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ABBREVIATIONS

APC	annual percent change
BRCA 1	tumor suppressor gene, Breast Cancer gene 1
BRCA 2	tumor suppressor gene, Breast Cancer gene 2
CI	Confidence interval
CIN	cervical intraepithelial neoplasia
dVIN	differentiated vulvar intraepithelial neoplasia
ECR	The Estonian Cancer Registry
EHIF	The Estonian Health Insurance Fund
FIGO	The International Federation of Gynecology and Obstetrics
HIPEC	hyperthermic intraperitoneal chemotherapy
HPV	human papilloma virus
HRT	hormone replacement therapy
ICD	International Classification of Diseases
PARP	enzyme, poly-ADP-ribose polymerase
RS	relative survival
RSR	relative survival ratio
TNM	tumor, nodulus, metastases staging system
UICC	The Union for International Cancer Control
UK	The United Kingdom
US	The United States of America
VAIN	vaginal intraepithelial neoplasia
VIN	vulvar intraepithelial neoplasia

1. INTRODUCTION

The increasing burden of cancer is widely recognized around the world. The main reason for the increase is considered to be the trend of a growing proportion of advanced aged people who are more vulnerable to cancer (Thun et al., 2010). The control of infectious and cardiovascular diseases in conjunction with an improving economic background has led to the increasing burden of cancer (Ginsburg et al., 2017). The knowledge of cancer development and behavior are comprehensively studied from observational studies of molecular characteristics (Hanahan et al., 2011) and cancer treatment has evolved rapidly over the past decades. Despite new technologies and advanced therapies, the deaths due to cancer have become the second cause of death after cardiovascular diseases in developed countries (WHO, 2019). In the majority of highly developed countries, cancer has become the main cause of premature deaths (age 0–69), while it ranks second in the Baltic countries and most Eastern European countries (Ferlay et al., 2018). Women contribute approximately 49% of the world population but more than 60% of people over 60 years (Population Reference Bureau, 2019). The rising cancer incidence among women is recognized in recent years (Ginsburg et al., 2017). The cancer incidence among young women aged 20–49 is estimated to be far higher than among men at that age (Ward et al., 2019). Women's cancer related premature deaths and disability have a strong impact on world cancer control efforts today. The socioeconomic disparities and rising cancer incidence among women have been brought out both in high- and low-income countries (Ginsburg et al., 2017).

Gynecological cancers comprise approximately 15% of all female malignant tumors in Europe (Ferlay et al., 2018; Ferlay et al., 2015) in 2018 and 13% of all female cancers in Estonia in 2016 (National Institute for Health Development, 2019). Uncontrolled growth of abnormal cells as cancer that develop from female genital organs have different patterns of growth and spread. Cancers of the ovaries, uterus, uterine cervix, fallopian tube, vagina and vulva are a heterogeneous group of malignant tumors that have distinct etiological factors, preventive and therapeutic approaches. The incidence rates of gynecological cancers have different long term trends that are found to be influenced by several societal, economic and health care factors like dietary intake and physical activity, sexual behavior and birth-control approaches (Hüsing et al., 2016; Nagle et al., 2018). In countries with well-organized cervical cancer screening programs the continuous decrease of cervical cancer incidence is detected (Vaccarella et al., 2013). The introduction of oral contraceptives in the 1960s is found to be related to the continuous decrease of ovarian cancer incidence (Sopik et al., 2015). Increasing prevalence of obesity is the main cause of the burden of endometrial cancer (Onstad et al., 2016). Cancer mortality is affected by incidence, but also the effectiveness of cancer management, which is mainly measured by population-based cancer survival. In EUROCARE-5 study (Sant et

al., 2015) the survival of gynecological cancers differed widely between countries. The best survival achievements were estimated in the Nordic countries and the lowest were shown in Eastern Europe. The comparison of estimates between an earlier study EUROCARE-3 (1990–1994) (Sant et al., 2003) and the latest EUROCARE-5 (1999–2007) showed significant improvements in gynecological cancers' survival in many European countries, but only modestly improved or unchanged estimates in Eastern Europe, including in Estonia.

Health care changes, socioeconomic background and societal transition during the previous decades have made Eastern Europe, including Estonia, a unique region which has been reflected also in dismal gynecological cancer trends.

The estimation of cancer incidence, mortality and survival is important to implement cancer control policies and adapt health care services. Knowing the epidemiologic cancer trends help to define the priorities for preventive, therapeutic and diagnostic strategies in each country and therefore evaluate the outcomes of interventions, i.e. screening activities in terms of cost and effectiveness.

The dismal estimates from previous pan-European studies encouraged more specific analysis.

This thesis contributes to a better understanding of the long-term trends of gynecological cancer in Estonia that reflect the socioeconomic changes of Estonian society and health care reforms. It is the first comprehensive gynecological cancer epidemiological study which provides an in-depth analysis of the incidence, mortality and survival of corpus uteri, cervical, ovarian and vulvovaginal cancer in Estonia. Special emphasis was put on age, morphology and stage. The results of the study have important implications for primary and secondary cancer prevention, reassessment of current screening policy as well as further development of cancer care.

2. REVIEW OF LITERATURE

2.1 Corpus uteri cancer

2.1.1 Natural history and morphological classification of corpus uteri cancer

Corpus uteri malignancies consist of 90% endometrial carcinomas and 10% uterine mesenchymal tumors, sarcomas. Endometrial cancer (carcinomas) arises from endometrial tissue which is a hormone responsive tissue. The growth is stimulated by estrogen and the cells' and glands' maturation is regulated by progesterone. In the condition of chronic unopposed estrogen, the endometrial cells' and glands' growth is not balanced, and abnormal proliferation and neoplastic transformation may occur. Atypical adenomatous hyperplasia is the premalignant stage of endometrial cancer. Regressed, atrophic endometrium could also be the source of intraepithelial cancer which develops into aggressive cancer. Endometrial cancer is divided into two main subgroups by histology, molecular biology and prognosis (Murali et al., 2017). Type I cancers mostly consist of well differentiated, estrogen receptor positive endometrioid adenocarcinomas. Type II includes mostly poorly differentiated and estrogen receptor negative tumors. The most common histological types are serous carcinomas and clear cell carcinomas.

Uterine sarcomas comprise approximately 5% of uterine corpus malignancies (Prat et al., 2015). These tumors arise from uterine corpus mesenchymal tissue. The most frequent histological type is leiomyosarcoma. Other types are atypical smooth muscle tumors, endometrial stromal tumors (low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma and undifferentiated endometrial sarcoma), adenosarcoma.

Carcinosarcoma (mixed Müllerian tumors) is also classified into type II endometrial cancers. These tumors consist of an epithelial component which is high grade serous or undifferentiated carcinoma, endometrioid carcinoma and high grade sarcoma component (Prat et al., 2015). In this thesis, these tumors are included into type II endometrial cancers.

2.1.2 Corpus uteri cancer risk factors

2.1.2.1 Obesity

The majority (90%) of corpus uteri cancers are endometrial cancers. Obesity is the main risk factor for endometrial cancer (Hüsing et al., 2016). It is estimated that endometrial cancer relative risk is increased 1.5 times for being overweight, 2.5 times for class I obesity, 4.5 times for class II obesity and 7.1 times for class 3 obesity (Lauby-Secretan et al., 2016). Estrogen induces endometrial proliferation even at an older age. After menopause the estrogen synthesis takes place in

adipose tissue. Adipose tissue produces androgens that are converted to estrogens with the help of aromatase. Aromatase function and levels are increased with age and adiposity. At postmenopausal age, as a result, adipose tissue produces unopposed estrogen. The mutagenic effect resulting in DNA double-strand breaks and genetic instability are also described as a result of estrogen metabolism (Onstad et al., 2016).

Increasing obesity has become a world-wide problem (Abarca-Gómez et al., 2017; Torre et al., 2017). Recent data indicate that approximately 16% of European women are obese (body mass index ≥30) and 31% are overweight (body mass index 25–29) (Marques et al., 2018). In Estonia, in 2018, the estimates showed that 26% of women aged 16–64 were overweight and 18% were obese (Tervise Arengu Instituut, 2018). Being overweight and obese are more prevalent in Northern and Eastern Europe than in Southern Europe (Marques et al., 2018). For example, obesity is estimated to affect 15–20% of Italian and French women, 20–25% of Finnish and Swedish women and 25–30% of Latvian, Belarussian and Ukrainian women.

2.1.2.2 Other risk factors

Nulliparity, estrogen-alone hormone replacement therapy (HRT) and diabetes as the consequences of being overweight and obese have also shown an unfavorable effect on endometrial cancer incidence (Hüsing et al., 2016). The use of oral contraceptives has shown a protective role against endometrial cancer (Hüsing et al., 2016).

2.1.3 Symptoms, pattern of spread and treatment of corpus uteri cancer

For the majority of corpus uteri cancer cases, vaginal bleeding is the first sign of the disease. The symptom occurs early in the course of the disease and leads to early detection and treatment.

Endometrial cancers' spread starts from the endometrium. Then the tumor grows through uterine serosa and invades adjacent structures i.e. urinary bladder and colon. Endometrial cancer spreads through the pelvic and paraaortic lymph nodes. Peritoneal spread and distant metastasis are revealed at a later stage of the disease.

FIGO and TNM classification of stages are used in Estonia and worldwide (Brierley et al., 2017).

The cornerstone of the treatment is surgery. Radical hysterectomy with or without pelvic lymphadenectomy is the standard of care. Adjuvant treatment is considered at early stages based on the tumor's clinical and pathological characteristics. Chemotherapy and radiation therapy are shown to benefit overall survival if performed as adjuvant treatment. Palliative surgery and palliative

chemotherapy are the standard if distant spread is revealed at diagnosis. 20% of early stage type I cancers and 50% of early type II cancers relapse (Suarez et al., 2017). Palliative chemotherapy with platinum compound, taxane and doxorubicin is the treatment of choice in this setting (NCCN, 2019). For Type I cancers, hormonal therapies with progestins can be considered.

2.1.4 Corpus uteri cancer incidence in the world, Europe and Estonia

The burden of corpus uteri cancer is recognized worldwide. The incidence is increasing in the United States (US), in Europe and in Southern Africa and in Asia (Lortet-Tieulent et al., 2018). In the US, the age-adjusted incidence rate is estimated to be as high as 27/100 000 women (world) per year (National Cancer Institute, 2019). In Europe, the corpus uteri cancer is the fourth most common cancer in women with the incidence rate of 20/100 000 women per year (European standard), contributing 6.5% of all female cancer cases in 2018 (Ferlay et al., 2018). The highest incidence rates are estimated in Northern and Eastern Europe (Lortet-Tieulent et al., 2018). In Bulgaria, Ukraine, Greece, Lithuania, Latvia and Slovakia, endometrial cancer has become the third most common cancer in women. Corpus uteri cancer was the most common gynecological malignancy in Estonia in 2016 (National Institute for Health Development, 2019). The Estonian age-standardized incidence rate in 2018 was 23/100 000 women per year (European standard) (J. Ferlay et al., 2018). The comparison of incidence rates of corpus uteri cancer in the Nordic and Baltic countries is shown in Table 1.

By histological subtypes, distinct incidence patterns have been observed. The United Kingdom (UK) data for the period of 1994–2006 showed that the increasing incidence of endometrial cancer was based on the increasing incidence of type I cancers while the type II cancers incidence rate did not change (Evans et al., 2011). In Denmark, in contrast, the type I incidence had been relatively stable during the past ten years, but the overall trend showed a decreasing incidence pattern over more than 3 decades (1978–2014). Type II cancers trend increased during the same period (Faber et al., 2017). The burden of corpus uteri cancer in different countries is based on type I endometrial cancers and is concluded as the concurrent effect of the burden of obesity (Onstad et al., 2016).

Table 1. Incidence (2018), mortality (2018) and survival (2000–2007) of gynecological cancers in selected European countries.

	Incidence[a]					Mortality[a]					5-year relative survival[b]			
	Corpus uteri cancer	Cervical cancer	Ovarian cancer	Vulvar cancer	Vaginal cancer	Corpus uteri cancer	Cervical cancer	Ovarian cancer	Vulvar cancer	Vaginal cancer	Corpus uteri cancer	Cervical cancer	Ovarian cancer	Vulvo-vaginal cancer
Finland	13.1	4.7	7.4	1.2	0.32	2.5	0.94	4.3	0.39	0.17	83.2	67.3	43.1	54.8
Sweden	13.5	9.0	6.4	1.4	0.29	2.0	2.0	3.8	0.31	0.05	85.5	66.8	44.1	58.0
Norway	15.8	10.7	7.0	1.5	0.25	2.5	1.7	5.4	0.38	0.02	82.9	71.0	41.4	64.8
Denmark	14.2	10.9	7.4	1.9	0.34	2.4	2.0	5.4	0.36	0.08	78.3	64.6	35.5	60.5
Latvia	17.4	25.0	14.3	1.1	0.41	5.0	6.5	7.8	0.58	0.18	69.8	51.0	33.7	44.3
Lithuania	24.0	18.9	12.2	1.3	0.28	3.7	7.2	7.8	0.46	0.12	73.4	56.0	31.7	48.6
Estonia	16.6	22.5	10.3	1.3	0.54	2.8	4.3	6.5	0.62	0.19	70.0	64.4	34.1	53.2
Europe	15.8	11.2	9.5	1.7	0.32	2.9	3.8	5.1	0.51	0.12	76.2	62.4	37.6	56.6

[a] The age-standardized incidence and mortality rates were calculated per 100 000 women/ year (world standard). The data on incidence and mortality obtained from the GLOBOCAN database, available at gco.iarc.fr/today/home, accessed 02/08/2019.

[b] The 5-year relative survival estimates were retrieved from EUROCARE-5 study for the period 2000–2007 (Sant et al., 2015).

2.1.5 Corpus uteri cancer mortality in the world, Europe and Estonia

The mortality rates have shown stable or decreasing rates in the world (Weiderpass et al., 2014). The estimated mortality rate in Europe in 2018 was 2.9/ 100 000 women per year (world standard) (Ferlay et al., 2018). In Estonia, an increasing mortality trend of corpus uteri cancer was observed in 1980–2008 (Weiderpass et al., 2014).

2.1.6 Corpus uteri cancer survival in Europe and in Estonia

The European average 5-year relative survival (RS) was 76% in EUROCARE-5 study (Sant et al., 2015). The significant improvement from 1990–1994 to 2000–2007 was seen in the 5-year RS estimates in the Nordic countries, reaching 86% in Sweden and 83% in Finland in the period of 2000–2007. In the Nordic countries the most recent 5-year RS of corpus uteri cancer for the period 2012–2016 was estimated as 83%–84% (Danckert et al., 2019). According to an earlier EUROCARE-3 study (Sant et al., 2003) (1990–1994), Estonian corpus uteri cancer survival estimates were one of the lowest in Europe. A later study EUROCARE-5 (Sant et al., 2015) (2000–2007) showed some improvement, but the Estonian estimates were still within the three lowest in Europe. The 5-year RS estimate was 64% in 1990–1994 and improved to 70% in 2000–2007 (Table 1). The European average survival rates for all age groups had also modestly improved (Sant et al., 2015).

2.2 Cervical cancer

2.2.1 Natural history and morphological classification of cervical cancer

Cervical cancer is a malignancy that originates from uterine cervix epithelium. Cancer mainly develops from the uterine cervix transformation zone. Transformation zone consists of columnar epithelial cells that transform to squamous cells in the ectocervix and to glandular cells in the endocervix. The two major histological types of cervical cancer are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinomas develop from the ectocervix and adenocarcinomas from the endocervix. The cancerous cells are preceded by precancerous intraepithelial neoplasia (Schiffman et al., 2007).

2.2.2 Cervical cancer risk factors

2.2.2.1 Human Papilloma Virus (HPV)

HPV is the main risk factor for cervical cancer (Schiffman et al., 2007). About 99% of all cervical cancers are caused by HPV. The spectrum of Human Papilloma viruses is broad, not all of them are found to be related to cervical cancer. The most cancerous HPV types for cervical cancer are 16 and 18. HPV 16 is the main cause of squamous cell carcinoma and HPV 18 contributes more to adenocarcinomas and adenosquamous carcinomas. HPV 16 and HPV 18 are found in 70% of cervical cancers and 50% of high grade intraepithelial neoplasia. The most common HPV types detected in cervical cancer are HPV 16, 18, 33 and 45 (Schiffman et al., 2007). Cervical cancer related HPV types transmit by skin-to-skin or by mucosa-to-mucosa contact. Different HPV types may transmit together. Cancer develops by certain phases: HPV transmission, HPV persistence, infected cervical cells transform to precancers and invasive cancer. Due to the long precancerous phase, the mean age at cervical cancer diagnosis is 35–55 years. The lifetime probability of acquiring HPV is high, estimated at 91% for men and 85% for women (Chesson et al., 2014).The probability of getting HPV infection during the first sexual intercourse is about 28% for women (Winer et al., 2005). HPV may disappear if once detected at screening. The median time for clearance is about 6–18 months. The longer the HPV infection persists the stronger the probability of the development of precancerous lesions. High risk HPV types (16 and 18) tend to have longer persistence (Schiffman et al., 2007). HPV 16 shows clinically detectable premalignant lesions while HPV 18 does not form as many precancerous lesions that makes the clinical prevention difficult. The new infections detected at advanced ages could be the previous infections that re-appear or that have been latent before.

2.2.2.2 Other risk factors

The risk of cervical cancer in women who use oral contraceptives for more than five years is twice higher than in those who never used them (International Collaboration of Epidemiological Studies of Cervical Cancer, 2007). The risk is also influenced by the number of sexual partners and more frequent screening. Smoking is an independent risk factor for cervical cancer development (Roura et al., 2014). The duration and intensity of smoking both increase the risk more than twice compared to never smokers. Quitting smoking inversely effects cancer development (Roura et al., 2014). Multiparity, having more than 3 children, is associated with a 2.2 times higher risk of developing precancerous high risk cervical intraepithelial neoplasia (CIN 3) (Luhn et al., 2013). The association was not consistent with developing invasive cancer.

Women affected with HIV and with a low CD4+ T-cell count are at a higher risk of developing invasive cervical cancer. The low CD4+ T-cell count is

associated with a longer persistence of high risk HPV types (Abraham et al., 2013).

2.2.3 Symptoms, pattern of spread and treatment of cervical cancer

Cervical cancer gives no symptoms at the precancerous phase or at an early stage. Bleeding after sexual intercourse or vaginal bleedings between menstrual periods or at menopausal age are the most common signs at the invasive cancer stage.

Cervical cancer grows locally and invades adjacent structures, urinary bladder and rectum. Lymphatic spread appears in pelvic lymph nodes. Distant metastases occur frequently in lungs, liver and bones.

FIGO (2009) and UICC TNM staging systems are currently used to stage cervical cancer in Estonia (Brierley et al., 2007).

The treatment of cervical cancer depends on the tumor stage (McMillian et al., 2019). Surgical treatment by conisation, trachelectomy or radical hysterectomy are the treatments of choice at the early stages. The surgical approach is chosen according to cancer's clinical and pathological characteristics. Radiation therapy with curative intent, both external beam radiation and brachytherapy, are applied to locally and regionally spread tumors. The concurrent radiosensitizing chemotherapy with platinum compound enhances the radiation treatment effect (Morris et al., 1999) and is established as a standard of care for locally advanced tumors. Distant metastatic disease is incurable and is mainly treated with palliative chemotherapy. Platinum agent combined with the taxane is the preferred regimen and the standard of care today. The newer biological agents have shown some effect on metastatic cervical cancer. Bevacizumab combined with chemotherapy has favorable outcomes in overall survival estimates compared to chemotherapy alone (Tewari et al., 2017). Bevacizumab is not reimbursed and not available for cervical cancer patients in Estonia at the moment. Immunotherapy has also shown some favorable effect on survival for cervical cancer patients (Chung et al., 2019). Pembrolizumab is indicated to patients with metastatic or recurrent cancer who have undergone previous chemotherapy with platinum compound and progressed. The tumors should be evaluated for PD-L1 (programmed death ligand 1) expression. Immunotherapy is indicated for cervical cancer patients in the US.

2.2.4 Cervical cancer incidence in the world, Europe and Estonia

Cervical cancer is the most common gynecological cancer in the world, with the highest incidence rates in less developed countries, in Latin America and in South Africa (Ferlay et al., 2018). The highest incidence rate in 1998–2002 has been estimated in Zimbabwe at 87/100 000 women per year and the lowest in

Finland at 8/100 000 women per year (world standard) (Vaccarella et al., 2013). In the US, the cervical cancer incidence trend is declining (National Cancer Institute, 2019). In 1992, the estimated age-standardized incidence rate was 11.2/100 000 women per year and reached 6.6/100 000 in 2016. In Europe, the mean age-standardized incidence rate was estimated at 13/100 000 women per year (Ferlay et al., 2018). In the Nordic countries the age-standardized incidence rate in 2016 was 8.3/100 000 women per year (Danckert et al., 2019) and the incidence trends have been constantly declining during the past decades. In contrast, in Eastern Europe (Estonia, Latvia, Lithuania, Russia, Belarus and Bulgaria), increasing trends were observed (Vaccarella et al., 2013). In Estonia the crude incidence rate was 21/100 000 women per year and the age-standardized incidence rate was 14.2/100 000 women per year (National Institute for Health Development, 2019). The comparison of incidence rates by countries is shown in Table 1 and demonstrates the gap between Nordic and Baltic countries in 2018. The falling incidence trends reflect the well-organized nation-wide screening programs (Vaccarella et al., 2014).

2.2.5 Cervical cancer mortality in the world, Europe and Estonia

Cervical cancer mortality rates differ largely in the world. The highest age-standardized rates above 50/100 000 per women per year were observed in the African region and the lowest rates of less than 2.0/100 000 per women per year (world standard) in Western and Northern Europe and the Arab countries (Ferlay et al., 2018). In most European countries the mortality rate of cervical cancer has declined (Arbyn et al., 2009). The lowest mortality rate of 1.1/100 000 was achieved in Finland in 2000–2004. Mortality rate has increased in Latvia, Lithuania, Romania and Bulgaria. The constant high mortality rate was observed in Estonia (Arbyn et al., 2009).

2.2.6 Cervical cancer survival in Europe and in Estonia

The survival rates of cervical cancer have risen very modestly during the past decades in Europe. The European mean 5-year RS estimate was 62% in 2000–2007 (Sant et al., 2015) (Table 1). According to EUROCARE-3 study (1990–1994), the highest 5-year relative survival estimates were observed in Norway and Sweden, at 69% in both countries. The lowest estimates were found in Poland (48%) and in Estonia (53%). In EUROCARE-5 (2000–2007) the survival was improved modestly in Norway (71%) and decreased in Sweden (67%). The larger improvement was observed in countries with a previous low relative survival – Estonia reached 64% and Poland showed 54% of 5-year RS.

The age-specific 5-year RS did not change between the EUROCARE-3 and EUROCARE-5 periods (Sant et al., 2003; Sant et al., 2015). The survival increase was shown for younger women (women aged 15–44 years) from 74% to

81% and also for women aged 45–54 years from 66% to 70%. The 5-year RS estimate decreased for women aged 65–74 years and was estimated at 51% in 2000–2007. In the Nordic countries the recent (2012–2016) age-specific 5-year RS estimates were 87%–91% for women under 50 years and 51% (Denmark) and less for women over 70 years (Danckert et al., 2019).

2.2.7 The rationale of cervical cancer screening

The purpose of cervical cancer screening is to prevent invasive cancer. The nation-wide cervical cancer screening programs had been implemented by 2016 in all European Union member states except Lithuania (Basu et al., 2018). The recommendations for the organization and quality assurance for the screening activities were composed by the International Agency for Research on Cancer under the program " Europe against cancer" and published in 2010 (Arbyn et al., 2010). The idea of cervical cancer screening is to detect preinvasive and pre-cancerous lesions that can be treated successfully and thus the development of invasive cancer can be prevented. The conventional screening is based on a Pap (Papanicolau) smear test. The test detects cervical cytology changes that could develop into cancer or detect already cancerous cells. The HPV-DNA testing is also in use in many countries and it could detect persistent moderate and high grade cervical intraepithelial neoplasia more often (Basu et al., 2018). The HPV-DNA testing is considered to be more sensitive than a conventional cytology test in detecting cervical adenocarcinoma, but it also may lead to overdiagnosis and unnecessary procedures as HPV infection may disappear naturally (Huh et al., 2015). The age of the target population of screening somewhat varies by countries, but most frequently the age group is set between 30–59 years (Anttila et al., 2009). The interval between tests is set to be three years in most countries.

The coverage of the target population is the key feature of a successful screening. The decline in incidence is seen in countries with high coverage, over 70% of the target population (Anttila et al., 2009; Elfström et al., 2015). Low coverage has not shown to result in incidence decline.

In the Nordic countries, the screening was established already in the beginning of the 1960s and it has shown a rapid and large decline in cervical cancer incidence and mortality (Vaccarella, et al., 2014). The cervical cancer incidence declines were also observed in the US, Canada and Australia after the implementation of screening programs (Dickinson et al., 2012; Vaccarella et al., 2013). Regular monitoring of the quality indicators in organized screening is a prerequisite for successful outcomes.

Regular participation in screening is estimated to prevent up to 83% of deaths due to cervical cancer (Landy et al., 2016).

2.2.8 HPV vaccination

The aim of HPV vaccination is to avoid the cell changes influenced by different HPV types that could lead to the development of precancerous lesions or cancer. The vaccine produces antibodies against HPV that could be detected within 10 years after the vaccination. Later, the prevention and the detection of HPV related cell damages could be examined by screening, cytological (Pap-smear test) or molecular HPV detection. Vaccination is most efficient during adolescence and for persons who had not become sexually active yet. The immunogenic boost after the vaccination is tested to be weak if a woman has already been infected with HPV and the cross-immunity had not been detected (Harper et al., 2017; Schiffman et al., 2007).

From 2007 the vaccination of girls was implemented into the national vaccination plan in Germany, France and Belgium (Bonanni et al., 2011) and more countries followed the action within the next few years. The vaccination for adolescents consists of two injections in a six month or a year interval. The vaccination schedule is recommended by the World Health Organisation (WHO, 2019).

2.3 Ovarian Cancer

2.3.1 Natural history and morphological classification of ovarian cancer

Ovarian cancer is a heterogeneous group of malignancies which arises from ovarian tissue or fallopian tubes' secretory epithelial cells or progenitor cells (Karnezis et al., 2017). Ovarian cancer is divided into two main subgroups based on histological type. Epithelial ovarian cancers comprise approximately 85–90% of all ovarian malignancies. They consist mainly of high grade serous carcinomas (70%), low grade serous carcinomas, endometrioid carcinomas, mucinous carcinomas and clear cell carcinomas. Non-epithelial ovarian malignancies cover 10–15% of cases. The main histological subtypes are germ-cell tumors and sex-cord tumors.

2.3.2 Ovarian cancer risk factors

There are certain established adverse risk factors and protective factors for ovarian cancer development. Based on distinct molecular and histological characteristics, ovarian cancer risk factors also vary by subtypes (Webb et al., 2017).

2.3.2.1 Ovarian cancer adverse risk factors

2.3.2.1.1 Genetic predisposition of ovarian cancer

It is well described that an individual woman's family history of ovarian cancer and breast cancer raises the likelihood of developing ovarian cancer. 14% of all epithelial ovarian cancers are found to have pathogenic mutations in BRCA 1 or BRCA 2 genes (Alsop et al., 2012). BRCA genes produce tumor suppressor proteins and are responsible for DNA repair (Venkitaraman, 2002). The most common genetic syndrome caused by pathogenic BRCA mutation is the hereditary breast and ovarian cancer. Women with BRCA 1 mutation have a lifetime risk to develop ovarian cancer of about 40% up to 70 years of age, and the risk is 16% for BRCA 2 mutation (King et al., 2003). Both breast and ovarian cancers represent 5% among BRCA 1 and 2% among BRCA 2 carriers (Rebbeck et al., 2015). BRCA-related ovarian cancer patients tend to be younger than sporadic ovarian cancer patients (Cass et al., 2003). The cancer is characterized by high grade histology and the tumors are very sensitive to platinum-based therapy (Cass et al., 2003). The overall survival of BRCA-related cancers is more favorable than for sporadic cancers (Bolton et al., 2012). BRCA mutation testing is recommended by international clinical guidelines for ovarian cancer patients (NCCN, 2019). The aim of BRCA testing is to guide the treatment choices (Mirza et al., 2018) and perform genetic counselling for family members for the prevention of BRCA-related cancers. BRCA testing has become a standard of care for epithelial ovarian cancer patients in Estonia.

2.3.2.1.2 Endometriosis

Endometriosis as a benign disease is found to be associated with certain types of epithelial ovarian cancers (Pearce et al., 2012). Clear cell, low-grade serous and endometrioid carcinomas are suggested to be associated with endometriosis while high grade serous and mucinous carcinomas are not. The exact underlying mechanism is not well clarified. ARID1A as a tumor suppressor gene is found to be mutated in 46% of clear cell ovarian cancers and 30% of endometrioid ovarian cancers (Wiegand et al., 2010).

2.3.2.1.3 Menopausal hormone therapy

Menopausal HRT is found to increase the risk of high grade serous and endometrioid ovarian cancer (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2015). A meta-analysis estimated the increased risk for all HRT users compared to never users. The risk increased with the duration of HRT and decreased after the cessation of therapy. The risk remained elevated even 10 years after the therapy for serous and endometrioid ovarian cancer. The conclusion was that one extra ovarian cancer case would be diagnosed per 1000 menopausal HRT users.

2.3.2.2 Ovarian cancer protective risk factors

2.3.2.2.1 Oral contraceptives

Oral contraceptives are established as protective factors of ovarian cancer. The combined mechanism of estrogen and progestin causes anovulation. It was estimated that by 2008, oral contraceptives had prevented 200 000 new ovarian cancer cases and 100 000 deaths (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008). The strongest effect is achieved in reducing ovarian cancer by using oral contraceptives among women under 30 years with a duration of 10 years and over (Havrilesky et al., 2013). Oral contraceptives were introduced to the world in 1960 in the US. More frequent use started in Estonia in the late 1990s. In 2018, oral contraceptives were the 15th most frequently prescribed medicine in Estonia (Sammul et al., 2018).

2.3.2.2.2 Breast feeding

Breast feeding is found to reduce ovarian cancer risk. The duration of breast feeding for more than 3 months is associated with a 27% reduced risk of ovarian cancer and it is estimated to last up to 30 years. The greater the duration of breastfeeding and the number of offspring, the more the risk is reduced compared to women who never breastfed (Modugno et al., 2019).

2.3.2.2.3 Pregnancy

Parous women are found to have a reduced ovarian cancer risk compared to nulliparous women (Koushik et al., 2017). The risk decreases with an increasing number of pregnancies. A woman with two pregnancies has a 50% lower risk of ovarian cancer than a woman without pregnancies.

2.3.2.3 Other factors

Mucinous ovarian cancer risk is found to be increased among tobacco users (Webb et al, 2017) but no other histological types. Obesity is found to be an adverse risk factor for endometrioid ovarian cancer but not for high grade serous cancers. Physical activity and alcohol consumption have not shown a relation to ovarian cancer risk (Webb et al., 2017).

2.3.3 Symptoms, pattern of spread and treatment of ovarian cancer

At early stages, ovarian cancer gives no specific symptoms. Tumors at early stages are found mostly incidentally by ultrasonography (Smith-Bindman et al., 2019). At later stages, abdominal mass, abdominal distention or increased girth, abdominal or pelvic pain, abdominal or pelvic bloating, and loss of appetite

may occur (Ebell et al., 2016). Symptoms are not specific for ovarian cancer and might lead to discover other health problems.

The high lethality of ovarian cancer is caused by its pattern of spread. The spread to peritoneal surfaces occurs early in the course of the disease and this makes ovarian cancer incurable. Regional spread to lymph nodes includes inguinal, pelvic and paraaortic nodes. Hematogenic spread is revealed mostly in the liver, pleura, lungs and non-regional lymph nodes.

FIGO and TNM staging systems are used to describe ovarian cancer stages (Brierley et al., 2017).

Treatment of ovarian cancer has evolved over the past decades and needs a multidisciplinary approach today. Surgery with the aim of cure at early stages (IA) and cytoreduction at later stages is the cornerstone of the treatment (NCCN, 2019). The standard approach is to remove both ovaries with adnexa, uterus and omentum. The goal of the surgery at later stages is to achieve optimal cytoreduction with no visible residual tumor in the peritoneal cavity (Du Bois et al., 2009.). Optimal cytoreduction for advanced stages (IIB-IV) is found to be the most powerful prognostic factor for survival. Hyperthermic intraperitoneal chemotherapy (HIPEC) has shown favorable outcomes in patients who underwent optimal cytoreduction (Van Driel et al., 2018), but the data are considered immature to perform HIPEC as standard of care. Chemotherapy is the standard approach for adjuvant treatment. Platinum-based combinations have been used for many decades. Chemotherapy might be used as neoadjuvant therapy when optimal cytoreduction as frontline therapy is impossible due to high tumor volume (Wright et al., 2016). The latest advances in ovarian cancer treatment apply mostly for epithelial ovarian cancer. Maintenance therapy for advanced stages has become a standard (Randall et al., 2019). PARP- inhibitors have shown significant improvement in progression free survival for high grade epithelial ovarian cancer both after frontline and after platinum-sensitive relapse. Bevacizumab maintenance therapy after frontline therapy and after platinum sensitive relapse has also shown favorable outcomes. At phases when epithelial ovarian cancer is considered platinum resistant, chemotherapy with other agents is the treatment of choice (Ledermann et al., 2013; NCCN, 2019).

2.3.4 Ovarian cancer incidence in the world, Europe and Estonia

Ovarian cancer incidence trends vary worldwide (Coburn et al., 2017) with the mean age-standardized incidence rate of 6.6/100 000 women per year (Ferlay et al., 2018b). The highest incidence rates are found in Eastern and Northern Europe (Ferlay et al., 2018) (Table 1). In the US, the age-adjusted incidence rate was 11/100 000 women per year (National Cancer Institute, 2019) in 2016 and in Europe the crude rate was 18/100 000 women per year, and the age-standardized incidence rate was 10/100 000 women per year. In Eastern Europe, the age-standardized incidence rate is the highest in Poland (14.7/100 000) and in Belarus (15.4/100 000) (Ferlay et al., 2018).

In the US, the incidence decline by APC 1.1% has been observed during 1988–2008 (Lowe et al., 2013). The decline was eminent both in women less than 65 years and over 65 years of age. In the Nordic countries the decline has been significant among women under 70 years during 1993–2013 (Gottschau et al., 2016) while the stable trend is observed among women over 70 years, except in Sweden, where the decline has been continuous during the studied period. In Estonia the incidence trend has been stable over the decades (Coburn et al., 2017).

The decline of the incidence is found to be related to more frequent oral contraceptive use and less frequent menopausal hormone therapy (Sopik et al., 2015). The countries where the incidence trends are increasing, the estimates are associated with decreased parity (Coburn et al., 2017).

2.3.5 Ovarian cancer mortality in the world, Europe and Estonia

Ovarian cancer is considered to be the most aggressive cancer of the female genital organs. The mean age-standardized mortality rate in the world was 3.9/100 000 women per year (world standard) in 2018 (Ferlay et al., 2018) with the highest estimates in Eastern Europe (7.8/100 000 in Poland, Latvia and Lithuania) and the lowest estimates under 1.0/100 000 women per year in Belize and in the Republic of Gambia. The European mean age-standardized mortality rate was 5.1/100 000 women per year which was lower than the estimate in Estonia (Table 1).

The trends in ovarian cancer mortality have been stable or declining in most parts of the world (Malvezzi et al., 2016). In countries of South America and South Korea increasing trends were observed. The only country in Europe with the increase in mortality (28%) was Bulgaria.

Mortality trend in Estonia from 2002 to 2012 showed the largest mortality decline in Europe (Malvezzi et al., 2016). The improvement was seen in every age group.

2.3.6 Ovarian cancer survival in Europe and in Estonia

The European average 5-year RS increased modestly from 1990–1994 to 2000 – 2007, from 37% to 38%, respectively (Sant et al., 2003; Sant et al., 2015). In Northern Europe the 5-year RS estimates were observed at 40% and over already in 1990–1994; in Sweden (41%) and Norway (40%). In EUROCARE-5, the average 5-year RS was 41% in the Nordic countries with the highest rate of 44% in Sweden (Table 1). The most recent estimates showed larger improvement in Denmark where the 5-year RS for the period 2012–2016 reached 41% and modest improvements in Norway (45%) and Sweden (49%) (Danckert et al., 2019). There has been no improvement in Finland (44%) during the past 10

years. The Estonian 5-year RS estimates improved from 26% in 1990–1994 to 34% in 2000–2007 (Sant et al., 2003; Sant et al., 2015).

The 5-year RS have improved very modestly during the past 25 years in countries with high quality cancer care. The rates have not exceeded 50% yet in Sweden or in Norway.

Despite of the improvements in short-term and 5-year RS, there were no improvements in 10-year survival observed in the Netherlands. 10-year RS estimate of 24% for ovarian cancer has not changed since the early 1990s (Timmermans et al., 2018).

2.3.7 Hereditary ovarian cancer prevention

There is no effective screening strategy for ovarian cancer. The detection of women with suspicious hereditary cancer syndromes is the only possibility to reduce the incidence of ovarian cancer within the high-risk family members. Hereditary cancer syndromes are detected and counselled by a clinical geneticist. International guidelines recommend BRCA testing for all epithelial ovarian cancer patients except mucinous cancers (NCCN, 2019). The Australian study found 14% of epithelial ovarian cancer were related BRCA gene mutations and 30% of these women did not have a family background of hereditary breast and ovarian cancer syndrome (Alsop et al., 2012). Prevention of ovarian cancer or other cancers of the hereditary syndrome could be considered if one family member is already found to have a hereditary high-risk cancer gene mutation. The same mutation could be detected in other blood related relatives. The prevalence of BRCA pathogenic mutations are about 1.0% to 2.5% of entire female population (Metcalfe et al., 2009). The idea of testing high risk cancer genes in all populations has already been put under discussion.

The international guidelines recommend to undergo preventive procedures before the age 40 (NCCN, 2019; Paluch-Shimon et al., 2016). Ovarian cancer prevention consists of the removal of the fallopian tubes and ovaries. As there is more etiological information that high grade serous ovarian cancer begins from the fallopian tubes (Kurman, 2013), the discussion about the removal of tubes only is underway (Gockley et al., 2018). Oral contraceptives are effective in preventing ovarian cancer and also among BRCA gene mutation carriers. Oral contraceptives are recommended as a preventive strategy for hereditary ovarian cancer (Paluch-Shimon et al., 2016).

None of the preventive measures can entirely avoid the development of ovarian cancer. Therefore the more frequent scheduled gynecologist visits with a transvaginal ultrasound and evaluation of cancer antigen CA 125 are recommended by guidelines and should be performed from the age of 35 years (NCCN, 2019; Paluch-Shimon et al., 2016).

2.4 Vulvar and vaginal cancer

2.4.1 Natural history and morphological classification of vulvar and vaginal cancers

The vulva consists of female outer genital organs: labia majora and minora, clitoris, vestibule, vaginal introitus and urethral meatus. About 95% of vulvar malignancies are squamous cell carcinomas.

The vagina is a female internal genital organ and lies in the pelvis and is surrounded in distal with the vulva and in proximal with the uterine cervix, while in the interior lies the urinary bladder and the rectum is located in the posterior. The majority of vaginal cancers are squamous cell cancers, approximately 10% are adenocarcinomas and a small entity consists of clear cell carcinomas. Vaginal adenocarcinomas and clear cell carcinomas are extremely rare cancers and are revealed in young women and adolescents.

2.4.2 Vulvar and vaginal cancer risk factors

2.4.2.1 Vulvar cancer risk factors

2.4.2.1.1 Lichen sclerosus

Lichen sclerosus is a chronic inflammatory skin disorder that usually affects the vulva and groin. It is found that with the ageing population, the incidence of lichen sclerosus has doubled during the past two decades (Bleeker et al., 2016). The average age of lichen sclerosus diagnosis is 60 years. Lichen sclerosus is the underlying condition for the development of differentiated vulvar intraepithelial neoplasia (dVIN). The cumulative incidence of vulvar cancer with lichen sclerosus is 7% in 10 years and it increases with age (Bleeker et al., 2016). Lichen sclerosus is not associated with HPV.

2.4.2.1.2 HPV

HPV is associated with high risk VIN (Alkatout et al., 2015). The main HPV type that has been found in high risk VIN is HPV type 16 (82%). The transmission of HPV is similar to what was previously described in the cervical cancer risk factors section. HPV induced VIN is found more in younger women (92% in women aged 50–59 versus 0% in women aged 80 years and over) (Wakeham et al., 2017). HPV-related vulvar carcinoma has shown better treatment outcomes. The 5-year survival is estimated 78% in HPV positive versus 49% in HPV negative women (Wakeham et al., 2017).

2.4.2.2 Vaginal cancer risk factors

The main risk factors for vaginal cancer are HPV types 16 and 18 (Daling et al., 2002). The premalignant lesions as vaginal intraepithelial neoplasia (VAIN) are associated with HPV. HPV transmission is similar as described in the cervical cancer and vulvar cancer section. 30% of vaginal cancer patients have suffered previously from another anogenital cancer. The other established risk factors are current smoking, early age (under 17 years) of first intercourse and more than five sexual partners.

2.4.3 Symptoms, pattern of spread and treatment of vulvovaginal cancer

The symptoms of vulvar cancer are pruritus, vulvar lump, vulvar bleeding, dysuria, discharge and pain (Alkatout et al., 2015).

The symptoms of vaginal cancer are commonly painless vaginal bleeding and discharge. In more advanced tumors the extension to adjacent organs and structures may mimic the symptoms of colorectal or bladder cancer (Di Donato et al., 2012).

Vulvar cancer grows first locally by invading adjacent structures (urethra, anus, vagina). The following regional lymphatic spread includes inguinal, femoral and pelvic lymph nodes. Distant metastasis is revealed most commonly in the liver, lungs and bones.

Vaginal cancer grows locally and spreads further onto adjacent organs and into the pelvic wall. Metastases in distant organs appear in the late course of the disease.

Vulvar and vaginal cancers are staged by FIGO and TNM staging systems (Brierley et al., 2017).

Three-quarters of patients suffering from vulvar or vaginal cancer are over 60 years old. The treatment of vulvar and vaginal cancers causes major effects on quality of life.

Surgery is the standard of care of locally and regionally spread vulvar tumors. Patients who are not candidates for surgery, radiotherapy or chemo-radiation is the preferred treatment modality. In case of distant metastatic disease, palliative chemotherapy with platinum compound is the standard of care (NCCN, 2018). Local small vaginal invasive cancers are treated with surgery alone. External beam radiotherapy and brachytherapy are the treatment of choice at a more advanced disease (Di Donato et al., 2012).

2.4.4 Vulvovaginal cancer incidence in the world, Europe and Estonia

Vulvovaginal cancers contribute 5% of all gynecological cancers in the world (Ferlay et al., 2018) and 7% in Europe. Vulvar cancer overall age-standardized incidence rate is observed at 0.88/ 100 000 per year (world standard) (Ferlay et al., 2018) in 2018 in the world and 1.7/100 000 in Europe. Vaginal cancer age-standardized incidence rates were 0.37/100 000 and 0.32/100 000, respectively. The increasing incidence trend of vulvar and vaginal cancers have been observed over the past decades in different countries (Barlow et al., 2017). The increasing prevalence of HPV is considered to be the main cause of vulvar cancer incidence increase among younger women (Hampl et al., 2008; Kang et al., 2017). In Australia, over the period 1982–2009 the overall incidence rate did not change (Barlow et al., 2015) but the significant increase of 82% was observed among younger women. In the UK, the significant increase of overall incidence was shown (Lai et al., n.d.) during the period 1990–2009. The increase was most prominent for the age group of 70 years and younger. The incidence decreased significantly for women age 80 and over. Despite the majority of vulvar cancer cases occurring in women 70 and older, the shift toward earlier stages at diagnosis has been observed in Germany and Australia.

2.4.5 Vulvovaginal cancer mortality in the world and Europe

The mortality of vulvar cancer is generally low, estimated age-standardized mortality rate of 0.27/100 000 per year in the world and 0.51/100 000 per year in Europe. Vaginal cancer showed the age-standardized mortality rate of 0.16/100 000 per year in the world and 0.12/100 000 per year in Europe (Ferlay et al., 2018a). Vulvar cancer mortality has significantly decreased for women aged 60 years and over during the past decades. Still, the mortality rates are higher at older age groups and estimated at 12/100 000 women per year (Barlow et al., 2015) and less than 0.5/100 000 women per year among women under 60 years.

2.4.6 Vulvovaginal cancer survival in Europe

According to EUROCARE-3 and 5 studies the survival of vulvovaginal cancer has improved. The European mean 5-year RS improved from 52% to 57% during the period 1990–2007. The dismal estimate of 34% of 5-year RS in Estonia in 1990–1994 had improved up to 53% in 2000–2007 (Sant et al., 2003; Sant et al., 2015). The relative survival in Europe improved for all age groups according to pan-European studies (Sant et al., 2015). The survival by stages have shown different long-term patterns. The 5-year RS for localized disease is about 80% and for distant metastatic disease the rate stays as low as 20% (Tanaka et al., 2019).

2.5 Cancer care, prevention and registration in Estonia

2.5.1 Health care organization for cancer care in Estonia

In Estonia, the Ministry for Social Affairs is responsible for the planning of health policy and its implementation, and ensuring the availability of health services, quality and safety (Ministry of Social Affairs, 2019). Primary care is organized based on family doctors who work as self-employed all-around Estonia. Specialist care is organized in the hospitals or in private offices. The services provided by different type of hospitals are laid down by the regulations of the Minister for Social Affairs in 2004 "Requirements for Hospitals' Types" (Sotsiaalminister, 2004).

Gynecological services are provided in every type of hospital and in private offices. No referral from a family doctor or other specialist is needed (Eesti Haigekassa, 2019).

Estonia has a solidary health insurance system that covers health care costs independently of patient's income, age or health care risks (Eesti Haigekassa, 2019). In addition to employed persons, the insurance covers treatment costs for children, seniors, mothers who are raising small children at home, the unemployed and pregnant women.

The major hospital reform took place during 1998–2001. According to the regulations by the minister for social affairs in 2004, cancer care can be performed only in regional and central hospitals. Currently, there are five hospitals which perform cancer treatment.

Estonia has no current National Cancer Plan. Previous plan ended in 2015 (Paat-Ahi et al., 2017). The plan was composed in 2006 and set the goals for the prevention and early detection of cancer, cancer care and rehabilitation, palliative care and hospice. The increasing cancer incidence and the lack of availability of cancer care were highlighted as the current situation in the strategy. The indicators to evaluate the progress were described. The overall cancer incidence and mortality were expected to decline by 5% and 10% accordingly during the strategy period. The indicator for cervical cancer incidence and mortality were defined and 20% of incidence and 30% of mortality reduction were expected. The indicator for cervical cancer screening was set to cover 70% of all the target population. The 5-year relative survival estimates were expected to improve for cervical cancer from 53% to 65% and for corpus uteri cancer from 64% to 75%.

The evaluation analysis of the National Cancer Plan in 2017 pointed out the dismal results (Paat-Ahi et al., 2017). The cancer incidence rose 25% and the mortality rose 9% for men and 17% for women during 2003–2014. Cervical cancer incidence and mortality continued to rise and the coverage by screening did not reach 50% of the target population. The goals were achieved in survival indicators – most cancers' survival increased.

The regulation for delivering and measuring cancer care services was adopted by the minister for social affairs in 2011 (Minister of Social Affairs, 2011). The aim of the regulation was to help to achieve the goals proposed in

the National Cancer Plan. The quality indicators set in the document are ongoing and compulsory to measure, monitor and report yearly by each hospital delivering cancer care.

2.5.2 Quality assurance

The quality of health services is monitored by the Estonian Health Insurance Fund (EHIF). EHIF is a governmental body founded in 2000 to organize the national health insurance, offer the health insurance and to ensure the health care, prevention and compensation for people with health insurance in Estonia.

The quality is monitored by controlling the health care institutions with the EHIF contracts of compensation of health services, conducting clinical audits and measuring clinical indicators.

The EHIF audits of treatment quality of cervical cancer and ovarian cancer were conducted in 2016 (Eesti Haigekassa, 2019). All four hospitals which provide gynecological cancer care were studied. 80 cases for ovarian and 80 cases for cervical cancer were evaluated for waiting-times, diagnostics, performance of multidisciplinary meetings, surgery, radiotherapy for cervical cancer, chemotherapy and documentation of follow-ups. Additionally, the expert opinion about the adherence to international guidelines was given. The main findings were incomplete documentation for waiting-times, only 75% of ovarian cancer cases were discussed in multidisciplinary meetings before any oncological treatment and prolonged waiting times (more than 42 days) for curative radiotherapy in cervical cancer cases were observed (Eesti Haigekassa, 2019).

In 2017 and 2018 the Treatment Quality Board and the Guideline Advisory Board was established and supported by EHIF (Eesti Haigekassa, 2019). The aim of the boards is to promote the collaboration of hospitals and specialists in developing and implementing quality care. The Treatment Quality Board focuses on the development of clinical quality indicators for monitoring the treatment quality. In 2018, 6 treatment quality indicators were adopted for the diagnostics and treatment of cervical cancer. The Treatment Guidelines Board produces treatment guidelines and patient management pathways. The management pathways of cancers are the suggested patient management algorithms from the suspicion of cancer by a primary care doctor or screening until death due to cancer. In 2016, patient management pathways for vulvar, cervical, corpus uteri cancer and ovarian cancer were adopted and published.

2.5.3 Diagnostics and treatment

The diagnostics with magnetic resonance tomography and computed tomography (CT) have been available for patients for more than 15 years. Ultrasound diagnostics for gynecological diseases were largely used from the end of the

1980s. Positron emission tomography for cancer diagnostics is available since 2002.

The implementation of new surgical modalities has been taken into practice. For example, in 2016, 57% of hysterectomies were performed by laparoscopic surgeries compared to 35% in 2011 (Veerus et al., 2015). The robotic surgery has not reached Estonia yet.

Globally, the advances in systemic treatment for gynecological cancers have recently made a major impact on prolonging patients' lives and improving quality of life. In Estonia, new systemic treatments are implemented into everyday practice with a delay compared to other European countries (Cherny et al., 2016). The procedure for drafting and amendment of a list of medicinal products of EHIF is regulated by the regulation of the Minister of Health and Labour which was implemented in 2018 (Minister of Health and Labour, 2018).

Radiation therapy for gynecological cancers has been performed in two hospitals – in the Tartu University Hospital and in the North Estonia Medical Center. Brachytherapy for cervical cancer was performed only in the North Estonia Medical Center until 2018. The first linear accelerator was received in the Tartu University Hospital in 1996. Today, there are six linear accelerators working in Estonia, four machines in the North Estonia Medical Center and two in the Tartu University Hospital. The availability of radiotherapy has been estimated as not optimal (Borras et al., 2015) and it should be improved in Estonia.

2.5.4 Estonian Cancer Registry (ECR)

ECR is a population-based registry and covers the whole Estonian population. The Registry was founded in 1978 and it collects the data about all incident invasive cancer cases diagnosed in Estonia since 1968. From 1994 all *in situ* cases and from 1998, brain and central nervous systems tumors and tumors of uncertainty for malignant potential or benign origin of endocrine organs locating in the brain area are collected. The data collection is regulated by law, and the current ECR legislation is in force from the 15th of March 2019. The aims of the registry are to analyze cancer incidence, prevalence and survival; to organize health care services and cancer control; to develop health policies; to evaluate cancer diagnostics and treatment and to facilitate cancer research. The reporting of cancer cases (diagnosis and treatment) is compulsory for all clinicians, pathologists and forensic doctors. There are reporting forms for physicians and pathologists who diagnose and treat cancer (Appendix 1 and 2). The form for clinicians consists of patient's personal data (name, personal identity code, gender, time of birth, the residence at the time of diagnosis), diagnosis (date of first diagnosis, the investigational methods that confirmed the diagnosis, morphologic diagnosis, tumor grade, extent of disease and TNM stage), frontline treatment by specialty (the intention of treatment, place of the treatment, date of the beginning of treatment, treatment method), the date of death

and the cause of death or the date of emigration and the data about the person who filled in the form (National Institute for Health Development, 2019). The data is tracked from multiple sources including the Estonian Population Register, Estonian Causes of Death Registry and through linkage with the databases of two regional hospitals. ECR uses the International Classification of Diseases for Oncology, currently the third edition (ICD-O-3) (Fritz et al., 2000), for tumor classification.

2.5.5 Cervical cancer screening in Estonia

From 2003, in Tallinn and in Tartu the first projects of cervical cancer screening activities were established. A nation-wide screening started in Estonia in 2006. Women aged 30, 35, 40, 45, 50 and 55 with valid health insurance are notified every five years by a letter to participate in a screening program and give a Pap-smear test. Women diagnosed with cervical cancer within the previous 60 months are not invited. The screening is voluntary and there are no restrictions if screening is skipped. The Pap test can be performed in the health care institutions holding a screening contract with the Estonian Health Insurance Fund (over 20 institutions in Estonia). The guidelines for taking the Pap test is adopted by the Estonian Gynaecologists' Society (Aavik et al., 2011). Estonian Cancer Screening Register is responsible for sending out the notification letters. The Register was established in 2015 with the aim to coordinate and analyze cancer screening data, evaluate the screening activities and offer the platform for future research. The cervical cancer screening in Estonia has been estimated as ineffective despite of more than 10 years of screening. Cervical cancer incidence has not decreased in Estonia (Vaccarella et al., 2016). The involvement of the target population has been low from the beginning of screening activities, only 20–40% (Kivistik et al., 2011). A study examined the reasons for the low participation rate and concluded that Estonian women did not have enough information about the program (Kivistik et al., 2011). One of the reasons not to attend the screening program was the recent Pap-smear test performed outside the program. The differences in socioeconomic background of women may affect the participation in cervical cancer screening. Higher level of education, younger screening age group and Estonian citizenship were shown to be positively associated with screening participation (Koreinik, 2019). In 2017, the overall participation rate published by the Estonian Cancer Screening Register was 31% (National Institute for Health Development, 2019). The rate of the screened target population differed by counties. The highest participation rate was shown in Järva county at 53% and the lowest was in Pärnu county and estimated at only 3%. The data gathered by the Register was compared to the Estonian Health Insurance Fund's data on performed Pap tests and the coverage of 67% of the target population was estimated overall.

From 2018 the HPV vaccination with the nonavalent vaccine was included into the Estonian national vaccination program for girls aged 12–14. In 2020,

only girls aged 12 will be included. The vaccination takes place at schools and is performed by a health care professional. The vaccination can be performed by a family doctor also. The vaccination is voluntary and for free. A consent from a parent is needed to perform the vaccination.

2.6 Summary of the literature review

Gynecological cancers contribute a large proportion of all cancers in women and affect deeply women's reproductive function, quality of life and cause premature death.

Globally, the trends of gynecological cancers are influenced by a number of individual, societal and health care factors. Incidence trends are affected by demographic changes, but also by changes in the prevalence of risk factors, such as obesity for corpus uteri cancer, oral contraceptive use for ovarian cancer, and sexual behavior for cervical cancer and vulvovaginal cancer, and by health care interventions, such as screening and HPV vaccination for cervical cancer. Survival trends show marked variations across Europe and are heavily dependent on the availability and quality of cancer care in a particular country.

Previous international and other studies of gynecological cancer trends have shown dismal results for Estonia. These patterns are not well understood. The transition from Soviet to Western society has made an impact on women's health behavior and brought along altered risk factor profiles. The changes in dietary preferences and physical activity, sexual behavior and birth control methods reached Estonia later than Western Europe. At the same time, major efforts have been undertaken to improve health care organization, the availability of modern diagnostic and treatment options, and the quality of cancer care. Nation-wide cervical cancer screening program has been in place in Estonia for over ten years. An in-depth analysis of long-term trends has not been carried out before and the need to examine whether the above-mentioned changes and cancer control activities have influenced recent outcomes of gynecological cancers in Estonia has been recognized. The results of the study are expected to provide input for health policy decisions in the future.

3. AIMS OF THE RESEARCH

The general aim of the research was to obtain a better understanding of the long-term epidemiological trends in the incidence, mortality and survival of gynecological cancers in Estonia, in the context of societal and healthcare transition, changing risk factor profiles and cancer screening activities.

The specific aims were:

1 To evaluate corpus uteri cancer incidence, mortality and survival trends in Estonia by age, stage and histological subtypes, with an emphasis on surgical treatment.

2 To examine cervical cancer incidence, mortality and survival by age, stage and histology in Estonia, with a particular focus on birth-cohort and period effects.

3 To analyze the incidence, mortality and survival trends of ovarian cancer by age and stage in Estonia.

4 To describe the incidence, mortality and survival of vulvar and vaginal cancers in Estonia.

4. MATERIALS AND METHODS

4.1 Data sources

The data on incident cases were obtained from the ECR, a population-based register collecting data on all newly diagnosed cancer cases in Estonia (see 2.5.4).

The data on deaths were provided by the Estonian Causes of Death Registry. The registry collects information on death certificates which are filled in by doctors or forensic doctors who ascertain the person's death. The registry was established and started to collect data on the 1st of January 2008. Before the date, the data about causes of death were collected by Statistics Estonia (National Institute for Health Development, 2019). Mortality data are available from 1984; causes of death have been classified according to International Classification of Diseases (ICD) starting from 1995.

Population denominator data were obtained from Statistics Estonia (Statistics Estonia, 2019).

Estonian Population Register that was used for vital status follow-up is a database which unites the main personal data on Estonian citizens and citizens of the European Union who have registered their residence in Estonia and aliens who have been granted a residence permit or right of residence in Estonia (Population Register, 2019).

Data definitions

The data on gynecological cancer cases diagnosed in adult women (age ≥15 years) were retrieved from ECR according to ICD-10 codes (Table 2). Cancer sites, overall time periods of analyses, morphology and stage definitions are specified in Table 2. Years of diagnosis were divided into three seven-year periods (1996–2002, 2003–2009, 2010–2016) to estimate the time trends of case distributions and survival (different time periods were used in papers I–IV due to data availability).

The ECR has collected data on stage at diagnosis since 1995. T, N and M stage according to current TNM (Union for International Cancer Control) classification is reported on clinical and pathological cancer notifications. Stage data is available in coded format only from 2012. Therefore, for the purposes of this study, TNM information was extracted from notifications, computerized and categorized into stage groupings based on the 7th edition of TNM or FIGO staging system (2009) (Table 2).

Age groups were defined according to the specifics of the cancer site studied and differed across cancer sites.

Table 2. Data definitions

Site	ICD-10	Period	Morphology (ICD-O-3)	Stage

Corpus uteri cancer	**C54** (C54.0, C54.1, C54.2, C54.3, C54.8, C54.9)	Incidence 1968–2016
		
		Mortality 1995–2016*
		
		Survival 1996–2016
			Type I
			endometrioid adenocarcinoma 83803;
			adenocarcinoma 81403;
			mucinous carcinomas 84803, 84813;
			adenocarcinoma with squamous metaplasia, adenosquamous carcinoma 85603, 85703.
			Type II
			papillary adenocarcinoma 82603;
			clear cell carcinoma 83103, 91103, 91203;
			serous carcinoma and cystadenocarcinoma 84403, 84413;
			carcinosarcoma 89803.
			Others
			sarcomas 88003–89513;
			other morphological entities and unspecified tumors 80003–80103;
				FIGO 2009
				stage I(a-b);
				stage II;
				stage III(a-c2);
				stage IV(a-b).

Cervical cancer	**C53** (C53.0, C53.1, C53.8, C53.9)	Incidence 1968–2016 Mortality 1984–2016 Survival 1996–2016	**Squamous cell carcinoma:** 80513–80833 **Adenocarcinoma**: 81403–85703 **NOS:** 80003–80103 **Other:** tumors of non-epithelial malignancies, carcinomas of neither squamous cell or adenocarcinoma origin 80123–80503; 80983–81303; 88003–94733	**TNM 7th edition** stage I T1(1a-1b2)N0M0; stage II T2(2a-2b)N0M0; stage III T3/3aN0M0; T3bNanyM0; T1–3N1M0; stage IV T4NanyM0; TanyNanyM1

Site	ICD-10	Period	Morphology (ICD-O-3)	Stage
Ovarian cancer	**C56**	Incidence 1968–2016 Mortality 1995–2016* Survival 1996–2016	**All**	**TNM 7th edition** stage I T1(1a-1c)N0M0 stage II T2(2a-2b)N0M0 stage III T1-2N0-1M0 T3aN0-1M0 T3bN0-1M0 T3cN0-1M0 stage IV TanyNanyM1a TanyNanyM1b
Vulvar and vaginal cancer	**C51**(C51.0, C51.1, C51.2, C51.8, C51.9) **C52**	Incidence 1968–2016 Mortality 1995–2016* Survival 1996–2016	**All**	N/A
Other and unspecified	**C55** **C57** (C57.0, C57.1, C57.2, C57.3, C57.4, C57.7, C57.8, C57.9) **C58**	N/A	**All**	N/A

* Mortality data prior to 1995 were available only for cervical cancer due to different classification systems used during the Soviet time.

Surgical treatment of corpus uteri cancer was classified based on the information reported on cancer notification (paper I). All patients reported to have undergone surgical treatment, regardless of intention were considered as surgically treated. The passive nature of reporting did not allow to distinguish between "surgical treatment not done" and "surgical treatment not reported", nor between types and intention of surgical treatment.

The percentage of microscopically verified cases, the percentage of death certificate only cases and cases diagnosed at autopsy were considered as data quality indicators.

4.2 Statistical methods

Incidence, mortality and relative survival were estimated for corpus uteri, cervical, ovarian and vulvovaginal cancers. Age-period-cohort analysis was performed to distinguish the effects of age, period and cohort on cervical cancer incidence. Both corrected and uncorrected mortality trends were analyzed for corpus uteri and cervical cancer.

Descriptive statistics

Chi-square test and two-sided p-values were used to test the statistical significance of the difference between proportions. P-value <0.05 was considered statistically significant. STATA 14.1 software (StataCorp LP, College Station, TX, USA) was used.

4.2.1 Incidence

The incidence rate was calculated by dividing the annual number of incident cases by the average annual number of the female population in a given year and expressed per 100 000 person-years. World standard population (1960) (Waterhouse et al., 1976) was used for calculating age-standardized rates. Joinpoint analysis with Joinpoint Regression Program (version 4.1.1.1) from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint/) was used to model the rates and calculate the estimated annual percent change (APC) with 95% confidence intervals (95% CI) (papers I-III). The minimum number of joinpoints (straight line) was zero and the maximum number suggested by the program for the dataset was five. Permutation test was used to assess the statistical significance of the APCs, where APC is significantly different from zero at alpha=0.05.

For paper IV, the crude incidence rate was calculated for women age 15–44 as a three-year moving average and the statistical significance of the trend was estimated and analyzed with linear regression. Microsoft Excel 2010 and STATA 11.2 software were used.

Age-period-cohort analysis

Cervical cancer incidence trends were separately analyzed with age-period-cohort analysis as shown by Carstensen (Carstensen, 2007). The analysis discerns the effects of age, period and cohort on cancer incidence.

In order to avoid age-period-cohort identification problems, arbitrary constraints were added to the model. 1935–1939 as a reference cohort was chosen. To evaluate the goodness of fit between models with different parametrization, Akaike Information Criterion (Akaike, 1974) was used. The age-function is shown as age-specific rates in reference cohort and adjusted for the period effect. The cohort function is a rate ratio relative to reference cohort and the period effects are a rate ratio relative to the age–cohort prediction (Carstensen, 2007).

For the age-period-cohort analysis, incident cases were aggregated into a five-year period and age groups. Due to small numbers, the cases younger than 30 years and older than 79 years were excluded. Thus, the analysis included 10 age groups (30–34…75–79), 9 periods (1970–1974…2010–2014) and 27 birth-cohorts (1895–1899…1980–1984). For the age-period-cohort calculations the Epi package's apc.fit function in R software (http://www.R-project.org) was used.

4.2.2 Mortality

The mortality rate was calculated by dividing the annual number of cancer deaths by the average annual number of the female population in a given year and expressed per 100 000 person-years. World standard population (1960) (Waterhouse et al., 1976) was used for calculating age-standardized rates. Joinpoint analysis with Joinpoint Regression Program (version 4.1.1.1) from the Surveillance Research Program of the US National Cancer Institute (http://surveillance.cancer.gov/joinpoint/) was used to model the rates and calculate the estimated annual percent change (APC) with 95% CI.

The certification problems of uterine cancer deaths i.e. causes of death recorded as "uterine cancer not otherwise specified (NOS)" may introduce problems in interpreting uterine cancer mortality (Loos et al., 2004; Weiderpass et al., 2014). To correct for these errors, the reallocation rule suggested by Loos et al. was used for corpus uteri and cervical cancer mortality estimation, under the assumption that cause of death NOS was allocated at random and the proportion of NOS of all uterine cancers was ≤25% (Loos et al., 2004; Weiderpass et al., 2014). Corrected mortality rates could be estimated from 1995, as the previously used Soviet causes of death classification did not allow to distinguish deaths due to uterine cancer NOS.

4.2.3 Survival

The patients were followed for vital status from the date of diagnosis until the 31st of December 2016 via linkage with the Estonian Population Register using unique personal identification numbers. The linkage was performed by the ECR. In case of death or emigration, the respective date was obtained.

Relative survival ratios (RSR) with 95% confidence intervals (CI) were calculated as the ratio of the observed survival to the expected survival of the underlying general population. The latter estimate was calculated according to the Ederer II (Ederer et al., 1959) method using national life tables for the female population stratified by single year of age and calendar year. Death certificate only (DCO) cases and those diagnosed at autopsy were excluded from survival analyses. Patients who were diagnosed and died on the same day were included with one day of survival time. Cohort analysis was used to estimate RSRs for patients diagnosed in earlier periods (1996–2002, 2003–2009). Period analysis was used for later cohorts not reaching 5 years of follow-up from diagnosis during the studied period (2010–2016). The International Cancer Survival Standards were used for age-standardizing overall RSRs (Corazziari et al., 2004). All calculations were conducted with STATA 14.1 (StataCorp LP, College Stations TX USA); survival analysis was performed using the *strs* module.

4.3 Ethics

The study protocol was approved by the Tallinn Medical Research Ethics Committee (Decision no. 284, May 16, 2013; Decision no 2636, February 14, 2019).

5. RESULTS

A total of 12 142 incident cases of gynecological cancer were diagnosed in adult women in Estonia in 1996–2016 (Table 3). 95% were microscopically verified cases. Death certificate only and autopsy cases comprised 1% of cases throughout the studied period.

The most frequent gynecological cancer was corpus uteri cancer (35%), followed by cervical cancer (29%), ovarian cancer (27%) and vulvovaginal cancer (6%). Other gynecological cancers and cancers not otherwise specified comprised 2% of cases. During the three time periods (1996–2002, 2003–2009, 2010–2016) the proportion of corpus uteri cancer increased from 34% in the earliest to 38% in the last period and ovarian cancer cases decreased from 28% in the earliest to 25% in the last period. Other gynecological cancer cases remained with unchanged proportions. Over the whole study period, 20% of cases were women under 50 years. The proportion of elderly women (age 80+ years) increased during the study period from 8% to 14%.

The microscopic verification rate was lowest for other cancers (66%) and ovarian cancer (90%), while it exceeded 97% for all other sites. The age distribution of gynecological cancer incident cases varied by cancer types during the study period (Table 4). The majority of cervical cancer cases (64%) were diagnosed in women aged 60 years and younger while 57% of corpus uteri cancer cases and 51% of ovarian cancer cases were observed in women age 60–79 years. The distribution of vulvovaginal cancer cases showed that 63% of incident cases were diagnosed in women aged 70 years and older (Table 4).

Table 3. Incident cases of gynecological cancers (ICD-10 C51–58) in adult women in Estonia by period of diagnosis, 1996–2016

	1996–2016		1996–2002		2003–2009		2010–2016		
	No	%	No	%	No	%	No	%	p-value[a]
Total	12142	100	3904	100	4039	100	4199	100	
Microscopic verification	11515	95	3753	96	3783	94	3979	95	<0.001
Death certificate only	114	1	27	1	50	1	37	1	0.037
Autopsy	87	1	28	1	40	1	19	0	0.015
Age at diagnosis (years)									
15–49	2472	20	811	21	915	23	746	18	<0.001
50–59	2594	21	888	23	830	21	876	21	
60–69	2995	25	1054	27	926	23	1015	24	
70–79	2748	23	825	21	940	23	983	23	
80+	1333	11	326	8	428	11	579	14	
Site (ICD-10)									
Vulvovaginal (C51, C52)	768	6	286	7	215	5	267	6	<0.001
Cervix (C53)	3568	29	1128	29	1239	31	1201	29	
Corpus uteri (C54)	4281	35	1322	34	1366	34	1593	38	
Ovary (C56)	3296	27	1101	28	1126	28	1069	25	
Other and unspecified (C55, C57, C58)	229	2	67	2	93	2	69	2	

[a] Chi-square test

Table 4. Incident cases of gynecological cancers in adult women in Estonia by site, 1996–2016

	Corpus uteri		Cervix uteri		Ovary		Vulvovaginal		Other and unspecified		
	No	%	No	%	No	%	No	%	No	%	p-value[a]
Total	4281	100	3568	100	3296	100	768	100	229	100	
Microscopic verification	4185	98	3460	97	2974	90	745	97	151	66	<0.001
Death certificate only	9	0	21	1	55	2	7	1	22	10	<0.001
Autopsy	29	1	14	0	36	1	3	0	5	2	0.004
Age at diagnosis (years)											
15–49	420	10	1449	41	529	16	40	5	34	15	<0.001
50–59	1004	23	821	23	646	20	79	10	44	19	
60–69	1317	31	628	18	838	25	165	21	47	21	
70–79	1104	26	461	13	852	26	284	37	47	21	
80+	436	10	209	6	431	13	200	26	57	25	

[a] Chi-square test; “other and unspecified” excluded

Corpus uteri cancer

The incidence of corpus uteri cancer increased significantly from 1968 to 1998 at a rate of 1.2% per year and from 2009 to 2016 at a rate of 2.8% per year (Figure 1).

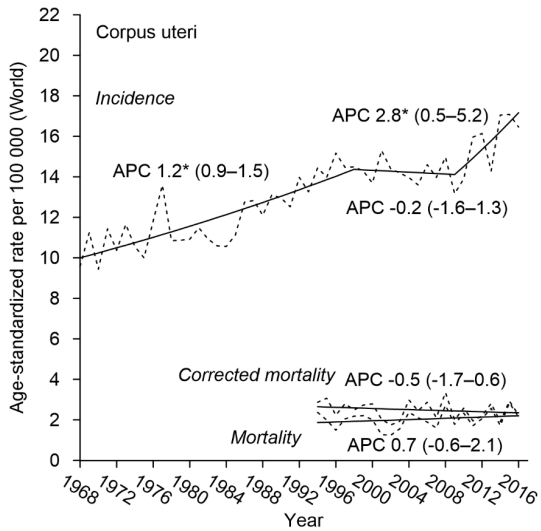

Figure 1. Observed (dotted line) and modelled (solid line) rates and annual percentage change (APC) for trends in age-standardized incidence (1968–2016) and corrected and uncorrected mortality (1994–2016) of corpus uteri cancer in Estonia. *The APC is significantly different from zero at alpha=0.05.

Incidence remained stable for women younger than 65 years and increased for women age 65–74 years, and ≥75 years (paper I, Figure 1). The overall incidence rate of corpus uteri cancer in young women aged 15–44 increased significantly during 1980–2009 (p=0.023) (paper IV, Figure 2). Incidence increase was limited to cancer of type I morphology, while the incidence of cancers of type II or other morphology decreased (paper I, Figure 2).

The uncorrected and corrected trends for corpus uteri mortality were slightly different, suggesting larger misclassification during earlier years. In general, age-standardized mortality remained stable (Figure 1). Mortality remained unchanged for all age groups below 75 years but increased at a rate of 1.6% per year for women age ≥75 years (paper I, Figure 1).

The proportion of stage II cases decreased significantly from 11% to 7% in 1996–2016 and stage IV declined from 11% to 8%, respectively. Surgical treatment became significantly more frequent comparing the earliest (1996–2002, 85%) to the latest (2010–2016, 89%) study period (paper I, Table 1). The proportion of surgically treated patients increased the most for elderly patients (from 58% to 79% in age group ≥75 years), and for stage IV (from 49% to 65%) and stage III (from 86% to 95%) (paper I, Table 3).

The overall age-standardized 5-year RSR significantly improved during the study period 1996–2016 and reached 78% in 2010–2016 (Table 5). The survival increased for all age groups and the age gap narrowed as the largest increase was seen in patients age 65 and older (paper I, Table 2). Survival increase was seen for all stages, but significant improvement was observed only in stage IV patients (paper I, Table 2).

Table 5. Age-standardized 5-year relative survival ratio (RSR) for gynecological cancers in Estonia, 1996–2016

	1996–2002		2003–2009		2010–2016		
	5-year RSR	95% CI	5-year RSR	95% CI	5-year RSR	95% CI	Change[a]
Corpus uteri	71	67–74	71	67–74	78	76–81	**+7**
Cervix	60	57–63	66	63–69	66	63–68	+6
Ovary	29	26–32	36	33–39	44	40–47	**+15**
Vulvovaginal	55	47–61	61	53–69	61	53–68	+6

[a] From first to last period; statistically significant findings in bold

Cervical cancer

The incidence of cervical cancer decreased significantly until 1980 and increased thereafter until the end of the study period at a rate of 0.6% per year (Figure 2).

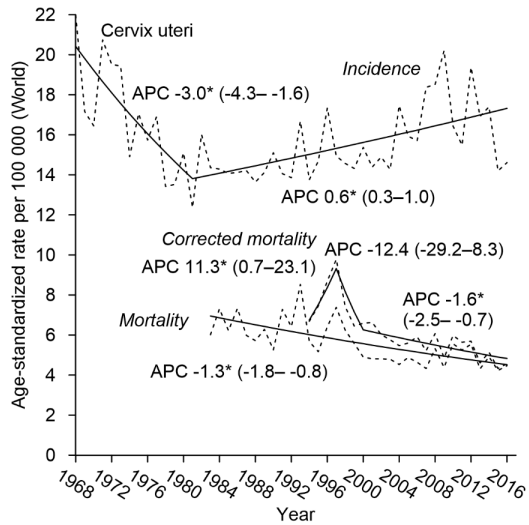

Figure 2. Observed (dotted line) and modelled (solid line) rates and annual percentage change (APC) for trends in age-standardized incidence (1968–2016) and corrected (1994–2016) and uncorrected (1984–2016) mortality of cervical cancer in Estonia. *The APC is significantly different from zero at alpha=0.05.

Significant incidence increase since the 1990s was observed for all age groups except 70+ years (paper II, Figure 1). In women age 15–44, the overall cervical cancer incidence rate increased significantly in 1980–2009 (paper IV, Figure 1). The age-period-cohort analysis showed a continuous increase in the relative risk of cervical cancer for all birth-cohorts younger than those born in 1940 (paper II, Figure 2). No period effects were seen.

The significant increase in squamous cell carcinoma incidence from 1980 was accompanied by a significant increase in adenocarcinoma incidence from the late 1990s (paper II, Figure 1).

The proportion of stage I cancers decreased from 40% in 2005–2009 to 35% in 2010–2014, while the proportion of stage IV increased from 13% in 2005–2009 to 18% in 2010–2014 (paper II, Table 1). 47% of all cases were observed in women aged 40–59 years. The proportion of incident cases of adenocarcinoma histology increased from 6% in 1995–1999 to 14% in 2010–2014. Squamous cell carcinoma cases decreased from 85% in 1995–1999 to 78% in 2010–2014 (paper II, Table 1). The shift towards later stages was observed for all age groups except women aged 40–49 years (paper II, Figure 2). The proportion of stage I cases decreased from 40 to 35% ($p=0.0096$) and the proportion of stage IV cases increased from 13 to 18% ($p=0.0019$) (paper II).

The overall age-standardized mortality trend for cervical cancer showed a modest decline by APC 1.3% (uncorrected) from 1985 to 2016 (Figure 1). The corrected mortality trend from 1995 to 2016 mimicked the longer uncorrected pattern with a slightly more prominent decline by APC 1.6% per year. Stable trends were observed for the age groups of 15–29 years, 40–49 years and 50–59 years. The significant declining mortality trend for women aged 60–69 years and 70+ years was observed (paper II, Figure 1).

The age-standardized 5-year RSR of cervical cancer patients increased significantly from 1996 to 2009 and stabilized thereafter and estimated at 66% in 2010–2016 (Table 5). The significant improvement was seen in the age groups of 30–39 and 40–49 (paper II, Table 2). In the oldest age group the 5-year RSR slightly decreased.

Ovarian cancer

The incidence of ovarian cancer has been stable over the study period 1968–2016 (Figure 3). For the age group of 50–59 years a significant decline by APC 3.4% per year was observed from 1995 to 2009 and followed by a significant increase until 2013 (paper III, Figure 1). Incidence rates for all other age groups have been stable. No significant changes in incidence were seen in women age 15–44 in 1980–2009 (paper IV, Figure 3).

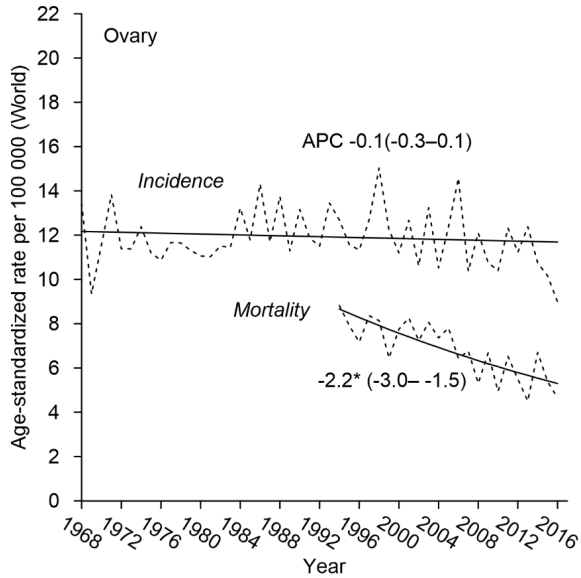

Figure 3. Observed (dotted line) and modelled (solid line) rates and annual percentage change (APC) for trends in age-standardized incidence (1968–2016) and mortality (1994–2016) of ovarian cancer in Estonia. *The APC is significantly different from zero at alpha=0.05.

The distribution of cases by age groups showed a decrease in the proportion of women aged 50–69 years and an increase in the proportion of women ≥70 years, the latter counting 42% of all cases in 2005–2009 (paper III, Table 1). An increase in the proportion of stage I disease from 14% in 1995–1999 to 16% in 2005–2009 was observed, while stage III and stage IV cases increased from 64% to 67% over the study period.

The overall mortality rate has been significantly declining since 1995 by APC 2.2% per year (Figure 1). A significant mortality decline was seen in the age groups of 50–59 and 60–69, while no changes were seen in the age group of 15–49 and a fluctuating trend was seen for the age group ≥70 with a significant decreasing segment from 2009 (paper III, Figure 1).

Ovarian cancer age-standardized RSR has significantly improved from 29% in 1996–2002 to 44% in 2010–2016 (Table 5). The survival has increased in all age groups and in all stages (paper III, Table 2).

Vulvar and vaginal cancers

The age-standardized incidence rate of vulvovaginal cancer has been stable over the study period, while mortality has declined by 1.0% per year since 1996 (Figure 4).

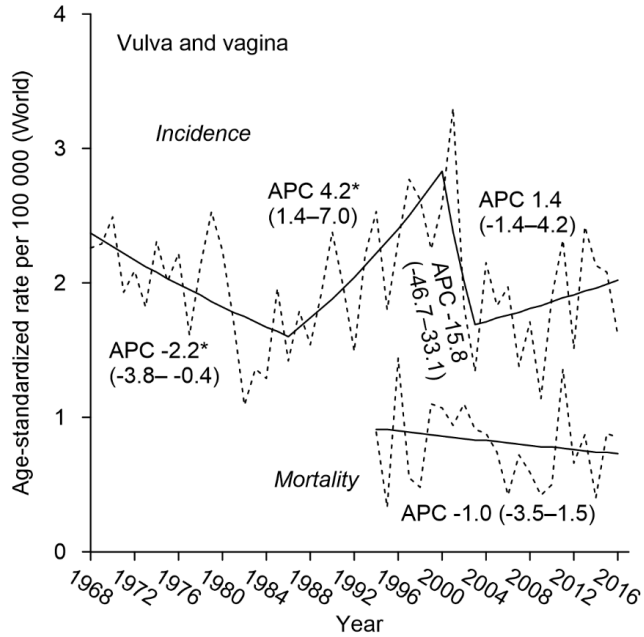

Figure 4. Observed (dotted line) and modelled (solid line) rates and annual percentage change (APC) for trends in age-standardized incidence (1968–2016) and mortality (1994–2016) of vulvovaginal cancer in Estonia. *The APC is significantly different from zero at alpha=0.05.

The stable trend was observed for both the younger and older age groups (Figure 5).

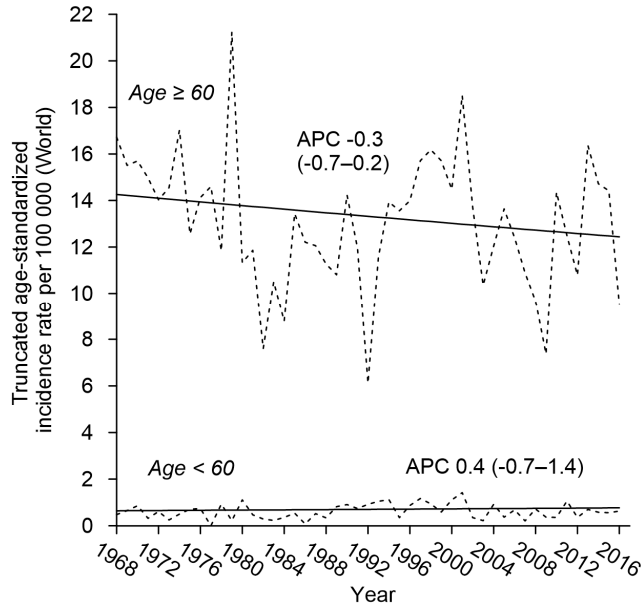

Figure 5. Observed (dotted line) and modelled (solid line) rates and annual percentage change (APC) for trends in truncated and crude age-standardized incidence (1968–2016) by age of vulvovaginal cancer in Estonia. *The APC is significantly different from zero at alpha=0.05.

The proportion of the youngest age group 15–49 developing vulvovaginal cancer has decreased and the oldest age group has increased during the studied period 1996–2016 (Figure 6).

The age-standardized 5-year RSR has increased from 55% in 1996–2002 to 61% in 2003–2009 and has been stable thereafter (Table 5).

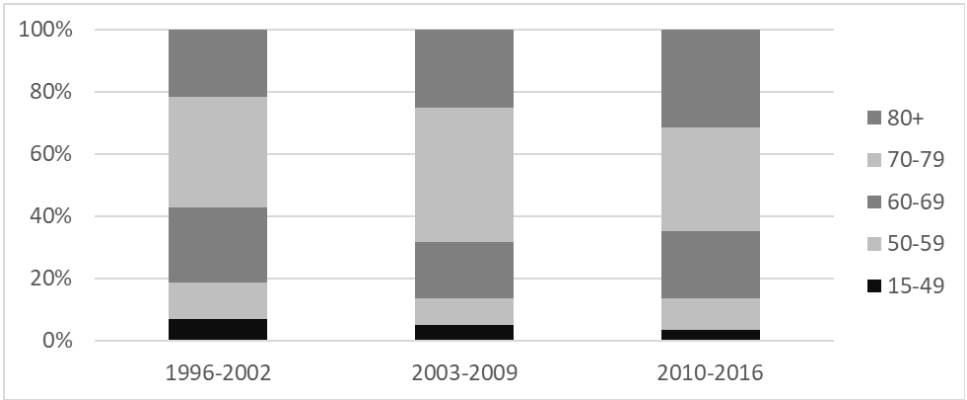

Figure 6. The age distribution of incident cases of vulvovaginal cancers, 1996–2016 (p=0.053)

6. DISCUSSION

This thesis provides an in-depth analysis of the long-term trends of all gynecological cancers in Estonia, using a variety of statistical methods. Incidence trends were examined over four decades, and mortality and survival trends over two decades. We observed a significant increase in the incidence of the two most common gynecological cancers, corpus uteri and cervical cancer. The trend for the latter site reflected the risk increase in successive birth cohorts born after the 1940s with no health-care related period effects to counteract those strong cohort effects. No particular changes were seen in the incidence of ovarian and vulvovaginal cancers. A significant mortality decrease has been apparent for ovarian cancer over the whole study period and for cervical cancer in more recent years. The largest survival improvement was seen for ovarian cancer (15% units over 20 years), while the progress was less rapid for other cancers. The proportion of older women among gynecological cancer patients almost doubled during the study period. A slight shift towards earlier diagnosis was seen only for corpus uteri cancer, whereas the stage distribution of cervical cancer shifted significantly towards the later stage.

Strengths and weaknesses of the thesis

The thesis is the first comprehensive overview of the long-term trends of gynecological cancers in Estonia. The main strength of the study was the use of uniformly collected population-based incidence data from the cancer registry that has nation-wide coverage since 1968 and adheres to international rules and principles, allowing specific analyses by morphology. The good quality of ECR data in terms of completeness, validity and vital status follow-up is evidenced by several quality analyses and international projects. The validity of ECR data is comparable to European cancer registries' estimates (Innoset al., 2015; Orumaa et al., 2015). The quality indicators (percentages of microscopically verified cases, autopsy cases and death certificate only cases) were similar to other registries in Western Europe (Innos et al., 2015; Orumaa et al., 2015). As an additional strength, data on tumor stage was available for a 20-year period. The study used a variety of statistical methods to better characterize changes over time and generations (i.e. join-point regression, age-period-cohort analysis) and took specific measures to overcome possible problems with data quality (i.e. corrected mortality analysis).

The main weakness of the study was limited information on the predictors of incidence or survival. Individual data on socioeconomic background, obstetrical status, place of residency or average income of women were not available for analysis. The data on performed hysterectomies and the detection mode of cervical cancers (screen-detected or not) were not available either.

Mortality analyses were limited by data availability and the use of a Soviet coding system used prior to the adoption of the ICD in 1995, which did not allow to distinguish several disease entities. Therefore, the time periods

included in mortality trend analyses differed across cancer sites and corrected mortality analysis for corpus uteri and cervical cancer was only possible from 1995. The comparison of uncorrected and corrected mortality rates demonstrated larger misclassification in earlier years, supporting the need for presenting corrected rates in order to avoid inaccurate interpretations of mortality trends. Furthermore, an evaluation of cause of death misclassification using linkage of individual incidence and death records is warranted in order to obtain a more precise estimate of the magnitude of possible misclassification. This study is ongoing.

Trends by histological types may have been influenced by the continuously improving accuracy of pathological diagnosis that has brought along lower proportions of NOS diagnoses and less misdiagnosis over the study period. Likewise, more thorough diagnostic work-up and the use of more accurate diagnostic methods in the later periods may have caused stage migration and led to some overestimation of stage-specific survival estimates.

Corpus uteri cancer

Corpus uteri cancer has become the most common gynecological cancer in Estonia. Its two types showed the distinct incidence trends. The rapid increase of type I endometrial cancer has been observed in developed countries and the main reason is considered to be the burden of obesity (Evans et al., 2011; Onstad et al., 2016). Being overweight and obese are increasing in Estonia (Tervise Arengu Instituut, 2018.) and this has likely contributed to the increase of the overall corpus uteri cancer incidence. The increase is more prominent in women aged over 65 years and an incidence increase driven by the same age group has also been observed in the Netherlands (Boll et al., 2013). Still, the trends in incidence are not consistent in all countries. In Denmark, overall decrease of corpus uteri cancer has been shown and the decrease of type I cancers was accompanied by the increase of type II cancers (Faber et al., 2017). The decline of the age-standardized incidence rate and the proportion of type II cancers in Estonia could reflect the possible misclassification of serous tumors during earlier periods. More accurate pathological diagnostics, e.g. immunohistochemistry, may detect more precisely the origin of the cancer.

The other possible underlying reasons for the increasing corpus uteri cancer trend in Estonia are the decrease of the number of children and deliveries per women. The average number of children per woman in 2018 was 1.7 (Statistics Estonia, 2019). The number of children per woman has been decreasing over time. For today's 55–59 years old women the mean number of children is 1.9 and for women 40–44 it is 1.7. The mean age at first birth has also risen from 22.7 years in 1992 to 28.3 years in 2017 (National Institute for Health Devlopment, 2019).

The use of menopausal HRT is not common among Estonian women (Sammul et al., 2018). HRT with estrogen compound only is permitted for women without a uterus and its use among women is very low.

The stage distribution with the increased proportion of stage I disease suggest more frequent early detection. The data is consistent with the type I cancers' clinical behavior which could be detected at an early stage due to the occurred symptoms.

The overall stable mortality trend of corpus uteri cancer is in line with most European countries' estimates (Weiderpass et al., 2014). However, more attention should be paid to the cause-of-death data among endometrial cancer patients in Estonia. Endometrial cancer patients might suffer from several comorbidities that could be life-limiting besides cancer itself. Comorbidities are frequently related to obesity e.g. hypertension and diabetes. Diabetes and two or more comorbidities are found to be negative predictors for corpus uteri cancer mortality (Nagle et al., 2018). Cardiovascular disease is the main cause of death for both younger and older patients with localized endometrial cancer (Ward et al., 2012). Type II cancers cause the most cancer related deaths among corpus uteri cancers (Torre et al., 2017; Ward et al., 2012). Therefore, the possible misattribution of cause of death could be suspected, considering the data on histological subtypes and stages.

Despite the significant improvement of corpus uteri cancer survival observed during the study period, the latest 5-year RS estimate of 78% is still lower than the estimate in the US (81%) in 2009–2015 (National Cancer Institute, 2019) and in the Nordic countries (83%) (Danckert et al., 2019) during the same period. The gap mostly remains for women age 65 and over, although this age group experienced the largest survival improvement. Large survival increases for both elderly women and stage IV patients occurred in parallel with a large increase in the proportion of patients treated surgically.

More frequent surgeries during the study period among elderly women could refer to better management of comorbidities. Even at late stages, surgical treatment is found to increase the survival for corpus uteri cancer patients (Barlin et al., 2010). The significant increase of surgically treated corpus uteri cancer patients during the past 20 years have also been observed in Norway (Trovik et al., 2012). The increasing surgery rate might be somewhat consistent with higher proportions of stage I disease which are frequently clinically managed by surgery only. However, comparing the data with the Norwegian 95% of patients who had undergone surgical treatment in 2001–2010 (Trovik et al., 2012) and the estimate found in the thesis which was only 89% in the last studied period, the need for the improvement in clinical care should be realized.

Cervical cancer

The increase in cervical cancer incidence with the shift towards later stages and older ages reflects the ineffectiveness of the nation-wide screening program in Estonia which was established in 2006 (Lynge et al., 2017). An effective screening program would have been expected to result in fewer cancer cases and the shift towards earlier stages and ages (Dickinson et al., 2012; Serraino et al., 2015). The major interventions made by countries e.g. nation-wide screening programs, have shown clear positive changes in the epidemiological

trends of cervical cancer in terms of the relative risk reductions in cervical cancer incidence by birth-cohorts and the decrease in incidence rates (Lynge et al., 2017; Vaccarella et al., 2013). The age-period-cohort analysis performed in the thesis showed the peak incidence in cervical cancer diagnosis around 50 years and a constantly increasing risk for all birth-cohorts from women born in 1940. No period effects were apparent. In the Nordic countries, more than 50 years of cervical cancer screening has set the peak incidence appearance around the age of 30 (Lynge et al., 2017; Serraino et al., 2015). This is the time when the first screening tests have been given by the first target age group. The increasing prevalence of HPV and changed sexual behavior have put birth-cohorts of women born after 1940 at an increasing risk of cervical cancer. This manifestation is common for all European countries (Vaccarella et al., 2014; Vaccarella et al., 2013). The period effect has shown a large decreasing cervical cancer incidence trend from the 1960s in the Nordic countries (Vaccarella et al., 2014). This is consistent with the beginning of screening in these countries. Our analysis showed a constantly stable period effect which refers to the lack of effective interventions against cervical cancer, including an opportunistic or organized screening program. It has been estimated that the screening program in the Nordic countries has prevented around 50% of cervical cancer cases from the beginning of the 1960s.

The high participation rate in organized screening programs is the corner-stone of a successful screening. In Denmark a stable participation rate of 75% in 2009–2015 was concluded as the reason for having one of the highest cervical cancer incidence rates (10/100 000, world) in the Nordic countries (Danckert et al., 2019; Lynge et al., 2017). The participation rate in Sweden has been 80% and the incidence rate is estimated at 9/100 000 (world) (Ferlay et al., 2018). In Estonia, the high incidence rate of 22/100 000 (world), reflects the low participation rate of the target population that has been estimated at only 51% in 2017 and even lower earlier (National Institute for Health Development, 2019). The nation-wide screening covers women with valid health insurance. In 2018, less than 95% of the Estonian population had valid health insurance (Organisation for Economic Co-operation and Development, 2019). Therefore, for the purposes of cervical cancer incidence decline in Estonia, women without health insurance should be included into the screening. The Nordic countries data have shown the second incidence peak among the elderly, women over 70 years old (Lynge et al., 2017). It is considered to be related to screening activities which were completed too early (aged 55). Therefore, the need to broaden the age frame up to the age of 70 years should be taken into account also in Estonia. For the strengthening of screening impact on cervical cancer incidence and survival, the addition of HPV-DNA detection besides the conventional Pap-smear test must be considered. Women with high risk HPV types need more frequent follow-up and accurate management.

In the thesis the corrected mortality showed a slightly decreasing trend from 1995 when even the rate above 4/100 000 per year is relatively high. In most of the European countries the mortality of cervical cancer is in a continuous

decline (Arbyn et al., 2009). In certain Eastern European countries, the trend has shown a stable or even an increasing pattern. Mortality rates are compatible with incidence rates. In countries with increasing or stable mortality rates, the cervical cancer screening is not working or is not established at all (Anttila et al., 2009; Lynge et al., 2017).

The aim of Pap-smear based screening is to prevent cervical cancer by treating premalignant lesions or find the cancer early when the cure is possible. It is estimated that Estonia would face an extra 1500 cervical cancer deaths by 2030 (Vaccarella et al., 2016) if strong preventive input won't be considered. From 2018 the vaccination of girls aged 12–14 has been integrated into the national vaccination plan. The decrease of pre-malignant cervical lesions and genital warts can be expected in 10 years (Drolet et al., 2015).

For the period 2010–2016, the 5-year RSR in Estonia was estimated at 66%. This is comparable to Nordic data during the same period 2012–2016 (Danckert et al., 2019) – 66% in Finland and the highest estimate of 73% in Norway. In Estonia, the significant improvement in survival from 1995–1999 to 2010–2016 was accompanied by dismal incidence rate, age and stage distributions.

The halted overall survival improvement in the later period of 2010–2016 reflects the shift towards later stages, but the small progress in implementing modern treatment modalities could also be considered. The conclusions of a clinical audit performed by EHIF in 2014–2015 referred to the limited availability of radiotherapy for cervical cancer patients. Furthermore, the new systemic treatments should be made available faster for patients suffering from cervical cancer.

Ovarian cancer

Stable incidence, significantly decreased mortality and rapidly increased survival of ovarian cancer patients have been observed in the thesis.

The long-time decline of ovarian cancer incidence has been observed in developed countries (Lowe et al., 2013; Sopik et al., 2015) and it is considered to be related to widespread oral contraceptive use which have a protective role against the cancer (Sopik et al., 2015). In the US approximately 85% of women born later than 1940 have used oral contraceptives at some period of their lives (Sopik et al., 2015). The real effect of oral contraceptives use on ovarian cancer incidence in Estonia could be expected within 10 years as the protective effect of the drugs lasts up to 30 years if ever used (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2008; Webb et al., 2017). The protective role of pregnancies could be considered, observing a significant incidence decline in the age group 50–59. The baby-boom took place in Estonia at the end of the 1980s and in the beginning of the 1990s. These women were at child-bearing age at that time which may have affected their cancer risk. The stage distribution of ovarian cancer over the studied period of 1995–2009 did not show any major changes. According to these findings no improved early detection could be concluded. As the ovarian cancer age-adjusted incidence rate increases with

age, the growing proportion of women over 70 years is the consequence of an ageing population.

The mortality of ovarian cancer has significantly declined in Estonia. Stable overall incidence trend and improved access to specialized care are the proposed reasons for better mortality estimates.

The overall survival of ovarian cancer has significantly improved from 1996 to 2016. The 5-year RSR of 26% observed in the EUROCARE-3 study has almost doubled by 2010–2016 reaching 44%. The estimate is highly comparable with countries with high quality cancer care like the Nordic countries (Danckert et al., 2019). The data on 5-year RSR on ovarian cancer survival in 2012–2016 showed 49% in Sweden, 45% in Norway, 44% in Finland and 41% in Denmark.

The progress in medicine has improved ovarian cancer patients' short-term survival, but the long-term survival has not improved in the world. Approximately 80% of ovarian cancer patients die due to the cancer within 10 years and only 13% are alive with advanced stages at 10 years from diagnosis (Timmermans et al., 2018).

The importance of optimal cytoreduction with no residual disease left in the advanced stages were introduced in the world in the beginning of the 2000s (Aletti et al., 2006; Du Bois et al., 2009) and it has remained the most powerful prognostic factor for ovarian cancer survival. Platinum-based chemotherapy, introduced in the beginning of the 1980s by cisplatin and replaced by carboplatin in the beginning of the 2000s, added an additional survival benefit and raised the overall 5-year RSRs over 4 years for advanced stages (Ozols et al., 2003). Today, maintenance therapy and evolving personalized medicine are expected to improve survival further (Mirza et al., 2018.).

Extensive surgeries with wide excisions and the management of postoperative complications could be performed only in high volume and well-equipped specialized hospitals. The audit in four hospitals performing ovarian cancer surgical treatment were carried out in 2014–2015 in Estonia. The audit was managed by the EHIF. The overall conclusion of ovarian cancer surgical treatment was good, and 79% of patients had undergone optimal cytoreduction. More efforts and unification were suggested for early stage surgical treatment (Eesti Haigekassa, 2019).

Vulvovaginal cancer

The incidence of vulvovaginal cancer showed a fluctuating trend from 1968 to 2016 due to a small number of cases, while mortality did not change significantly in 1995–2016. The increase of vulvovaginal cancer incidence has been previously observed in Germany and in England (Holleczek et al., 2017; Lai et al., 2014). The incidence increase in these countries has been significantly based on the increasing incidence among women under 60 years old. The proportion of women 54 years and younger diagnosed with vulvar cancer has increased from 11% in 1989–1993 to 23% in 2009–2013 in Germany (Holleczek et al., 2017). In contrast the proportion of elderly women 75 years and older has decreased from 44% to 35% during the same period. The increase in

the number of overall cases were also observed. In this thesis, contrary to German trends, the number of cases during the studied period did not change and the proportion of women 70 years and older increased from 57% in 1996–2002 to 65% in 2010–2016 and the proportion of younger women aged 60 years and less, decreased from 19% to 14% during the same period. The observed age standardized incidence rates in Estonia have been stable for both younger and older women. The increase of the incidence among younger women has been explained by the widespread prevalence of HPV and its cancerous type 16 (Barlow et al., 2015) as the main risk factor. The incidence pattern observed in the thesis over the study period might refer to a smaller prevalence of high-risk HPV type 16 among middle-age women than among the counterparts in countries with higher incidence rates.

The estimated stable mortality trend refers to stable and unchanged incidence trends.

The stable survival rates during the latest periods (5-year RSR in 2003–2009 and 2010–2016, respectively) were lower than the estimates in the Nordic countries (Danckert et al., 2019.), England (Lai et al., 2014) and in Germany (Holleczek et al., 2017). The rise in detection of early stage tumors in concordance to the incidence increase of younger women have been described in these countries. Treatment at earlier stages has a more favorable outcome in terms of overall survival. High proportions of elderly patients with more advanced tumors could be the reason for dismal overall survival in Estonia.

7. CONCLUSIONS

The thesis provides a comprehensive overview of long-term gynecological cancer incidence, mortality and survival trends in Estonia that reflected the societal and economic transition in the country during the past decades. The results of the study identified a major pitfall in cancer control in Estonia by revealing dismal cervical cancer trends resulting from an underpowered national cervical cancer screening program. The changing risk factor profile cannot be underestimated in the increasing incidence trend of corpus uteri cancer and also cervical cancer. Women's health issues should be of high importance in the state health policy and women's cancer prevention and early detection should be highlighted in cancer control.

The results of the thesis contribute to evidence-based health policy by helping to define the future perspective in women's cancer and giving the directions for the improvement in health care organization, public health policies and cancer care.

1. Corpus uteri cancer is the most frequent gynecological cancer in Estonia. The incidence of corpus uteri cancer has increased driven by the type I cancer trend. The most likely underlying cause of the trend is the increasing prevalence of obesity in female population. The observed survival increase was most likely associated with more frequent surgical treatment among all age groups and stages. The importance of the management of comorbidities for corpus uteri cancer outcomes is widely recognized, therefore the improvement in the management of comorbidities, especially at older ages would lead to further survival gain. Corpus uteri cancer mortality has not turned to a decline.
2. The study demonstrated increasing cervical cancer incidence rates in women under 70 years of age. Increases were seen for both major histological subtypes. The overall rising incidence trend reflected the increasing risk in successive birth cohorts born after 1940s with no interventions to counteract this. The corrected mortality trend showed a modest decline while mortality rate remained high. Although cervical cancer survival has somewhat improved, the observed shift towards older ages and later stages is not consistent with the outcomes expected from ongoing nation-wide screening.
3. The incidence of ovarian cancer has been stable over the past decades in Estonia. The rapid mortality decline was accompanied by significant improvement of survival, which has now reached estimates comparable with European countries of high-quality cancer care. The pattern was even more remarkable if considering the increased proportion of elderly women and the survival gain both in elderly women and most advanced stages.
4. A stable incidence trend of vulvovaginal cancer was shown over the study period. No shift towards younger ages or the increase in the incidence of younger women was observed. The stable mortality rates and only modestly improved survival indicate the need to pay more attention to elderly women.

8. IMPLICATIONS FOR PRACTICE

Corpus uteri cancer

The country's public health strategy for tackling obesity should incorporate measures for increasing awareness about obesity related cancers, including endometrial cancer in women, among other health problems. Clinicians should put more effort into advising overweight and obese women. The detection and consideration of the patient's individual risk factors would lead to tailored diagnostics of suspicious premalignant conditions and more frequent early detection of corpus uteri cancer. The implementation of relevant guidelines for early detection and optimal management of endometrial hyperplasia to prevent corpus uteri cancer should be emphasized. The prevention and treatment of comorbidities (diabetes, cardiovascular disease) are essential for longer survival and for the ability to apply different treatment modalities to endometrial cancer patients.

Cervical cancer

The trends found in the study are similar to other Eastern European countries and lead to the conclusions that the Pap-smear-based screening strategy has been ineffective. There is an urgent need to acknowledge that screening activities must be improved. The participation rate needs to be increased. Quality assurance measures have to be implemented in the program. Opportunistic screening should be replaced by program-based activities. Further activities and a follow-up in case of an abnormal Pap-smear finding are of the greatest importance in preventing cervical cancer. The addition of HPV-DNA detection could help to detect women with high risk lesions and plan specific treatment and follow-ups. Upper age limit for screening should be increased. Home-testing should be offered to women who have not participated for more than 7 years in screening. Women without health insurance are the highest risk group for cervical cancer and therefore must be included into the screening. More accurate data and feedback on participation, Pap-smear results and screening service providers should be gathered in Estonia. Regular monitoring of quality indicators for screening activities might help to define possible pitfalls in data accuracy and timely adequacy. Altogether, both the strengthening of screening activities and treating cervical cancer patients should be addressed. HPV vaccination for girls started in 2018 and the results in terms of cervical cancer incidence decrease could be expected no earlier than in 10 years. The data on vaccination should be registered on individual level that would help to adapt further screening. Vaccination of boys against HPV should be considered.

Ovarian cancer

New approaches are needed to reduce ovarian cancer incidence, improve early detection and prolong survival. Genetic counselling and prevention should be emphasized as the only effective prevention strategy for hereditary ovarian

cancer. Implementation of new treatment modalities both in surgery and in systemic therapy are essential for better survival outcomes. Collaboration in clinical and scientific projects with hospitals and institutions together with neighboring countries would bring benefit for both patients and clinicians. The timely access to high quality care is the key prerequisite for better outcomes.

Vulvovaginal cancer

The importance of the follow-up and treatment of lichen sclerosus and low-risk VIN are important to reduce vulvar cancer incidence in Estonia. Elderly women should be informed about vulvar cancer symptoms and about the need to visit a gynecologist regularly. Taking into account the trends of cervical cancer as HPV induced cancer, vigilance regarding the increasing incidence of vulvovaginal cancer in younger women should be kept in mind by clinicians in future. Regular gynecological check-ups and the knowledge about the symptoms of vulvovaginal cancer should be emphasized to achieve earlier detection. Tackling and preventing health problems caused by HPV should be the focus in the future.

9. FUTURE DIRECTIONS

The continuous evaluation of gynecological cancer trends is necessary for cancer control and health policy implementation. Further studies should take into account individual data on the place of residence, average income and the level of education to study relevant associations. As cancer treatment might result in major disabilities, the quality of life of gynecological cancer patients needs to be studied and improved.

More in-depth research on corpus uteri cancer incidence and mortality should be carried out to describe the influence of risk factors and the presence of co-morbidities. Mortality trend needs to be re-evaluated by taking into account all-cause mortality and disease specific mortality. The evaluation of different treatment modalities would have an important value in planning cancer care.

Cervical cancer incidence trend reflects the ineffectiveness of nation-wide screening program. Therefore, the studies on incidence and mortality trends are needed to improve the screening program. Further studies should take into account the woman's participation in screening, previous Pap-smear test results and socioeconomic background.

Ovarian cancer is a heterogeneous disease and the analysis of incidence trends of distinct subtypes' with the consideration of known risk factors should be carried out. Hereditary ovarian cancer prevention should become of more interest in further studies. The evaluation and the prevention of hereditary ovarian cancer are important topics to discuss in near future in Estonia.

Vulvovaginal cancer incidence is expected to rise in the future. The study on incidence rates among younger women with the assessment of the prevalence of different HPV types would give more information and the insight of future perspective.

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SUMMARY IN ESTONIAN

Günekoloogiliste pahaloomuliste kasvajate epidemioloogia Eestis

Rahvastiku vananemine on toonud kaasa vähihaigestumuse tõusu üle kogu maailma. Arenenud riikides on vähk surmapõhjusena tõusnud sageduselt teisele kohale südame-veresoonkonna haiguste järel. Vähihaigestumuse, -suremuse ja -elulemuse mõõtmine on oluline vähitõrje ja tervishoiukorralduse planeerimiseks ja tõhususe hindamiseks.

Naised moodustavad poole maailma elanikkonnast. Noorte naiste hulgas on haigestumus pahaloomulistesse kasvajatesse oluliselt kõrgem kui noorte meeste hulgas. Naiste vähist tingitud enneaegsete surmade vältimine ja tervisekao vähendamine on vähitõrje oluline eesmärk kogu maailmas.

Günekoloogiliste paikmete vähid moodustavad kõigist naistel diagnoositavatest pahaloomulistest kasvajatest Euroopas 15% ja Eestis 13%. Munasarja-, emakakeha-, emakakaela-, häbeme- ja tupevähi riskitegurid erinevad ning nende paikmete kasvajate esinemist mõjutavad ühtlasi muutused ühiskonnas, sotsiaal-majanduslikus seisundis ja tervishoiukorralduses. Eelnevad uuringud on Eestis näidanud kõrget haigestumust ja suremust günekoloogilistesse kasvajatesse ning Euroopa keskmisest madalamat elulemust.

Emakakehavähi peamiseks riskiteguriks on ülekaal ja rasvumine. Selle kasvaja haigestumus on viimastel aastakümnetel maailmas tõusnud, suremus aga langenud või püsinud stabiilsena. Üleeuroopalise vähielulemusuuringu EUROCARE andmetel oli aastatel 2000–2007 emakakehavähi patsientide elulemus Eestis Euroopa viimase kolme kõige madalama tulemuse hulgas.

Emakakaelavähi peamine riskitegur on seksuaalsel teel leviv inimese papilloomiviirus (HPV). Emakakaelavähki on võimalik ennetada riiklikul tasandil organiseeritud sõeluuringuga. Euroopas, välja arvatud Ida-Euroopa riikides, on täheldatud emakakaelavähi haigestumuse pidevat langust. Eestis on emakakaelavähi haigestumus aga üks kõrgemaid Euroopas. Selle vähipaikme elulemus Eestis on Euroopa keskmisel tasemel.

Munasarjavähi kõrge risk on peamiselt seotud geneetilise eelsoodumusega ning kaitsvaks teguriks on suukaudsete rasestumisvastaste vahendite kasutamine. Viimastel aastakümnetel on maailmas täheldatud haigestumuse langust, suremus on aga stabiilne või langemas. Munasarjavähi elulemus on võrreldes teiste günekoloogiliste kasvajatega madal. Üleeuroopalised vähielulemusuuringud on näidanud teatavat elulemuse paranemist, kuid viie aasta suhteline elulemus ei ole ületanud 50%.

Häbeme- ja tupevähi peamiseks riskiteguriks on samuti HPV. Vanematel naistel võib häbemevähk areneda ka naha krooniliselt põletikulisest seisundist – *lichen sclerosusest*. Häbeme- ja tupevähi haigestumus on maailmas püsinud stabiilsena ning suremus on üldiselt madal. Häbeme- ja tupevähi elulemus on Euroopas viimastel kümnenditel paranenud.

Töö eesmärk

Töö peamine eesmärk oli paremini mõista günekoloogiliste pahaloomuliste kasvajate pikaajalisi haigestumuse, suremuse ja elulemuse trende Eestis, hinnates neid ühiskonnas aset leidnud sotsiaalsete ja tervishoiukorralduslike muutuste, riskitegurite trendide ja emakakaelavähi sõeluuringu kontekstis.

Töö alaeesmärgid:

1. Hinnata emakakehavähi haigestumust, suremust ja elulemust Eestis, keskendudes vanusele, staadiumile, histoloogilisele alatüübile ja kirurgilisele ravile.
2. Analüüsida emakakaelavähi haigestumust, suremust ja elulemust Eestis vanuse, staadiumi ja histoloogilise alatüübi järgi, rõhuasetusega sünnikohordi- ja perioodiefektidel.
3. Hinnata munasarjavähi haigestumust, suremust ja elulemust Eestis vanuse ja staadiumi järgi.
4. Kirjeldada häbeme- ja tupevähi haigestumust, suremust ja elulemust Eestis.

Materjalid ja metoodika

Töö peamise andmeallikana kasutati Eesti Vähiregistrit. See on rahvastikupõhine register, mis kogub andmeid kõigi Eestis diagnoositud vähijuhtude kohta. Register loodi 1978. aastal ja sisaldab andmeid alates 1968. aastast. Andmed surmajuhtude kohta saadi Eesti Surmapõhjuste Registrist ja rahvastikuandmed Statistikaametist.

Andmed täiskasvanud naistel (vanus ≥15 aastat) diagnoositud günekoloogiliste pahaloomuliste kasvajate kohta koguti vähiregistrist vastavalt Rahvusvahelise Haiguste Klassifikatsiooni (RHK) 10. versioonile. Histoloogilised tüübid defineeriti RHK Onkoloogia osa 3. versiooni järgi. Staadiumid grupeeriti TNM ja FIGO (Rahvusvaheline Günekoloogia ja Sünnitusabi Föderatsioon) klassifikatsiooni alusel. Vanuserühmad moodustati vastavalt kasvajapaikme spetsiifikale. Andmed emakakehavähi kirurgilise ravi kohta pärinesid vähiteatistelt.

Haigestumus- ja suremuskordajad arvutati kasutades aastakeskmist naisrahvastikku ja väljendati 100 000 inimaasta kohta. Vanusele kohandamiseks kasutati maailma standardrahvastikku. Kordajate modelleerimiseks ja aastase protsentuaalse muutuse ning 95% usaldusintervalli arvutamiseks kasutati *joinpoint* regressioonanalüüsi. Haigestumust vaadeldi perioodil 1968–2016 ning suremust 1995–2016. Elulemusanalüüsi kaasati aastatel 1996–2016 diagnoositud esmasjuhud.

Emakakaelavähi haigestumustrende analüüsiti täiendavalt vanus-periood-kohort-mudeli abil. Arvutati eri sünnikohortide ja ajaperioodide suhteline risk.

Emakakeha- ja emakakaelavähi suremuse analüüsimisel kasutati suremuskordajate korrigeerimist võimalike vigade suhtes, mis võivad tuleneda surmapõhjuse valest kodeerimisest. Vead võivad esineda juhul, kui korrektse paikmespetsiifilise koodi asemel märgitakse surma põhjusena täpsustamata emakakehavähk.

Elulemusanalüüsi jaoks jälgiti patsientide elustaatust kuni 31. detsembrini 2016, linkides vähiregistri andmed isikukoodi alusel Rahvastikuregistri andmetega. Isiku surma või riigist lahkumise korral saadi teada vastav kuupäev.

Suhteline elulemusmäär koos 95% usaldusintervalliga saadi tegeliku elulemuse jagamisel eeldatava elulemusega. Viimane leiti vastavalt Ederer II meetodile kasutades naisrahvastiku elutabeleid. Lahangul diagnoositud ja ainult surmatunnistuse juhud jäeti elulemusanalüüsist välja. Varasemate perioodide puhul kasutati suhtelise elulemusmäära arvutamiseks kohort-analüüsi, hilisemate perioodide puhul, mil kohordid polnud veel läbinud viieaastast jälgimisperioodi, kasutati periood-analüüsi. Vanusele kohandatud elulemusmäärade arvutamiseks kasutati rahvusvahelisi standardeid.

Tulemused ja arutelu

Kokku diagnoositi aastatel 1996–2016 Eestis 12 142 günekoloogilise pahaloomulise kasvaja esmasjuhtu. Kõige sagedasem günekoloogiline pahaloomuline kasvaja oli sel perioodil emakakehavähk, mis moodustas 35% kõikidest juhtudest. Kõige vähem esines häbeme- ja tupevähi juhte (6%). 20% kõikidest juhtudest diagnoositi alla 50-aastastel naistel. Üle 80-aastaste naiste osakaal suurenes uuringuperioodi vältel 8%-lt 14%-le.

Emakakehavähi haigestumus tõusis uuritud perioodil oluliselt, tingituna I tüüpi kasvajate haigestumuse suurenemisest. See omakorda on seostatav ülekaalulisuse ja rasvumise tõusuga rahvastikus. Korrigeeritud suremustrend oli stabiilne. I tüüpi emakakehavähk avastatakse sageli varases staadiumis, mil ravitulemused on head. Selle kasvajatüübi puhul on leitud, et 40% patsientidest sureb pigem kaasuva kardiovaskulaarse haiguse tõttu, mitte kasvajast tingitud põhjustel. Emakakehavähi viie aasta suhteline elulemus on oluliselt paranenud, ulatudes viimasel perioodil 78%-ni, mis jääb siiski alla Põhjamaades ja USA-s saavutatud tulemustele. Elulemus paranes enim eakatel patsientidel ja IV staadiumi puhul. Samaaegselt suurenes oluliselt kirurgiliselt ravitud patsientide osakaal, mis on tõenäoliselt seotud kaasuvate haiguste tõhusama käsitluse ja väheinvasiivsete kirurgiliste meetodite arenguga. Võttes arvesse haigestumus- ja elulemustrende, viitab suremuskordajate püsimine samal tasemel võimalikele ebatäpsustele surmapõhjuste määramisel.

Emakakaelavähi haigestumus on oluliselt tõusnud. Haigestumuse tõusu võis täheldada kõikides vanuserühmades, välja arvatud üle 70-aastaste naiste hulgas, ning nii lamerakuliste kui ka adenokartsinoomide puhul. Vanus-periood-kohortmudeli analüüsist selgus, et kõige madalam risk haigestuda emakakaelavähki on 1940. aastatel sündinud naistel ja risk suureneb ühtlaselt kõikides hilisemates sünnikohortides. Perioodi-efekt oli stabiilne, millest järeldub, et alates 1970. aastatest ei ole toimunud olulisi ennetustegevusi, mis vähendaksid emakakaelavähi haigestumust. Olulise negatiivse leiuna ilmnes staadiumijaotuse nihe kaugelearenenud kasvajate suunas. Aastatel 2010–2014 diagnoositi I staadiumis 35% juhtudest ning III ja IV staadiumis kokku 42% juhtudest. Hästi toimiva sõeluuringuga riikides ulatub I staadiumis diagnoositud juhtude osakaal üle 60%. Viie aasta suhteline elulemus on viimastel aastatel jäänud samale tasemele (66%). Elulemuse tulemuste stabiliseerumist saab seostada hilisema staadiumiga diagnoosimisel ja kiiritusravi piiratud kättesaadavusega. Uuringu tulemus-

test järeldub Eestis alates 2006. aastast läbi viidava emakakaelavähi sõeluuringu ebaefektiivsus.

Munasarjavähi üldine haigestumus on olnud kogu vaadeldud perioodi vältel stabiilne, samuti kõikides vanuserühmades. Arvestades sagedast suukaudsete rasedusvastaste vahendite kasutust ning suurt sünnitajate arvu 1990-ndate aastate alguses, võib edaspidi eeldada pigem haigestumuse langust. Suremus on uuringuperioodil oluliselt langenud, eriti 50–59- ja 60–69-aastaste naiste hulgas. Oluliselt on tõusnud munasarjavähi viie aasta suhteline elulemus, ulatudes perioodil 2010–2016 44%-ni. Elulemuse tõus oli täheldatav kõikides vanuserühmades ja kõikide staadiumite puhul. Eesti elulemusmäär uuringu viimasel perioodil on võrreldav riikidega, kus vähiravi on väga kõrgel tasemel. Uuringutulemusi saab seostada vähiravi parema kvaliteedi ja kättesaadavusega Eestis.

Häbeme- ja tupevähi haigestumus on olnud stabiilne, sh nii nooremate ja vanemate naiste seas. Samuti on püsinud muutumatuna nende kasvajate suremus. Häbeme- ja tupevähi viie aasta suhteline elulemus on paranenud ja jõudnud 61%-ni, kuid viimasel uuringuperioodil on jäänud samaks. Uuringu tulemused näitavad, et Eestis ei esine Lääne-Euroopale iseloomulikku sagedasemat nooremate naiste haigestumuse trendi, mis võib olla seotud vähema HPV levikuga rahvastikus.

Järeldused

Uurimistöö annab esmakordselt tervikliku ülevaate günekoloogiliste kasvajate pikaajalistest haigestumuse, suremuse ja elulemuse trendidest Eestis. Trende on mõjutanud Eesti ühiskonnas aset leidnud sotsiaalsed ja tervishoiukorralduslikud muutused.

1. Emakakehavähi haigestumus on tõusnud, peamiselt tingituna I tüüpi kasvajate haigestumuse tõusust. Suremus on olnud stabiilne. Emakakehavähi elulemus on märkimisväärselt paranenud, mis on tõenäoliselt seotud oluliselt sagenenud kirurgilise raviga kõikides vanuserühmades ja staadiumites.
2. Emakakaelavähi haigestumus suurenes uuringuperioodil oluliselt. Haigestumustrend on tingitud riski suurenemisest rahvastikus, mida ei ole tasakaalustanud tõhus ennetustegevus. Emakakaelavähi suremus püsis kõrgel tasemel. Elulemus on küll paranenud, kuid I staadiumis diagnoositud juhtude osakaalu langus ning vanemaealiste osakaalu tõus ei ole kooskõlas sõeluuringu oodatavate tulemustega. Võib järeldada, et emakakaelavähi sõeluuring on seni olnud ebaefektiivne.
3. Munasarjavähi suremus ja elulemus on uuritud perioodi jooksul näidanud olulist positiivset trendi. Suremuse langus ja elulemuse pikenemine on toimunud vaatamata vanemaealiste ja enam levinud staadiumiga juhtude osakaalu suurenemisele.
4. Häbeme- ja tupevähi haigestumus on püsinud uuringuperioodi vältel stabiilsena nii nooremas kui vanemas vanuserühmas. Elulemus on mõnevõrra paranenud.

Praktilised soovitused

Uuringu tulemused näitavad vajadust muutuste läbiviimiseks tervishoiukorralduses ja tervislike eluviiside suuremaks tähtsustamiseks ühiskonnas, vältimaks naiste enneaegseid surmasid tulevikus. Vajalik on teadlikkuse tõstmine ülekaalust kui emakakehavähi peamisest riskitegurist. Elulemuse parandamiseks tuleb pöörata tähelepanu kaasuvate haiguste ennetamisele ja ravile. Emakakaelavähi vähieelsete seisundite ja varajaste kasvajate diagnoosimise tõhustamiseks tuleb tagada riikliku sõeluuringu kvaliteet, kaasata uuringusse ravikindlustamata naised ning kaaluda HPV-DNA määramise lisamist sõeluuringu kavasse. Rõhutada ja selgitada tuleb tüdrukute vaktsineerimise tähtsust ning kaaluda poiste kaasamist vaktsineerimiskavasse. Munasarjavähi suremuse vähendamiseks tuleb järgida rahvusvahelisi ravijuhiseid, arendada personaalset meditsiini ja võimaldada selle kättesaadavust. Häbeme- ja tupevähi varaseks avastamiseks tuleb rõhutada korrapäraste günekoloogiliste läbivaatuste olulisust.

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APPENDIX 1

TEATIS VÄHIREGISTRILE

Isikukood | 1☐ Mees 2☐ Naine | Haigusloo või haigekaardi nr.

Perekonnanimi **Eesnimi**

Sünniaeg päev kuu aasta

Elukoht
Vald/alev/linn
Maakond
Tn./küla maja krt.

Varem diagnoositud pahaloomulised kasvajad
Millises organis
Kus diagnoositud või ravitud Kuupäev

DIAGNOOS (üksikasjaline paige)
Diagnoosimise aeg
päev kuu aasta

Diagnoosi kinnitanud uurimismeetodid
1☐ Kliiniline
2☐ Instrumentaalne kliiniline uuring (röntg., ultraheli, endosk., rad.isot. jne)
3☐ Operatsioon ilma histoloogilise uuringuta
4☐ Biokeemiline või immunoloogiline eriuuring
5☐ Tsütoloogiline või hematoloogiline uuring
6☐ Metastaasi histoloogiline uuring
7☐ Algkolde histoloogiline uuring
8☐ Lahang histoloogilise uuringuga
9☐ Lahang ilma histoloogilise uuringuta

Morfoloogiline diagnoos ja pahaloomulisuse aste kood

LEVIK
Staadium:
T N M
1☐ In situ
2☐ Lokaalne
3☐ Metastaseerunud **ainult** regionaalsetesse lümfisõlmedesse
4☐ Levik naaberorganitesse
5☐ Kaugmetastaasid
6☐ Kaugelearenenud protsess, täpsed andmed puuduvad
7☐ Määratlemata

RAVI

1☐ Kirurgiline ravi
1☐ Radikaalne
2☐ Palliatiivne
3☐ Määratlemata
Tervishoiuasutus Kuupäev
Operatsioon

2☐ Kiiritusravi
1☐ Radikaalne
2☐ Palliatiivne
3☐ Määratlemata
Tervishoiuasutus Kuupäev
Kiiritusdoos ja meetod

3☐ Keemiaravi
Tervishoiuasutus Kuupäev
Milline ravi

4☐ Hormoonravi
Tervishoiuasutus Kuupäev
Milline ravi

5☐ Muu ravi
Tervishoiuasutus Kuupäev
Milline ravi

6☐ Ei saanud eriravi
1☐ Kõrge vanus või kaasuvad haigused
2☐ Kaugelearenenud kasvaja
3☐ Haige keeldumine
4☐ Suunatud teise tervishoiuasutusse (kuhu)
5☐ Muu põhjus (milline)

7☐ Andmed ravi kohta puuduvad

Andmete esitaja nimi……..... Ametikoht……..……

Surmaaeg päev kuu aasta

Surmapõhjus

Tervishoiutöötaja kood…….....Telefon ……...……

Tervishoiuasutus……...……Kuupäev ……...……..

Allkiri ……

APPENDIX 2

PATOLOOGIA OSAKONNA TEATIS VÄHIREGISTRILE

Isikukood	1 ☐ Mees 2 ☐ Naine	Sünniaeg päev kuu aasta
Perekonnanimi	**Eesnimi**	
Preparaadi saatja Tervishoiuasutus Arsti nimi	Preparaadi nr.	Kuupäev päev kuu aasta
1 ☐ Lahang 2 ☐ Histoloogiline uuring 3 ☐ Tsütoloogiline uuring	**ALGKOLLE** (üksikasjaline paige)	
Muudes elundites leitud kasvajakude		
Uuring tehtud 1 ☐ Algkoldest 2 ☐ Metastaasist 3 ☐ Määratlemata	**Morfoloogiline diagnoos ja diferentseerumise aste** kood **G P T N M**	
Patoloogi nimi	Andmete esitaja ametikoht…….....	
Kliiniline diagnoos	Nimi.....…… Kuupäev……..... Labor……Telefon ..... Tervishoiutöötaja kood ja allkiri……..……....	

PUBLICATIONS

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3. Ojamaa K, Veerus P, Baburin A, Everaus H, Innos K. Time trends in ovarian cancer survival in Estonia by age and stage. Int J Gynecol Cancer 27:44–49; 2017.
4. Ojamaa K, Tammaru M, Kase M, Mägi M, Jõgi T, Jaal J. Günekoloogi-listesse pahaloomulistesse kasvajatesse haigestumus 15–44 aastaste Eesti noorte naiste hulgas ajavahemikul 1980–2009. Eesti Arst 93:395–398; 2014.

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1. Ojamaa K, Veerus P, Baburin A, Everaus H, Innos K. Increasing incidence and survival of corpus uteri cancer in Estonia over the past two decades. Cancer Epidemiol 62:101566; 2019.
2. Ojamaa K, Innos K, Baburin A, Everaus H, Veerus P. Trends in cervical cancer incidence and survival in Estonia from 1995 to 2014. BMC Cancer 18:1075; 2018.
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