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Faculty of Health Sciences Department of Community Medicine

Epidemiology of cervical cancer and high risk of HPV infection with a focus on Arkhangelsk City and County, Northwest Russia

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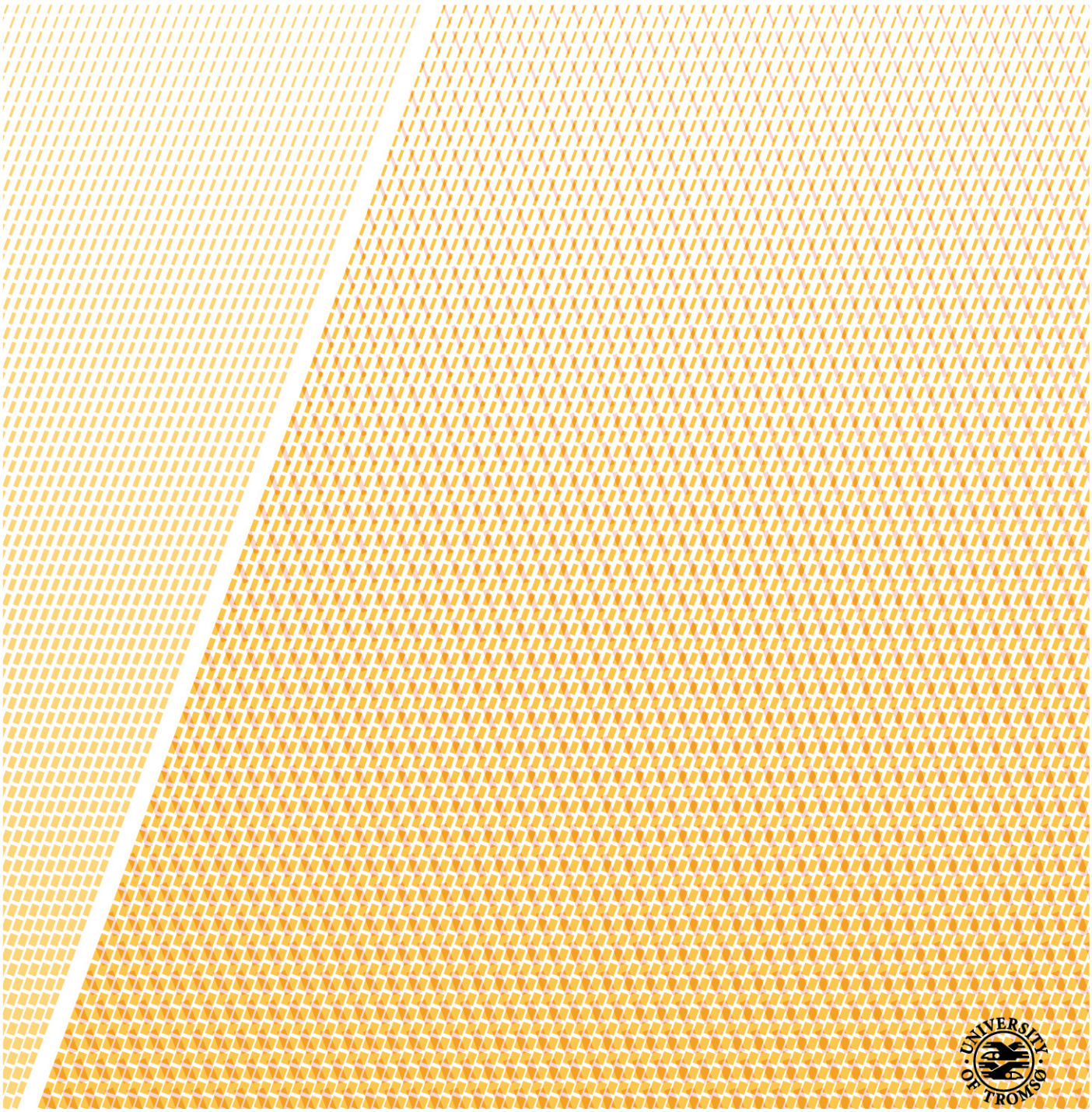
A dissertation for the degree of Philosophiae Doctor – October 2018

ISM skriftserie nr. _____



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A dissertation for the degree of Philosophiae Doctor (PhD)

Department of Community Medicine

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Tromsø, Norway

2018

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Preface

The idea of studying the epidemiology of cervical cancer (CC) and of high-risk HPV in Arkhangelsk County occurred to me long before my PhD studies. In 2006, I started my work as a medical doctor in Arkhangelsk, Russia with a special focus on CC prevention and its early diagnosis. At that time I was enrolled as a co-teacher of a Health Promotion course in the Arkhangelsk International School of Public Health, which was a collaboration project between UiT-The Arctic University of Norway (Tromso, Norway), the Northern State Medical University, Arkhangelsk (NSMU) and other Nordic institutions.

During the early years of my career, I began to understand the importance of fighting the stigma associated with sexually transmitted diseases. Tests for HPV and related vaccinations were not conducted in Russia at that time. Most cancer events were reported only as descriptive statistics by official national statistical institutions. In Arkhangelsk, however, a cancer registry was operational that included detailed information about every cancer event reported in the region. As a gynecologist, I understood how important it was for health care providers, health practitioners, nurses, and the general population to obtain more detailed and precise information about CC prevention, diagnostics, and treatment. To ensure that cancer control actions are effective, it is essential to have access to precise data on a regular basis.

When a PhD position became available at UiT in an area related to my medical practice, I decided to apply. The data analyses and research findings described in this thesis illustrate not only the content of the Arkhangelsk Regional Cancer Registry and the importance of CC screening, but also identify knowledge gaps about prevention of the disease.

Acknowledgements

First of all, I would like to thank my supervisor, Jon Oyvind Odland, for his ongoing support and the confidence he instilled in me along the way.

I also need to thank all my co-authors for their valuable contributions, encouragement, and team work. Evert Nieboer served as the scientific and linguistic editor. Thank you, Evert, for all your help, your patience in drafting the manuscripts, and for the independence you granted me.

This thesis would not have been possible without my fellow students, namely Anton Kovalenko, Anna Usinina, Vitaly Postoev, and Yuri Sumarokov. Thank you for preventing my PhD life from being a boring process. You were not only a part of my scientific ventures, but you brightened the evenings after the seminars, courses, and conferences. Olga Kharkova and Ekaterina Sharashova ─ thank you for being my friends and my personal psychologists during the entire journey. Without your support I would surely not have reached this point.

Odd Nielsen, my life will never be the same after meeting you and getting to know your sense of humor.

I am grateful to everyone at the Institute of Community Medicine, Faculty of Health Sciences, Uit – The Arctic University of Norway (Tromsø, Norway) for friendly discussions and for providing such a good working environment.

I am also grateful for the support received from my parents, especially for sharing their time and caring for my children.

Abstract (in English)

Background

Cytological screening for the detection of precancerous stages of CC has been shown to be effective in reducing the incidence and mortality rates of this disease. In order to develop successful CC prevention programs in Russia, the epidemiology of CC and high-risk HPV infection must be established. To contribute to this effort, the current study focuses on Arkhangelsk County and Arkhangelsk, Northwest Russia.

Aims

The specific objectives were to: i) compare those patients diagnosed with CC through routine screening to those diagnosed with CC through other methods using Arkhangelsk cancer registry data; ii) examine associations between knowledge of HPV and CC prevention and sociodemographic and behavioral characteristics of women who visited a clinical maternity hospital in Arkhangelsk; and iii), explore high-risk HPV infection positivity in relation to sociodemographic factors, sexual behavior characteristics and knowledge about HPV and CC prevention among women who visited the aforementioned hospital.

Methods

We used registry-based and cross-sectional study designs. Specifically, for the first objective (diagnoses by screening *versus* other methods), we analyzed 1548 cervical cancer cases documented in the Arkhangelsk Cancer Registry; for the second and third specific objectives (i.e., knowledge and high risk positivity of HPV vis-à-vis sociodemographic and behavioral factors), we included 300 women who visited an Arkhangelsk clinical maternity hospital in the cross-sectional study.

Results

Our data show that deaths from CC among women who had the diagnoses made without opportunistic screening ─ after adjustment by year, for cancer stage, patient residence, histological tumor type, and age at diagnosis ─ was 37 percent higher compared to those who were diagnosed through screening. Women diagnosed with CC by screening in the early stages (I and II) of the disease survived longer when compared to those diagnosed without screening. However, we did not find such difference for the advanced stages (III and IV).

Our cross-sectional study demonstrated that the majority of women in Arkhangelsk had a sufficient level of knowledge about HPV and CC prevention, and this was associated with the women's level of education, parity, age of initiating of intercourse, and source of information about HPV and CC prevention. After adjustment, women with a university level of education were more likely to have a higher score of correct answers on knowledge about HPV and CC prevention compared to those without a university education.

Of the 300 women recruited and examined in our study, 16.7% (n = 50) were positive for HR-HPV. In the crude analysis, the risk of being positive for HR-HPV infection increased gradually with being younger ($p_{trend} = 0.012$) and with lower parity ($p_{trend} = 0.007$). Odds of having a positive HR-HPV status increased with an increased lifetime number of sexual partners and with a younger age at sexual debut. After adjustment for all variables, the association with the number of sexual partners was no longer significant.

Conclusions

Diagnosis of CC made via the screening program prolonged survival. We identified educational gaps that might be used to tailor interventions in CC prevention. Exploring women's awareness about existing CC screening programs should be considered in efforts to enhance participation rates.

Abstract (in Norwegian)

Bakgrunn.

Cytologisk screening for å oppdage forstadier til livmorhalskreft (CC) har vist seg å være effektivt i å oppdage og redusere forekomst og dødelighet av sykdommen. For å utvikle vellykkede forebyggingsprogrammer i Russland må det etableres kunnskaper og diagnostiske verktøy for å oppdage livmorhalskreft og høy-risiko Human Papilloma Virus (HPV) infeksjoner. Denne studien er tenkt å bidra til en positiv utvikling i forebygging og diagnostisering i Arkhangelsk fylke og byen Arkhangelsk i Nord-Vest Russland.

Formål.

Formål med studien var å i) sammenlikne pasienter diagnostisert med CC gjennom rutine screening med de som var oppdaget med andre metoder ved hjelp av kreftregisteret i Arkhangelsk; ii) undersøke sammenhenger mellom kunnskaper om HPV og CC forebygging og sosiodemografiske og adferdsmessige karakteristika hos kvinner som besøkte en kvinneklinikk i Arkhangelsk; iii) undersøke høy-risiko HPV status i relasjon til sosiodemografisk status og seksuell adferd, samt kunnskaper om HPV og CC forebygging hos kvinner som oppsøkte eller ble henvist til klinikken.

Metode.

For å oppnå den ønskede informasjon ble det brukt både registerbaserte data og en tverrsnittstudie. For det første formålet (screening sammenliknet med andre metoder) ble det analysert 1,548 kreftkasus dokumenterte i kreftregisteret. For tverrsnittstudien (kunnskap om høy-risiko HPV eksponering relatert til sosiodemografiske og adferdsmessige faktorer) ble det inkludert 300 kvinner som konsulterte kvinneklinikken.

Resultater.

Våre data viste at død relater til CC hos kvinner diagnostisert uten opportunistisk screening — etter justering for år, kreftstadium, bosted, histologisk krefttype og alder ved oppdaging – var 37 % høyere når man sammenliknet med de som var oppdaget ved screening. Kvinner diagnostisert med CC på et tidlig stadium (I og II) av sykdommen levde lenger sammenliknet med de som ble diagnostisert uten bruk av screening. Denne forskjellen kunne ikke gjenfinnes i de mer avanserte stadier (III og IV).

Vår tverrsnittsstudie viste at majoriteten av kvinner i Arkhangelsk hadde tilstrekkelige kunnskaper om HPV og CC forebygging. Dette var sterkt assosiert med utdanningsnivå, paritet, alder for

seksuell debut og informasjonskilder om HPV og CC forebygging. Etter justering hadde kvinner med akademisk utdannelse høyere andel korrekte svar vedrørende kunnskaper om HPV og CC forebygging sammenliknet med kvinner uten universitetsutdanning.

Av de 300 kvinner som ble rekruttert og undersøkt i tverrsnittsstudien var 16.7% (n = 50) positive for HR-HPV. I basisanalysen var risikoen for HR-HPV infeksjon økende ved minkende alder ($p_{trend} = 0.012$) og med lavere paritet ($p_{trend} = 0.007$). Oddsen for å ha en positiv HR-HPV status økte med totalt antall partnere og med lavere alder for seksuell debut. Etter justering for alle variabler var sammenhengen med antall partnere ikke lenger siginfikant.

Konklusjoner.

Diagnose av CC gjennom et screening program økte overlevelsen. Det ble påvist at forskjeller i utdanningsnivå kan brukes til fornuftige intervensjonsprosedyrer i forebyggingen. Det må settes et øket fokus på kvinners kunnskaper og oppmerksomhet knyttet til eksisterende screening programmer for å øke deltakelsen.

Abstract (in Russian)

Введение.

Внедрение цитологического скрининга на рак шейки матки вызвало снижение показателей инцидентности и смертности от этого заболевания в мире. Одним из условий разработки успешной программы профилактики раковых заболеваний в России, является исследование региональных эпидемиологических особенностей рака шейки матки и вируса папилломы человека. Эпидемиология данного заболевания в Арктическом регионе, таком как Архангельская область также важна для разработки программы.

Цели исследования.

i) сравнить пациентов с диагнозом рак шейки матки, диагностированных с помощью скрининга и без него, используя Архангельский раковый регистр; ii) исследовать возможные взаимосвязи между уровнем знаний о ВПЧ, профилактике рака шейки матки и социально-демографическими характеристиками женщин, наблюдающихся в Архангельском клиническом родильном доме им. К.Н. Самойловой; iii) изучить социально-десографические, поведенческие характеристики женщин с положительным ВПЧ статусом.

Методы исследования.

В настоящей работе использованы данные Архангельского Ракового Регистра (АРГ). Было проанализировано 1548 случаев рака шейки матки. Также были использованы данные поперечного исследования – 300 женщин наблюдающихся в Архангельском клиническом родильном доме им. К.Н. Самойловой

Результаты исследования.

Пациенты диагностированные с помощью скрининга имели лучшую выживаемость по сравнению с теми кому диагноз был поставлен без скрининга. С помощью скрининга диагноз рака шейки матки устанавливался на более ранних стадиях.

Результаты поперечного исследования демонстрируют достаточный уровень знаний о ВПЧ и раке шейки матки у женщин Архангельска. Достаточный уровень знаний был ассоциирован с уровнем образования, паритетом, возрастом начала половой жизни, и источником информации о ВПЧ и профилактике рака шейки матки. Из 300 участников у 50 (16.7%) был выявлен ВПЧ высокого риска. Риск положительного статуса значительно повышался с юным возрастом ($p_{trend} = 0.012$) и отсутствием родов ($p_{trend} = 0.007$). Вероятность положительного

статуса ВПЧ была больше с увеличением количества половых партнеров и ранним началом половой жизни. После поправки на все переменные, ассоциация с количеством половых партнеров была статистически незначима.

Заключение.

Рак шейки матки выявленный во время скрининга обеспечивает лучшую выживаемость.

Были выявлены информационные пробелы, которые могут быть использованы для формирования программ профилактики рака шейки матки.

List of papers

This thesis is based on the research papers listed below.

Paper 1

Roik EE, Nieboer E, Kharkova OA, Grjibovski AM, Postoev VA, Odland JO. **Do Cervical Cancer Patients Diagnosed with Opportunistic Screening Live Longer? An Arkhangelsk Cancer Registry Study**. Int J Environ Res Public Health. 2017 Nov 26;14(12).

Paper 2

Roik EE, Sharashova EE, Nieboer E, Kharkova OA, Postoev VA, Odland JO. **Knowledge about Human Papillomavirus and Prevention of Cervical Cancer Among Women of Arkhangelsk, Northwest Russia**. PLoS One. 2017 Dec 13;12(12):e0189534.

Paper 3

Roik EE, Sharashova EE, Kharkova OA, Nieboer E, Postoev VA, Odland JO. **Sociodemographic Characteristics, Sexual Behavior and Knowledge about Cervical Cancer Prevention as Risk Factors for High-Risk Human Papillomavirus Infection in Arkhangelsk, North-West Russia**. Int J Circumpolar Health .2018;77:1498681.

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Abbreviations

WHO	World Health Organization
ACR	Arkhangelsk Cancer Registry
ACC	Adenoid cystic carcinoma
CC	Cervical cancer
CIN	Cervical intraepithelial neoplasia
EU	European Union
HPV	Human papilloma virus
HR-HPV	High-risk human papilloma virus
ICD	International Classification of Diseases
LBC	Liquid based cytology
OR	Odds ratio
PCR	Polymerase chain reaction
SCC	Squamous cell carcinoma
95 % CI	95 % Confidence interval

1. Introduction

1.1 Epidemiology of Cervical Cancer

CC is the fourth most common female cancer worldwide and is an important public health problem with an estimated 528,000 cases in 2012 [1, 2]. In 2015, approximately 266,000 women died from this preventable disease [1]. Cancer is usually more common in older people, but with CC the majority of cases appear between the ages of 35 to 50. If changes in prevention and cancer control are not implemented, the number of deaths from CC in low and middle-income countries may rise to 430,000 by 2030 [3]. CC screening aims to detect precancerous lesions and early stage cancer, thereby avoiding new cancer cases and circumventing the development of advanced stages and deaths from this disease [2]. Over the last 50 years, the incidence and mortality rates of CC have shown remarkable reductions in countries with organized cytology-based screening programs [4, 5]. The latest recommendations by the European Union (EU) states that cancer screening should only be offered on a population basis in organized screening programs, with quality control protocols at all levels [6]. Nevertheless, there is wide variation in the structures of such screening programs, which appears to reflect the resources available.

1.1.1 Pathology and natural history of CC

CC is considered a preventable disease. Its development passes through premalignant stages that may be detected by cervical cytology long before CC appears. From the initial infection on, steps occur that lead to cancer development. HPV must be persistent within the epithelial cells of the host to progress toward neoplastic changes. The traditional view has been that this process takes years or decades to occur after the initial contraction of HPV infection. A recent study suggests that these changes may develop more quickly than was previously understood [7]. Winer et al [7] followed women after HPV acquisition and documented the development of cervical intraepithelial neoplasia (CIN); one third of the study participants had progression within 36 months. The risk of CC gradually increases with age, peaking between 45-49 years [8]. CC is ranked as the second most common female cancer worldwide in the 15-44 year age group [8].

There are two main histological types of CC, namely squamous cell carcinoma (SCC) and adenocarcinoma. Until the late 1960s, SCC was the most common type and accounted for nearly 95% of all invasive CCs, while adenocarcinomas accounted for only 5% [9, 10]. The difficulty of anatomic accessibility has been suggested as one of the main causes for the low detection rates of adenoid cystic carcinoma (ACC) [11]. Most recently, the SCC type has accounted for approximately 75% of CC, whereas adenocarcinomas contributed 25% [12]. This change is likely due to the introduction of CC screening and HPV testing as an additional screening tool [13, 14].

Different histological classifications have been proposed for the cervical pre-cancer cellular changes [15]. Initially, cellular changes were graded into mild, moderate, severe dysplasia, and carcinoma *in situ* when the full thickness of the epithelium is involved. In order to highlight that dysplasia and carcinoma *in situ* constituted two distinct components of one process, Richart in 1968 proposed three grades (1 to 3) for CIN according to their severity [16]. Currently there are multiple systems in use in different parts of the world for classifying precancerous conditions of the cervix. According to the World Health Organization (WHO), the CIN classification is still widely used in many countries for cytological reports, although it should done so only for histological reports [17]. The Bethesda system for reporting cervical cytologic diagnoses was developed in the 1990s at the United States National Cancer Institute [18]. As implied, it was created to be used only for cytological reports and combines CIN II and CIN III into one group (referred to as high-grade squamous intraepithelial lesions) and designates CIN I as low-grade squamous intraepithelial lesions.

Several studies suggested that invasive cancer is a result of the progression from mild dysplasia to severe dysplasia, and later on to carcinoma *in situ* [19, 20]. The natural history of CC is still being studied. It is known that in the majority (70-90%) of high-grade lesions (CIN II-III), HPV DNA will be detected [21]. Four types of HPV (16, 18, 45, and 31) account for approximately 80% of cancer cases [22]. Although a great number of HPV infections resolve spontaneously, HPV is qualified as a "necessary cause" of CC (i.e., if there is no infection there is no disease). Cervical infections with oncogenic HPV increase the risk of CIN II and III, while co-infection with certain HPV types (e.g., HPV-16 and HPV -31) has the lowest chance of clearance [23]. However, it is known that mild dysplasia found in cytological smears (CIN I) frequently regresses to normal (as do half of moderate dysplasia cases). Most regressions occur within two years, while those that persist longer are associated with increased risk of developing precancerous lesions and cancer. However, Holowaty et al. [19] state that progression from mild to severe dysplasia takes about ten years [20]. For precancerous lesions to develop, to be maintained and progress, the persistence of HPV is

essential. Once CIN III is established, it is unlikely to undergo spontaneous regression [24]. The number of dysplasia cases diagnosed far exceeds the number of invasive CCs [25]. In the 1980s, McIndoe et al. [25] showed that for every case of invasive CC, there are more than 10 cases of pre-invasive cancers. This finding supports the understanding that not all precancerous lesions progress into cancer.

1.1.2 Incidence and mortality of CC

There is wide variation in the reported incidence and mortality rates for CC worldwide. The incidence and death rates are substantially higher in low- and middle-income countries due to limited access to preventive measures [2]. Reported incidences range from 42.7/100.000 in the Eastern Africa population to 4.4 /100.000 for Western Asia [26].

The incidence of CC in Eastern Europe is four times higher than in Western European countries [26], and such East-West health disparities within Europe have previously been noted by Mackenbach [27]. Fortunately, the incidence and mortality rates of CC have shown remarkable reductions in countries where screening programs were introduced [4, 5].

In Russia, CC continues to be a major public health problem; it ranks as the fifth leading female cancer and about 15,342 new cases are diagnosed annually [8]. The reported crude CC incidence rate for the country is somewhat lower than that in Arkhangelsk County (21.27 *versus* 24.25 in 2015). Arkhangelsk County is the biggest Arctic region in Europe, and its gross regional product places it as a middle-income region within the Russian Federation [28].

1.1.3 Risk factors for CC

Various biological, social, cultural, and economic factors have been shown to be involved in the development of CC. Of course, the primary risk factor for CC is persistent infection with HPV [29]. Behavioral practices that increase the risk of sexual transmission of HPV contribute. Most studies do not differentiate between histological types when assessing CC risk factors. Indeed, it has been confirmed that most risk factors for both pathologic types are similar [30], although high parity and current smoking may increase the risk of SCC among HPV-positive women [30].

It has been observed that the incidence of CC increases with age. It starts to rise at the age of 30-35 years and reaches its peak at about 60-65 [22]. Cancer is usually considered to be an age-related disease because the incidence of most cancers increases with age [31]. However, a peak of CC incidence around the age of 50 appears to occur among unscreened or under-screened birth–cohorts [32]. High parity [33, 34], long term use of oral contraceptives (more than five years) [33,

35], and smoking [33] are co-factors that can increase the risk of CC up to 5 times among those infected by HPV.

Immunosuppressive conditions, including HIV, are also associated with increased risk of CC [36], as are higher lifetime numbers of sexual partners and early age at first intercourse [37, 38]. Male partners may contribute to the risk of CC development in their female partners because men can carry and transmit HPV and male circumcision reduces the risk of transmitting HPV [39, 40].

1.2 Epidemiology of human papillomavirus

More than 30 years ago, Harald zur Hausen and his research group established a causal link between human papillomavirus infection of the cervix and CC. Their finding ─ that HPV16 can be detected in wart and CC tissues ─ was followed by worldwide research activities. In recent decades, the latter has resulted in the development of prophylactic vaccines for HPV. In 2008, Harald zur Hausen received the Nobel Prize in Physiology or Medicine in recognition of his discovery [41]. Currently, more than 100 HPV types have been identified, of which over 40 infect the genital tract through sexual transmission and at least 15 can cause cancer of the cervix and other sites [2].

1.2.1 Natural history and prevalence of human papillomavirus

HPV is the most common sexually transmitted infection worldwide, and most sexually active individuals of both sexes will acquire it at some point in their lives [42, 43]. Worldwide HPV prevalence in women with normal cytology is approximately 10%, although it is higher (around 17%) in women younger than 25 [44]. HPV prevalence is also elevated in low and middle-income countries [45, 46].

More than 90% of HPV infections may regress in 6-18 months [47]. Persistent infection of oncogenic HPV types is a necessary cause of malignant epithelial lesions of the cervix, vulva, vagina, penis, anus, and oropharynx. The probability of HPV clearance depends on the duration of the infection [48, 49] ─ the longer the persistence, the lower chance of clearance.

HPV types have been classified as either oncogenic (high-risk human papillomavirus) or probably oncogenic (low-risk human papillomavirus) based on their ability to induce cancer [50]. HPV 16 and 18 are the two most common oncogenic types and cause around 70% of all CCs worldwide [51].

1.2.2 Risk factors for human papillomavirus

Because HPV is predominantly transmitted through sexual intercourse, the risk factors associated with cervical infection by HPV are clearly related to sexual behavior. Epidemiological studies investigating risk factors for HPV infection have shown that the key determinants in women are the number of sexual partners, the age at which sexual intercourse was initiated, and the likelihood of having a HPV-carrying partner because the epidemiological chain of infection involves both women and men [39, 52]. Both sexes can be asymptomatic carriers and transmitters and both can experience active infection [40].

The only clear risk factors for the persistence and progression of HPV are immunodeficiency and HPV type [53]. Long-term use of oral contraceptives [54], high parity[34], and tobacco smoking [55] are other risk factors that may influence the virus progression [33]. Some studies also mention co-infection with other sexually transmitted diseases (namely Chlamydia trachomatis and Herpex Simplex Virus) [33, 56, 57].

1.3 Cervical Cancer and human papillomavirus prevention

1.3.1 Screening

The WHO defines screening as "the presumptive identification of unrecognized disease by means of tests or examinations that can be applied rapidly" [58], and was the first international organization to provide criteria for screening, including a recommended screening test [59]. The objectives of CC screening are to detect precancerous lesions and early stage cancers, thereby avoiding new cancer cases, the development of advanced CC stages, and mortality [2]. There are two main types of screening programs: organized (population based or nationwide) and opportunistic/spontaneous screening (i.e., screening on demand) [60]. Canada and United States have been regarded as leaders in CC screening. The majority of research on screening implementation has taken place in US settings, where it is predominantly opportunistic. In Canada, a combination of opportunistic and organized screening is common [61, 62]. Cancer screening programs in Northern Europe are known for their accomplishments in decreasing the incidence and mortality rates [63]. Finland was the first country to successfully establish organized screening of CC, and its implementation resulted in rapid decreases in the incidence of invasive CC and related mortality [63]. The Finnish screening program has also generated changes in the staging and histological distribution of CC [4, 14]. The latest EU recommendations state that cancer screening

programs should be offered on a population basis and in an organized fashion. They must include quality control protocols at all levels [6] and screening should commence at the age of 20-30 and continue at 3-5 years intervals up to 60-65 years of age. Furthermore, the EU guidelines state that initiating screening earlier or screening at shorter intervals show no additional benefits because annual screening has been shown to prevent 93% of all squamous ICC, while screening every third year circumvented 91% and screening every 5 years prevented 84% [64]. National and WHO guidelines that describe how to start and organize a screening program are available [65]. As noted, wide variation in the structure of CC screening programs reflects the resources available in the country or region [66]. In the United States, the recommended age of initiating screening is 21 or within 3 years of the start of sexual activity with screening intervals of 2-3 years. In the UK, the recommended age for the initiation of screening is 25 with intervals of 3-5 years (depending on the age of the participant) [67, 68].

Screening tools for the detection of precancerous lesions vary from country to country. Cervical cytology is the most common method employed in CC screening worldwide [69]. A meta-analysis on the efficacy of cytology as the screening test claims that it has low sensitivity and high variability [70]. HPV DNA testing is another tool recommended for cervical screening of high risk HPVs. In April 2014, the USA Food and Drug Administration approved the use of the HPV DNA test as a primary (first-line) screening of CC [71]. It can be used alone or with cytology co-testing, and is often recommended for women over 30 [67, 72].

A successful screening program requires the inclusion of a high proportion of women. When limited resources are available, high population coverage with long screening intervals (every fifth year) is more effective than screening a lower proportion every three years [73]. The EU guidelines and those issued by the WHO recommend that at least 70% of a population be covered [6, 58].

Factors shown to increase participation in screening include knowledge about screening intervals, regular consultation with a gynecologist, urban residence, invitation letters, and telephone reminders [15, 74, 75]. Non-participation in screening is associated with younger age [76, 77], single status [76, 78], lower level of education [76, 77, 79] and smoking [76], and possibly a low level of HPV awareness [80, 81]. Ethnicity [82], psychological barriers [83], and rural residence are other factors that have been linked with participation rates in screening programs [66].

Cytological screening for CC was introduced in the Soviet Union in the mid-sixties [84]. Since that time, the screening has been opportunistic and cytology-based with Ayre's spatula as the cell-collection instrument. For the staining of samples, the Romanovski-Gimse method has been used. Order № 50 issued by the Ministry of Health of the Russian Federation in 2003 delineated the

CC screening procedure [85]. It declared that testing for CC should begin at the age of 18 with no upper age limit, be performed annually, and should be combined with a gynecological examination. The Order also stated that, when possible, the instrument of choice for sample acquisition is cytobrush. In 2012, new regulations were issued by the Ministry of Health of the Russian Federation (Order № 572n) to replace Order № 50. Order № 572n includes standards of medical care in the field of obstetrics and gynecology, and is based on the International Classification of Diseases (ICD) codes for specific conditions. However, it does not provide specific instructions for CC screening (e.g., age limits, its frequency, or sampling procedure) [86]. No new guidelines for regulating CC screening procedure have been established since 2012, and currently there is no national screening registry in Russia.

1.3.2 Vaccination

CC can be prevented by prophylactic vaccine against HPV. Three HPV vaccines exist on the market, namely: bivalent (Cervarix produced by GlaxoSmithKline), quadrivalent (Gardasil), and 9-valent vaccine (Gardasil 9, produced by Merck) [87]. All three vaccines are non-infectious, made of HPV-like particles, and protect against the two HPV types most commonly associated with cancer (16 and 18), while the quadrivalent and 9-valent vaccines also protect against HPV types 6 and 11 that cause anogenital warts. In addition, the 9-valent vaccine targets five additional cancer-causing HPV types (31, 33, 45, 52, and 58). The US Centers for Disease Control and Prevention (CDC) recommend two doses of HPV vaccine (0, 6-12 month) for those who start vaccination before the age of 15 [88]. In the case of immunosuppressing conditions, or if the vaccination was started after the age of 15, three doses of HPV vaccine are recommended (0, 1-2, 6 month schedule) [89]. Ideally, vaccination should be administered before exposure to HPV occurs. However, those who have been infected earlier with one or several HPV types can still get protection from other HPV types with the vaccine. The recommended age range for routine vaccination is 9-12 years [87]. The CDC Advisory Committee on Immunization Practices also recommends the vaccination of females aged 13 through 26 years and males aged 13 through 21 years when not previously adequately vaccinated [87]. Moreover, vaccination is recommended until the age of 26 years for gay, bisexual, and transgender individuals, and for immunocompromised persons (including those with HIV infection) who were not vaccinated previously [87]. Most HPV vaccines are licensed for use in both females and males. Currently, in Russia vaccination against HPV is available on demand for a fee, but is not included in the national vaccine calendar.

In summary, vaccination strategies are a supplement to cytological screening but do not constitute an alternative. Lynge et al [32] and the WHO emphasize that it will take several decades before most women will benefit from vaccination. Until then, cervical screening will remain the primary preventive strategy [32, 58].

1.3.3 Knowledge

Information about HPV and CC prevention and the specific sources for the information are important in terms of building preventive strategies and improving participation in screening. Relevant specific knowledge is important in tailoring screening programs [90]. Knowledge about CC risk factors and the benefits of CC prevention motivate women to participate in screening [91]. However, there is a significant HPV knowledge deficit worldwide [36, 92-96]. Lima et al. [97] demonstrated that HPV knowledge level was associated with age, education, marital status, household income, and multiple pregnancies. Results of the Lima et al. study show that younger women expressed less knowledge about CC when compared to older women. The study also reported that married women, women living with a partner, those with higher income, higher educational attainment, and who had been pregnant all exhibited better knowledge about HPV and CC [97]. Similarly, Hanisch et al. [91] found an association between HPV knowledge level with age and education. However, they found no relationship between marital status and knowledge about HPV.

HPV-related knowledge has been explored and described in countries worldwide [36, 92-96], although little is known about the situation in Russia. Although studies have been conducted in countries of the former Soviet Union, research has been focused on specific study groups such as medical students and health professionals and not the general public [93-95]. Nevertheless, these investigations have shown that there was a relatively low level of knowledge and awareness about HPV and CC risk factors among study participants.

2. Aims of the Thesis

Exploring the epidemiology of CC and high-risk HPV infections with a focus on Arkhangelsk City and County, Northwest Russia, was the overarching aim of this thesis

Specific objectives were:

1) To compare patients diagnosed with CC through screening to those diagnosed through other methods using the Arkhangelsk Cancer Registry (Paper 1);

2) To examine associations between knowledge of HPV and CC prevention and sociodemographic and behavioral characteristics of women who visited *the Samoylova* Clinical Maternity Hospital in Arkhangelsk City (Paper 2);

3) To explore high-risk HPV infection in relation to sociodemographic and sexual behavior characteristics as well as knowledge about HPV and CC prevention among women who visited *the Samoylova* Clinical Maternity Hospital (Paper 3).

3. Material and Methods

3.1 Data source and study design

The research project described focuses on Arkhangelsk County (AC) and its administrative center, namely the city of Arkhangelsk. The latter was founded in 1584 and is located in the northwestern region of the Russian Federation. AC covers an area of 589,900 square km and had a population of 1,155,028 on January 1, 2018 [28], while the city of Arkhangelsk covers an area of 294,420 square km with 351,488 inhabitants in 2017 [28]. As shown in Figure 1, AC is in the Barents region and borders the White Sea, which separates AC from Murmansk County (Oblast). AC borders the counties of Vologda and Kirov, the Republics of Karelia and Komi and the Nenets Autonomous District.

Figure 1. Map of Arkhangelsk County and neighbouring counties.

According to the 2010 Census, the largest ethnic groups in AC were [98]: Russians (95.5%), Ukrainians (1.4%), Nenets (0.6%), Belorussians (0.4%), Komi (0.3%), Azeris (0.2 %); and 83% of the population were urban residents [98]. In 2016, the average life expectancy in AC was 66.4 years for men and 76.9 for women [99]. Life expectancy was higher in urban than in rural areas [99]. The most frequent causes of death were cardio-vascular diseases and cancer [99]. The AC is rich in natural resources, with pulp mills, logging, ship repair, diamond mining and electric power-production [28] constituting the region's main industries.

In order to achieve our research's specific objectives, we applied registry-based and cross-sectional study designs as depicted in Figure 2.

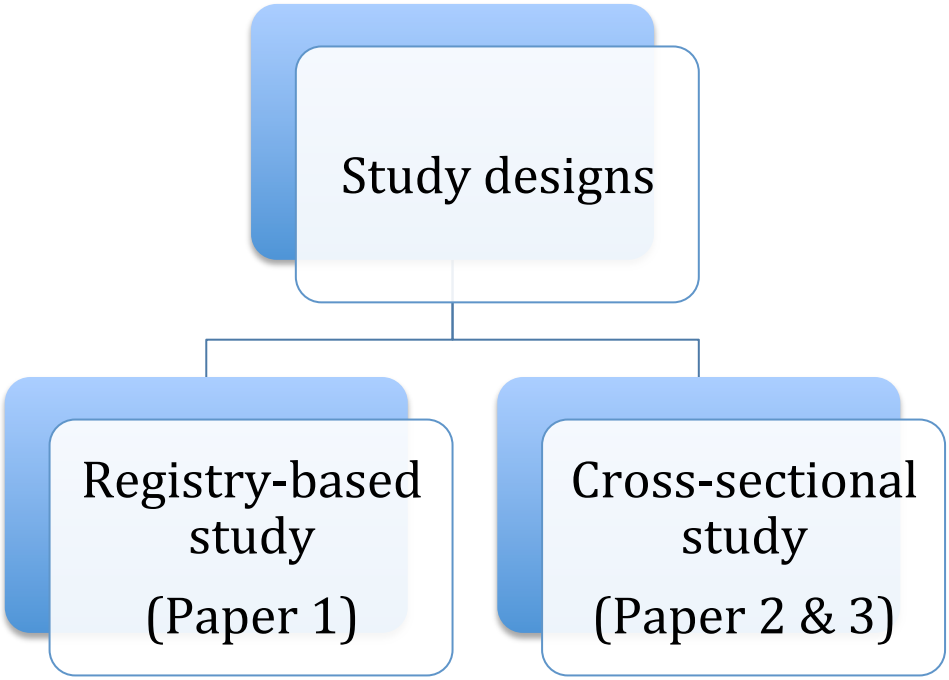

Figure 2. Chart illustrating study designs used in the thesis research

The data for Paper 1 was obtained from the Arkhangelsk Cancer Registry (ACR), which is a joint effort of the University of Tromsø (Norway) and the Arkhangelsk Regional Oncological Hospital (Russia); it was established in 1999. It includes all cancer cases that occur in the Arkhangelsk Oblast. Even though the systematic registration started in 1999, all cancer cases from 1993 on were identified and added to the database retrospectively. A quality control assessment of the ACR data was conducted twice (in November 2003 and May 2003), and on this basis was recognized as valid for epidemiological studies [100].

Every Russian citizen has the right to receive medical care free of charge. According to Russian legislation (order № 135, issued by the Russian Ministry of Health on April 19, 1999), every newly diagnosed cancer case must be reported by physicians to the oncological hospital within three days using a prescribed form [101]. Notification has been obligatory since the 1960s. The mentioned order contains instructions for filling out the pertinent form. For example, if the doctor is uncertain about the diagnosis, the patient must be referred to a larger hospital or to a oncological hospital. The notification form also contains a field for a description of the treatment assigned and the progress of the disease. When completing the form, both the International Classification of Diseases (ICD) codes and their descriptions are to be used. If the Oncological Hospital receives a form with a disagreement between the given code and its description, clarification from the local hospital is to be sought. When a resident of AC is diagnosed with cancer elsewhere in Russia, the completed form must be sent by the diagnosing institution to the Oncological Hospital in Arkhangelsk, and *vice versa*. For example, reports of cancer cases among students from other republics and oblasts in Russia are forwarded to the regions in Russia where they have permanent residence.

Initially, three trained individuals entered the data from the forms into the Cancer Registry database. In 2000, software was installed to monitor the accuracy of the entered data [100]. The ACR contains the following data: date of birth, sex, ethnicity, occupation, date of diagnosis, ICD-9, 10 code, histological tumor type, morphology code, the TNM (Tumor, Node, Metastasis staging system) stage, method by which the cancer was diagnosed, how the tumor was revealed, type of treatment and its result, the appearance of cancer metastases, cancer recurrence and, if applicable, date and cause of death.

For research Papers 2 and 3, a cross-sectional study was conducted in the city of Arkhangelsk. For both, the enrollment period was January 1, 2015 to April 30, 2015 at the *Samoylova* Clinical Maternity Hospital.

3.2 Study population

The study population of Paper 1 consisted of 1548 women from Arkhangelsk County who were diagnosed with malignant neoplasm of the uterine cervix and whose cases were registered in the ACR between January 1, 2005 and November 11, 2016. The inclusion criterion was the presence of a newly diagnosed malignant neoplasm of the uterine cervix. Out of the total number of cases,

371 were excluded due to repeated disease episodes (cancer recurrences) and 21 were dropped due to lack of follow up, leaving 1,940 women as the cohort for the analysis.

For Papers 2 and 3, 350 female residents of Arkhangelsk city aged 25 to 65 years of age who came to the gynecologist for any reason were invited to participate in the study. Women (n = 300) who met the study criteria and signed the informed consent form were enrolled. The sample size was calculated to satisfy the following conditions: HPV prevalence of 10%, $(1-\beta) \geq 0.80$ at $\alpha = 0.05$. Due to the absence of national screening guidelines for CC in Russia, we used the age range specified in the United Kingdom's National Health Service Cervical Screening Programme guidelines [68].

3.3 Data collection

As already indicated, the data used for Paper 1 came from the ACR. CC cases registered in the ACR during the period 1 of January 2005 to November 2016 were included.

For Papers 2 and 3, we used a questionnaire with questions based on published studies and reports by international health care agencies [2, 43, 102, 103]. Most of the questions were formulated to provide one answer, while for some questions more than one response was allowed. We tried to keep the questionnaire short to ensure it could be completed while in a gynecologist's waiting room. The questions (in English) are provided below. Please refer to Appendix 1 for the Russian language version.

1. How old are you? _____Years

2. What is your education level?
- ☐ Secondary school
- ☐ College
- ☐ University
- ☐ Other (specify)_____

3. What is your marital status?
- ☐ Married
- ☐ Single
- ☐ Cohabiting
- ☐ Divorced or widowed
- ☐ Other_____ (specify)

4. How old were you when you first had your sexual intercourse?
_____Years

5. How many sexual partners have you had during your lifetime?
- ☐ 1-3
- ☐ More than 3

6. Have you ever been pregnant? (Including abortions and miscarriages)
- ☐ Yes

- Number of deliveries _____
- Number of abortions _____
- Number of miscarriages _____

☐ No

8. Do you smoke?

☐ Yes (specify for how many years _____)
☐ No

9. Do you use contraception?

☐ Yes
- Hormonal contraceptive pills
- Condom
- Intrauterine device
- Other (specify) _____

☐ No

11. Have you ever had sexually transmitted diseases?

☐ Yes
☐ No
☐ Do not remember or Do not know

12. Before participating in this survey, have you ever heard about human papilloma virus (HPV)?

☐ Yes
☐ No

13. If you have answered «YES» on previous question, please specify your main source of information:

☐ TV, internet, newspaper or magazine, radio
☐ Doctor
☐ Family or friends

14. Human papilloma virus (HPV) is very common in women

☐ True
☐ False

15. Human papilloma virus (HPV) can be transmitted during vaginal sexual intercourse.

☐ True
☐ False

16. The larger the number of sexual partners, the greater is the chance of getting human papilloma virus (HPV)

☐ True
☐ False

17. Human papilloma virus (HPV) is a known risk factor for the development of cervical cancer.

☐ True
☐ False

18. Most HPV types can clear up on their own if left untreated.

☐ True
☐ False

19. A person usually does not have symptoms when infected with HPV.
☐ True
☐ False

20. Most sexually active women will never get HPV during their life.
☐ True
☐ False

21. In accordance with the Russian legislation how often routine screening for CC should be done?
☐ Once in six months
☐ Once in a year
☐ Once in three years
☐ Once in five years

22. Cytological cervix smear (Pap test) can detect changes that can lead to cancer if left untreated?
☐ True
☐ False

23. HPV vaccine can prevent CC?
☐ True
☐ False

24. HPV vaccination is most effective when given prior to the first sexual intercourse.
☐ True
☐ False

25. Someone who has undergone HPV vaccination cannot develop CC.
☐ True
☐ False

26. Women who have undergone HPV vaccination do not need a Pap test later in life.
☐ True
☐ False

For the purpose of the analysis about HPV knowledge, 14 of the 26 questions on knowledge about HPV and CC prevention were used (specifically, questions 12 and 14-26). We also solicited information (questions 2-11) on sociodemographic status (age, education, marital status, parity and smoking), sexual behavior (including the age of initiation of intercourse), history of sexually transmitted infection, contraception use and history of CC.

In Paper 3 we used the results of cervical cytology and HR-HPV DNA genotyping. After the participants were enrolled in the study, tissue samples were collected and sent (on the date of collection) to the central laboratory for cytological diagnosis, HPV detection, and genotyping

(Central Research Institute of Epidemiology Rospotrebnadzor, Moscow, Russia). Pap smears were assessed blindly with regard to the HPV results. Cytological results were reported in accordance with the Bethesda System 2001 [104]. Women with abnormal and uncertain results were recommended to repeat the test in 6 months or to have a colposcopy and histological confirmation.

In our study, we used the AmpliSens® HR-HPV screen-titre kit, Inter-Lab-Service, Moscow, Russia, to determine HPV positivity. It involves an *in vitro* nucleic acid amplification test for qualitative and quantitative detection in biological materials of DNA of HPV of high carcinogenic risk. It is able to detect DNA of HR-HPV of the following types: 18, 39, 45, 59, 16, 31, 33, 35, 52, 58, 51 and 56. Samples were considered to be positive when they reached the HPV-DNA threshold of 1pg/ml, which is recommended by the United States Food and Drug Administration.

3.4 Variables

When analyzing the Arkhangelsk Cancer Registry data (Paper 1), we obtained the following information from the subjects medical records: CC diagnostic method (diagnosed with or without screening), cancer location and stage, year-end vital status, histological type of tumor, age at diagnosis, date of birth, residence, and, if applicable, date of death. Residence was defined as urban or rural. Most study participants were diagnosed during a regular health check and thus they comprised a non-selected population. Some participants were diagnosed without screening due to the presence of CC symptoms. Symptoms exhibited by the latter group included vaginal discharge, inter-menstrual bleeding, post-coital bleeding, postmenopausal bleeding, and backache. In both settings, the diagnostic procedure for CC was similar. Patients with an *in situ* cancer were not included in the registry or in the survival analysis. Histologic subtypes were classified according to the ICD for Oncology, 2nd ed. Histopathological types were grouped as squamous cell carcinomas, adenocarcinomas, and other/unspecified malignant neoplasms. Ages at the time of diagnosis and time of death were presented as continuous variables. We used the International Cancer Survival Standard weights for CC, with age at diagnosis divided into five groups: 15–44, 45–54, 55–64, 65–74 y, and over 75 y for CC survival analyses [105]. In the ACR database, vital status by the end of each year was defined as: (i) death from CC, ii) death from other reasons, and (iii) alive. Survival time was calculated in months, with the initial date being the day of diagnosis. For patients whose cause of death was CC, the final date was that date of their death; for those who did not die it was November 11, 2016. Stage-specific survival analysis was carried out for each stage separately. Furthermore, due to a small number of observations, data for stages I and II were combined to

generate an early cancer variable. The same procedure was adopted for stages III and IV to define an advanced stage variable.

In Paper 2, participants' knowledge about HPV and CC prevention was used as both a discrete and binary variable. For the latter, we defined the level of knowledge as sufficient (7-14 out of the 14 questions answered correctly) or poor (6 or less out of the 14 questions answered correctly). Sources of knowledge about HPV and CC prevention were defined as TV/media, physician, or other (including family and friends). The frequency of screening for CC was categorized as once in six months, annually (the national recommendation until 2013), and once every 3-5 years. The last time the participants underwent screening for CC was categorized into: less than 3 years ago, more than 3 years ago, never, and do not know. Age as a variable was used as both continuous (years) and categorical (25-44 or ≥ 45 years). Education was designated as university level or less than university level. Based on their marital status, study participants were divided into three groups: married, cohabiting, or single (including divorced or widowed). Parity was divided into 0, 1, or ≥ 2 deliveries. Smoking was designated as ever (yes) and never (no). Age of initiating intercourse was considered as continuous (years) or categorical variable (≤17, 18-21, and > 21 years), and the number of lifetime sexual partners was grouped into three and less or more than three. The history of sexually transmitted infections was categorized into either 'ever had' or 'never had.'

In Paper 3, women were grouped by age (25-29, 30-39, ≥ 40), marital status (married, cohabiting, or single including divorced and/or widowed), parity (0, 1, or ≥ 2 deliveries), and education (university level or less). Age of initiating intercourse (years) was used as a continuous variable and the number of lifetime sexual partners was designated as three or less and more than three. Abortions and condom use were categorized as yes or no, and the sexually transmitted infections variable as 'ever had' or 'never had'. Participants' knowledge about HPV and CC prevention was used as both a discrete and a binary variable. The status for HR-HPV infection was defined as positive or negative for any type of HR HPV infection.

3.5 Data analysis

All statistical analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL). The p-value <0.05 was considered to be statistically significant.

In Paper 1 we applied the Pearson's chi-squared test in the analysis of categorical variables, while the T-test was used in the comparison of continuous variables. The Kaplan-Meier method was applied in the determination of mean CC survival times, while the log-rank method was used in the comparison of accumulated survival curves. Hazard ratios (HRs) were calculated for the independent study variables employing the Cox proportional risk model. The multivariable Cox proportional risk model was adjusted for age, cancer stage and histology, residence and year of diagnosis.

A histogram was used in Paper 2 to describe the distribution of HPV and CC prevention knowledge (presented as a discrete variable) among the study participants. For each level of knowledge (poor and sufficient), we calculated the mean and standard deviation for maternal age and age of sexual début, and applied the independent Student's t-test in the comparisons of continuous variables and Pearson's χ^2 test for categorical variables. Linear regression was employed to estimate possible associations between the level of knowledge about HPV and CC prevention and sociodemographic and sexual behavior characteristics. Crude and adjusted regression coefficients were calculated with 95% confidence intervals.

The distribution of high-risk HR-HPV types among the study participants are reported in Paper 3. The age of sexual debut and number of correct answers on the "HPV and CC Related Factors Questionnaire" are presented as the median and the first and third quartiles. We used the Mann-Whitney test for comparisons of continuous variables and the Pearson's χ^2 test for categorical variables between the two HR-HPV status groups (negative/positive). Logistic regression was employed to estimate possible associations between the outcome (HR-HPV status) and predictors (age, parity, age at sexual debut, and number of sexual partners). Certain predictors were chosen on the basis of published knowledge. Crude and adjusted odds ratios (ORs) were calculated with 95% CIs.

3.6 Ethical aspects

In order to achieve the first aim of the thesis, we obtained anonymized data from the Arkhangelsk Cancer Registry. Our study database does not contain personal data, and because the project was not interventional in nature, informed consent was not required for this component of the study. Ethical approval was granted by the Ethical Committee of the Northern State Medical University, Arkhangelsk, Russia (Этический комитет Северного Государственного Медицинского Университета) (Report Number 01/02-17 obtained on 01/03/2017), and by the

Norwegian Regional Committee for Medical and Health Research Ethics (RECNorth), Tromsø, Norway (Registered Report Number 2014/1670).

For the second and third aims of the thesis, ethical approval was obtained from the Research Ethics Committee of Northern State Medical University of Arkhangelsk, Northwest Russia (Registered Report Number 08/12-14 from 10.12.2014), and from the Norwegian Regional Committee for Medical and Health Research Ethics, Tromsø, Norway (Registered Report Number 2014/1670). All study participants provided written informed consent.

4. Main Results

4.1 Paper 1: Do Cervical Cancer Patients Diagnosed with Opportunistic Screening Live Longer? An Arkhangelsk Cancer Registry Study

Cases (n = 1940) of primary invasive cancers of the cervix were confirmed and registered in Arkhangelsk during the study period, January 1, 2005 to November 11, 2016. Of these, 1548 records matched the selection criteria and constitute the study sample. Most of the 1548 cases were diagnosed at stage I and SCC was the predominant histological form and 514 died from CC.

Most participants diagnosed by screening were at stage I ($p < 0.001$) and died less frequently from CC ($p < 0.001$) than those not so. The latter group was diagnosed at a younger age ($p = 0.013$) and died younger ($p = 0.002$). Compared to women with CC, those diagnosed by screening, tumor histology and the patients' place of residence did not differ for those diagnosed without screening.

Kaplan-Meier survival curves illustrated a significant difference in survival time between the two groups ($p = 0.001$). The five- and ten-year survival was approximately 60% among CC patients diagnosed without screening and more than 70% for those diagnosed by it. Moreover, five-year survival was about 97% for stage I, 64% for stage II, 28% for stage III, and 20% for stage IV. In the stage-specific analyses, we observed a significant difference in survival for those diagnosed with screening compared to those diagnosed without it only for stage II ($p = 0.052$). ; while for stage I $p = 0.379$, for stage III $p = 0.495$, and for stage IV $p = 0.789$.

Women diagnosed with CC through early-stage (I and II) screening of the disease survived longer when compared to those diagnosed without screening ($p = 0.003$). For the advanced stages (III and IV), however, we did not find a similar difference ($p = 0.890$).

At the end of the follow-up, respectively 59 (22.5%) and 455 (35.4%) of the women diagnosed with and without screening had died. Younger, urban residents diagnosed with stage I and II had somewhat longer survival times. Cox regression modeling indicated that the hazard ratio for death among women with CC diagnosed without screening was 1.61 (unadjusted with 95% CI: 1.22-2.10) and 1.37 (adjusted with 95% CI: 1.04-1.80.

4.2 Paper 2: Knowledge about human papillomavirus and prevention of CC among women of Arkhangelsk, Northwest Russia

Responses to 14 questions about awareness of the disease administered using the "HPV and CC Related factors Questionnaire" indicated that the number of correct answers was distributed normally among the study participants. The mean number of correct answers was 8.5 (2.2), with a median of 9.0, and first and third quartiles of 7.0 and 10.0, respectively.

Of the survey respondents (n = 300), 74.7% were generally aware about the role of having multiple sexual partners as a risk factor for CC, while 67% did so about the prevalence of HPV and that sexually active people will likely contract HPV in their lifetime. By contrast, 35.7% of the study subjects were aware about the existence of a vaccine against HPV, while only 9.7% did so about a need for screening after vaccination. Moreover, 79.3% of study participants answered incorrectly that the HPV vaccine prevents the development of CC, while a large majority (90%) indicated incorrectly that most HPV types clear up on their own.

In terms of screening, 37.1% of the participants had been given a cytological smear (cervix, or Pap test) within the previous three years; 7.0% had done so more than three years before the study; and 38.0% never had a Pap test, while 17.7% claimed not to know. Among those who were aware that screening can detect CC in its early stages, 48.5% had had a Pap test within the previous three years, 8.6% had the test more than 3 years before, 29.3% never had a Pap test, while 13.6% did not know ($p < 0.001$).

About one third of the study participants reported that their doctor was their main source of information about HPV and CC prevention. Interestingly, TV/media was cited as a source by 53.3% and 12.7% mentioned other sources.

Sixty (20.0%) of the 300 participants had a poor level of knowledge about HPV and CC prevention, while 240 (80.0%) had sufficient knowledge. Our demographic information on the study

participants indicates that women in both groups were of comparable age, namely in their mid-thirties. Associations of the level of knowledge about HPV and CC prevention were evident for maternal education ($p = 0.049$), parity ($p = 0.049$), age of sexual activity initiation ($p = 0.014$), as well having their physician as the primary information source about HPV and CC prevention ($p = 0.006$) more frequently. In this context, a university education, early sexual debut, and giving birth to two or more children were predictors. Overall, the most common source of information about CC and its prevention was the mass media (more than 50%). Furthermore, women with a poor knowledge level received the information from their social surroundings more often compared to those with sufficient level ($p = 0.005$). Associations between the level of HPV and CC prevention knowledge and age, marital status, smoking, history of sexually transmitted infections and contraception use were not observed.

The crude difference between the number of correct answers on the 14 questions about HPV and CC prevention was significant depending on the educational level of respondents ($p = 0.029$), and was even more pronounced after adjustment ($p = 0.021$). Women with a university education were more likely to have higher knowledge about HPV and CC prevention compared to women with lower educational levels. Having two or more deliveries was associated with having more correctly answered questions on HPV and CC prevention when compared to nulliparous women ($p = 0.012$). However, this difference was not statistically significant after adjustment ($p = 0.071$). In the crude and adjusted linear regression models, age, marital status, smoking, age of initiation of intercourse, number of partners, and history of STDs were not associated with the number of correct answers to the 14 questions about HPV and CC prevention.

4.3 Paper 3: Sociodemographic characteristics, sexual behavior and knowledge about CC prevention as risk factors for high-risk human papillomavirus infection in Arkhangelsk, North-West Russia

Of the women recruited and examined in the study, 16.7% ($n = 50$) were positive for HR-HPV. The most commonly detected HPV types were group A9 (62%), followed by group A7 (24%). Multiple infections were detected in 14% ($n = 7$) of participants. Approximately 97 % ($n = 292$) of the study participants had no pathological findings in the Pap smear, while 2% ($n = 6$) had L-SIL and 0.7% ($n = 2$) of the abnormal Pap smear results had atypical squamous cells of undetermined significance.

Women from 25-29 years of age (p = 0.013), those cohabiting with sexual partners (p = 0.011), those who were *nulliparae* (p = 0.009), smokers (p = 0.011) and having more than three sexual partners (p = 0.034) were more likely to have positive HR-HPV status. The latter group, debuted sexually at earlier ages than women with a negative HR-HPV status (p = 0.001). The prevalence of positive and negative HR-HPV infections did not differ among women with different educational levels, nor for those with previous abortions, hormonal contraceptive and condom use, and a history of sexually transmitted infections.

Independent of their HR-HPV status, the study participants provided correct answers more frequently to the following survey questions/statements: "The chance of getting HPV increases with number of sexual partners"; "What is the main hazard of HPV for females?"; and "HPV vaccine is most effective if given to individuals who have never had sex." The statement "Most HPV types can clear up on their own if left untreated" was the question answered incorrectly most frequently. We observed no difference in the number of correct answers between women with positive and negative HPV status (p = 0.716). The prevalence of poor knowledge was not significantly different for participants with positive and negative HPV status (28.0 % *versus* 18.4 % respectively, with p = 0.121).

In the crude analyses, the risk of being positive for HR-HPV infection increased gradually with being younger and having lower parity; the p values for trend were 0.012 and 0.007, respectively. Odds of having positive HR-HPV status increased with increased age, higher number of sexual partners, and with a younger age at sexual debut. After adjustment for all variables (specifically age, parity sexual partners, and sexual activity debut), associations with age and the number of sexual partners were no longer significant.

5. Discussion

5.1 Methodological considerations

A registry is defined as "an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s)" [106]. A primary objective of cancer registries is to collect and classify information on all cancer cases. This allows the determination of incidences of specific cancer types in a defined population. The data collected becomes even more useful when it is accumulated over a

long period of time. A cancer registry is an essential component of any cancer control program [107]. The use of registries is time- and cost-effective, and allows the investigation of hypotheses that would not be feasible without sufficient numbers of observations. Cancer registries provide information on the distribution of all cancers, including non-fatal cases. Systematic presentations of registry data can identify determinants of the disease and can delineate groups at risk. When both outcome and exposure are available from the same registry or registries that can be linked, associations of different factors with a specific outcome can be investigated. However, cancer registry information is of limited value for etiological research in terms of factors that may influence the outcome [100, 108]. In cancer epidemiology, the latency is usually long or unknown and therefore cancer registries lack data about most potential etiological factors.

When studying causes of cancer, a registry can be the source of outcome data that otherwise would be difficult to obtain. Moreover, a collection of all cancer patient records in a defined population minimizes the selection bias that is often found in clinical studies.

The usefulness of a registry is not only defined by the quantity of information it contains, but also its quality. The main methodological challenge is to minimize random and systematic errors to achieve high validity and precision in statistical findings. The quality of a registry can be evaluated in terms of the correctness of its data (validity), completeness of data for each record, population coverage and potential limitations in fulfilling its purpose [100, 108].

Currently, there are numerous cancer registries worldwide. All the Nordic countries have ongoing population-based cancer registries, in addition to birth registries and hospital-based registries. A number of regional cancer registries exist in Russia. However, only two are recognized to meet internationally defined quality standards. The Cancer Registry in St. Petersburg was established in 1993 and is considered to be the first population-based cancer registry in Russia [109]. Data quality control for the Arkhangelsk Cancer Registry was conducted twice, specifically in November 2003 and May 2003, and the quality of the registered information was suitable for epidemiological studies [100]. Data from the Arkhangelsk Cancer Register were included in the CONCORD-2 study [110], which compared worldwide cancer survival statistics .

In a cross-sectional study, data are collected on a population at one specific point in time to examine relationships between specific health issues and potential risk factors. They provide a snapshot of disease frequency in a specific population at a given point in time, and can be used to assess the burden of disease or health issues of a population. Such information can be highly useful in planning and allocating health resources. Cross-sectional studies are observational and are known

as descriptive research, not causal or relational, and thus cannot be used to determine the cause of a disease. This study design is often employed to make inferences about possible relationships to risk factors or to gather preliminary data to support further research and experimentation.

Cross-sectional studies are known for being relatively inexpensive and quick. They enable assessments of incidence although this study design is not suitable for rare diseases or those of short duration. Since the worldwide prevalence of HPV is relatively high (10%), a cross-sectional study is quite adequate to investigate potential risk factors such age, educational status, or even income.

5.2 Discussion of main study results

5.2.1 Comparison of CC patients diagnosed with and without screening using the Arkhangelsk Cancer Registry

The observed mean age at diagnosis of CC was 48.5 y, which is comparable to values reported in other studies. One British study [62] reports that the median age at diagnosis for CC approached 50 y. Most commonly, screening ages for studies are between the late 40s to middle 60s. The significant difference in the mean age of CC cases diagnosed with and without screening (namely 48.1 and 50.6 y, respectively) is consistent with that observed in a Swedish study [14]. The latter authors report a slight increase in the mean age at diagnosis for all CC stages after screening was introduced. By contrast, other studies indicate no significant differences in the median age at diagnosis [62, 111]. The age of screening initiation varies between countries. In the Russian Federation, screening protocols are regulated nationally by the Ministry of Health Orders No. 50 and 808, which specify that CC screening should begin at the age of 18 or at initiation of sexual activity (whichever comes first) without an upper age limit. Initiation of screening at an early age can lead to overestimation of CC risk. Landy et al. have concluded that screening from age 20 y on would lead to over-treatment and over-testing, without having little impact on CC prevention [112].

Our data show that place of residence was not associated with CC diagnosis made with or without screening. Low participation rates in CC screening have been reported for rural areas of the USA [113]. It appears that rural residents have a higher risk of late cancer detection due to barriers that include lack of convenient access to or availability of preventive health care services (including early detection screening) [114] and of awareness and knowledge about the existence of screening

programs [115]. By contrast, for cancers diagnosed at late stages no significant associations between rural/urban places of residence and survival have been reported [116].

The fraction of the participants with a positive CC diagnosis decreased across the four CC stages; specifically 39.1% (I), 26.1% (II), 22.7 (III) and 12.0 (IV) %. At stage I, the % of CC cases diagnosed with screening was higher compared to those without (51.3 versus 36.7%). This concurs with the findings of Hellman et al. [14], who observed an increase in stage I diagnosis that exceeded 50% of all CC cases. Contrary results have also been reported. For example, Nowakowski et al. [111] have indicated that advanced stages of CC dominated in a cervical screening program in Poland. Women diagnosed with CC through screening (stages I and II) in our study had longer survival rates when compared to those diagnosed without screening, although we did not observe this difference for the advanced stages of CC. This may partly be due to speedier examination of those diagnosed by screening. In this context, women diagnosed without screening have to wait for a colposcopy and biopsy appointment as long as six months.

The number of primary health care centers and medical workers have decreased in Russia after the collapse of Soviet Union and in about 17,500 municipalities there is no health care infrastructure. Furthermore, 35% of settlements are not covered by public transportation systems or ambulance services [117]. Relative isolation may well be an explanation for the low level of participation in CC screening programs. Several factors are known to influence participation in CC prevention measures: (i) underfunding at the system level; (ii) suitable screening intervals are not recommended by healthcare providers and treatments/follow-up visits are not carried out in a timely manner; and (iii), lack of transportation and/or childcare which can impede clinical visits. In this context, a 2010 Norwegian study identifies the importance of pertinent knowledge in enhancing public participation, including an awareness of screening intervals and CC risk factors [78]. Sporadic screening or a lack of communication among health care professionals that lead to misunderstanding between cytologists and gynecologists and low screening coverage (on average 43-45%, with a range of 11.5% to 61.9% in 2009 and 23.6-24.6% in 2001-2007) were also believed to contribute, as well as low attendance rates across a region due to a women's lack of awareness about the risk of CC [118]. Lack of training in smear sampling and the use of older instruments have also been suggested as reasons for screening failure [118], as well as demographic changes in population size and distribution by age and sex [84]. It has also been reported that one-fifth of patients diagnosed with CC in the Republic of Karelia died within the first year of the disease [118].

SCC was the predominant histological type and accounted for more than 80% of all CC cases, of which 9.1% were adenocarcinomas. In the 1950s and 1960s, worldwide nearly 95% of all invasive CCs were squamous cell carcinomas with adenocarcinomas accounting for the remainder [9, 10]. More recently the approximate percentages were 75% (squamous type) and 25% (adenocarcinomas) [12]. This change in distribution likely reflects the introduction of screening with cytological testing as the primary screening tool [9, 13]. Anatomic accessibility difficulty has been suggested as the main reason for both the low detection rates and the occurrence of late-stage adenocarcinomas [119]. One way for improving the early detection of adenocarcinoma is to employ a combination of cytology and diagnosis of high-risk HPV type [119]. Factors believed to have contributed to the changes in CC distribution by age, stage and histopathology are the availability of health care providers, wide use of contraceptive pills, changes in smoking habits and in sexual behavior, and increased awareness of CC risk [14].

Our study group of women diagnosed with CC through screening survived longer than those who were diagnosed after presenting symptoms. The 5-y survival from CC worldwide varies widely from < 50% to > 70%, even though in most countries it has increased somewhat in the past 10 y. The Nordic countries (78%) have reported the highest 5-y survival times, while the lowest occurred in Malta (44%) [110]. According to the American Cancer Society (ACS) in 2010, the overall 5-y survival was 72% in the USA [72]. Even though the 5-year survival for our Stage I patients with that reported by the ACS (≥ 93%), their percentages were a little higher for the other 3 stages than ours, namely: ≥ 63% (stage II), ≤35% (stage III) and around 15% (stage IV) [72].

Since the prevalence of other diseases (e.g., hypertension and cardiovascular diseases) may mitigate receiving optimal treatment for CC or for a favorable result to occur, age as a prognostic survival factor can thus be confounded by age-dependent factors [11]. Survivals up to 87% for women aged 30 y and 45.5% for those >70 y are typical [11]. Our findings closely match the relative 5 y survival ages at diagnosis in the EUROCARE-3 study, namely that for the 15–44 y group at diagnosis it was more than two-fold higher compared to women aged ≥75 (respectively 74% and 34%).

According to IARC [64], the CC stage at diagnosis is generally the most important factor in patient survival [11]. The women in our study with late stage CC had substantially lower survival times after first CC diagnosis (<5 y). Improvement in survival is often used as an indicator of

screening success. In Finland, implementation of CC screening resulted in only a slight decrease in survival [120]. This was attributed to a growing proportion of cases with advanced cancers in those not previously screened. By contrast, studies of CC in most counties have shown improvements in survival for those receiving adequate diagnostic and treatment (including screening).

5.2.2 Possible associations between knowledge of HPV and CC prevention and sociodemographic and behavioral characteristics of women who visited the clinical maternity hospital in Arkhangelsk

In documents from the Institut Català d'Oncologia (ICO) HPV Information Centre it is speculated that women's knowledge and awareness about HPV and CC prevention are critical for the development of successful preventive approaches [91]. Our results indicate that most women in our sample knew about the potential consequences of having an HPV infection but this did not appear to reduce prevention rates. This suggests that other factors might also be critical, such the availability of health care, transportation and childcare. Several studies worldwide have reported findings that differ from ours in that a significant deficit in HPV knowledge among women appears to exist worldwide [36, 91-94, 97].

Many participants in our study were aware of sexual transmission of HPV. Nevertheless gaps in knowledge about symptoms and treatment of HPV infection occurred. Even though HPV is the most common sexually transmitted infection, it is transient and therefore women tend not to seek treatment. We show that close to 90% of women understand that HPV should be treated. Perhaps this result in part can explained by misinformation provided by some health care professionals and pharmaceutical companies, namely that HPV detection of requires antiviral treatment. However, the HPV test is commercially and widely available in Russia. Another possibility is the wide use of colposcopy in Russia, even though the number of educational courses and available literature on how to perform this procedure properly are limited [121, 122]. This can lead to over-diagnosis of cervical lesions. Lack of guidelines and training among doctors has also been identified as pertinent to over diagnoses and treatment [122].

Women in our study had a pretty good understanding of CC risk factors. We also demonstrate that pertinent knowledge about these risk factors and CC screening process is of great relevance. The women who knew that Pap tests screen for CC chose to have them more often than those who lacked this knowledge. Nevertheless, our analysis does reveal that there was insufficient

knowledge that HPV vaccination can prevent the development of CC. Unfortunately, vaccination is not yet included in the Russian state vaccination program.

Our study suggests that a woman's age does not appear to be associated with her knowledge about HPV and CC prevention. Although an earlier study did find that younger women had a higher level of this knowledge [123], their main sources for pertinent information about HPV were the Internet and other mass media. Our Arkhangelsk study findings imply that simple educational efforts designed for and targeting older women would likely increase their participation in CC screening. This would reveal CC cases at earlier stages of the disease, and thus would constitute a successful effort to reduce the overall CC burden. This focus on older women would ideally be necessary for only a number of years as subsequent generations would hear about it. Indeed, Williams et al. [124] report that in their study conducted in the USA most of the respondents with higher HPV knowledge now receive this information in school. Given that the average age of onset of sexual activity and the fact that vaccination is only effective for virgins, we suggest that HPV education would be effective in reducing the population disease burden when given at early ages (elementary school or earlier).

Women of all ages (25-65 years old) in our study were at risk of getting an HPV infection and thus developing CC. The age group that would benefit most from directed preventive measures such as CC screening is clearly broad and likely extends beyond the scope of our study. However, Tiro et al. [125] have shown that older and less educated women would benefit from improved awareness of HPV and CC prevention. While not identifying a specific age, our findings reinforce the importance that university educational level was independently associated with a higher level of knowledge about HPV and CC prevention [91, 123].

Smoking, a known risk factor for CC, was not associated with the level of HPV knowledge in our study [125, 126]. The relatively low smoking rate (12-13%) among our study subjects possibly accounts for this observation. A recent study in the Murmansk County of North-west Russia for the period 2006-2011 indicates that the prevalence of smoking among women of child-bearing age was 25.2% prior to pregnancy [127]. Differences in age, education level, and socioeconomic factors might account for this discrepancy.

Risky behaviors, specifically early initiation of intercourse and high number of sexual partners, are understood to enhance the risk of HPV infection [128]. An association between the number of sexual partners and level of knowledge about HPV and CC prevention was not observed, even though individuals in our knowledge sufficient group were slightly older ($p = 0.014$). In this

context, an earlier USA study indicated that neither age of intercourse initiation nor number of lifetime sexual partners were associated with knowledge scores [126].

No association was evident between the level of HPV and CC knowledge and history of sexually transmitted infections. More specifically, women with a history of STDs and consulted a saw physicians about their infections had not been informed about HPV or had forgotten it. This suggests that clinicians need to pay more attention to informing their patients' about HPV and associated cancers, including details other sexually transmitted infections.

The absence of an association between the type of contraception women used and HPV knowledge levels might be assigned to the fact that 50% percent of the respondents in our study did not use contraception at all. One possible explanation for this could be that the respondents in our study were more concerned about chlamydia or gonorrhea risks than that of HPV. Consequently, they may have had an underestimation of the seriousness of an HPV infection and thereby failed to seek information on its prevention, nor took the initiative to be tested/screened for it.

Our analysis of questionnaire data indicated that levels of HPV and CC prevention knowledge were associated with the respondents' source of information. Those who identified their doctor as the primary source of information on HPV were more likely to have an adequate level of knowledge about it. Holcombe et al. [126] also observed this. Our data show that women with poor knowledge received their information about CC and its prevention from media and TV more often. On this basis, we conclude that health care professionals provide more precise and accurate knowledge about CC and its prevention than does the media. In order enhance the broad acceptability of CC screening, it seems important that physicians be encouraged to share pertinent information more frequently and that targeted education and/or information sources for women on the importance of routine screening for CC prevention be implemented. It also seems prudent to encourage general educational campaigns for women to supplement targeted healthcare system efforts because socioeconomic status is a factor in HPV knowledge levels and, as demonstrated, some social situations constitute a source of information leading to poor levels of knowledge. Holcomb et al. [126] also observed that the sexual behavior of women with a higher level of knowledge did not differ from that of those with low knowledge. Interestingly, Tiro et al. [125] state that women who reported to distrust of all sources of health information were less likely to report HPV awareness.

Poor levels of knowledge about HPV and CC are found among demographically diverse groups worldwide, even among medical professionals. Several Russian studies and those conducted in former Soviet countries have evaluated awareness and understanding of HPV and CC among

specific groups, such as medical students and health professionals [93-95]. All these investigations indicated a relatively low level of knowledge about HPV among the study participants. Kahn et al. [128] describe a similar situation among USA pediatricians. Comparable findings in distinct societies indicate that the lack of educational efforts about HPV infection is a widespread health issue. Although scientific knowledge about HPV is growing (especially in terms of virus detection), the need for improved understanding about the prevalence of HPV and the efficacy of CC prevention exists in both the general population and among health professionals in disparate countries.

5.2.3 High-risk HPV infection positivity in relation to sociodemographic status, sexual patterns, and HPV and CC prevention knowledge among women in the Arkhangelsk maternity hospital.

The prevalence of HR-HPV infection in our study was 16.7% and thus exceeds the 11–12% worldwide in women without cervical abnormalities. Infection rates higher than those in the Arkhangelsk study have been reported for the Caribbean (35.4%), sub-Saharan African (24%) and Eastern Europe (21%), while rates reported for North America (4.7%) and Western Asia (1.7%) were lower than our estimate [29]. The varying estimates of HR-HPV prevalence between regions could be due in part to different ages of study populations and, possibly, use of different HPV tests.

HPV prevalence among women in Russia is not well documented as the available data are mostly restricted to research conducted in the city of Saint-Petersburg. For the latter, an HR-HPV positivity of 13% (n=107) has been documented [129] . One study that investigated cohorts of women at risk for HPV infection in three former USSR states suggested an overall HPV prevalence of 33.4% [130]. These differences in prevalence estimates within the former USSR are likely partly explained by disparities in the study populations. Age is a major determinant in HPV infection prevalence. In our study group, younger aged women (age groups 25-29 and 30-39) tended to be HPV positive more often than those aged 40 years or older. These findings corroborate other studies that show a steep decrease in HPV infection with age [131, 132]. In general, the younger a population the higher the rates of HPV infection. It has been suggested that in young women most HR-HPV infections are transient and often result from new sexual contacts and that persistent infections occur in a small proportion of women [132].

Our Archangelsk study indicated that cohabiting was associated with HPV infection. This observation might be related to the time of last exposure to HPV, as this is longer in married women

than in singles. Moreover, sexual activity in single people tends to be sporadic. Increasing rates of sex outside of marriage indicate that marital status is less of a reliable safeguard of sexual-health status.

An association between HR-HPV infection and reproductive factors was demonstrated in our study. The negative trend observed for parity is consistent with the observation by Munoz et al.[47] that it serves as a protective factor against positive HPV status. This negative trend could be due to changes in the cervical transformation zone resulting from hormonal shifts during pregnancy that potentially could hinder the acquisition of HPV infection during intercourse. An important and related finding that does not necessarily contradict our and Munoz et al.'s observations is the negative trend for parity reported in a USA study. It showed that high parity increased the risk of squamous-cell carcinoma of the cervix among HPV-positive women [133].

In spite of the relatively low smoking rates (13%) among Arkhangelsk study subjects, our results corroborate other research that report that HPV status is positively associated with this habit.. A recent study on smoking before and during pregnancy in Murmansk County of North-west Russia reports that its prevalence among this cohort of women was 25.2% during 2006-2011 [127]. Differences in the time frames and the average age and education level of the cohorts might have contributed to the marked discrepancy in smoking rates. While smoking is associated with an increased risk of CC [134], the precise influence of smoking on a woman's chance of contracting HPV is unclear. A few studies have investigated possibly links and found that smoking has the potential to increase the risk of HPV infection through localized impairment of cervical cell-mediated immunity, although the observed magnitude of the effect was small [135]. Even though there appears to be a solid medical consensus that smokers are more likely to develop CC if they are HPV positive, there is no such agreement about whether increased risks of contracting HPV is associated with smoking. Some studies report an enhanced risk of HPV infection among smokers as we observed [131], but others found a reduced risk [136].

Consistent with previous studies [37, 131, 132, 137], our study found that age at sexual debut and the number of lifetime sexual partners are associated with positive HPV status. The average age that women become sexually active appears to be declining over time [138], which has clear implications for their health. Most young women and men become sexually active during their teenage years, and they generally do so without any protection. Poor general understanding of the various risks of unprotected sex (beyond unwanted pregnancies), coupled with a lack of access to birth control services, can explain the low rates of their use and the high rates of improper and ineffective application when used. Greenberg et al. [139] demonstrated that risky behaviors are

associated with early first sexual intercourse in a female population, including tendencies to have multiple sexual partners and having sex with riskier partners (e.g., bisexual or HIV-infected men). Previous research [37, 133] has established that risky life-styles, including multiple sexual partners and frequency of intercourse, are associated with HPV infection and particularly that by high oncogenic HPV types. In addition, having a high number of sexual partners has most consistently been associated with high rates of HPV infection [131, 132, 137]. Data that associate multiple sexual partners with higher HPV rates can be problematic as women tend to underreport the number of lifetime sexual partners [131, 140, 141].

Our findings indicate that condom use was not associated with HPV status. In their meta-analysis, Manhart et al. [142] found no consistent evidence that condom use reduces the risk of contracting HPV. Authors do suggest that while condoms might not prevent HPV infection, they may protect against genital warts and invasive cervical cancer [142]. Research has shown that very few women used condoms consistently [143, 144] and that they might be underestimating their potential protective effects.

Long-term use of oral hormonal contraceptives (i.e., the pill) could be a cofactor that increases the risk of cervical carcinoma [145]. Previous studies indicate that patients who used oral contraceptives fewer than 5 years did not have an increased risk of cervical cancer when compared to those who never used them [35, 146]. Nevertheless, the use of the pill for over 5 years has resulted in higher risks of cervical cancer [34, 145]. Almost 30 years ago, it was hypothesized that oestrogen and other hormones are capable of reactivating HPV or increasing its viral expression [147, 148]. However this relation is not likely causal as contraceptive users may differ from nonusers in aspects other than sexual behavior/contraception use.

Although our study participants demonstrated sufficient levels of knowledge about HPV and CC prevention, this awareness yielded no apparent protection against positive HPV status. Furthermore, while our more educated participants were more likely to be informed about HPV and CC, there was no association between education levels and rates of HPV infection. More educated women with good understanding of HPV and CC prevention were as likely to have HPV as less educated women with poor understanding. A possible explanation for the lack of difference in actual HPV rates between these two groups is that even though healthcare providers informed some women in a scientific and matter-of-fact manner that lead to greater understanding, the communication occurred with little or no attention to a problem's complexity. Neither was there a focus on the basics of prevention, the socioeconomic and the cultural context of a patient's life style and sex life. In short, if healthcare providers are indeed providing information, they are not doing so

in an effective way. We propose that it could be beneficial to re-conceptualize the education of healthcare workers to include not just a better understanding of HPV but also *how to effectively communicate* the risks and prevention of HPV and other STDs. The involvement of healthcare workers in planning such programs seems essential.

Little doubt remains that women who were positive for HPV can be distinguished from those who were HPV negative by a number of factors in their reproductive health, sexual behavior and preferences. However, many sociodemographic characteristics and variables used to measure sexual behavior are closely interrelated and thus could be potential confounders and/or mediators in a multivariable analysis. Moreover, the total impact of some key risk factors, such as marital status and smoking, could not be assessed fully due to the cross-sectional design of our study. Consequently, it was difficult to design an optimum regression model to evaluate their influence. Despite this limitation, our central findings have clear health care implications: specifically that age at sexual debut and parity (and not age itself or the lifetime number of sexual partners) are identified as independent predictors for cervical HR-HPV infection.

5.3 Implications for public health practice and research

Our findings corroborate previous studies in concluding that screening for CC is effective in improving survival rates for women. CC morbidity and mortality rates are still high in the Archangelsk region, and a near-certain contributor to this health problem is a lack of CC screening programs in Northwest Russia. From 1964 to 2012, various Soviet and Russian federal laws addressed CC screening guidelines. As mentioned in Section 1.3.1 of this thesis, in 2003 the Ministry of Health of the Russian Federation issued order № 50, which delineates the preferred CC screening procedure [149]. The order states that cytological testing for CC should commence at the age of 18 and should have no upper age limit. The testing is to be performed annually and should be combined with a thorough gynecological examination. It also specified that when cytobrush is available it is the preferred instrument for acquiring samples.

In section 1.3.1 of this thesis it is mentioned that the Ministry of Health of the Russian Federation issued a new order (№ 572n) in 2012 to establish the standards for medical care in the field of obstetrics and gynecology [150]. This order focused on the International Classification of Disease (ICD) cancer codes and did not specify instructions on screening in terms of a recommended age of initiation, the ideal frequency of tests, nor specific tissue sampling instruments

and staining methods). There is therefore no national screening registry in Russia currently, nor detailed guidelines for the management of women with cervical pathology. In the absence of official instructions, healthcare practitioners still recommend following the annual cytological sampling schedule and this practice was common during our study period. The research findings described in this thesis provide some information and data pertinent to updating the CC screening guidelines in Russia.

Notwithstanding our finding that more educated women were more likely to understand HPV and CC, the present research reveals a gap in specific knowledge about CC prevention. As noted above, most women with a sufficient level of knowledge named their physician as their main source of information. To address this knowledge gap, it is vital to provide all women with accurate information about HIV in the context of developing CC and to support the creation of effective educational programs for both women and their health-care providers.

In summary, our Arkhangelsk study found that women with positive HPV status were more likely to be younger, nulliparae and smokers, as well as having an earlier age of sexual debut and more than three sexual partners. As we have described in this report, the development and availability of specifically targeted sexual education programs would prevent the high occurrence of CC in Arkhangelsk.

6. Concluding Remarks

Based on our studies, we make the following conclusions:

1) Women diagnosed with CC through screening in its early stages survived longer when compared to those diagnosed without screening. The latter group was also diagnosed with CC at a younger age ($p = 0.013$) and died younger ($p = 0.002$). These findings are unequivocal in their significance for health care practitioners in that the CC death rate for women diagnosed without screening was 37 percent higher than of those diagnosed through screening.
2) Women with a university education, those who had an early sexual debut, had two or more children and/or whose physician was their primary source of information had higher levels of knowledge about HPV and CC prevention.
3) HR-HPV infection was more prevalent in women aged 25-29, as well as for nulliparous, smokers, cohabitants or those having had more than three sexual partners. Women with a positive HR-HPV status started having sex at an earlier age than those without. We found no difference in the numbers of correct answers for those with a positive or negative HPV status.

7. Implications and Research Recommendations

First of all, I and my co-authors recommend that the Cancer Registry in Arkhangelsk should continue and be expanded. Currently, the ACR does not include data on economic status, ethnicity, or Pap screening results. We have illustrated the critical importance of this information and conclude that it would facilitate and help to define and enhance future research, notably the investigation of cancer survival.

Secondly, to facilitate CC and related research we recommend the establishment of formal nationwide CC screening guidelines and a CC registry that can be linked to regional databases. This is a fundamental prerequisite for understanding the effectiveness of screening and enhancing participation rates in regions and nationally.

Thirdly, our examination of knowledge about CC in relation to the sociodemographic characteristics of women identified the development of CC educational programs for women, men and healthcare providers to be sound public policy. Furthermore, the research described in this thesis clearly demonstrates the importance of reliable sources of knowledge on HPV and CC prevention, and the need for effective communication methods.

Our final recommendation is that an effective HPV vaccination program be developed in the Arkhangelsk region.

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Paper 1

Paper 2

Paper 3

1. Сколько Вам полных лет? _____

2.Ваше образование?

- ☐ Средняя школа
- ☐ Колледж
- ☐ Университет
- ☐ Другое(укажите)_____

3. Ваш семейный статус?

- ☐ Замужем
- ☐ Одинока
- ☐ Проживаю с партнером
- ☐ Разведена/Вдова
- ☐ Другое_____ (укажите)

4. В каком возрасте Вы начали половую жизнь?

_____

5. Сколько сексуальных партнеров у вас было??

- ☐ 1-3
- ☐ Больше 3

6. Вы были беременны? (включая выкидыши и аборты)

- ☐ да
  - o Количество родов_____
  - o Количество абортов_____
  - o Количество выкидышей _____
- ☐ No

8. В настоящее время Вы курите?

- ☐ Да (уточните как долго _____)
- ☐ Нет

9. Пользуетесь ли вы какими либо методами защиты от беременности?

- ☐ Да
  - o Гормональные контрацептивные препараты
  - o Презерватив
  - o Внутриматочная спираль
  - o Другое (уточните) _____
- ☐ Нет

11. Были ли у вас когда-нибудь инфекции передающиеся половым путем?

- ☐ Да
- ☐ Нет
- ☐ Не помню/ Не знаю

12. До заполнения этой анкеты вы когда –нибудь слышали о вирусе папилломы человека (ВПЧ)?

- ☐ Да
- ☐ Нет

13. Если вы ответили «ДА» на предыдущий вопрос, пожалуйста уточните откуда Вы получили информацию:

- ☐ ТВ, ИНТЕРНЕТ, газеты, радио, журнал
- ☐ Врач
- ☐ Семья, друзья

14. Вирус папилломы человека (ВПЧ) часто встречается у женщин

- □ Да
- □ Нет

15. Самый часто встречающийся путь передачи вируса папилломы человека это половой путь.

- □ Да
- □ Нет

16. Большое количество половых партнеров в течение жизни повышает риск развития рака шейки матки.

- □ Да
- □ Нет

17. Вирус папилломы человека - известный фактор риска развития рака шейки матки.

- □ Да
- □ Нет

18. Как вы думаете, вирус папилломы человека может пройти без назначения лечения?

- □ Да
- □ Нет

19. У человека с вирусом папилломы нет проявлений инфекции

- □ Да
- □ Нет

20. Большинство женщин никогда в течение жизни не встретятся с вирусом папилломы человека.

- □ Да
- □ Нет

21. Согласно Российского законодательства как часто необходимо обследоваться на рак шейки матки?

- □ Один раз в шесть месяцев
- □ Один раз в год
- □ Один раз в три года
- □ Один раз в пять лет

22. До заполнения этой анкеты знали ли вы что цитологическое исследование соскоба с шейки матки (мазок на “раковые клетки”) может определить изменения на шейке матки, которые, если их не лечить, могут привести к развитию рака шейки матки?

- □ Да
- □ Нет

23. Вакцина против ВПЧ может предупредить развитие рака шейки матки

- □ Да
- □ Нет

24. Вакцинация против ВПЧ наиболее эффективна, если провести ее до начала половой жизни

- □ Да
- □ Нет

25. У человека вакцинированного от ВПЧ не может развиться рак шейки матки

- ☐ Да
- ☐ Нет

26. Женщинам привитым от ВПЧ не нужно больше участвовать в скрининге на рак шейки матки

- ☐ Да
- ☐ Нет