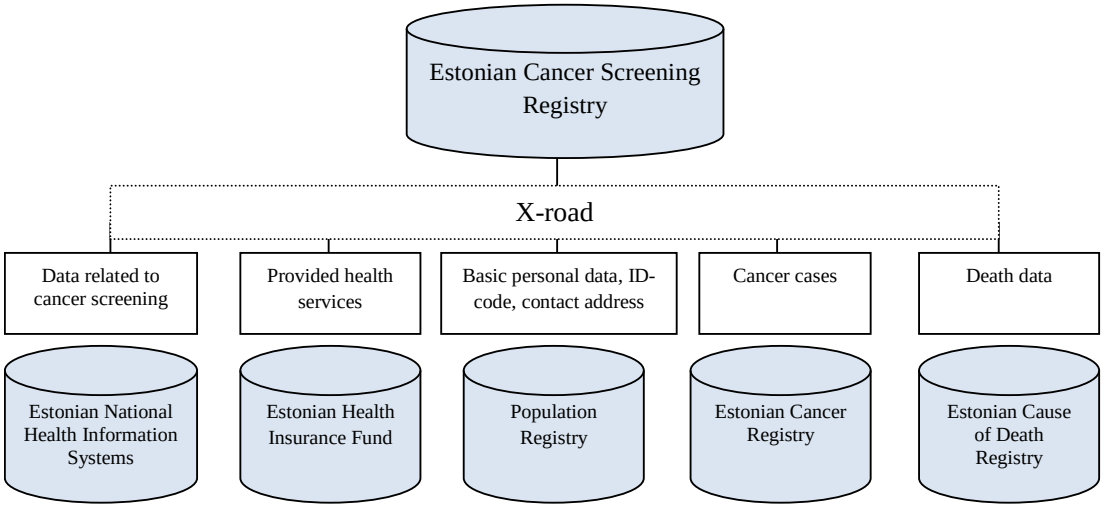

Figure 3. Databases and data exchange services in the cancer screening process (Adapted from [33]).

2.5.2 Data documentation

All healthcare providers who have performed initial screening test, additional analysis and treatment of the woman in the target population, send the result(s) to the ENHIS. Initial screening can be documented either as ambulatory epicrisis or test report and additional investigation as ambulatory or stationary epicrisis. The sample taker (midwives take the initial screening sample in organized and gynaecologists in opportunistic programs) documents the case report in his/her own hospital information system and composes ambulatory epicrisis including also the test report from the laboratory [32].

The Estonian Health Services Organization Act stipulates that the classifications, directories, address details of the State Information System and standards of the Health Information System must be used for documenting health services [35]. In Estonia, the Health and Welfare Information Systems Centre (*In Estonian:* Tervise ja Heaolu Infosüsteemide Keskus - TEHIK) develops and administrates the standards and classifiers and interfacing instructions through the Publication Centre to health care service providers and software developers. The health care institution itself is responsible for organizing the development and management of standards, classifications, and lists in its

field of activity [36]. Latest versions of defined document standards and national classifications (available in the Publication Centre webpage http://pub.e-tervis.ee) are recommended to be used in hospital information systems in standardized documenting and result reporting to ENHIS [37].

The data collection about the screening results starts when the registry queries relevant nationally established codes (e.g. EHIF pricelist, LOINC, SNOMED CT, ICD-10) from ENHIS and in turn receives document numbers where these diagnosis codes where found [38]. EHIF pricelist codes are used for performed PAP tests, additional investigations and treatments, SNOMED CT codes to describe anatomic sites, NOMESCO codes for surgical procedures and LOINC codes for HPV-tests and also Pap tests [38]. Then ECSR requests the documents based on obtained numbers and the central system responds with the documents from which ECSR machine-reads the necessary information into its own database [36].

According to the legislation given by the Statute (Estonian Cancer Screening Registry Act) [34], ECSR collects the following data from test reports and ambulatory or stationary epicrisis in ENHIS:

a) data about the medical document
b) patient's personal identification number
c) anamnesis
d) number of the referral letter
e) procedure code, name, execution date, description, result and data about the performer (institution and health care worker)
f) pathology analysis code, name, sample material (location and adequacy), evaluation date and result, data about the performer (institution and health care worker)
g) data about laboratory analysis ordering, sample material, result, the cause of refusal, evaluation date and performer (institution and health care worker)
h) description of the decision
i) code and name of the primary disease
j) pathomorphological diagnosis code and name
k) the scope of malignant tumor (TNM, stage, histological differentiation)
l) concomitant disease (code and name)

The availability and utilization of relevant standards and classifications for documentation in the health care service providers' information systems is the prerequisite for sending data to ENHIS. The classifications are essential for mutual

understanding, and the standards ensure the correct transmission of data to the data warehouse. It is important that the service provider uses the versions of document standards recommended in the Publication Centre for documenting the test results and ambulatory and stationary epicrisis to be machine-readable and processable [36]. Standardized medical data in the right and properly filled data fields in the e-health document give the ECSR an opportunity to benefit from e-health and use the data in the central system for national statistics that have not been executed in Estonia before.

3 Research objectives

1. To measure the following test performance indicators by means of screening registry and additionally collected data analysis:
    a) Distribution of screened women by the results of cytology
    b) The proportion of women with colposcopy
    c) Positive Predictive Value (PPV) of colposcopy
    d) Detection Rate (DR) of histologically confirmed CIN+
    e) Test specificity
2. To describe the screening test data quality in the ECSR

4 Methodology

This section gives the details of the selected study population, time-frame, data collection methods, and explanatory descriptions and adjusted formulas of the quality indicators.

4.1 Study population

The study population consisted of women belonging to the cervical cancer screening target group in 2016 (year of birth 1956, 1961, 1966, 1971, 1976, 1981 and 1986) who had screening test taken (cervical cytology registered) in the period 01.01.2016-31.12.2016 and subsequent additional investigations (colposcopy and histopathological analysis of biopsy specimen) performed in the period of 01.01.2016 - 23.05.2017.

4.2 Data collection

Data about the Pap test results was obtained from ECSR database. Merely the cervical screening tests performed nationally by the 21 healthcare service providers participating in the organized cervical cancer screening in 2016 were included in the analysis.

Data about the results of histological analyses necessary for computing some of the selected parameters is not collected in the ECSR database. Retrieving this data through inquiries from ENHIS is complicated due to the uneven machine-readable quality of histology reports and also because the anatomic site from which the biopsy was taken was not documented with its histology procedure code before 2018. Furthermore, the retrieved data about performed cervical cytology results and colposcopies is also frequently incomplete. Therefore, to improve the quality of screening test results in the registry's database and collect additional data about colposcopies and subsequent histopathological biopsy results, 21 individual institution-specific data tables in Microsoft Excel format were created to be filled directly by the institutions. The tables included personal identification codes of women who belonged to the target group in 2016 and had been screened for cervical cancer in the corresponding health care facility but were missing the result(s) of the screening test and/or subsequent examination in the registry's database. Detailed information about the test result, date of the medical act or registration and performer's name was requested for each woman separately for cytology, histology and

colposcopy analysis. The standardized data tables (one for each) were sent to the respective service providers for offline data entry and were requested to be sent back in encrypted form via email to the ECSR.

4.3 Time reference

The data collected in the Excel tables was requested for the period of 01.01.2016-31.01.2017 regarding Pap tests and for the period of 01.01.2016-23.05.2017 concerning colposcopic evaluation and histological analysis. The dates were chosen to be in concordance with the existing data in the registry's database. Encrypted tables were sent by e-mail or delivered personally to the contact persons to all 21 selected health service providers in December 2017. The individual responses and test results received up to the 1st of February were incorporated in the study.

4.4 Variables

Quality indicators of screening test performance used in this study were adopted from the second edition of European guidelines for quality assurance on cervical cancer screening [39]. The selected performance parameters included the following:

1) The distribution of screened women by the results of cytology

Seven laboratories were providing the diagnostic service of evaluating the Pap tests for the cervical cancer screening program in 2016. These diagnostic units are located in pathology departments of Tartu University Hospital, North Estonian Medical Centre, East-Tallinn Central Hospital, West-Tallinn Central Hospital, Pärnu Hospital and Viljandi Hospital, in addition to dr. I.Reinmaa private laboratory.

The international standardized Bethesda System (TBS) is mainly used for reporting cervical cytology in Estonia [40]. According to this classification Pap test results can be divided into the following categories:

1) negative for intraepithelial lesion or malignancy (NILM);
2) epithelial cell abnormalities, including
    a) atypical squamous cells of undetermined significance (ASC-US)

b) atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
c) low-grade squamous intraepithelial lesion (LSIL)
d) high-grade squamous intraepithelial lesion (HSIL)
e) squamous cell carcinoma
f) atypical glandular cells (AGC)
g) adenocarcinoma

The cervical cytodiagnoses are determined according to the severity in a hierarchical manner as: carcinoma > HSIL > LSIL > AGC/ASC-H > ASCUS > negative (i.e., benign cellular changes and within normal limits). Pap test results categorized using the latest Bethesda System (2014) provide information about the types of cell changes found in addition to the information about specimens' adequacy, general categorization and interpretation [40].

The distribution of screened women by the results of cytology will be calculated using the following formula:

$$\frac{\text{N screened women with each cytological diagnosis}}{\text{N screened women in the program}}$$

The indicator is being calculated separately for all subgroups of women and overall. If a woman has multiple Pap tests performed in the 12-month period, the index Pap test was recorded to be the Pap test with the most severe result as ranked from a) to e) in case of changes in squamous epithelial cells and f) to g) for changes in glandular epithelial cells in the context of the aforementioned categories. Thus, only the most severe diagnosis of cervical cytology in the study period was included in the assessment.

2) Proportion of women with colposcopy

Further assessment is needed depending on the severity of cellular abnormalities found in cervical smear test. In Estonia, women with the initial cervical smear result of ASC-H, AGC, HSIL or higher and women older than 25 years with LSIL are recommended to be referred to colposcopy according to national cervical screening guidelines [10]. During the colposcopical procedure the cervix is examined at a higher magnification to find and locate suspicious lesions and to assess their extent and severity.

The proportion of women with colposcopy is calculated according to the following formula:

$$\frac{\text{N screened women who underwent colposcopy}}{\text{N screened women}}$$

3) Positive predictive value (PPV) of colposcopy

Targeted biopsies are also taken during the colposcopic examination process if needed to confirm the cervical abnormality. The biopsy result determines whether a treatment is required by excision of the transformation zone to prevent the progression. Three-tiered cervical intraepithelial neoplasia classification (CIN1, 2, 3) is used for histopathology reporting and it parallels with the two-tiered (LSIL and HSIL) terminology of the Bethesda System for cytology – LSIL corresponds to CIN1 and HSIL to CIN2 and 3 [41].

The PPV of referral for colposcopy represents the proportion of women with truly positive Pap test result for being confirmed by histology as CIN1, CIN2 or CIN3. It is thus a measure of the predictive validity of a positive test or also known as the cytology-histology agreement [42].

Referral rate for colposcopy in this study was changed for performed colposcopies and the PPV of referral for colposcopy is calculated based on the actual number of women having colposcopies and the subsequent biopsies taken according to this formula:

$$\frac{\text{N screened women who had colposcopy with histologically confirmed CIN+}}{\text{N screened women with colposcopy}}$$

The parameters for histology (CIN1+, CIN2+, CIN3+, invasive Ca) are being calculated separately and overall.

4) Detection rates (DRs) of histologically proven CIN+

Cervical screening tests can identify pre-cancerous lesions that may be successfully treated, thereby preventing the development of cervical cancer. The DRs by histological diagnosis is a measure that provides feedback about effective cervical cancer control and

prevention [42] since CIN2+ lesions have higher probability to progress into cervical cancer.

The DRs of histologically proven CIN+ is the number of cervical intraepithelial neoplasias (CIN) detected per screened women in the 12-month period and can be computed by using this formula:

$$\frac{\text{N screened women with each histological diagnosis (CIN1+/CIN2+/CIN3+)}}{\text{N screened women in program}}$$

This parameter will be calculated separately for the results of histology (CIN1, CIN2, CIN3 and Ca) per 1000 screened women.

5) Test specificity

The specificity reflects the ability to identify normal outcomes. The specificity of a Pap test will show how correctly cytology identifies the proportion of women who do not have high grade lesions or cancer (true negative cases).

Test specificity cannot be calculated directly from screening program data, because the true denominator is unknown [42]. The following formula can be used for the calculation of approximate specificity:

$$\frac{\text{N screened women with normal screening test results}}{\text{N screened women who had no histologically confirmed CIN+}}$$

In the formula the normal test results refer to NILM diagnosis (negative for intraepithelial lesions of malignancy) of the Pap test and the denominator is calculated as number of women screened minus the number of women with confirmed CIN+.

4.5 Ethical considerations

The author of this thesis signed a confidentiality agreement and a contract with the NIHD which gave her the authority to use and process the necessary data from the ECSR database and to enquire additional information regarding the performed screening tests from healthcare service providers according to the legislation of Cancer Screening Registry Act [34].

5 Results

This section provides the information on the amount and status of the performed screening tests, reports the feedback of the requested data-tables, and gives the measurements of the quality indicators.

5.1 Feedback on the requested data tables

Altogether, 21 encrypted Excel tables were sent to the health care service providers. These tables included more than 13 000 personal identification codes of women who belonged to the target group in 2016 and had PAP test taken during the relevant year but were missing the smear test and/or additional investigation/analysis result in ECSR database. During the determined time frame (from the 15th of December 2017 to the 1st of February 2018) 10 data-filled tables were received from the institutions. One of the returned tables contained information only about abnormal Pap test results and their further assessments that were forwarded in the former table format used for data transmission before the establishment of cancer screening registry. In total, additional data was obtained for 1054 women. Ten service providers responded that filling the tables with supplementary data could only be done manually one by one and is very time-consuming requiring additional resources and was therefore impossible to execute. One health service provider did not return its table nor gave an explanation for non-cooperation. The obtained data was incorporated into the screening registry's database and was considered in computing the selected parameters. The completeness of Pap test results for 2016 in screening registry was 51% before and 55% after the incorporation of the current study materials. The detailed information on screening test results, completeness of information and additionally collected data is presented in Table 1.

The flowchart of the study population is shown in Figure 4. Altogether over 56 000 women belonged to the cervical screening target group in 2016 and 23 840 of them were screened by the institutions participating in organized cervical screening that year. After the inclusion of additionally collected data the screening test and additional investigation results were available for 11 913 of them.

Table 1. Information on screened, requested and received Pap test results for the year 2016.

Service provider*	N screened women	Completeness of data in ECSR (%)	N women in requested data tables	Received data on N women
1	322	0	322	0
2	1075	0	1075	0
3	152	0	152	152
4	4436	82.7	1024	0
5	625	0	625	0
6	294	94.2	17	17
7	546	98.2	36	36
8	554	100.0	68	68
9	393	0	393	0
10	327	72.8	169	169
11	3227	0	3227	90
12	2043	0	2043	0
13	1104	0	1104	0
14	1584	97.8	220	0
15	344	93.9	21	21
16	1694	0	1694	0
17	628	95.7	38	38
18	427	88.1	77	0
19	4240	99.5	255	0
20	163	0	163	163
21	662	60	300	300
Total	23840	51.0	13023	1054

*The service providers included (in alphabetical order) – Arvenos, East-Tallinn Central Hospital, Fertilitas, Hiiumaa Hospital, Ida-Viru Central Hospital, Jõgeva Hospital, Järvamaa Hospital, Kuressaare Hospital, Läänemaa Hospital, Medicum, Narva Hospital, North Estonia Medical Centre, Põlva Hospital, Pärnu Hospital, Rakvere Hospital, Raplamaa Hospital, South-Estonian Hospital, Tartu University Clinic, Valga Hospital, Viljandi Hospital and West-Tallinn Central Hospital.

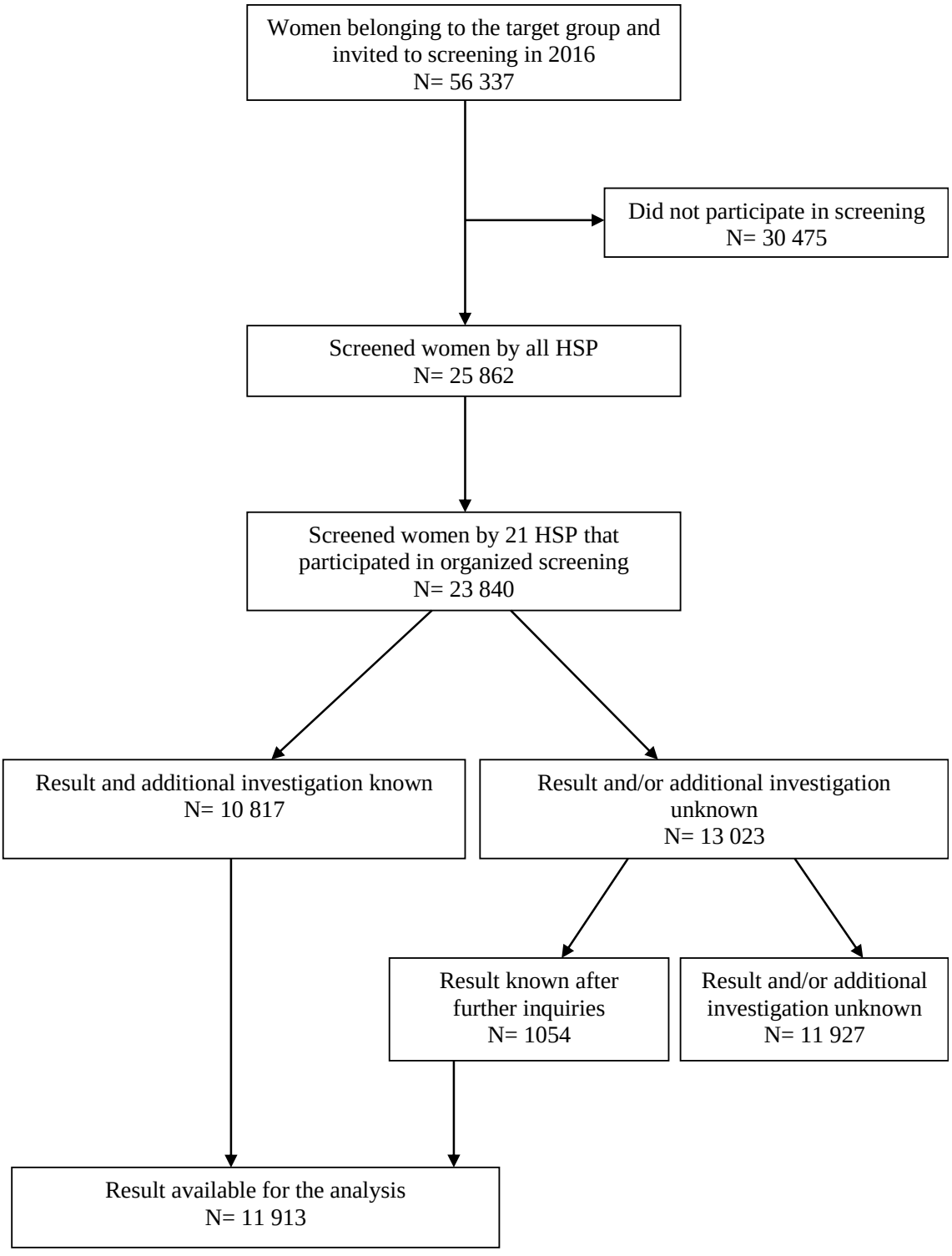

Figure 4. Study flowchart. Abbreviations: HSP, health service provider.

5.2 Test performance indicators

5.2.1 Distribution of women by the results of cytology

Merely half of the smears (11 913) were eligible to be included in the calculation of the proportion of screened women with different results of cytology. Table 2 demonstrates the distribution of cytological diagnoses among screened women in 2016 with available test results. Approximately 93% of samples had normal results and were diagnosed as NILM. The proportion of women with abnormal cytology findings (i.e. atypical squamous cells of undetermined significance (ASC-US) or worse) was 7.24%. The most prevalent results of pathological smears were ASC-US, contributing to 3.74 of all known cytological findings, followed by the results of LSIL - 1.47% and HSIL - 1.18%. Atypical squamous cells cannot exclude HSIL (ASC-H) were detected in 0.65% and atypical glandular cells (AGC) in 0.17% of all smears. There were 5 cervical squamous cell carcinoma diagnoses in women screened within cervical screening program in 2016. Cancer cases constituted to 0.04% of all available test results.

Table 2. Diagnostic profile of cervical smear results

Result of screening cytology	**N women**	**% of all known results**	**% of abnormal results**
Negative for epithelial lesion of malignancy (NILM)	11050	92.76	
Abnormal findings:	863	7.24	
Atypical squamous cells of undetermined significance (ASCUS)	446	3.74	45.7
Atypical squamous cells cannot exclude HSIL (ASC-H)	77	0.65	7.9
Low-grade intraepithelial lesion (LSIL)	175	1.47	17.3
High-grade intraepithelial lesion (HSIL)	140	1.18	14.3
Squamous cell carcinoma	5	0.04	0.51
Atypical glandular cells (AGC)	20	0.17	2.05
Result available	**11913**		
Result unavailable	**11927**		
Total	**23840**	100	100

Abnormal results were further grouped as 1) malignant cells, 2) HSIL, 3) LSIL and 4) ASC-US+ASC-H+AGUS (Figure 4). Malignant cells and HSIL lesions represent the smears with the most significant and severe abnormalities among cervical cancer screening test results that require velocious further investigation and active management whereas LSIL and ASC-US/ASC-H/AGC findings are considered as abnormalities of a lesser degree. Out of 863 abnormal findings 543 (55.6%) belong to the ASC-US/ASC-H/AGUS group and 145 (14.9%) to the high-grade pathology group.

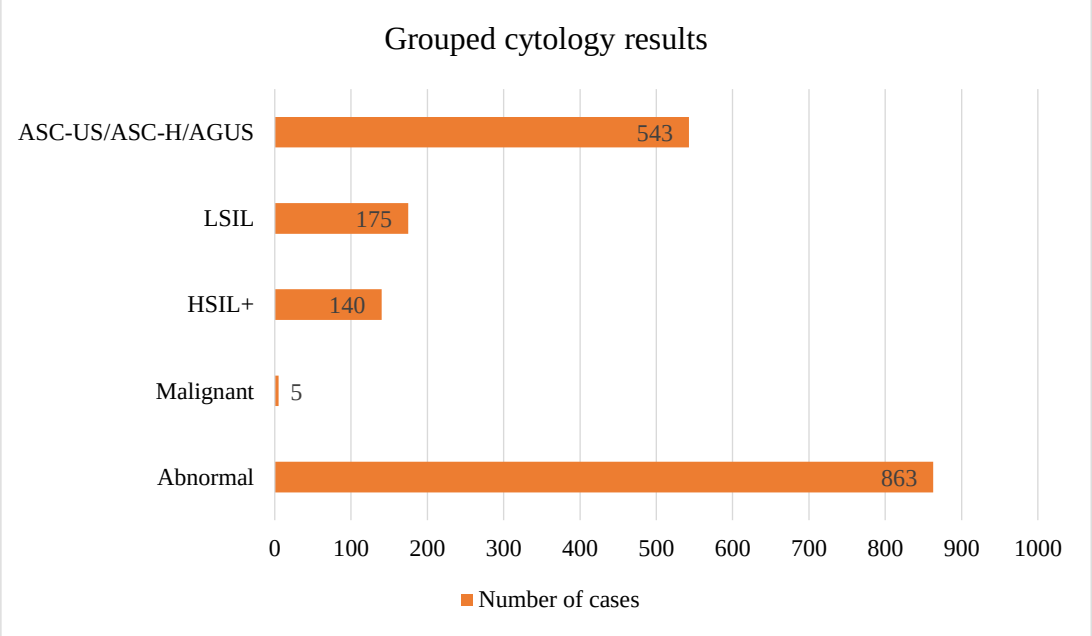

Figure 5. Proportion of screened women with abnormal cytology by grouped results

5.2.2 Proportion of women with colposcopy

There were 516 colposcopies performed of women belonging to the target group in 2016 by the selected health care providers according to the screening registry´s database. The proportion of women who underwent colposcopy within cervical screening program in 2016 was **2.16%** of all women who had PAP test taken in the relevant year.

5.2.3 Positive predictive value (PPV) of colposcopy

In the calculation of the third indicator - PPV for colposcopy - only the data related to the responding health care providers was included. Biopsy results with CIN+ diagnosis were taken into account in the numerator and all women who underwent colposcopy in relevant (responding) institutions according to the screening registry database (N=166) in the denominator. The overall PPV of colposcopy for CIN2+ and CIN3+ were 22.3% and 6% respectively. Based on separate cytology result calculations the PPV for ASC-H was 5.4%, for HSIL 12.7% and for AGC 1.8%.

The collected data about subsequent histology results of biopsies also enabled the evaluation of the cytology-histology correlation, which gives valuable data that can be used to improve the diagnostic testing and screening process [43]. The correlation estimates shown in Table 3 indicate that 33.3% of ASC-US, 66.7% of ASC-H and 78.6% of AGUS cytological diagnoses were histologically negative, whereas 87.5% of HSIL lesions were histologically also high-grade findings (CIN 2+). Equally good correlation could be noted for LSIL results where the majority of smear test results (88.2%) confirmed to be either CIN 1 or 2 lesions. However, the 41.2% of low grade lesions and 28.6% of ASC-US smears were found to be histologically high-grade. This discordance is substantial and has relevance in follow-up and monitoring guidelines of the patient.

Table 3. Correlation of cytology with histological biopsy findings[1].

	Histology										
	Negative		CIN 1		CIN 2		CIN 3		CIN		
Cytology	N	%	N	%	N	%	N	%	N	%	Total
ASCUS	7	33.3	8	38.1	6	28.6	0	0	0	0	21
ASC-H	18	66.7	2	7.4	3	11.1	2	7.4	2	7.4	27
AGUS	11	78.6	0	0	3	21.4	0	0	0	0	14
LSIL	2	11.8	8	47.1	7	41.2	0	0	0	0	17
HSIL	3	12.5	3	12.5	8	33.3	8	33.3	2	8.3	24
Total	41	39.8	21	20.4	27	26.2	10	9.7	4	13.6	103

[1] The data is based on an audit sample from responding service providers.

5.2.4 Detection rates (DRs) of histologically proven CIN+

For this estimation, merely the data about cytology and histology results from responding screening institutions were used. The DRs by histological diagnoses were calculated separately for different grades of CIN and according to the available data the DR for CIN1, CIN2 and CIN3 were 3.0, 3.7 and 1.4 per 1000 screened women respectively. For the purpose of comparability with screening programs in other EU member states, the rate for CIN2+ was computed to be 5.36/1000 and for CIN3+ it was 1.4/1000 screened women.

5.2.5 Test specificity

The data of cytology test results in the registry´s database and collected data of histology test results concerning the responding service providers enabled the calculation of the overall test specificity, but not separately by cytology and histology results. All the women with Pap-test negative results were included in the numerator and all women who had no confirmed positive histology results were considered in the denominator. The overall test specificity was found to be 99.4%.

6 Discussion

This section explains the results of the measurements and compares them with the findings from other studies, while commenting on the data quality and possible factors influencing it. Also, the underlying meaning of the study is presented, and the limitations of the study are acknowledged.

6.1 Significance of the study

The present thesis provides an overview of the test performance indicators in the Estonian cervical cancer screening program in 2016, calculated on digitally collected data in the ECSR database and additionally collected data from the healthcare service providers. The establishment of the ECSR created the opportunity to more effectively monitor screening programs performance by using the collected data. Previously, all the data about pathological cytology results of only organized screening were collected in aggregated, impersonalized tables filled manually by institutions excluding opportunistic screening findings completely. In addition, the amount of performed Pap smears among the target group each year was acquired from EHIF based on paid invoices. After the formation of the population-based screening registry, the actual coverage of the target population and performed tests could be estimated. Most importantly, the necessary data retrieval came from genuine test results present in the ENHIS about both organized as well as opportunistic screening.

Measuring the performance indicators by ECSR is essential in regular screening process monitoring and evaluation to ensure continuous quality improvement by facilitating the proposal of necessary improvements. It also provides an opportunity to compare Estonian screening program performance with other EU member states, especially with northern European countries such as Finland, Sweden and Denmark, whose well-established screening programs have been functioning for many decades and have thereby decreased cervical cancer incidence significantly.

The quality indicators can be calculated only if access is provided to the necessary data and therefore it is very important that the collected data completeness and quality in the registry´s database are high. According to the screening test results observed in this study

there is a noticeable problem with the insufficient quality of the collected data that needs to be addressed to provide ECSR proper tools for monitoring the screening programs.

6.2 Performance measures

The selected quality indicators of the cervical cancer screening program were analysed for the year 2016 because the screening test data transmission and retrieval was somewhat improved compared to the first-year activity of a newly established screening registry. Furthermore, 2016 was the last year with complete follow-up after detected cervical lesions before the beginning of the study. It would have been too laborious for health service providers to fill Excel tables with additional data about test results for two consecutive years, especially for the year 2015 when the amount of unknown Pap smear results was even bigger than in 2016. The results for the requested data in individually delivered tables were received from almost half of the providers, representing a notable extra work for the contact persons in the institutions. Nevertheless, the willingness to cooperate in the quality improvement of screening data was noticed also in those institutions that had to decline participation.

In this study, five test performance parameters were chosen recommended in the European guidelines [39]. First, the distribution of screened women by the result of cytology was calculated and the amount of abnormal results were found to be 7.24%. In the beginning of the establishment of organised cervical screening in Estonia (2003-2008) the proportion of abnormal results were 5.4% on average (3.80-6.66%) including only organized screening test results [44]. The value has remained to be between 3-7% of all results in organised screening so far. The increase in abnormality rate in this study is probably attributable to the addition of opportunistic test results in the estimation.

The Estonian abnormality rate of Pap tests in 2016 is comparable with international values, where the average proportion of detected pathologies in screening is usually 6-8%, and also with northern European countries. In the recent study about a registry-based assessment in Sweden**,** approximately 91% of samples were found to be cytologically normal [45]. In Finland, on average of 6% of women have an abnormal test result in organized screening [46], [47] and in Denmark, during 2013-2015 in total 10.7% of satisfactory cytology samples showed abnormalities as defined by ASC-US+ [48].

The rate of referral for colposcopy is a measure of economic cost but also can cause unnecessary stress, time expenditure and anxiety to the woman, which can be a measure of an excess burden as well [4]. Therefore, this parameter should be kept as low as possible. Although the EU guideline recommends determining the referral rate for colposcopy as a performance indicator, this was not feasible for Estonia. The referral for colposcopy is not generated in the ENHIS (there is no national requirement for that) and thus the second variable was calculated as the proportion of women who attended colposcopy. This rate for 2016 was in concordance with other European countries where the PPV for referral has been shown to be between 0.5% and 4% [42] and is strongly dependent on adopted national screening management protocols particularly for ASC-US and LSIL in triaging of the HPV positive women. The colposcopy referral rates in EU member states vary, but the mean is 2.1% [21]. It is equivalent to the actual attendance rate for Estonia in 2016, meaning that the referral rate could be a bit higher due to the reason that usually all referred women might not attend colposcopy.

The PPV of colposcopy for histology-proven CIN2+ and CIN3+ measured in this study are likely underestimated due to incomplete data on histology reports. The mean values in EU are considerably higher – PPV for CIN2+ is 33.8% and 22.9% for CIN3+ compared to 22.3% and 6% respectively in this analysis [21]. The DR of histology proven CIN2+ lesions is an important measure representing the number of women that were possibly saved from developing cervical cancer in the future (a checkpoint of disease progression). This rate should be observed and compared to European screening programs identifying the variation in quality and the trend in the prevalence or increase of CIN lesions [21]. In Estonia based on the analysis of the limited data, the DR of CIN2+ (5.36/1000 screened women) were in concordance with European mean (4.4/1000 screened women) ranging from 2.9/1000 in Finland to 10.1/1000 in Denmark according to the published report for the years 2013-2014 [21]. These rates are important indicators of screening program effectiveness and therefore should be calculated regularly, but until the implementation of the exact anatomical site coding in the cervical histology reports by all institutions performing colposcopies and treatment of screen-detected lesions it is almost impossible to calculate the exact number of the DRs and PPVs concerning all the screening tests and diagnostic assessment and treatments.

The Pap test is considered to be highly specific for detecting high-grade lesions, meaning that it correctly identifies the women that do not have the disease. The specificity of the Pap smear has been proven to be over 95% in many studies [49]. In this analysis including the cytology and histology results from the responders, the overall specificity was very high. It should be taken into consideration that histology results were most probably not available for all cervical screening tests and thus the actual specificity might be slightly lower.

In Estonia, the established cervical cancer screening program is not very effective and needs improvement. Low coverage of target population and the absence of quality assurance have been brought out to be the main causes of ineffectiveness [7]. According to a study conducted among Estonian women in 2012, the main reasons for non-participation in the national organized cervical cancer screening program were a recent visit to a gynaecologist, fear to give a Pap test, in addition to long waiting and inconvenient reception time [50]. To encourage the participation, a home mailing of a self-sampling kit could be an alternative method to reach non-attenders that has been shown to provide adequate accuracy in HPV testing [51]. One recommendation has also been to replace the Pap smear as primary screening test with more sensitive HPV test. Extending the screening range might also be a measure to decrease the incidence of invasive cancer. According to the national statistics for the years 2000-2015, more than one third (39.9%) of cervical cancer incidence cases are diagnosed outside the age range of the target group, especially in women older than 60 years of age [52]. The quality of the cytology laboratories participating in the screening is different and there is no reference laboratory [26]. Thus, to lower the incidence of cervical cancer in Estonia, it is important to increase the screening coverage and implement a quality assurance system that monitors the performance of screening program activities at all levels.

6.3 Data completeness and quality

ECSR has been operating for 3 years and despite the initial assessment to use the existing data in ENHIS for cancer screening registry purposes, the activity has revealed that the quality of centrally collected data is incomplete. Also, the use of terms and definitions sometimes differs between institutions. Preliminary investigations before the employment might have foreseen the status of screening test report quality in the central system.

The screening data in the registry is mediated through ENHIS. The prerequisite for sending data correctly to the central system is the availability and use of valid standards and classifications in the providers´ own information system(s). Due to the submission and incompatibility problems of the health care service providers' IT solutions, the data is sometimes incomplete and unobtainable for secondary use [53]. Implementing and updating IT solutions is costly and time-consuming for the institution but ignoring national data transmission standards results in incorrect data input. In 2016, there were five different information systems used by 21 institutions participating in organized cervical cancer screening (L. Mokrik, personal communication, April 30, 2018). One single information system for all service providers would decrease costs, harmonize data standardization and improve its quality but seems currently impossible to be realized.

The completeness of information for cytology tests in 2016 was found to be approximately 50% indicating the need for further improvement. The large proportion of incomplete data in the screening registry could be the result that test report documents were not sent to the ENHIS, the valid standards are not used in providers' information systems or information on test results is provided in free text format and relevant data fields are not machine-readable. Despite the fact that it is compulsory for the service provider to send documents to the central system, 6 out of 21 health service providers involved in cervical cancer screening had not sent any documents according to the screening registry's statistics for the year 2016 [54]. The underlying reasons needs to be investigated since all health service providers that perform screening have information systems that support data exchange with ENHIS.

In Sweden and Finland for example, the registry coverage is 100% for both cytological and histological analyses of cervical screening. In Sweden, the laboratories send a copy of the same report to the registry that they forward to the clinic that requested the analysis ensuring thus the completeness and correctness of data [45]. In Finland, Mass Screening Registry covers all health care providers that provide cervical screening tests and it comprises the detailed information on the results of all tests in addition to subsequent necessary diagnostic procedures and treatments [46].

To increase the completeness and acquisition of medical data both in the ENHIS and thereby also in the ECSR, health care providers should send all data to the central system by using the valid national data transmission standards and make the necessary

developments in their IT systems. In addition, all the data fields should be standardized and contain either encoded information or inserted by using nationally agreed classifications, because the main problem has been the usage of free text in documenting the test results. According to the legislative framework, the ENHIS has right to perform regular check-ups to verify the data quality and give consistent feedback to service providers [55]. This is presently carried out but needs more resources to be done more actively. Another possibility to increase the data acquisition would be to send the test report after confirmation by relevant health care worker directly from the laboratory to the ENHIS and some institutions already have started this with Pap tests (T. Lasn, personal communication, April 20, 2018).

Due to the submission and incompatibility problems of the health care service providers' IT solutions, the data is sometimes incomplete and unobtainable for secondary use [53] but timely and accurately provided data will ensure the proper functioning of the registry, avoid excessive manual data input and enable better treatment and results for the patients [1]. Although the quality of the screening tests and report submission is improving every year, additional investments to ENHIS, ECSR and service providers are required to accelerate the process for monitoring the data quality, measuring regularly the quality indicators and aligning the institutions´ information systems to required standards.

6.4 Study limitations

This study was limited by the amount of information available on cytology results and subsequent histology results, which hindered the measurement of the complete values of test performance parameters for the cervical cancer screening program in 2016. Some indicators were adjusted to fit with the available data for example referral rate for colposcopy was replaced with attendance rate. Furthermore, it was not possible to calculate all test performance indicators recommended in EU guidelines due to the limitations of the availability of relevant data. In the future there is a need to analyse further in collaboration with Estonian Health and Welfare Information Systems Centre the underlying reasons for the absence of the necessary information in test reporting to make relevant amendments.

7 Summary

The primary aim of the thesis was to analyse five test performance indicators of the Estonian cervical cancer screening program in 2016 based on the data of ECSR and with the help of additional data collection from institutions participating in organized screening program. Secondary aim was to observe the data completeness and quality in the screening registry´s database.

The quality indicators were estimated according the European Guidelines for Quality Assurance in Cervical Cancer Screening. The proportion of screened women with abnormal cytology findings was found to be 7.24%. The most prevalent results were ASC-US (3.74% of all results), followed by LSIL (1.47%) and HSIL (1.18%) lesions. The proportion of women with colposcopy was 2.1% and the PPV of colposcopy for CIN2+ and CIN3+ were 22.3% and 6% respectively. The estimates for DRs of CIN1, CIN2 and CIN3 were 3.0, 3.7 and 1.4 per 1000 screened women respectively. The overall test specificity was 99.4%.

The completeness of Pap tests in ECSR was 51% before and 55% after the inclusion of additionally collected information. Therefore, because of the insufficient quality of the collected data, the results represented in this master´s thesis are limited with the available data set and might be different when complete data on cervical cytology and histology results were obtainable.

In conclusion, it is extremely important for the cancer screening registry to have complete data on all screening test results, additional investigations and treatments to measure the effectiveness of the screening program by using the quality indicators. It enables to react the potential problems in time, give valuable feedback to the service providers and improvement proposals to the policy makers. The increase in data quality and acquisition can be achieved when health service providers keep their information systems up-to-date with recommended documenting standards and send all documents to ENHIS. Efforts need to be made to ensure consistency and enhanced quality of the data collected for the screening reports.

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References

[1] J. Ferlay *et al.*, "Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012," *Int. J. Cancer*, vol. 136, no. 5, pp. E359–E386, 2015.

[2] M. N. Nawal, "Cervical Cancer: A Preventable Death," *Rev. Obstet. Gynecol.*, vol. 2, no. 4, pp. 240–244, 2009.

[3] M. Hakama, M. P. Coleman, D. M. Alexe, and A. Auvinen, "Cancer screening: Evidence and practice in Europe 2008," *Eur. J. Cancer*, vol. 44, no. 10, pp. 1404–1413, 2008.

[4] M. Arbyn *et al.*, "European Guidelines for Quality Assurance in Cervical Cancer Screening. [2nd edition].," 2008.

[5] Tervise Arengu Instituut, "Vähi sõeluuringute register." [Online]. Available: http://tai.ee/et/tegevused/registrid/vahi-soeluuringute-register. [Accessed: 17-Dec-2017].

[6] J. Ferlay *et al.*, "Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012," *Eur. J. Cancer*, vol. 49, no. 6, pp. 1374–1403, 2013.

[7] S. Vaccarella *et al.*, "Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017–40: a population-based study," *Lancet Oncol.*, vol. 17, no. 10, pp. 1445–1452, 2016.

[8] T. Rosso, P. Bertuccio, C. La Vecchia, E. Negri, and M. Malvezzi, "Cancer mortality trend analysis in Italy, 1980-2010, and predictions for 2015," *Tumori*, vol. 101, no. 6, pp. 664–675, 2015.

[9] Cancer Research UK, "Cancer Mortality Statistics." [Online]. Available: http://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality. [Accessed: 24-Mar-2018].

[10] I. Aavik, L. Padrik, T. Raud, and P. Veerus, "Emakakaela, tupe ja vulva vähieelsete muutuste diagnoosimine, jälgimine ja ravi.," 2015.

[11] L. Bruni *et al.*, "ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 27 July 2017." .

[12] E. R. Myers, D. C. McCrory, K. Nanda, L. Bastian, and D. B. Matchar, "Mathematical model for the natural history of human history of human papillomavirus infection and cervical carcinogenesis.," *Am J Epidemid*, vol. 151, no. 12, pp. 1158–1170, 2000.

[13] P. M. Miranda *et al.*, "Persistence or clearance of human papillomavirus infections in women in Ouro Preto, Brazil," *Biomed Res. Int.*, vol. 2013, 2013.

[14] G. M. Clifford, J. S. Smith, M. Plummer, N. Muñoz, and S. Franceschi, "Human

papillomavirus types in invasive cervical cancer worldwide: A meta-analysis," *Br. J. Cancer*, vol. 88, no. 1, pp. 63–69, 2003.

[15] R. L. Stanberry and D. I. Bernstein, Eds., *Sexually Transmitted Diseases: Vaccines, Prevention, and Control*, 1st ed. Academic Press, 2000.

[16] M. Griffiths, "Screening for cervical cancer in developing countries. Report of a WHO consultation.," 2002.

[17] C. B. J. Woodman, S. I. Collins, and L. S. Young, "The natural history of cervical HPV infection: Unresolved issues," *Nat. Rev. Cancer*, vol. 7, no. 1, pp. 11–22, 2007.

[18] Eesti Haigekassa, "HPV-vastane vaktsineerimine." [Online]. Available: https://www.haigekassa.ee/inimesele/haiguste-ennetus/vahi-soeluuringud-naistele/hpv-vastane-vaktsineerimine. [Accessed: 24-Apr-2018].

[19] National Cancer Institute, "Pap and HPV testing." [Online]. Available: https://www.cancer.gov/types/cervical/pap-hpv-testing-fact-sheet. [Accessed: 20-Feb-2018].

[20] M. Arbyn *et al.*, "European guidelines for quality assurance in cervical cancer screening. Second edition-summary document," *Ann. Oncol.*, vol. 21, no. 3, pp. 448–458, 2010.

[21] International Agency for Research on Cancer, "Cancer screening in the European Union (2017). Report on the implementation of the Council Recommendation on cancer screening.," 2017.

[22] IARC, *Cervix Cancer Screening. IARC Handbook of Cancer Prevention.*, vol. 10. IARC Press, 2005.

[23] R. Sankaranarayanan *et al.*, "HPV Screening for Cervical Cancer in Rural India," *N Engl J Med.*, vol. 360(14), pp. 1385–94, 2009.

[24] "EU-topia." [Online]. Available: http://eu-topia.org/. [Accessed: 09-Apr-2018].

[25] "Nordscreen." [Online]. Available: http://nordscreen.org/. [Accessed: 09-Mar-2018].

[26] P. Veerus *et al.*, "Emakakaelavähi sõeluuringute juhend," 2011.

[27] Eesti Haigekassa, "Eesti Haigekassa haiguste ennetamise arengukava 2016-2019," 2016.

[28] I. Aavik, L. Padrik, T. Raud, K. Täär, and P. Veerus, "Emakakaela, tupe ja vulva vähieelsete muutuste diagnoosimine, jälgimine ja ravi. HPV-vastase vaktsineerimise soovitused.," *ENS ravijuhend, versioon 3*, pp. 1–74, 2014.

[29] V. Kesic, M. Poljak, and S. Rogovskaya, "Cervical cancer burden and prevention activities in Europe," *Cancer Epidemiol. Biomarkers Prev.*, vol. 21, no. 9, pp. 1423–1433, 2012.

[30] Tervise Arengu Instituut, "Tervisestatistika ja terviseuuringute andmebaas." [Online]. Available: http://pxweb.tai.ee/PXWeb2015/index.html. [Accessed: 20-Dec-2018].

[31] Tervise Arengu Instituut, "Vähi sõeluuringute register." [Online]. Available: http://www.tai.ee/et/tegevused/registrid/vahi-soeluuringute-register. [Accessed: 09-Dec-2018].

[32] Tervise ja heaolu infosüsteemide keskus, "Vähi sõeluuringute dokumenteerimise nõuded." [Online]. Available: http://pub.e-tervis.ee/manuals/Vähi sõeluuringu

dokumenteerimise juhend/1. [Accessed: 11-Jan-2018].

[33] S. Reisberg, H.-A. Talvik, K. Koppel, S. Laur, and J. Vilo, “Description of the current status and future needs of the Information Architecture and Data Management solutions for the national personalised medicine pilot project,” 2015.

[34] “Vähi sõeluuringute registri asutamine ja registri pidamise põhimäärus (13.01.2015),” *Riigi Teataja I.* .

[35] “Tervishoiuteenuste korraldamise seadus (09.05.2001),” *Riigi Teataja I.* .

[36] “Tervise ja Heaolu Infosüsteemide Keskus.” [Online]. Available: https://www.tehik.ee/. [Accessed: 28-Dec-2017].

[37] Tervise ja heaolu infosüsteemide keskus, “Standardite ja klassifikaatorite publitseerimiskeskus.” [Online]. Available: http://pub.e-tervis.ee/. [Accessed: 14-Jan-2018].

[38] T. Lasn, “Sõeluuringu andmevahetusprotsessid ja nõutavad standardid.” presented at Tervise Arengu Instiuud (TAI) emakakaelavähii koostöökohtumine Tallinn 26.10.2017.

[39] M. Arbyn *et al.*, “European guidelines for quality assurance in cervical cancer screening: recommendations for collecting samples for conventional and liquid-based cytology,” *Cytopathology*, vol. 18, no. 3, pp. 133–139, 2007.

[40] R. Nayar and D. C. Wilbur, “The Pap test and Bethesda 2014,” *Cancer Cytopathol.*, vol. 123, no. 5, pp. 271–281, 2015.

[41] A. G. Waxman, D. Chelmow, T. M. Darragh, H. Lawson, and A.-B. Moscicki, “Revised Terminology for Cervical Histopathology and Its Implications for Management of High-Grade Squamous Intraepithelial Lesions of the Cervix HHS Public Access,” *Obs. Gynecol. Obs. Gynecol*, vol. 120, no. 6, pp. 1465–1471, 2012.

[42] G. Ronco *et al.*, “Process performance of cervical screening programmes in Europe,” *Eur. J. Cancer*, vol. 45, no. 15, pp. 2659–2670, 2009.

[43] S. S. Raab and D. M. Grzybicki, “Cytologic-histologic correlation,” *Cancer Cytopathol.*, vol. 119, no. 5, pp. 293–309, 2011.

[44] S. Vaask, T. Raud, and U. Klaar, “Emakakaelavähi sõeluuringu korraldus ja tulemused Eestis,” *Eesti Arst*, vol. 88, no. 11, pp. 748–754, 2009.

[45] K. M. Elfström, P. Sparén, P. Olausson, P. Almstedt, B. Strander, and J. Dillner, “Registry-based assessment of the status of cervical screening in Sweden,” *J. Med. Screen.*, vol. 23, no. 4, pp. 217–226, 2016.

[46] H. Salo *et al.*, “Divergent coverage, frequency and costs of organised and opportunistic Pap testing in Finland,” *Int. J. Cancer*, vol. 135, no. 1, pp. 204–213, 2014.

[47] M. Pankakoski, S. Heinävaara, T. Sarkeala, and A. Anttila, “High lifetime probability of screen-detected cervical abnormalities,” *J. Med. Screen.*, vol. 24, no. 4, pp. 201–207, 2017.

[48] E. Lynge *et al.*, “Cervical screening in Denmark – a success followed by stagnation,” *Acta Oncol. (Madr).*, vol. 57, no. 3, pp. 354–361, 2018.

[49] M.-H. Mayrand *et al.*, “Human Papillomavirus DNA versus Papanicolaou Screening Tests for Cervical Cancer,” *N. Engl. J. Med.*, vol. 357, no. 16, pp. 2163–2173, 2007.

[50] A. Kivistik, K. Lang, P. Baili, A. Anttila, and P. Veerus, “Women’s knowledge about cervical cancer risk factors, screening, and reasons for non-participation in cervical cancer screening programme in Estonia,” *BMC Womens. Health*, vol. 11, pp. 7–12, 2011.

[51] K. Haguenoer *et al.*, “Vaginal self-sampling is a cost-effective way to increase participation in a cervical cancer screening programme: A randomised trial,” *Br. J. Cancer*, vol. 111, no. 11, pp. 2187–2196, 2014.

[52] Tervise Arengu Instituut, “Eesti Vähiregister.” [Online]. Available: http://www.tai.ee/et/tegevused/registrid/vahiregister/statistika. [Accessed: 19-Dec-2018].

[53] J. Idavain, P. Liisi, and N. Eigo, “Pahaloomuliste kasvajate valitud paikmete ja näitajate andmeallikate analüüs,” 2017.

[54] T. Mändla, “Vähi sõeluuringute register Eestis : võimalused täna ja tulevikus,” 2016. [Online]. Available: https://tervis.ut.ee/sites/default/files/www_ut/tth2016_mandla_vahi_soeluuringute_register.pdf. [Accessed: 07-Jan-2018].

[55] “Tervise infosüsteemi põhimäärus (01.12.2016),” *Riigi Teataja I*.