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COMPARISON OF DIFFERENT CERVICAL CANCER SCREENING STRATEGIES BASED ON SIMULATION MODELLING

Master's thesis

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SIMULATSIOONI MUDELIL PÕHINEVATE ERINEVATE EMAKAKAELAVÄHI SÕELUURINGUSTRATEEGIATE VÕRDLUS

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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.

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Abstract

The aim of this study is to compare different cervical cancer screening strategies using a validated web-based tool for modelling, EU-TOPIA (Towards improved screening for breast, cervical and colorectal cancer in all of Europe) to determine which works best.

Cervical cancer (CC) incidence has become a global concern in women's health with high prevalence rates. It is the fourth most frequent cancer in women in the world. Some specific types of the Human papillomavirus (HPV) have been found to be the cause of about 70% of CCs. Although prophylactic vaccines offer great hope for future generations, already sexually active women will have to depend on screening as it will take several decades to benefit from such intervention. Despite a successful implementation of cervical cancer screening programme in Estonia since 2006, its cervical cancer incidence is third highest in Europe.

Analysis and investigations to assess the benefits and potential risks associated with cervical screening strategies varying by primary screening test, screening frequency, target age range, triage test for abnormal results and adherence rate were carried out using the tool. The natural history of cervical cancer was modelled in a projected population of Estonian females from 2018 up to the year 2050, using the base case scenario and a total of nine cervical cancer screening strategies were simulated and compared with the current screening strategy used in the Estonian organized cervical cancer screening programme.

According to our data, an increase in the mortality reduction rates was observed in the simulation with vaccination when compared to the simulation with no vaccination. Findings from this study in accordance with recommendations from guidelines on weighing the benefits and harms of screening, show that HPV-test with cytology triage in the 30 to 60 years age group is the optimal strategy to save more life-years with less harms. The number of overdiagnosed cases and false positives are lower with this strategy when compared with strategies having higher mortality reduction rates in the simulation of unvaccinated cohort. However, it requires more triage tests. Simulation modelling approach provides an infrastructure for making comparative analysis quickly and

efficiently and should be encouraged in making health care policy decisions. However, to achieve reliable model outcomes such as with using the EU-TOPIA tool, the availability of good quality medical data is highly crucial.

This thesis is written in English and is 38 pages long, including 5 chapters, 8 figures and 5 tables.

Annotatsioon

Simulatsiooni mudelil põhinevate erinevate emakakaelavähi sõeluuringustrateegiate võrdlus

Selle uuringu eesmärk on võrrelda erinevaid emakakaelavähi sõeluuringute strateegiaid, kasutades valideeritud veebipõhist modelleerimisvahendit, EU-TOPIA (Rinna-, emakakaela- ja kolorektaalvähi parema sõeluuringu suunas kogu Euroopas), et teha kindlaks, milline neist töötab paremini.

Emakakaelavähi esinemissagedus on muutunud naiste tervise ülemaailmseks probleemiks, sest tema levimus on kõrge. Emakakaelavähk on naiste seas neljas sagedamini esinev vähk maailmas. On leitud, et mõned inimese papilloomiviiruse konkreetsed tüübid põhjustavad umbes 70% emakakaelavähi juhtudest. Ehkki profülaktilised vaktsiinid pakuvad tulevastele põlvedele suurt lootust, peavad juba seksuaalselt aktiivsed naised sõltuma sõeluuringutest, kuna sellisest sekkumisest on kasu mitu aastakümmet. Hoolimata riikliku emakakaelavähi sõeluuringuprogrammi rakendamisest Eestis alates 2006. aastast, on semakakaelavähi esinemissagedus Eestis Euroopas kolmandal kohal.

Modelleerimisle põhineva veebipõhise tööriista abil viidi läbi analüüsid ja uuriti emakakaela sõeluuringute strateegiatega seotud eeliseid ja võimalikke riske, varieerudes sõeluuringu esmastesti, testimise sageduse, sihtrühma vanusevahemiku, patoloogiliste tulemuste triaažitesti ja osalusmäära vahel. Emakakaelavähi loomulik ajalugu modelleeriti Eesti naiste prognoositavas populatsioonis 2018. aastast kuni aastani 2050, kasutades alusstsenaariumi ning simuleeriti kokku üheksa emakakaelavähi sõeluuringu strateegiat ja võrreldi neid praegu Eestis kasutatava sõelumisstrateegiaga organiseeritud emakakaelavähi sõeluuringute programmiga.

Meie andmetel täheldati vaktsineerimise simulatsioonides suremuse vähenemise suurenemist, võrreldes stsenaariumitega, kus vaktsineerimine puudub. Selle uuringu tulemused vastavalt sõeluuringu eeliste ja kahjude kaalumise juhendite soovitustele

näitavad, et tsütoloogia triaažiga HPV test 30–60-aastaste vanuserühmas on kõige tõhusam strateegia, et päästa rohkem eluaastaid väiksema kahjustusega. Ülediagnoosimine ja valepositiivsed tulemused on selle strateegia korral madalamad, kui võrrelda strateegiaid, mille suremus on vaktsineerimata kohordi simulatsiooni korral kõrgem. Kuid see nõuab rohkem triaažikatseid.

Kokkuvõtteks võib öelda, et modelleerimise modelleerimine pakub infrastruktuuri võrdleva analüüsi kiireks ja tõhusaks tegemiseks ning seda tuleks tervishoiupoliitiliste otsuste tegemisel julgustada. Usaldusväärse mudeli tulemuse saavutamiseks, näiteks EU-TOPIA tööriista kasutamisel, on kvaliteetsete meditsiiniliste andmete kättesaadavus väga oluline.

Lõputöö on kirjutatud inglise keeles ning sisaldab teksti 38 leheküljel, 5 peatükki, 8 joonist, 5 tabelit.

Terminology

Screening strategy

The screening strategy of an organized screening programme determines between which ages women are invited for screening, with which interval they are invited, which primary test is performed and which triage tests are performed after a positive primary test.

Primary test

A primary test is the initial screening test a woman is invited to. Based on the result of this test, the woman will be referred to colposcopy or triage testing. The primary test can either be cytology (checking for abnormal cells), HPV-test (checking for the presence of hr-HPV) or a co-test, which is a combination of both.

Triage test

A triage test is a screening test that is performed after a woman has had a positive primary screening test, but before the decision is made whether or not to refer her for a colposcopy (e.g. a cytology test after a positive primary HPV-test). The triage test can be performed either directly after the primary test, or after a waiting period of several months or years, depending on the screening strategy.

Colposcopy

A colposcopy is a diagnostic exam by a gynaecologist to determine the presence of disease. This might include taking a biopsy [29].

List of abbreviations and terms

AGC	Atypical Glandular Cell
ASC-H	Atypical Squamous Cells - cannot exclude HSIL
ASC-US	Atypical Squamous Cells of Undetermined Significance
ATHENA	Addressing the Need for Advanced HPV Diagnostics
CIN	Cervical Intraepithelial Lesion
EHIF	Estonian Health Insurance Fund
ENHIS	Estonian National Health Information System
EU	European Union
EU-TOPIA	Towards improved screening for breast, cervical and colorectal cancer in all of Europe
FIGO	International Federation of Gynaecology and Obstetrics
HPV DNA	Human Papillomavirus Deoxyribonucleic Acid
HPV	Human Papillomavirus
hrHPV	High Risk Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
IARC	International Agency for Research on Cancer
ICER	Incremental Cost-Effectiveness Ratio
LBC	Liquid-Based Cytology
LSIL	Low-grade Squamous Intraepithelial Lesion
QALY	Quality-Adjusted Life-Years
TAI	Terevise Arengu Instituut
TNM	Tumour Nodes Metastases
VIA	Visual Inspection by Acetic Acid
VILI	Visual Inspection with Lugol's Iodine
WHO	World Health Organization
USPSTF	US Preventive Services Task Force

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1 Introduction

The burden of cancer continues to rise globally exerting physical, emotional and financial strain on individuals, families, communities and health care systems. With an estimated 570, 000 new cases, 311, 000 deaths in 2018 and representing 6.6% of all female cancers, cervical cancer is the fourth most frequent cancer in women in the world [1]. In Estonia, cervical cancer is the second most common gynaecological cancer [2]. It has been established that some specific types of the human papillomavirus (HPV) such as HPV 16 and 18 are responsible for causing about 70% of cervical cancers and pre-cancerous cervical lesions [3].

The HPV is the most common viral infection of the reproductive tract and the most sexually active women will contract this virus once or even more than once in their lifetime [3]. Studies conducted by the International Agency for Research on Cancer (IARC), identified HPV DNA in 99.7% of cases of cervical cancers [4]. Although prophylactic vaccines offer great hope for future generations, women who have initiated sexual intercourse will mostly have to depend on screening for the prevention of cervical cancer as it will take several decades for most women in the age group of concern who already are at the risk of exposure to the virus to benefit from such intervention [5].

Cervical screening programmes have proven to be effective in reducing cervical cancer incidence and mortality. However, the level of success varies widely between countries [6]. Even though Estonia has an organized screening programme put in place since 2006, the incidence of the cervical cancer is third highest in Europe [2]. The efficacy of screening depends on epidemiologically evidence-based target group, participation rate, screening interval, screening and diagnostic test characteristics, treatment efficacy, and compliance to follow-up visits. For a screening programme to be effective, it is important that screening is done within certain age groups, at appropriate intervals and that the adherence rates are high. Good quality must be maintained, continuous monitoring systems and evidence-based indicators must also be put in place [7]. Otherwise, avoidable mortality will not be prevented.

In several European countries, screening has been introduced to mitigate the burden of cancer. However, these programmes vary considerably, and the long-term effectiveness of screening has only been assessed in a few. In an effort to identify opportunities to improve cancer outcomes across Europe, EU-TOPIA (Towards improved screening for breast, cervical and colorectal cancer in all of Europe), a five-year project (2015-2020) funded by the European Commission's Horizon 2020 was implemented. The programme aims to improve health outcomes and equity of breast, cervical and colorectal cancer screening programmes in ways that take full account of the different demographical, medical, political, economic and cultural contexts across Europe by providing national, regional, and local policymakers with tools to evaluate and quantify their cancer screening programmes. EU-TOPIA has developed and validated innovative dedicated microsimulation models of the natural history of the three cancers for the evaluation of screening, tailored specifically to the different countries in Europe [8].

Simulation modelling approach provides an infrastructure for the comparative analysis of population-based screening models to answer important policy-based questions [9]. It allows the flexibility of changing risk factor profiles of the population, new screening modalities, and treatment regimens giving a full range of the benefits and costs of the interventions. To assess the costs and effects of such interventions as screening programmes, one could monitor the existing programmes or set up trials to evaluate different screening strategies. However, setting up large trials is expensive, needs a long follow-up time and might have ethical concerns. Also, the outcomes of such trials will be dependent on several factors, which might be different across countries, so the results might not be applicable to another country [10].

1.1 Aim, research questions and objectives

Despite having an organized screening programme put in place since 2006, Estonia has the third highest cervical cancer incidence in Europe [2]. The aim of this study is to compare different cervical cancer screening strategies using a web-based tool (EU-TOPIA) to determine best possible solutions to improve the current screening programme.

Research questions:

1. Which screening strategy is most beneficial in reducing the incidence and mortality of cervical cancer among Estonian female population?
2. Which screening strategy will cause the most harm?
3. Which strategy will increase the number of primary tests and additional investigations the most?

Research objectives:

1. To model the natural history of cervical cancer in a projected population of Estonian females from 2018 up to the year 2050 using a web-based evaluation tool
2. To analyse and compare the outcomes of modelling different screening strategies
3. To determine which works best for the population

Literature overview

This section explains the importance of screening, types of cervical cancer screening programmes and different screening strategies by primary test, target age range and screening interval as recommended by guidelines or previous literature in tackling the incidence of cervical cancer. It also explores different approaches used to compare screening strategies.

1.2 Importance of screening

The aim of screening is to identify people who are at greater risk of a disease or health condition in an otherwise healthy population, so that an early diagnosis or intervention can be proffered. This may result in better health outcomes for some of the individuals being screened [11]. Mortality rates from cervical cancer can be reduced or averted using appropriate primary and secondary preventive measures. These interventions form a holistic approach which includes programmes for prevention/vaccination, early detection, effective screening and treatment. An example of a productive and cost-effective cervical cancer intervention is population-based screening for which evidence-based, feasible and efficient screening strategies exist. Its effectiveness and appropriate balances of health benefits and harm is well established through randomized controlled trials and observational studies [12]. In cervical cancer screening, the main objective is to detect precancerous lesions caused by the human papillomavirus (HPV) in order to remove them and prevent the development of invasive cancers. The early detection of cervical cancers while they can be successfully treated is a secondary objective [13].

1.3 Types of cervical cancer screening methods

The utilization of the Pap test in national screening programmes can be traced back to the mid-twentieth century [14], and it is still a cornerstone in most current programmes. Furthermore, the International Agency for Research on Cancer (IARC) determined that the incidence of invasive cervical cancer can be reduced by at least 80% with the

implementation of cytology-based (Pap test) cervical screening programmes every three to five years for women aged 35 to 64 years [15]. However, with the advent of the ability to test for HPV, there are currently three approaches to cervical cancer screening: HPV testing, which searches for the presence of high-risk HPV types in cervical cells; Pap testing (cytology) which looks for cervical cell changes; and co-testing which examines the same cell sample for high-risk HPV strains and changes in the cells of the cervix [12]. Despite an increasing body of evidence in support of primary HPV screening to be a more cost-effective means of prevention than conventional cytology under most scenarios, most European countries tend only to use HPV testing as triage for cytological abnormalities [16]. In Estonia the primary screening test currently in use is the conventional cytology with HPV testing for population-based screening.

1.3.1 Conventional cytology or Pap test

Cytology-based screening using Pap smear test is one of the commonest and most accepted methods [17]. A notable reduction has been observed in the incidence and mortality of cervical cancer in countries where organized screening using Pap test has been implemented. Even though it is effective in curbing the disease, one of the major challenges in the practical implementation of this method is that it requires a lot of resources such as professionals who are skilled enough to identify a handful of abnormal cells among few hundred thousand cells, motivating the need to automate the screening methodology [16]. It also has some important limitations such as time-consuming staining procedure, poor reproducibility, susceptibility to blood and mucus obscuration amongst others which can contribute to errors while analysing results. [14].

1.3.2 Liquid-based cytology (LBC)

Liquid-based technology was developed with the goal of enhancing cervical smear sample preparation. It is a more recent method of preparing cervical samples for cytological examination. Contrary to the conventional ‘smear’ preparation where the sample is applied directly to a slide for microscopic investigation, LBC involves making a suspension of cells from the sample and this is used to produce a thin layer of cells on a slide. Instead of being directly fixed on a slide, cervical cell samples are first transferred to a vial which contains a preservative solution to enable uniform distribution. Since only a portion of the sample is used for cytology, the remainder can be used for further testing including human papillomavirus (HPV) testing [14]. The potential benefits of LBC

include a decrease in the number of inadequate slides, increased test sensitivity and increased smear reader productivity.

1.3.3 Human papillomavirus testing

The main risk factor for developing cervical cancer is HPV infection [18]. Twelve HPV genotypes have been widely recognized as indicating higher risk of the high-grade precancerous lesion or cancer (high-risk HPV). According to the WHO, these twelve types are carcinogenic (class 1), and they include: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. The carcinogenic HPV types can vary by an order of magnitude in risk for cervical cancer. With the discovery that human papillomavirus (HPV) is the leading cause of cervical cancer development, it has become clear that screening by HPV testing is much more sensitive and objective, but less specific for cervical cancer screening than cytology. Based on evidence, clinically validated HPV DNA test in women 30 years of age and older in primary screening has proven to be more effective than Pap test. Surveillance/triage tests are therefore required to compensate for the lower specificity [19].

In screening for cervical cancer, the HPV test is commonly used in combination with a Pap test. This combination is otherwise known as co-testing. The American Cancer Society recommends co-testing for women aged 30 and above. It is not appropriate in women below 30 years because they are more sexually active and have a higher probability to contract an HPV infection that will clear up on its own. Within this category of younger women, HPV tests results may be confusing and insignificant. The HPV test is also used to further investigate the need for more testing or treatment in women who have moderately abnormal test results such as Atypical Squamous Cells of Undetermined Significance [17].

1.3.4 Visual inspection by acetic acid and visual inspection with Lugol's iodine

A simple method of identifying precancerous lesions of the cervix and invasive cancer early is by visually inspecting the cervix after applying 5% acetic acid (VIA) and/or Lugol's iodine (VILI). The use of VILI was discontinued after the emergence of cervical cytology testing in the mid-twentieth century [20]. Due to the potential difficulties associated with the implementation of cytology-based screening in low resource settings, researches have been conducted to investigate the accuracy of other screening options

such as the VIA and VILI in the early detection of cervical cancer [20]. Results from both tests are categorized based on the colour changes seen on the cervix and are readily available without the use of laboratories. However, a good knowledge of the anatomy, physiology and pathology of the cervix is important for understanding the basis of screening and for interpreting the outcome of screening while using this method. According to Qureshi et al. 2010, VIA and VILI tests are more sensitive but less specific in detecting pre-invasive lesions when compared to the cytology, making both tests suitable for use in low-resource settings [21]. The WHO suggested the use of VIA and VILI in developing countries as a substitute for failed cytology screening programmes in these countries.

1.4 Cervical screening programmes

Before introducing a screening programme, it is essential for researchers and policy makers to understand and consider what makes a screening programme effective. The EU Council in 2003, recommended that cancer screening programmes are based on scientific evidence of efficacy [22]. In addition, it said that efficacy is a required condition but not adequate to provide screening to the target population. Rather, the balance between harms and benefits should be clearly shown to be in favour of the benefits and the programme should be cost-effective, affordable and acceptable for the population. The challenge for policymakers is to consider all the potential benefits and harms and decide in the context of their health system and their values or ethics whether the screening programme is expected to produce benefits at a reasonable cost [23]. Some of the challenges to be considered as presented by the WHO are shown in Figure 1 below.

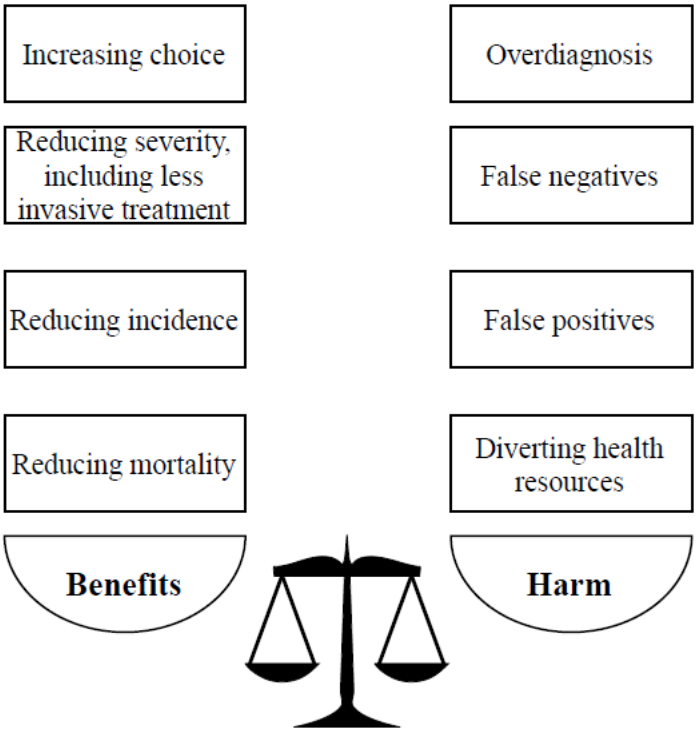

Figure 1. Balancing benefits and harm (Adapted from [23])

There must be a national policy which defines screening age, interval and screening method used. Adequate political and financial investment are also required. A screening programme should be a seamless, integrated system in which women are recruited, screened, the results communicated and understood. Also, women are referred for treatment as required and/or return for repeat screening as determined by the policy [24]. The effectiveness of a programme in achieving health gains is largely dependent upon the interaction of many elements within and outside the health system, such as an accurate register identifying the target population and a strategy to ensure and monitor follow up [25]. When compared with other countries where cervical cancer programmes have been reported to be more successful for example Finland and Australia, screening adherence and coverage in Estonia is quite low. Measures to increase participations in screenings should be advocated. One way could be through self-collection of screening test samples. Currently, smear samples are being taken by specially trained midwives in about 21 clinics around Estonia.

1.4.1 Non-organized or opportunistic screening

Opportunistic screening is screening outside an organized or population-based screening programme. Opportunistic screening is recommendations made during a routine medical consultation for a woman, during consultation for an unrelated condition or on the basis

of a possibly increased risk for developing cervical cancer or by self-referral [24]. Opportunistic screening wastes human and financial resources and exacerbates social inequalities. For example, having high coverage in selected parts of the population which are frequently screened while having low coverage in other parts of the population with less socioeconomic status. Women should be strongly encouraged to be given a prophylactic Pap test only within a screening programme [28].

1.4.2 Organized population-based screening

Organized screening programmes designed and managed at the central level to reach most women at risk are preferable to opportunistic screening [26] as screening is only effective if there is a well-organized system for follow-up and treatment. Organized screening entails 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 target population [24]. A well-organized screening programme is considered more effective in cancer prevention, more cost-effective and with less harm due to over screening and overtreatment than opportunistic testing. In well-organized population-based screening all women are followed from the invitation and test to the possible treatment registering all data from each step. Data collection is important for monitoring and evaluating the quality and effectiveness of screening. However, these benefits are often lost in opportunistic testing as a result of incomplete follow-up and lack of registration. The appropriate age range and test interval may also not be clearly defined or followed [27].

1.4.3 Screening strategies

The screening strategy of an organized screening programme determines the age women who are invited for screening and with which interval they are invited. Also, it determines which primary test and which triage tests are performed after a positive primary test [29]. A primary test is the initial screening test a woman is invited to. Based on the result of this test, the woman will be referred to colposcopy or triage testing. The primary test can either be cytology (checking for abnormal cells), HPV-test (checking for the presence of high risk-HPV) or a co-test, which is a combination of both. A triage/surveillance test is a screening test that is performed after a woman has had a positive primary screening test but before the decision is made whether or not to refer her for a colposcopy (e.g. a

cytology test after a positive primary HPV-test). The triage test can be performed either directly after the primary test or after a waiting period of several months or years, depending on the screening strategy. A colposcopy is a diagnostic exam by a gynaecologist to determine the presence of disease. This might include taking a biopsy [29].

According to the European guidelines for quality assurance in cervical cancer screening, cervical cytology is recommended as the standard primary test for screening the cervix and it should begin within the age range of 20 and 30 years [28]. However, it is preferred not to start earlier than 25 or 30 years depending on the diseases burden in the population and the resources available [27]. The recommended screening method is the Pap test with the HPV test (co-test), or the HPV test every 5 years (preferred) or the Pap test alone every 3 years (allowed) is recommended for women aged 30 to 65 years old [31]. Screening is recommended up until the age of 60 years at 3 to 5 years interval. It is also advised to stop screening in older women who have already had three or more consecutive previous (recent) normal cytology results. Women below the age of 30 years should not be screened for HPV due to the high rate of viral clearance in this age group [30].

It is not recommended to start a cervical Pap test, regardless of the onset of sexual activity or other risk factors before the age of 21 [31] because cervical cancer is rare among teenagers and young women. Rapid progression of cervical cancer in this age group cannot be prevented by screening. Therefore, screening adolescents leads to unnecessary evaluation and treatment of pre-invasive cervical lesions that have a high probability of regressing spontaneously [31]. Adolescent cervical cancer prevention programmes that start before the onset of sexual activity must focus on anti-HPV vaccination that is safe and has a high efficacy [32] and is cost-effective. In women aged 30 to 65 years the recommendation of performing Pap test alone every 3 years is allowed. An interval of 3 years provides an appropriate balance between the benefits and harms of screening in this age group. There is no need to take an additional Pap test from a woman who has taken a national screening in the last three years [31]. Monitoring in women over 65 years may be discontinued if previous tests have been negative and there has been no history of CIN2 (Cervical intraepithelial neoplasia: classification of cervical dysplasia) or higher grade within the previous 20 years. Previous negative follow-up means 3 negative Pap tests or 2 negative co-tests (Pap test with HPV test) in the last 10 years [31]. In the absence of

strong evidence-based proof it is not appropriate to screen women of all ages by any method on an annual basis. An annual screening leads to a large number of unnecessary examinations and treatments but very little increase in the number of preventable cancers. Randomized studies do not provide a sufficiently high level of evidence to increase screening intervals beyond 3 years in any age group with a previous negative Pap test. Due to the high prevalence of HPV in women under the age of 30 years, as confirmed by a study in Estonia, it is not appropriate to screen women 21-29 years with HPV tests either by a standalone test or as a co-test [31].

1.5 Population-based cervical cancer screening in Estonia

Population-based cervical cancer screening programme in Estonia was implemented in 2006 under the authority of the Estonian Health Insurance Fund (EHIF), and the National Institute for Health and Development [6]. The primary screening method is conventional cytology or Pap test and test samples are taken by specially trained midwives in clinics that participate in the programme (altogether 21 clinics all over Estonia in 2016). The national target age group range is from 30 to 59 years with an interval of 5 years between negative screens. The program excludes women with prior cervical cancer and eligible women with valid mailing address receive mailed information letters. However, the whole target group can participate without the invitation and information is also available online in personal patient portal. The informational letter includes information about the screening procedure and contact information of all clinics where screening services are offered. Population data which includes the women's names, mailing addresses, and status (alive, dead, or emigrated from Estonia) are retrieved from the Estonian Population Registry. The criteria for a follow-up screening test or for referral for diagnostic confirmation according to the Pap-smear results are as follows:

1. Atypical Squamous Cells of Undetermined Significance (ASCUS) -> HPV test immediately or repeat Pap in 12 months;
    - if HPV turns out to be negative, then normal screening policy,
    - if positive, then treat like Low-grade Squamous Intraepithelial Lesion (LSIL);
2. Atypical Squamous Cells - cannot exclude HSIL (ASCH) - > colposcopy;
3. LSIL -> take HPV,

- if negative, then repeat Pap and HPV in 12 months,
- if positive, then colposcopy;

4. High-grade Squamous Intraepithelial Lesion (HSIL) -> immediate colposcopy;
5. Atypical Glandular Cell (AGC) -> colposcopy and curettage

Individual level screening test data are retrieved from the Estonian National Health Information System (ENHIS). The Estonian Cancer Screening Registry which was established in 2015 collects data about the primary test, additional investigations (HPV, colposcopy, histology) and treatment offered by the clinics; this data is retrieved from ENHIS which is a nationwide central digital database while the screening registry makes regular linkages with the Estonian cancer registry and Estonian Cause of Death Registry [33].

1.6 Methods of comparing screening strategies

To assess the costs and effects of screening programs it is possible to monitor the existing programs or set up trials to evaluate different screening strategies. Cox et al., 2013 compared 9 cervical cancer screening strategies to the current screening standard (cytology with HPV triage of atypical squamous cells of undetermined significance) for the detection of high-grade cervical disease from the ATHENA (Addressing the Need for Advanced HPV Diagnostics) HPV study. The ATHENA HPV study is a prospective 3-year cervical cancer screening trial designed to compare the performance of the newly introduced cobas HPV Test both alone and in combination with cervical cytology among women aged 21 years and older in the United States [34]. The study enrolled more than 47,000 women aged 21 years and older who presented for cervical cancer screening; all eligible participants had both Papanicolaou testing and HPV testing (by Amplicor HPV test, Linear Array high-risk HPV genotyping test, and the cobas HPV Test) [34]. Setting up such large trial is expensive, needs a long follow-up time and might have ethical concerns. Also, the outcomes of such trials will be dependent on several factors, which might be different across countries, so the results might not be applicable to another country [10].

Shen and Parmigiani 2005, made a comparison of breast cancer screening strategies. Microsimulation model was used for systematic evaluation of the relative expenses and

projected benefits of combining the two screening modalities: mammograms and clinical breast examinations. According to the study, the microsimulation model uses the best available evidence to simulate health histories of women at risk of breast cancer under various screening strategies. A total of 48 screening strategies, depending on the age range, the examination interval and whether mammography or clinical breast examination is given at every one or two exams was examined [35]. The study reported that screening sensitivities generated from simulations showed a reasonable range of variations, consistent with data from breast cancer screening trials, suggesting that the model can accurately represent the effects of screening.

Recognizing that simulation models provide a way to extrapolate available evidence and predict long-term outcomes, the US Preventive Services Task Force (USPSTF) requested simulation modelling to assess the benefits, burden, and harms of various screening strategies for the general population for its update to the 2008 colorectal cancer screening recommendations. To inform the USPSTF colorectal cancer screening recommendations Amy B. et al., 2016 modelled the benefits, burden, and harms of colorectal cancer screening strategies. The authors estimated the optimal ages to begin and end screening and identified a set of model-recommendable strategies that provide similar life-years gained and a comparable balance between life-years gained and screening burden. A total of 204 screening strategies were evaluated using three independently created microsimulation models of colorectal cancer (CRC) developed within the National Cancer Institute-funded Cancer Intervention and Surveillance Modelling Network (CISNET). The three models used for the analysis are: Simulation Model of CRC (SimCRC), Microsimulation Screening Analysis (MISCAN) for CRC (MISCAN for cervical cancer is used in this present research), and Simulated Population Model for Incidence and Natural History (CRC-SPIN) [36].

Võrno et al., 2019 carried out a cost-effectiveness analysis study of cervical cancer screening in Estonia using a Markov cohort model to estimate costs and quality-adjusted life-years (QALYs) of eight cervical cancer screening strategies. The strategies varied by primary screening tests and triage scenarios, upper age limit of screening, and testing interval. Incremental cost-effectiveness ratios (ICERs) were calculated in comparison to current screening practice as well as to the next best option [37]. The study concluded that decreasing Pap-test based screening interval or changing to HPV-test based screening can both improve the effectiveness of cervical cancer screening programme in Estonia.

However, based on the current cost-effectiveness study Pap-test based screening every three years should be preferred [37].

Much focus has been placed in the last few decades on the introduction of quality assurance systems, thus generating and interpreting interim data and indicators for screening. Innovations such as simulation models could enhance the effects of screening by quantifying the lifetime benefits and harms of existing cancer screening programmes in Europe because the evaluation of the actual effects of cancer screening in terms of benefits and harms on citizens is lacking. How screening outcomes can be optimized also remains unclear [8]. It is crucial to know how much resources that is required for a country to implement a screening programme. Other than being able to estimate required resources, modelling can help guide health policy makers in ministries and health insurance funds because it provides a means to assess the effectiveness of the current programme when compared to no screening [8]. If screening age, screening intervals or adherence rates are increased within a projected population using a model, it is possible to predict how many deaths can be prevented. It is also possible to evaluate the effectiveness of the current population-based screening programme when compared with no screening. It is mandatory to analyse the quality and impact of screening programmes in reducing incidence and mortality rates as public funds spent on preventive measures rather than treatment must be justified.

2 Methodology

Analysis and investigations to assess the benefits and potential risks associated with cervical screening strategies were carried out using a validated web-based tool for modelling, EU-TOPIA. This section describes the study design, model, data sources, data collection, data quality and simulation process.

2.1 Study design

This research is a modelling-based study. A validated web-based model platform (EU-TOPIA) was used to analyse and investigate research questions. The EU-TOPIA evaluation tool has been calibrated on data from a number of countries exemplary for all European regions where Estonia belongs [38].

2.1.1 EU-TOPIA

The EU-TOPIA evaluation tool was designed to allow users simulate outcomes of several cancer screening strategies for their own country. It is a web-based evaluation tool and its development was funded by the European Union (EU) Commission's Horizon 2020 programme. It uses a well-established microsimulation model for cancer (MISCAN-Cervix) [38]. MISCAN-Cervix is a stochastic (which means that sequences of events are simulated by drawing from distributions of probabilities and durations instead of using fixed values, therefore, the outcomes of the model are subject to random variation), semi-Markov microsimulation model which is able to simulate the population of a country, including the development of cervical cancer [29]. The three main aims of MISCAN-Cervix are:

1. To quantify the long-term harms, benefits and costs of primary prevention and cervical cancer screening strategies.

2. To compare screening strategies, allowing the user to improve existing screening programmes as well advising countries on the effects of implementing a cervical cancer screening programme.

3. To quantify the effects of removing barriers to screening, which can be used to prioritize which barriers should be removed first.

2.1.2 Model description and assumptions

The program consists of three main parts which are demography, natural history and the screening.

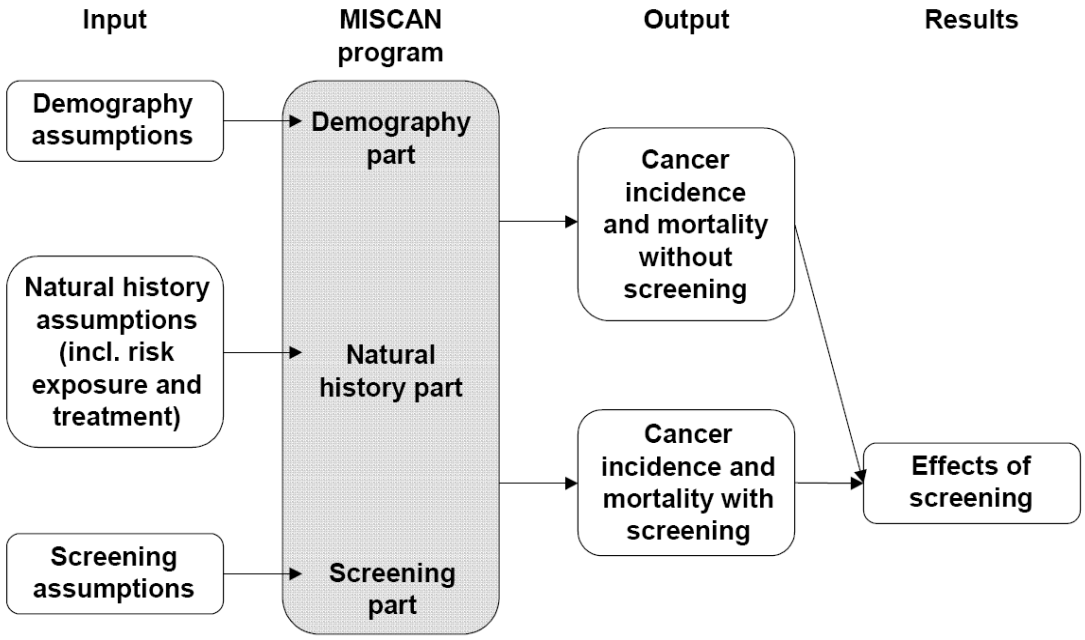

Figure 2. Basic structure of the MISCAN-Cervix model [29]

Demography assumptions: The following demography assumptions were made, which affect the characteristics of the population without the presence of cervical cancer [29].

- One cohort is simulated with one life table. All women are born at the same time but will die from cervical cancer or from other causes at different moments in time.
- In the model it is assumed that death from cervical cancer is independent from death from other causes. Whichever comes first determines the actual moment of death.

Natural history assumptions: Many characteristics of the natural history of cervical cancer cannot be observed because the disease starts to develop unnoticed. Once a diagnosis is made, it is in most cases unethical not to intervene. Therefore, assumptions have to made

about the natural history of cervical cancer. These assumptions are based on expert opinion or derived from observed data such as detection rates. [29].

Screening assumptions: Several assumptions have to be made regarding the performance of the screening tests, the consequences of colposcopy and the screening behaviour of the women [29].

Performance of the screening tests

- The probability of having a positive test result depends on the lesion grade and the HPV status of the woman for both cytology and the HPV-test.
- No differences in test characteristics are assumed for different HPV genotypes, both for cytology and the HPV-test.
- Systematic positive and systematic negative test results over time are possible for cytology for certain persons, infections or lesions.

Screening behaviour

- Women invited to screening can either attend or not attend the primary screening test. The probability to attend is dependent on age. If a woman attends, she will do so exactly at the invited age.

Colposcopy

- When a woman is referred to colposcopy, all prevalent CIN lesions will be diagnosed and removed/treated.
- Colposcopy is 100% accurate and will show the highest prevalent lesion.
- Women with a prevalent HPV infection but without a prevalent CIN will not be treated. The HPV infection may still progress to CIN after the colposcopy.
- As screen-detected cancers tend to have a better stage-specific survival than clinically detected cancers, detection of cervical cancer by screening in the model may prevent death from cervical cancer. However, if the death from cervical cancer is not prevented, the duration until death from cervical cancer will not be different from clinically detected cancers [29].

2.2 Study population

The study modelled the female population in Estonia, by age distribution, from 2018 to 2050 (population projection), using the base case scenario (i.e. the scenario based on current population trends).

2.3 Approval

In order to gain full access to this tool, permission was requested to the EU-TOPIA team for the author to be registered in October of 2019. Confirmation of approval was received via e-mail one month later in November. The cervical cancer model template, user guide and model description were downloaded, after the author had read and agreed to the end user license agreement. The process of data collection from different data sources started in December 2019.

2.4 Description of data requirements and sources

The cervical cancer data template for the tool (EU-TOPIA) consists of twenty-four tables with different categories and types of data requirements, which are further classified by level of importance; 'mandatory', 'should have' and 'non-mandatory'. The core set of tables labelled as mandatory is required for the model to run the simulations. These include Table0, eTable2, sTable1a, sTable1b and sTable2b. The tables labelled as 'should have' are eTable4, eTable6, sTable5 and sTable9. Other non-mandatory data improves the information generated by the model for the country, validates results and provides data for screening monitoring reports.

Data for modelling were obtained by the author from the following sources:

- Estonian Population Registry
- Estonian Cancer Registry
- Estonian Cancer Screening Registry
- Estonian Causes of Death Registry
- Human Mortality Database
- Website of Estonian Society of Gynaecologists

- Estonian vaccination website, Vaktsineeri
- Publications from scientific databases

The Estonian Population Registry was accessed via the website of Statistics Estonia while the other three registries; Estonian Cancer Registry, Estonian Cancer Screening Registry and the Estonian Causes of Death Registry were accessed through the National Institute for Health Development (Terevise Arengu Instituut – TAI) website. The Human Mortality Database was accessed via the website: 'http://www.mortality.org/' as provided in the user guide. The Estonian Society of Gynaecologists' website was accessed via 'https://emakakaelajuhis.weebly.com/'. Information about the implementation of HPV vaccination in the national immunization plan and type of HPV vaccine used (nonavalent gardasil 9) was obtained from the Terviseamet managed website: 'https://www.vaktsineeri.ee/en/diseases-and-vaccines/haigused/hpv' while scientific database searches were carried out using relevant keywords to access publications from PubMed and NordScreen.

2.4.1 Description of type and format of data by table

The tables are categorized and named in two parts based on the type of data: epidemiological data and screening programme related monitoring data. Demographic and epidemiological data tables are marked as "eTablex" while the screening data tables are marked "sTablex" where "x" represents different numbers from 1 to 9.

Table0 requires information about country, region and cancer site. Estonia, national data and cervical cancer were selected in this table, respectively.

eTable1 requires the 2018 female population age distribution and population projections up to 2050 separated by calendar year and five-year age groups. This information was obtained from the Estonian Population Registry using the base case scenario, which is based on the current population trends of the country.

eTable2 requires the number of incident cervical cancer cases and person years at risk over the most recent five-year period available. Incidence of cervical cancer cases (ICD-10: C53) from 2013 to 2017 by five-year age groups were gotten from the Estonian Cancer Registry while the population data for this period were obtained from the Estonian Population Registry.

eTable3 requires mortality due to cervical cancer data for the most recent five-year period available by five-year age groups. This information, number of deaths caused by cervical cancer (ICD-10: C53) from 2013 to 2017 was retrieved from the Estonian Causes of Death Registry. Population data for this period were retrieved from the Population Registry.

eTable4 requires 5-and-10-years relative survival observed in five most recent years by stage. The author made an advanced search in the PubMed database in January 2020. The search strategy included citations between 2010 and 2020 which are available in full free text and in English language. Keywords used for this search were: cervical cancer, relative survival, Estonia. As a result of the search, 3 articles were returned. The articles were screened by title and 2 of them were excluded, and a publication of 5 years relative survival rate 2010 to 2014 was found and used for this table. Relative survival rates from this publication which is reported in the TNM (Tumour Nodes Metastases) classification of malignant tumours staging system was translated into FIGO (International Federation of Gynaecology and Obstetrics) classification of malignant tumours staging by the author using the recommended website provided in the model user guide.

eTable5 requires the stage distribution of cervical cancer in the five most recent years and in FIGO staging format. Information required for this table was also found through database search. The author made a search in the PubMed database in January 2020. The search strategy included citations published in the last 10 years which are available in full free text and in English language. Keywords used for this search were: cervical cancer, stage distribution, Estonia. Two articles were returned and screened by title. A publication about the trends of cervical cancer incidence which had the number of cases reported by stage distribution using the TNM staging system was found and used for this table. Stage distribution in TNM staging system was translated into FIGO staging by the author.

eTable6 requires current, all-cause mortality rate for women by single ages from 0 to 100 years. Age-specific mortality rates data was obtained from the Human Mortality Database, using Estonia's life tables as recommended in the EU-TOPIA MISCAN-Cervix user guide. The Human Mortality Database was assessed via the website: 'http://www.mortality.org/' as provided in the user guide.

eTable9 requires information about the sexual behaviour of Estonian men and women separated by sex. Data about the average age of sexual debut was found via the website of Estonian Society of Gynaecologists.

sTable1a requires the characteristics of the organized screening programme on screening test, ages, interval, invitation protocol and roll-out. Information about the screening protocol, target population, screening interval, invitation protocol, start date of screening programme, roll-out completion status and year of roll-out completion of the Estonian cervical cancer screening programme was obtained from the cervix-fact-sheet-Estonia-2017 from the NordScreen database.

sTable1b requires the index year (most recent calendar year for which complete data are available- 2016 at latest) of screening data and the size of the target population in absolute numbers and separated by five-year age groups. The data for cervical cancer screening target population in the year 2016 was used in filling this table. This information was retrieved from a data table in the Estonian Cancer Screening Registry and is coded VSR11.

sTable2a requires data on actual number of invitations and participation in the organized screening programme in absolute numbers and separated by five-year age groups. Data about the number of women invited, and the number of women screened out of invited both in 2016 and in the most recent round as defined in the template, were extracted from the data tables in the Estonian Cancer Screening Registry coded VSR12, VSR13 and VSR14.

sTable2b requires data on the number of women eligible for screening and screening coverage in absolute numbers, separated by five-year age groups in the most recent screening round and during the years 2003 to 2007. Organized cervical cancer screening started in Estonia in 2006 and the Estonian Cancer Screening Registry was established in 2015, therefore the data required for this time period is unavailable. However, recommendations (use of alternative data or estimates derived from period when data is available) from user guide on troubleshooting this problem was applied. Available data from the screening registry data set coded VSR12 were used.

sTable3 to sTable9 requires more detailed and specific data which are unavailable in the screening registry. This information includes screening history and treatment data. An

example is “the number of women personally invited in 2016 for the first time”. Information about initial and subsequent screening are unavailable from the registers. Other inaccessible data were data about, triage testing, participations in colposcopy, histology, treatment and staging of detected lesions. An overview of each of these data tables are shown in Table 1. These are however non-mandatory tables, which are not obligatory for running a simulation on the model. They are important for improving the information generated by the model for the country and were substituted with respective data from the exemplary country (Finland) for Northern European region in which Estonia was categorized according to the user guide. More details about the exemplary country are explained in section 3.5 of this chapter. Disease data about high risk HPV prevalence and type distribution among Estonian women, required for eTable7 and eTable8 were searched and found from databases but the format in which they were presented in the publications were incompatible with the EU-TOPIA format. These are also non-mandatory tables.

sTable8b and sTable8c are not applicable to Estonia’s organized screening because information about co-testing and HPV as a stand-alone primary test is required whereas, the country’s current primary test method is conventional cytology.

Table 1. Overview of all data requirements and sources for the EU-TOPIA evaluation tool [38]

Table name	Brief description	Data sources
Table 0*	Country data	Author
eTable1	Population size by year and five-year age group	Estonian Population Registry
eTable2*	Cancer Incidence for the five most recent years available by 5-year age group	Estonian Cancer Registry, Population Registry
eTable3	Mortality for the five most recent years available by 5-year age group	Estonian Causes of Death Registry, Population Registry
eTable4	Relative survival by stage	PubMed database/Finland
eTable5	Stage distribution	PubMed database
eTable6	All-cause mortality by age	Human Mortality Database
eTable7	hrHPV prevalence by 5-year age group	N/A
eTable8	hrHPV type distribution in women by age	N/A
eTable9	Sexual behaviour	Estonian Society of Gynaecologists' website
sTable1a*	Current screening programme characteristics	NordScreen database
sTable1b*	Index year and target population	Estonian Cancer Screening Registry
sTable2a	Screening invitations and participation	Estonian Cancer Screening Registry
sTable2b*	Screening coverage including opportunistic screening	Estonian Cancer Screening Registry
sTable3	Screening invitations and screening tests by Screening History	N/A
sTable4	Further assessment indication after a primary test	N/A
sTable5	Participation in colposcopy after referral	Finland
sTable6a	Histology outcome (highest diagnosis per women)	N/A
sTable6b	Treatment of detected lesions	N/A
sTable7	Stages of screen detected cancers	N/A
sTable8a	Interval cancers (in case of cytology)	N/A
sTable8b	Interval cancers (in case of HPV + cytology)	N/A
sTable8c	Interval cancers (in case of standalone HPV)	N/A
sTable9	Triage (in case of cytology)	Finland

*=Mandatory tables

hrHPV=High-risk human papillomavirus

N/A=Not applicable

2.5 Data quality check

After the submission of data in the tool, automatic checks on data quality and completeness, was carried out by the web-based tool to ensure that the inputs are within a reasonable range and in the correct formats. For situations where data provided by the author were either incomplete or unavailable in the non-mandatory tables, respective data from the exemplary country (Finland) were used. If the data quality uploaded for mandatory tables are low or insufficient, such data will be rejected.

Exemplary country: The overall aim of the EU-TOPIA project is to improve existing cancer screening programmes in Europe. It was developed to allow European policymakers and researchers to simulate outcomes of multiple cancer strategies for their own country. Thus, requiring users to upload specific demographic and screening data for their own country [38]. Because the values of the calibrated parameters might differ across Europe, four different models were calibrated for the tool.

From each European region, an exemplary country with high quality data was selected to be representative for that region (Finland for Northern Europe, The Netherlands for Western Europe, Slovenia for Eastern Europe and Italy for Southern Europe) [29]. Based on the country selected in Table0 which is Estonia, Northern Europe is assigned because Estonia is categorized under Northern Europe alongside Denmark, Faroe Islands, Iceland, Latvia, Lithuania, Norway and Sweden [38]. Therefore, model parameters from the exemplary country which in the case of this research is Finland is used, where 'non-mandatory' data but 'should have' tables are not available. These include: eTable4, sTable5 and sTable9.

2.6 Simulation process

The tool allows users to be able to change the screening test, target age, screening interval, adherence, HPV vaccination coverage and HPV types included in vaccine, to create a maximum of five scenarios in one simulation. The author simulated two sets of five comparative scenarios each, one without vaccination and the other with 70% vaccination coverage assumption.

Selection of screening scenarios – In the first set of scenarios simulated, the current screening method which is cytology with HPV triage is compared with four others:

cytology with co-testing triage, HPV-test with cytology triage, HPV-test with co-testing triage and co-testing with co-testing triage as shown in Table 2. Same values were selected for other parameters which were target age, screening interval, adherence and vaccination coverage. Simulation was submitted for processing; the author was notified by e-mail as soon as simulation was finished, and the results were downloaded.

Table 2. Screening strategies without vaccination

Scenario	Screening test	Target age (years)	Screening interval	Adherence	Vaccination coverage	HPV types included in vaccine
1	Cytology with HPV triage	30-60	5 years	Current adherence*	0% coverage	No vaccination
2	Cytology with co-testing triage	30-60	5 years	Current adherence*	0% coverage	No vaccination
3	HPV-test with cytology triage	30-60	5 years	Current adherence*	0% coverage	No vaccination
4	HPV-test with co-testing triage	30-60	5 years	Current adherence*	0% coverage	No vaccination
5	Co-testing with co-testing triage	30-60	5 years	Current adherence*	0% coverage	No vaccination

Scenario 1 is defined based on the current screening in Estonia

*Current adherence by age group: **20-24** 45.4%, **25-29** 45.4%, **30-34** 45.4%, **35-39** 45.9%, **40-44** 46.4%, **45-49** 46.7%, **50-54** 47.5%, **55-59** 44.2%, **60-64** 44.2%, **65-69** 44.2%, **70-74** 44.2%, **75-79** 44.2%.

The second set of scenarios/screening strategies shown in Table 3 was selected based on the methods which performed best in the first scenario, guideline recommendations on target age and screening interval, and previous literature. Information about the implementation of HPV vaccination in the national immunization plan and type of HPV vaccine used (nonavalent gardasil 9) [39] was obtained from the Terviseamet managed website: www.vaktsineeri.ee. Further details about the selection are discussed in chapters four and five.

Table 3. Screening strategies with vaccination

Scenario	Screening test	Target age (years)	Screening interval	Adherence	Vaccination coverage	HPV types included in vaccine
1	Cytology with HPV triage	30-60	5 years	Increase of 30%	70% girls only	HPV16/18/31/33/45/52/58
2	Cytology with HPV triage	25-65	3 years	Increase of 30%	70% girls only	HPV16/18/31/33/45/52/58
3	HPV-test with HPV triage	30-65	5 years	Increase of 30%	70% girls only	HPV16/18/31/33/45/52/58
4	HPV-test with co-testing triage	30-65	5 years	Increase of 30%	70% girls only	HPV16/18/31/33/45/52/58
5	Co-testing with co-testing triage	30-65	5 years	Increase of 30%	70% girls only	HPV16/18/31/33/45/52/58

3 Results

This chapter presents the results of the simulation of two sets of five comparative scenarios. The first set of scenarios analysed without vaccination correspond to the current situation in Estonian cervical cancer screening programme. The purpose of this simulation is to make a comparison between different screening methods, to identify the strategies which will give the most benefits (lowest incidence and mortalities caused by cervical cancer) and cause the least harm. The second simulation assumes a vaccination coverage of 70% with nonavalent HPV vaccine (gardasil 9) that is recently implemented in Estonian national immunization plan. The second simulation aims to analyse the impact of vaccination on screening strategies. Results are presented using tables and figures to illustrate the comparison of different cervical cancer screening strategies and the impact of vaccination between vaccinated and unvaccinated cohorts.

3.1 Simulation outcomes in unvaccinated cohort

The simulation modelled five different screening methods which are: cytology with HPV triage (current screening method in Estonia), cytology with co-testing triage, HPV-test with cytology triage, HPV-test with co-testing triage and co-testing with co-testing triage. Same options were selected for all other parameters in this simulation which are: target age (30-60 years), screening interval (5 years), adherence (shown Table 2 of the previous chapter) and vaccine coverage (no vaccination).

3.1.1 Benefits outcomes

As shown in the Figure 3, co-testing with co-testing triage and HPV-test with co-testing triage have a similar performance. Detailed results from simulation showed that both strategies were most effective in reducing the incidence and mortality rates of cervical cancer. Both strategies have a higher mortality reduction percentage (58.6% and 57.4% respectively) when compared to a no screening scenario.

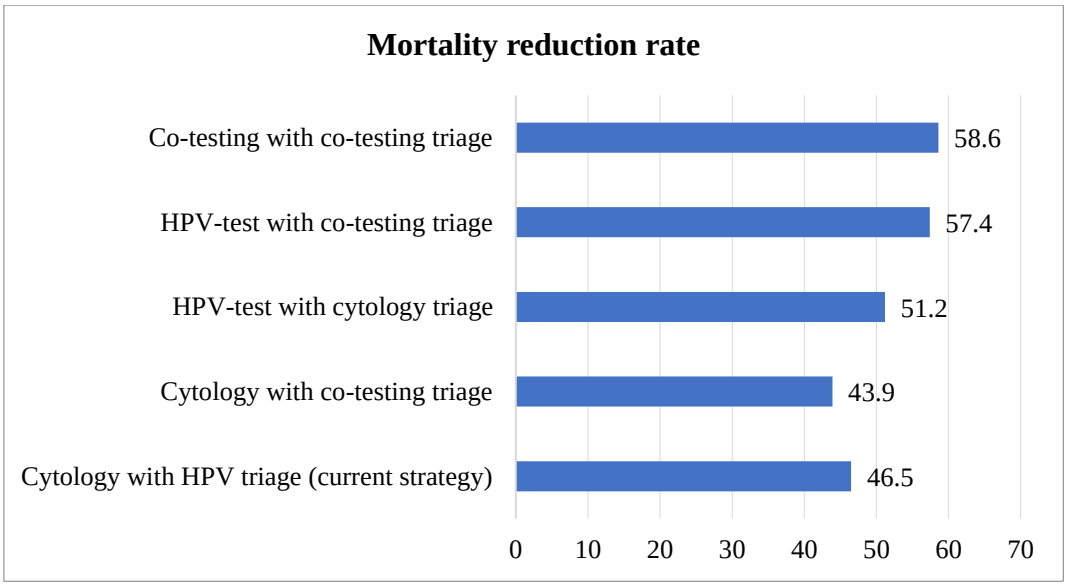

Figure 3. Mortality reduction rate in unvaccinated cohort when compared with no screening by strategy

3.1.2 Harm outcomes

In this study, co-testing with co-testing triage, and HPV-test with co-testing triage had the highest number of overdiagnosed cases per 100,000 women and in the same pattern both strategies also had the highest number of false positive tests. Number of false positives tests was estimated using the simulation outcome of number of women referred to colposcopy without CIN1+. HPV-test with cytology triage has a mortality reduction rate of 51.2 %. Overdiagnosis and false positives are lower with this strategy when compared with co-testing with the two strategies with higher mortality reduction rates (co-testing triage and HPV-test with co-testing triage). However, it requires more triage tests.

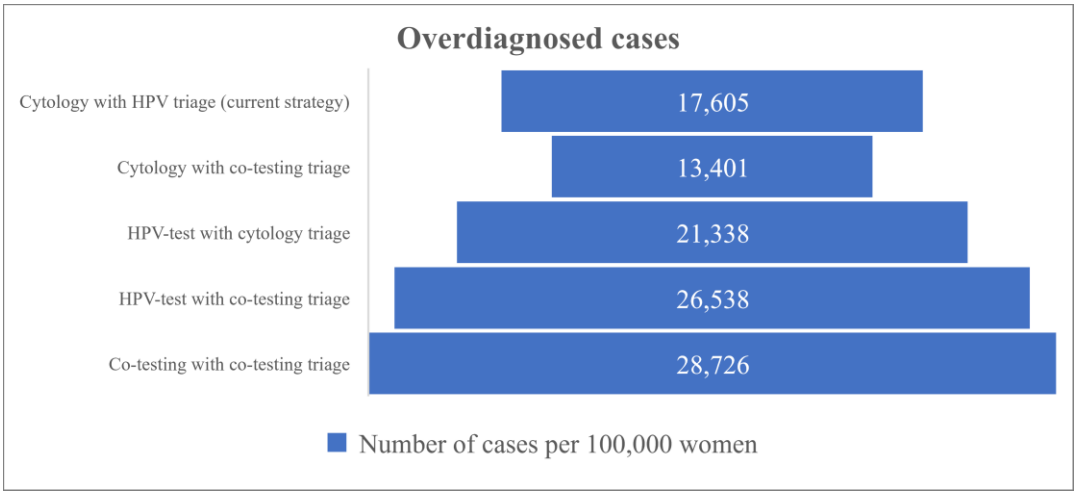

Figure 4. Number of overdiagnosed cases per 100,000 women by strategy

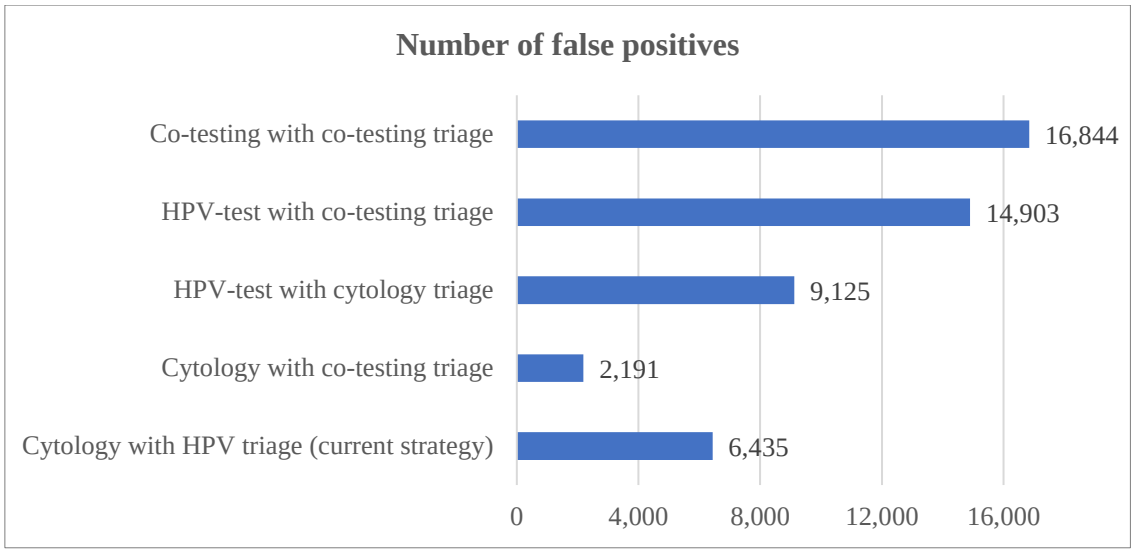

Figure 5. Number of false positives per 100,000 women by strategy

3.1.3 Additional investigations needed

The number of primary tests across all five strategies are almost the same, while the triage tests show a different trend. Tests increased the most in the HPV-test based strategies. Cytology-based test numbers are lower while co-testing with co-testing triage falls within the mid-range.

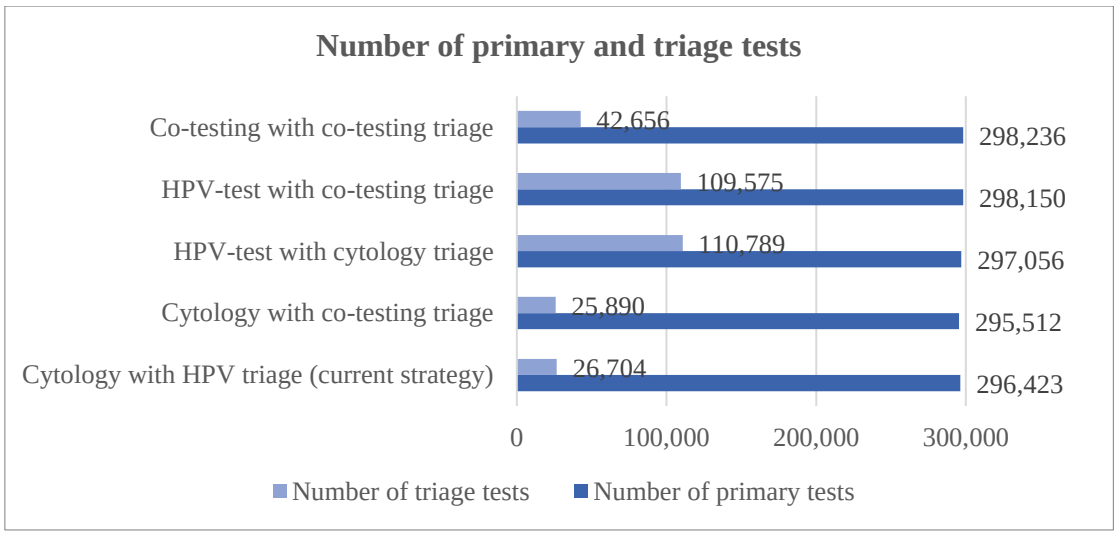

Figure 6. Number of primary and triage tests per 100,000 women by strategy

Co-testing strategy had the highest number of colposcopy referrals when compared to others as shown in Figure 7. This is nearly double the number of colposcopy referrals in the current strategy. An additional 21,957 colposcopy referrals will be needed if co-testing is employed as primary testing method and 6,611 if HPV-test with cytology triage used.

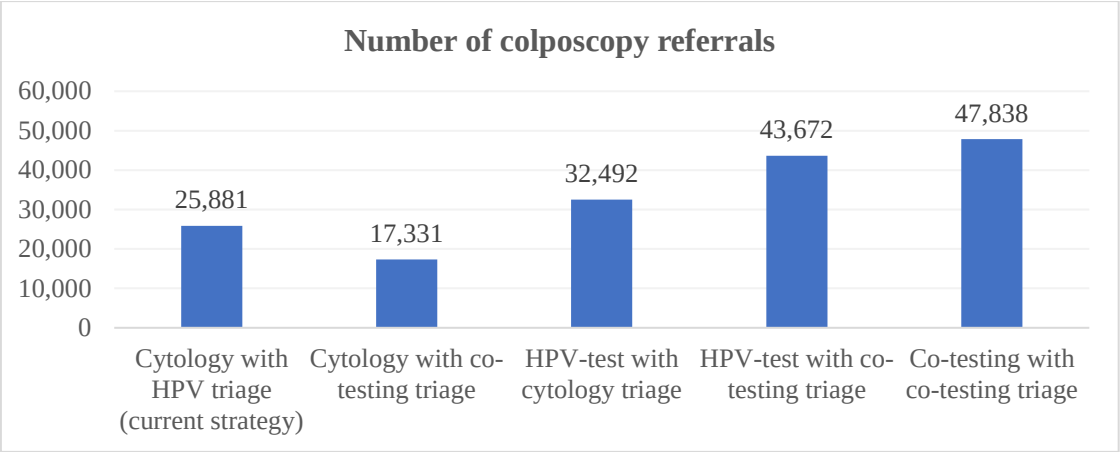

Figure 7. Number of colposcopy referrals per 100,000 women by strategy

3.1.4 Optimal strategy

Co-testing as primary test had a higher mortality reduction rate (benefit) when compared with the current cytology-based screening. However, co-testing had the highest number of colposcopy referrals, primary tests and overdiagnosed cases (harm). Findings from this study in accordance with recommendations from guidelines on weighing the benefits and harms of screening, shows that HPV-test with cytology triage in the 30 to 60 years age group is the most efficient strategy to save more life-years with less harms. The number of overdiagnosed cases and false positives are lower with this strategy when compared with strategies having higher mortality reduction rates in the simulation of unvaccinated cohort. However, it requires more triage tests.

Table 4. Results summary

Outcomes	**Strategies**
Benefits	
Reduces the most deaths and incidence	Co-testing with co-testing triage
Detection of lesions CIN3 and adenocarcinoma in situ	Co-testing with co-testing triage
Harm	
Highest number of false positives, overdiagnosis and colposcopy referrals	Co-testing with co-testing triage
Requires the most additional tests and investigations	
Highest number of primary tests	Co-testing with co-testing triage
Highest number of triage tests	HPV-test with cytology triage
Optimal strategy	HPV-test with cytology triage

3.2 Simulation outcomes in vaccinated cohort

In order to investigate the impact of vaccination on future screening practices, the effect of 70% coverage of nonavalent HPV vaccines was modelled in the second simulation of this study. Adherence was increase with 30% higher than the first simulation. In 2018, vaccination against HPV became implemented in the Estonian national immunization plan and was offered free of charge to girls aged from 12 to 14. As of 2020, it is being offered to girls aged 12 years. This scenario was simulated with an assumption of 70% coverage as demonstrated by previous research [50] and compared with the current screening without vaccination. Four other strategies were simulated with different combinations of primary test methods, target age and screening intervals. Combinations were guided by recommendations from guidelines. For instance, HPV-based strategies were not simulated in women below 30 years of age due to the high possibility of HPV clearing up or becoming undetectable within two years of infection [31]. Instead, cytology-based strategy was used. Two strategies which had the highest mortality reduction rates from the previous simulation, co-testing with co-testing triage and HPV-test with co-testing triage were again simulated with increased target age range by five years, adherence and vaccination to examine the effect of increased participation and vaccination. As shown in Figure 8 there is an increase in the mortality reduction rates compared to the scenarios with no vaccination. When the screening interval of cytology with HPV triage was increased to 3 years and target age extended to 25 to 65years in this simulation, the outcome was improved, and mortality reduction rate increased to 74.3 percent from 58.5%.

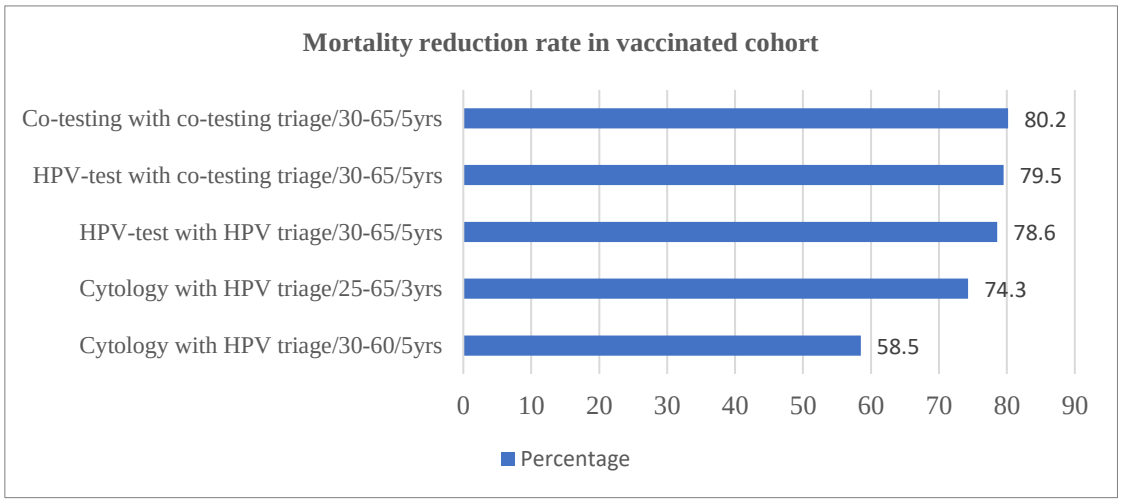

Figure 8. Mortality reduction rate when compared to no screening in vaccinated cohort by strategy

Table 5 shows comparison between the results of simulations of the current strategies. One in unvaccinated cohort and the other in vaccinated cohort. The purpose of this comparison is to show the impact of vaccination and adherence on incidence and mortality rates and also to give an insight on the number of additional tests and investigations, colposcopy referrals when adherence is increased. There was a 12% increase in mortality reduction and the need for a total of 195,945 additional primary tests. The triage tests were fairly similar, while the number of colposcopy referrals reduced by 6,328.

Table 5. Comparison to show the impact of vaccination and adherence between vaccinated and unvaccinated cohort

Outcomes per 100,000 women simulated	**Current strategy**	**Current strategy with vaccination and 30% increase in adherence**
Mortality reduction (%) **	46.5	58.5
Number of primary tests	296,423	492,368
Number of triage tests	26,704	26,413
Number of colposcopy referrals	25,881	19,553
False positives	6,435	6,633
Number of overdiagnosed cases	17,605	12,190

** percentage reduction due to screening compared to a no screening scenario with the same vaccination coverage

4 Discussion

This section explains the analysis and interpretation of the results of the simulations. The results are compared with previous studies while study limitations and recommendations are discussed at the end of the chapter.

A screening programme is only effective when evidence-based efficient screening strategies exist. The effectiveness of a programme in achieving health gains is largely dependent upon the interaction of many elements within and outside the health system, such as an accurate register identifying the target population and a strategy to ensure and monitor follow up. In all cancer screening programmes it is necessary to specify the type of primary screening test, triage test, the age at which people should first be invited for the test, the age at which they should no longer be invited and screening frequency. The combination of these parameters all defines the efficacy of the screening strategy of the programme. In screening for cervical cancer, the primary test can either be cytology (checking for abnormal cells), HPV-test (checking for the presence of high risk-HPV) or a co-test, which is a combination of both. An optimal strategy for cervical cancer screening would have a high sensitivity to minimize the possibility of missing the disease and provide maximum specificity to reduce the number of false positive results and over referrals. Regrettably, strategies that maximize sensitivity usually have quite poor specificity [34].

Different screening strategies were compared in order to determine the best strategy for cervical cancer in this study. Comparison of screening strategies can be achieved through randomized trials. However, setting up large trials is expensive and need a long follow-up time. Also, the outcomes of such trials will be dependent on several factors, which might be different across countries and the results might not be applicable to another country [10]. Simulation modelling approach provides an infrastructure for testing different screening methods and different target groups, but it can be done quickly and efficiently. Simulation modelling allows the comparative analysis of population-based

screening models to answer important policy-based questions, the flexibility of changing risk factor profiles of the population, new screening modalities, treatment regimens. Also, simulation modelling gives access to data on full range of the benefits, harms and costs of the interventions [9].

The EU-TOPIA evaluation tool is a modelling web-based tool developed to allow users simulate outcomes of several cancer screening strategies. EU-TOPIA development was funded by the European Union (EU) Commission's Horizon 2020 programme. It uses a well-established microsimulation model for cancer (MISCAN-Cervix) [38]. MISCAN-Cervix is a stochastic semi-Markov microsimulation model (which means that sequences of events are simulated by drawing from distributions of probabilities and durations instead of using fixed values the outcomes of the model are subject to random variation) [29]. The MISCAN-Cervix was developed in the 1970s at the Department of Public Health of Erasmus MC, University Medical Centre Rotterdam and was designed for evaluating the effect of cancer screening [38]. It simulates individual life histories and assesses the consequences of introducing a screening programme on these life histories. In these simulations, different screening strategies can be applied to quantify the effects of screening on the population. Because the population characteristics in the model and their background risk for cervical cancer can be tailored to those of a specific country, it is possible to make country specific estimations of costs and effects for different screening strategies [29].

Even though the use of this tool is inexpensive when compared to setting up trials for evaluating screenings strategies, the availability of good quality medical data is highly important to effectively use this tool. It requires very specific and detailed screening and treatment data to run simulations and improve the information generated by the model. This can be challenging for countries that lack good health information systems. While collecting data for this research, we observed that a lot of information is missing from the Estonian Cancer Screening Registry. High quality data input is crucial for monitoring and evaluating the quality and effectiveness of screening. Hence, the need for hospitals and other health service providers to embrace timely submission of data to the central systems and databases is paramount.

Results from this study showed that co-testing as primary test screening for women aged 30 to 60 years is the most beneficial in reducing incidence and mortality because it has the highest mortality reduction rate (58.6%) when each strategy is compared with a no screening scenario. Our findings confirm data from earlier studies [31]. The same strategy also detected the highest number of lesions; however, it required the most colposcopies. Ideally, screening tests should efficiently and accurately identify women with precancer condition who are at significant risk for developing cancer and appropriate intervention will prevent progression to invasive cancers. Detection of CIN3 was used as the measure of a test's sensitivity for precancer condition because a substantial proportion of women with CIN3 would develop invasive cervical cancer if left untreated [42]. Similarly, two other strategies based on HPV primary screening test also had more than 50% mortality reduction rate. This is also consistent with a previous recent study which concluded that HPV-test based screening can improve the effectiveness of the cervical cancer screening programme in Estonia when compared with cytology [37]. In 2017, Australia transitioned from cytology-based screening to an HPV primary screening. The screening is performed every five years for women aged 25 to 69 years with partial genotyping for HPV types 16 and 18 and liquid-based cytology triage for other HPV types [43]. A 2019 modelling study used the Policy1-Cervix (a validated dynamic model) to model the effect of the transition to primary HPV screening in Australia. The results demonstrated that by 2066 the annual incidence of cervical cancer will decrease and remain at fewer than one case per 100,000 women if screening for HPV continues every five years for cohorts who have been offered nonavalent vaccine or fewer than three cases per 100,000 if these cohorts are not screened [44]. Large-scale randomized trials also suggest that primary HPV-based screening is more effective when compared with cytology-based screening and support its introduction from the age of 30 years and the extension of screening intervals to at least five years [45].

Harm from screening is unintended and unavoidable. It encompasses all the possible adverse effects of the entire screening pathway [46] which can result from the complications of a screening test, further investigations or the non-justified treatments. Examples of such effects include overdiagnosis, false positives, false negatives and diversion of health resources. Overdiagnosis identifies a condition that would never cause a person harm during their lifetime [49]. Overtreatment which means that additional extensive or invasive treatment can occur alongside overdiagnosis. In this study, co-

testing with co-testing triage, and HPV-test with co-testing triage had the highest number of overdiagnosed cases per 100,000 women and in the same pattern both strategies also had the highest number of false positive tests. Most HPV infections are transient and asymptomatic with more than 90% of new HPV infections including those caused by high-risk HPV types, clearing up or becoming undetectable within two years [47]. After a positive screen by cytology or by different combinations of cytology and HPV screening methods, colposcopy referrals are made for a diagnostic evaluation and biopsy of evident lesions in cervical screening programmes [48]. Interestingly, colposcopy may produce also harm. In the first place, there are potential harms associated with detecting these transient lesions. The problems may include anxiety associated with a "positive" cancer screening test, potential stigmatization from the diagnosis of a sexually transmitted infection, discomfort from additional diagnostic and treatment procedures, bleeding from treatment and longer term, an increased risk of pregnancy complications such as preterm delivery due to treatment [49]. Consequently, the American Cancer Society cervical cancer screening guidelines indeed used the number of colposcopies as the primary measure of harm [31]. It is important to note that it was specifically stated in the guidelines' publication that financial costs were not taken into consideration in making recommendations. Benefits associated with the expenditure of health resources on screening programmes rather than treatments must be justifiable. Obviously, benefits should outweigh the harms and resources should be allocated in right proportion to the need [23].

4.1 Study limitations

As with any modelling study, the findings presented from this research is dependent on the assumptions made. Such assumptions include the 30% increase in adherence and 70% vaccinations coverage in the second simulation (vaccinated cohort). However, these assumptions are informed by guidelines and previous literature. If a higher coverage will be achieved in reality, then the effect of vaccination in reducing the incidence and mortality of cervical cancer might have been underestimated.

Secondly, the EU-TOPIA evaluation tool used in this study has a limited number (seven) of sets of predefined cervical screening strategies which were combined differently in this research. If there were more, the combinations made by the author could differ slightly.

Also, for the current screening strategy in Estonia, the target age is 30 to 59 years, this age option is not available in the options from the tool. The author however selected the closest option of 30 to 60 years, due to the fact that the protective effect of the last screen at 55 years lasts up to 60 years.

Another limitation was the inability to find certain screening and treatment information from the Estonian Cancer Registry and Estonian Cancer Screening Registry due to the incompleteness or unavailability of data. It was however replaced with data from Finland as recommended in the user guide of the tool.

4.2 Recommendations

The quality and completeness of data reported in screening registers needs improvement. IT systems should be upgraded to facilitate a better link and communication of statistical data between databases and registers such as the screening registers and the Estonian National Health Information Systems, while maintaining patient information privacy and confidentiality.

Finally, there is a need for further research on the cost-effectiveness analysis of HPV-based screening tests and co-testing strategies in Estonia, as new evidence such as in randomized trials about the potential benefits of these strategies are beginning to emerge. The author made a database search and found only one modelling cost-effectiveness study about this topic. Although the study acknowledges the potential of HPV-based test screenings, detailed information about the strategies compared were unknown because the author could not access the full text of this publication.

5 Summary

Emerging technologies such as screening tests and prophylactic vaccines provide opportunities for innovative and efficient cancer screening programmes, however decision making for policymakers becomes challenging due to the complex and long natural history of the disease and the various time points along the disease spectrum at which interventions are applied [41]. The aim of this thesis is to compare different cervical cancer screening strategies using a web-based tool (EU-TOPIA) to determine best possible solutions to improve the current screening programme.

The natural history of cervical cancer was modelled in a projected population of Estonian females from 2018 up to the year 2050 to analyse and compare the outcomes of modelling different screening strategies. A total of nine different combinations of cervical cancer screening strategies based on primary screening test, target age and screening interval were simulated and compared to the current screening standard (cytology with HPV-test triage).

Comparison was made using two different types of simulations in our analysis. One simulation without and the other with vaccination. According to our data, an increase in the mortality reduction rates was observed in the simulation with vaccination when compared to the simulation with no vaccination. Co-testing as primary test had a higher mortality reduction rate (benefit) when compared with the current cytology-based screening. However, co-testing had the highest number of colposcopy referrals, false positives, overdiagnosed cases (harms).

In conclusion, findings from this study in accordance with recommendations from guidelines on weighing the benefits and harms of screening, shows that HPV-test with cytology triage in the 30 to 60 years age group is the optimal strategy to save more life-years with less harms. The number of overdiagnosed cases and false positives are lower with this strategy when compared with strategies having higher mortality reduction rates in the simulation of unvaccinated cohort. However, it requires more triage tests.

Simulation modelling approach provides an infrastructure for making comparative analysis quickly and efficiently and should be encouraged in making health care policy decisions. Asides being inexpensive, studies have reported that screening sensitivities generated from simulations show a reasonable range of variations when compared with randomized trials suggesting that models can accurately represent the effects of screening. However, to achieve reliable model outcomes such as with using the EU-TOPIA tool, the availability of good quality medical data is highly important. High quality data input is crucial for monitoring and evaluating the quality and effectiveness of screening. Hence, the need for hospitals and other health service providers to embrace timely submission of data to the central systems and databases is paramount.

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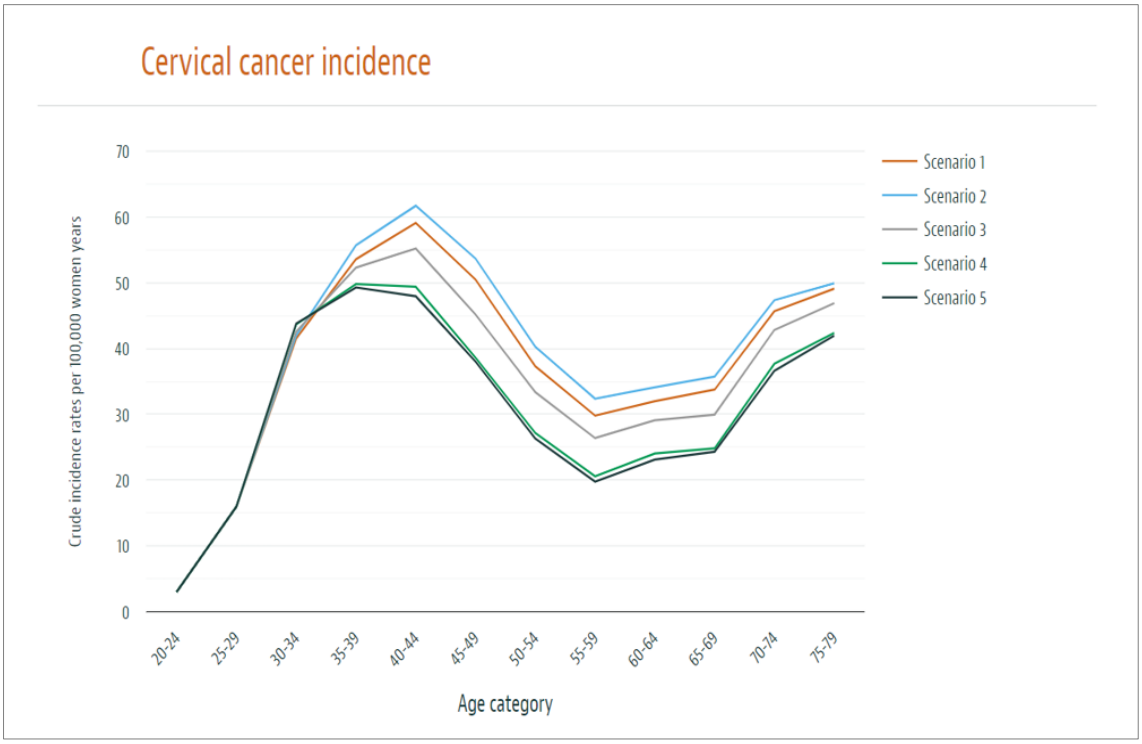
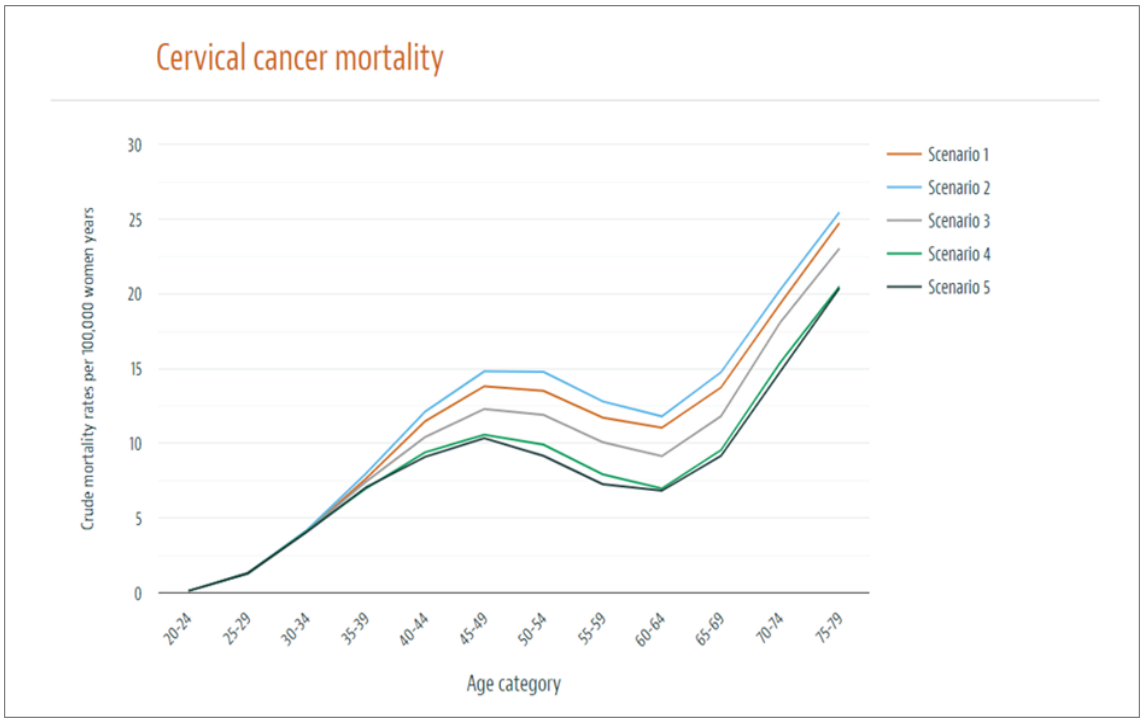
Appendix 1 – Result figures



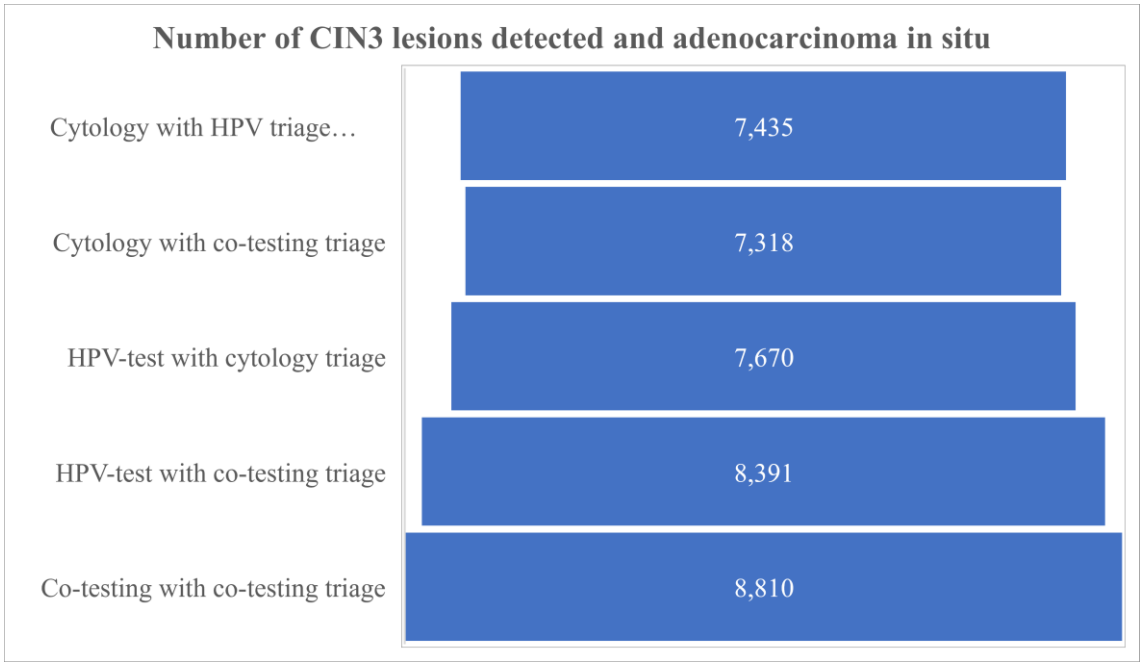
Cervical cancer incidence in unvaccinated cohort

Scenario 1-Cytology with HPV triage **Scenario 2**-Cytology with co-testing triage **Scenario 3**-HPV-test with cytology triage **Scenario 4**-HPV-test with co-testing triage **Scenario 5**-Co-testing with co-testing triage



Cervical cancer mortality in unvaccinated cohort

Scenario 1-Cytology with HPV triage **Scenario 2**-Cytology with co-testing triage **Scenario 3**-HPV-test with cytology triage **Scenario 4**-HPV-test with co-testing triage **Scenario 5**-Co-testing with co-testing triage



Number of CIN3 lesions detected and adenocarcinoma in situ per 100,000 women by strategy

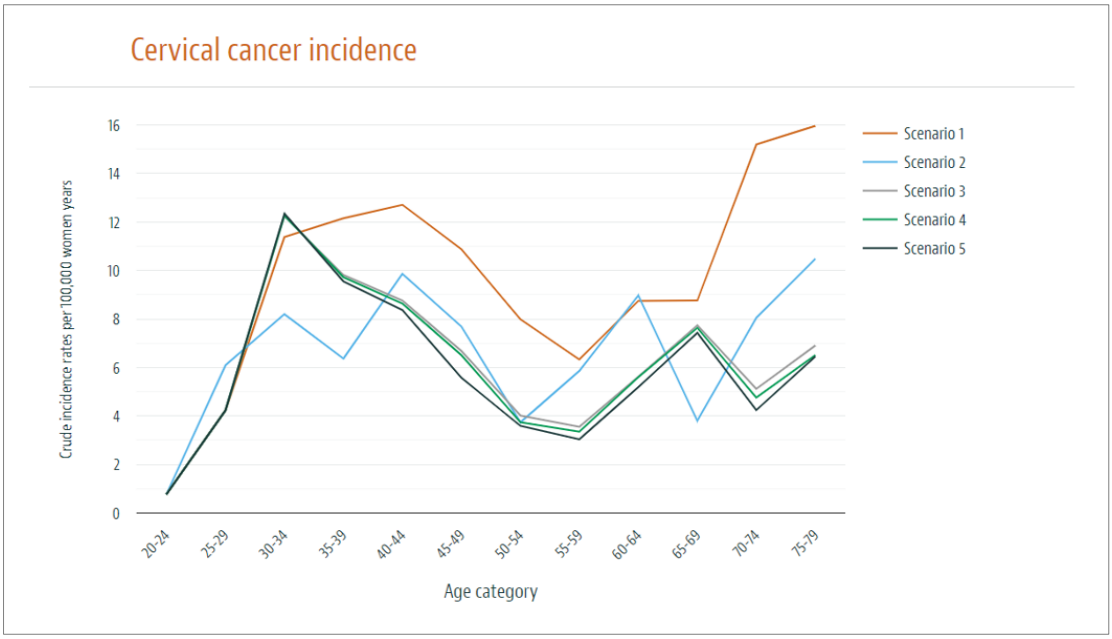
Results in unvaccinated cohort

Outcomes per 100,000 women simulated	**Cytology with HPV triage**	**Cytology with co-testing triage**	**HPV-test with cytology triage**	**HPV-test with co-testing triage**	**Co-testing with co-testing triage**
Number of primary tests	296,423	295,512	297,056	298,150	298,236
Number of triage tests	26,704	25,890	110,789	109,575	42,656
Number of colposcopy referrals	25,881	17,331	32,492	43,672	47,838
Number of women referred to colposcopy without CIN1+	6,435	2,191	9,125	14,903	16,844
Number of lesions detected CIN1	6,643	3,545	8,918	11,535	12,793
Number of lesions detected CIN2	4,813	3,727	6,176	8,258	8,804
Number of lesions detected CIN3 + AIS	7,435	7,318	7,670	8,391	8,810
Number of lesions detected CC	2,320	2,417	2,180	1,959	1,925
Number of overdiagnosed cases*	17,605	13,401	21,338	26,538	28,726
Number of cervical cancer deaths	729	766	666	581	565
Cervical cancer mortality reduction due to screening (%) **	46.5	43.9	51.2	57.4	58.6
Number of tests needed to prevent 1 CC incidence	251	270	286	248	203
Number of tests needed to prevent 1 CC death	509	537	584	520	426
Number of colposcopy referrals needed to prevent 1 CC incidence	20	15	23	27	28
Number of colposcopy referrals needed to prevent 1 CC death	41	29	47	56	60

CC = cervical cancer CIN = cervical intraepithelial neoplasia AIS = adeno in situ

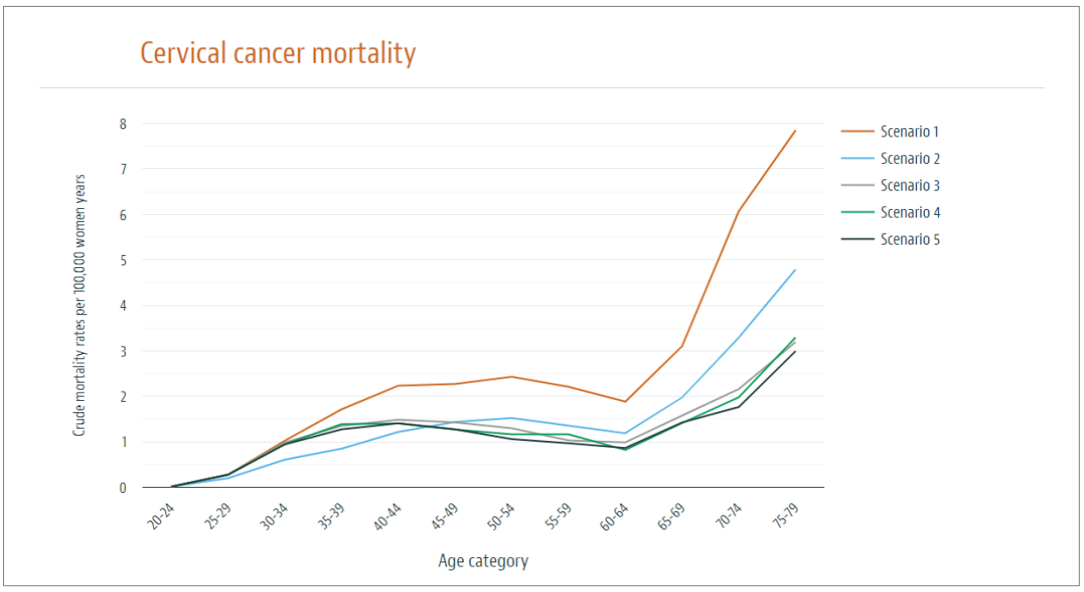
* Overdiagnosis is defined as the extra number of diagnosed cases of CIN1+ due to screening, compared with a no screening scenario [40]

** percentage reduction due to screening compared to a no screening scenario



Cervical cancer incidence in vaccinated cohort

Scenario 1-Cytology with HPV triage, 30-60 years, 5 years interval **Scenario 2**-Cytology with HPV triage, 25-65years, 3 years interval **Scenario 3**-HPV-test with HPV triage, 30-65 years, 5 years interval **Scenario 4**-HPV-test with co-testing triage, 30-65 years, 5 years interval **Scenario 5**-Co-testing with co-testing triage, 30-65 years, 5 years interval



Cervical cancer mortality in vaccinated cohort

Scenario 1-Cytology with HPV triage, 30-60 years, 5 years interval **Scenario 2**-Cytology with HPV triage, 25-65years, 3 years interval **Scenario 3**-HPV-test with HPV triage, 30-65 years, 5 years interval **Scenario 4**-HPV-test with co-testing triage, 30-65 years, 5 years interval **Scenario 5**-Co-testing with co-testing triage, 30-65 years, 5 years interval

Results in vaccinated cohort

Outcomes per 100,000 women simulated	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Number of primary tests	492,368	987,217	554,911	555,161	555,944
Number of triage tests	26,413	57,185	106,027	105,984	46,524
Number of colposcopy referrals	19,553	39,646	33,832	35,430	41,545
Number of women referred to colposcopy without CIN1+	6,633	16,813	14,572	15,545	18,772
Number of lesions detected CIN1	5,704	12,145	9,832	10,389	12,045
Number of lesions detected CIN2	3,202	5,684	5,311	5,369	6,015
Number of lesions detected CIN3 + AIS	3,826	4,807	3,924	3,935	4,526
Number of lesions detected CC	606	427	396	387	372
Number of overdiagnosed cases*	12,190	21,916	18,316	18,934	21,811
Number of cervical cancer deaths	181	112	93	89	86
Cervical cancer mortality reduction due to screening (%) **	58.5	74.3	78.6	79.5	80.2
Number of tests needed to prevent 1 CC incidence	958	1,450	880	870	777
Number of tests needed to prevent 1 CC death	2,039	3,233	1,933	1,912	1,726
Number of colposcopy referrals needed to prevent 1 CC incidence	36	55	45	47	54
Number of colposcopy referrals needed to prevent 1 CC death	77	123	99	102	119

CC = cervical cancer CIN = cervical intraepithelial neoplasia AIS = adeno in situ

* Overdiagnosis is defined as the extra number of diagnosed cases of CIN1+ due to screening, compared with a no screening scenario [40]

** percentage reduction due to screening compared to a no screening scenario