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

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Elena Roik

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A dissertation for the degree of Philosophiae Doctor (PhD)

Department of Community Medicine

Faculty of Health Sciences

Uit The Arctic University of Norway

Tromsø, Norway

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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.

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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.

List of Tables and Figures

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,

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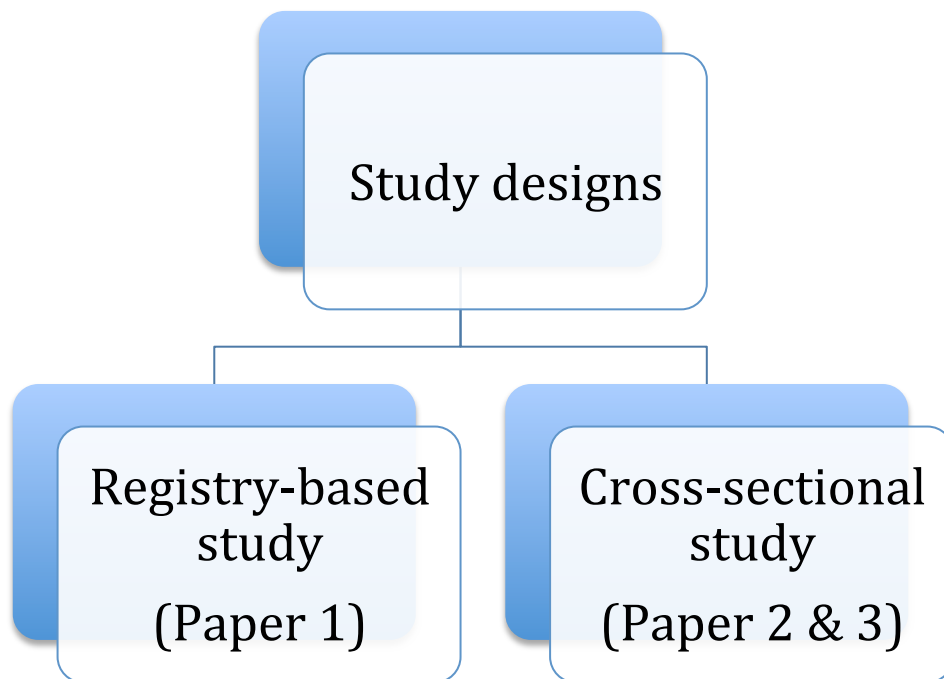
Figure 2. Chart illustrating study designs used in the thesis research

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-β) ≥ 0.80 at α = 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

- o   Number of deliveries _____
- o   Number of abortions _____
- o   Number of miscarriages _____
□   No

8. Do you smoke?
□   Yes   (specify for how many years _____)
□   No

9. Do you use contraception?
□   Yes
- o   Hormonal contraceptive pills
- o   Condom
- o   Intrauterine device
- o   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 $\geq$ 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 $\geq$ 2 deliveries. Smoking was designated as ever (yes) and never (no). Age of initiating intercourse was considered as continuous (years) or categorical variable ($\leq$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, $\geq$ 40), marital status (married, cohabiting, or single including divorced and/or widowed), parity (0, 1, or $\geq$ 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 ($\geq$ 93%), their percentages were a little higher for the other 3 stages than ours, namely: $\geq$ 63% (stage II), $\leq$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 $\geq$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.

8. References

1. de Sanjose S, Serrano B, Castellsague X, Brotons M, Munoz J, Bruni L, Bosch FX: **Human papillomavirus (HPV) and related cancers in the Global Alliance for Vaccines and Immunization (GAVI) countries. A WHO/ICO HPV Information Centre Report**. *Vaccine* 2012, **30 Suppl 4**:D1-83, vi.
2. **Media centre: Human papillomavirus (HPV) and cervical cancer. Fact sheet № 380.** [http://www.who.int/mediacentre/factsheets/fs380/en/]
3. **Fact Sheet HPV GAVI** [http://www.who.int/immunization/hpv/plan/fact_sheet_hpv_gavi_2013.pdf]
4. Hakama M, Rasanen-Virtanen U: **Effect of a mass screening program on the risk of cervical cancer**. *Am J Epidemiol* 1976, **103**(5):512-517.
5. Laara E, Day NE, Hakama M: **Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes**. *Lancet* 1987, **1**(8544):1247-1249.
6. Union TCotE: **Council recommendation of 2 December 2003 on cancer screening**. *Official Journal of the European Union* 2003(878):327–334.
7. Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee SK, Kuypers JM, Koutsky LA: **Development and duration of human papillomavirus lesions, after initial infection**. *J Infect Dis* 2005, **191**(5):731-738.
8. **ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Russian Federation. Summary Report** [http://www.who.int/mediacentre/factsheets/fs380/en/]
9. Smith HO, Tiffany MF, Qualls CR, Key CR: **The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study**. *Gynecol Oncol* 2000, **78**(2):97-105.
10. Vinh-Hung V, Bourgain C, Vlastos G, Cserni G, De Ridder M, Storme G, Vlastos AT: **Prognostic value of histopathology and trends in cervical cancer: a SEER population study**. *BMC Cancer* 2007, **7**:164.
11. Kosary CL: **FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina**. *Semin Surg Oncol* 1994, **10**(1):31-46.
12. Vizcaino AP, Moreno V, Bosch FX, Munoz N, Barros-Dios XM, Borras J, Parkin DM: **International trends in incidence of cervical cancer: II. Squamous-cell carcinoma**. *Int J Cancer* 2000, **86**(3):429-435.
13. Mathew A, George PS: **Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix--worldwide**. *Asian Pac J Cancer Prev* 2009, **10**(4):645-650.
14. Hellman K, Hellstrom AC, Pettersson BF: **Uterine cervix cancer treatment at Radiumhemmet: 90 years' experience. Time trends of age, stage, and histopathology distribution**. *Cancer Med* 2014, **3**(2):284-292.
15. Cancer. IAfRo: **Cervix Cancer Screening. IARC Handbooks of Cancer prevention**. *IARC Handbooks of Cancer prevention* 2005, **Vol. 10. Lyon: IARC Press**.
16. Richart RM, Fu YS: **DES and CIN**. *Obstet Gynecol* 1982, **60**(5):668-669.
17. **Comprehensive Cervical Cancer Control: A Guide to Essential Practice. 2nd edition.** [https://www.ncbi.nlm.nih.gov/books/NBK269605/]

18. **The revised Bethesda System for reporting cervical/vaginal cytologic diagnoses: report of the 1991 Bethesda workshop**. *J Reprod Med* 1992, **37**(5):383-386.
19. Tranbaloc P: **[Natural history of precursor lesions of cervical cancer]**. *Gynecol Obstet Fertil* 2008, **36**(6):650-655.
20. Holowaty P, Miller AB, Rohan T, To T: **Natural history of dysplasia of the uterine cervix**. *J Natl Cancer Inst* 1999, **91**(3):252-258.
21. Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, Tortolero-Luna G, Kjaer SK, Munoz N: **Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia**. *Vaccine* 2008, **26 Suppl 10**:K1-16.
22. Bosch FX, Munoz N, de Sanjose S: **Human papillomavirus and other risk factors for cervical cancer**. *Biomed Pharmacother* 1997, **51**(6-7):268-275.
23. Jaisamrarn U, Castellsague X, Garland SM, Naud P, Palmroth J, Del Rosario-Raymundo MR, Wheeler CM, Salmeron J, Chow SN, Apter D *et al*: **Natural history of progression of HPV infection to cervical lesion or clearance: analysis of the control arm of the large, randomised PATRICIA study**. *PLoS One* 2013, **8**(11):e79260.
24. MacLehose RF, Harpster A, Lanier AP, Schiff MA, Koehler K, Murphy N, Becker TM: **Risk factors for cervical intraepithelial neoplasm in Alaska Native women: a pilot study**. *Alaska Med* 1999, **41**(4):76-85.
25. Boyes DA, Morrison B, Knox EG, Draper GJ, Miller AB: **A cohort study of cervical cancer screening in British Columbia**. *Clin Invest Med* 1982, **5**(1):1-29.
26. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM: **Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008**. *Int J Cancer* 2010, **127**(12):2893-2917.
27. **Health inequalities: Europe in profile. Rotterdam.** [http://www.who.int/social_determinants/resources/european_inequalities.pdf]
28. **Territorial office of the federal state statistics service of the Arkhangelsk region.** [http://arhangelskstat.gks.ru/wps/wcm/connect/rosstat_ts/arhangelskstat/ru/statistics/population/]
29. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M *et al*: **Global burden of human papillomavirus and related diseases**. *Vaccine* 2012, **30 Suppl 5**:F12-23.
30. International Collaboration of Epidemiological Studies of Cervical C: **Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies**. *Int J Cancer* 2007, **120**(4):885-891.
31. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ: **Age and cancer risk: a potentially modifiable relationship**. *Am J Prev Med* 2014, **46**(3 Suppl 1):S7-15.
32. Lynge E, Lonnberg S, Tornberg S: **Cervical cancer incidence in elderly women-biology or screening history?** *Eur J Cancer* 2017, **74**:82-88.
33. Castellsague X, Munoz N: **Chapter 3: Cofactors in human papillomavirus carcinogenesis--role of parity, oral contraceptives, and tobacco smoking**. *J Natl Cancer Inst Monogr* 2003(31):20-28.
34. Munoz N, Franceschi S, Bosetti C, Moreno V, Herrero R, Smith JS, Shah KV, Meijer CJ, Bosch FX, International Agency for Research on Cancer. Multicentric Cervical Cancer Study G: **Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study**. *Lancet* 2002, **359**(9312):1093-1101.

35. Moreno V, Bosch FX, Munoz N, Meijer CJ, Shah KV, Walboomers JM, Herrero R, Franceschi S, International Agency for Research on Cancer. Multicentric Cervical Cancer Study G: **Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study**. *Lancet* 2002, **359**(9312):1085-1092.

36. Massad LS, Evans CT, Wilson TE, Goderre JL, Hessol NA, Henry D, Colie C, Strickler HD, Levine AM, Watts DH *et al*: **Knowledge of cervical cancer prevention and human papillomavirus among women with HIV**. *Gynecol Oncol* 2010, **117**(1):70-76.

37. Vaccarella S, Franceschi S, Herrero R, Munoz N, Snijders PJ, Clifford GM, Smith JS, Lazcano-Ponce E, Sukvirach S, Shin HR *et al*: **Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys**. *Cancer Epidemiol Biomarkers Prev* 2006, **15**(2):326-333.

38. Louie KS, de Sanjose S, Diaz M, Castellsague X, Herrero R, Meijer CJ, Shah K, Franceschi S, Munoz N, Bosch FX *et al*: **Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries**. *Br J Cancer* 2009, **100**(7):1191-1197.

39. Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, de Sanjose S, Eluf-Neto J, Ngelangel CA, Chichareon S, Smith JS *et al*: **Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners**. *N Engl J Med* 2002, **346**(15):1105-1112.

40. Castellsague X, Bosch FX, Munoz N: **The male role in cervical cancer**. *Salud Publica Mex* 2003, **45 Suppl 3**:S345-353.

41. **The Nobel Assembly at Karolinska Institutet** [http://nobelprize.org/nobel_prizes/medicine/laureates/2008/press.html.]

42. Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, Markowitz LE: **Prevalence of HPV infection among females in the United States**. *JAMA* 2007, **297**(8):813-819.

43. **Human Papillomavirus (HPV) Statistics** [https://www.cdc.gov/std/hpv/stats.htm]

44. de Sanjose S, Diaz M, Castellsague X, Clifford G, Bruni L, Munoz N, Bosch FX: **Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis**. *Lancet Infect Dis* 2007, **7**(7):453-459.

45. Franceschi S, Herrero R, Clifford GM, Snijders PJ, Arslan A, Anh PT, Bosch FX, Ferreccio C, Hieu NT, Lazcano-Ponce E *et al*: **Variations in the age-specific curves of human papillomavirus prevalence in women worldwide**. *Int J Cancer* 2006, **119**(11):2677-2684.

46. Hammouda D, Clifford GM, Pallardy S, Ayyach G, Chekiri A, Boudrich A, Snijders PJ, van Kemenade FJ, Meijer CJ, Bouhadef A *et al*: **Human papillomavirus infection in a population-based sample of women in Algiers, Algeria**. *Int J Cancer* 2011, **128**(9):2224-2229.

47. Munoz N, Mendez F, Posso H, Molano M, van den Brule AJ, Ronderos M, Meijer C, Munoz A, Instituto Nacional de Cancerologia HPVSG: **Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results**. *J Infect Dis* 2004, **190**(12):2077-2087.

48. Maucort-Boulch D, Plummer M, Castle PE, Demuth F, Safaeian M, Wheeler CM, Schiffman M: **Predictors of human papillomavirus persistence among women with equivocal or mildly abnormal cytology**. *Int J Cancer* 2010, **126**(3):684-691.

49. Rodriguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, Solomon D, Guillen D, Alfaro M, Morales J *et al*: **Longitudinal study of human papillomavirus**

persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection**. *J Natl Cancer Inst* 2010, **102**(5):315-324.

50. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, Snijders PJ, Meijer CJ, International Agency for Research on Cancer Multicenter Cervical Cancer Study G: **Epidemiologic classification of human papillomavirus types associated with cervical cancer**. *N Engl J Med* 2003, **348**(6):518-527.

51. Castellsague X: **Natural history and epidemiology of HPV infection and cervical cancer**. *Gynecol Oncol* 2008, **110**(3 Suppl 2):S4-7.

52. Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM, Schiller JT, Bock JE, Sherman ME, Lowy DR *et al*: **High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse)**. *Cancer Epidemiol Biomarkers Prev* 2001, **10**(2):101-106.

53. Humans IWGotEoCRt: **Biological agents. Volume 100 B. A review of human carcinogens**. *IARC Monogr Eval Carcinog Risks Hum* 2012, **100**(Pt B):1-441.

54. International Collaboration of Epidemiological Studies of Cervical C, Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodhill A, Green J, Peto J, Plummer M *et al*: **Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies**. *Lancet* 2007, **370**(9599):1609-1621.

55. International Collaboration of Epidemiological Studies of Cervical C, Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, Goodill A, Green J, Peto J, Plummer M *et al*: **Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies**. *Int J Cancer* 2006, **118**(6):1481-1495.

56. Arnheim Dahlstrom L, Andersson K, Luostarinen T, Thoresen S, Ogmundsdottir H, Tryggvadottir L, Wiklund F, Skare GB, Eklund C, Sjolin K *et al*: **Prospective seroepidemiologic study of human papillomavirus and other risk factors in cervical cancer**. *Cancer Epidemiol Biomarkers Prev* 2011, **20**(12):2541-2550.

57. Smith JS, Bosetti C, Munoz N, Herrero R, Bosch FX, Eluf-Neto J, Meijer CJ, Van Den Brule AJ, Franceschi S, Peeling RW *et al*: **Chlamydia trachomatis and invasive cervical cancer: a pooled analysis of the IARC multicentric case-control study**. *Int J Cancer* 2004, **111**(3):431-439.

58. **World Health Organization. Cancer screening.** [http://www.who.int/cancer/prevention/diagnosis-screening/screening/en/]

59. **Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years** [http://www.who.int/bulletin/volumes/86/4/07-050112/en/]

60. Hakama M, Coleman MP, Alexe DM, Auvinen A: **Cancer screening: evidence and practice in Europe 2008**. *Eur J Cancer* 2008, **44**(10):1404-1413.

61. **Screening for cervical cancer.** [http://www.cancer.ca/en/prevention-and-screening/early-detection-and-screening/screening/screening-for-cervical-cancer/?region=on]

62. Sasieni P, Castanon A, Cuzick J: **Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data**. *BMJ* 2009, **339**:b2968.

63. Vaccarella S, Franceschi S, Engholm G, Lonnberg S, Khan S, Bray F: **50 years of screening in the Nordic countries: quantifying the effects on cervical cancer incidence**. *Br J Cancer* 2014, **111**(5):965-969.

64. Cancer IAfRo: **Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. IARC Working Group on evaluation of cervical cancer screening programmes.** *BMJ*, **293**(6548):659-664.

65. **World Health Organization. Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.** [http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf]

66. Webb R, Richardson J, Esmail A, Pickles A: **Uptake for cervical screening by ethnicity and place-of-birth: a population-based cross-sectional study**. *J Public Health (Oxf)* 2004, **26**(3):293-296.

67. **The Cervical Cancer Screening Guidelines chart.** [http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf]

68. **NHS Cervical Screening Programme. Colposcopy and Programme Management** [https://www.bsccp.org.uk/assets/file/uploads/resources/NHSCSP_20_Colposcopy_and_Programme_Management_(3rd_Edition)_(2).pdf]

69. Kobayashi D, Takahashi O, Hikosaka C, Okubo T, Fukui T: **Optimal cervical cytology mass screening interval for cervical cancer**. *Arch Gynecol Obstet* 2013, **287**(3):549-554.

70. Fahey MT, Irwig L, Macaskill P: **Meta-analysis of Pap test accuracy**. *Am J Epidemiol* 1995, **141**(7):680-689.

71. **FDA approves first HPV test for use with SurePath Preservative Fluid** [https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm510251.htm]

72. **HPV and HPV testing.** [https://www.cancer.org/cancer/cancer-causes/infectious-agents/hpv/hpv-and-hpv-testing.html]

73. Care. CTFoPH: **Recommendations on screening for cervical cancer.** *CMAJ : Canadian Medical Association Journal* 2013, **185**(1):35-45.

74. Eaker S, Adami HO, Granath F, Wilander E, Sparen P: **A large population-based randomized controlled trial to increase attendance at screening for cervical cancer**. *Cancer Epidemiol Biomarkers Prev* 2004, **13**(3):346-354.

75. Eaker S, Adami HO, Sparen P: **Reasons women do not attend screening for cervical cancer: a population-based study in Sweden**. *Prev Med* 2001, **32**(6):482-491.

76. Seidel D, Becker N, Rohrmann S, Nimptsch K, Linseisen J: **Socio-demographic characteristics of participation in the opportunistic German cervical cancer screening programme: results from the EPIC-Heidelberg cohort**. *J Cancer Res Clin Oncol* 2009, **135**(4):533-541.

77. Ronco G, Senore C, Giordano L, Quadrino S, Ponti A, Segnan N: **Who does Pap-test? The effect of one call program on coverage and determinants of compliance**. *Epidemiol Prev* 1994, **18**(61):218-223.

78. Hansen BT, Hukkelberg SS, Haldorsen T, Eriksen T, Skare GB, Nygard M: **Factors associated with non-attendance, opportunistic attendance and reminded attendance to cervical screening in an organized screening program: a cross-sectional study of 12,058 Norwegian women**. *BMC Public Health* 2011, **11**:264.

79.   Coleman D, Day N, Douglas G, Farmery E, Lynge E, Philip J, Segnan N: **European Guidelines for Quality Assurance in Cervical Cancer Screening. Europe against cancer programme**. *Eur J Cancer* 1993, **29A Suppl 4**:S1-38.

80.   van der Aa MA, Pukkala E, Coebergh JW, Anttila A, Siesling S: **Mass screening programmes and trends in cervical cancer in Finland and the Netherlands**. *Int J Cancer* 2008, **122**(8):1854-1858.

81.   Harper DM, Nieminen P, Paavonen J, Lehtinen M: **Cervical cancer incidence can increase despite HPV vaccination**. *Lancet Infect Dis* 2010, **10**(9):594-595; author reply 595.

82.   Moser K, Patnick J, Beral V: **Inequalities in reported use of breast and cervical screening in Great Britain: analysis of cross sectional survey data**. *BMJ* 2009, **338**:b2025.

83.   Azerkan F, Widmark C, Sparen P, Weiderpass E, Tillgren P, Faxelid E: **When Life Got in the Way: How Danish and Norwegian Immigrant Women in Sweden Reason about Cervical Screening and Why They Postpone Attendance**. *PLoS One* 2015, **10**(7):e0107624.

84.   Petrova GVK, A.D.; Gretzova , O.P.; Starisky ,V.V. : **Malignant neoplasms in Russia. Overview of statistical data 1993-2013.** . *Overview of statistical data 1993-2013 Moscow* 2015.

85.   **Order of the Ministry of Health of the Russian Federation of 10.02.2003 №50 "On the improvement of obstetric and gynecological care in outpatient clinics".** [http://www.med-pravo.ru/PRICMZ/PricMZ2003/50/50_2-1.html]

86.   **Order of the Ministry of Health of the Russian Federation of November 1, 2012 No. 572n "On the Approval of the Procedure for the provision of medical assistance in the field of obstetrics and gynecology** [https://www.rosminzdrav.ru/documents/9154-prikaz-ministerstva-zdravoohraneniya-rossiyskoy-federatsii-ot-1-noyabrya-2012-g-572n-ob-utverzhdenii-poryadka-okazaniya-meditsinskoy-pomoschi-po-profilyu-akusherstvo-i-ginekologiya-za-isklyucheniem-ispolzovaniya-vspomogatelnyh-reproduktivnyh-tehnologiy]

87.   **Centers for Disease Control and Prevention. Vaccine Recommendations.** [https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html]

88.   **Clinician FAQ: CDC Recommendations for HPV Vaccine 2-Dose Schedules** [https://www.cdc.gov/hpv/downloads/HCVG15-PTT-HPV-2Dose.pdf]

89.   **Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices** [https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm]

90.   Andersson S BK, Demirbüker SS, Mints M, Östensson E.: **Perceived cervical cancer risk among women treated for high-grade cervical intraepithelial neoplasia: The importance of specific knowledge.** *PLoS ONE* 2017, **12**(12).

91.   Hanisch R, Gustat J, Hagensee ME, Baena A, Salazar JE, Castro MV, Gaviria AM, Sanchez GI: **Knowledge of Pap screening and human papillomavirus among women attending clinics in Medellin, Colombia**. *Int J Gynecol Cancer* 2008, **18**(5):1020-1026.

92.   Moreira ED, Jr., Oliveira BG, Ferraz FM, Costa S, Costa Filho JO, Karic G: **Knowledge and attitudes about human papillomavirus, Pap smears, and cervical cancer among young women in Brazil: implications for health education and prevention**. *Int J Gynecol Cancer* 2006, **16**(2):599-603.

93. AN V: **Dynamics of cervical cancer incidence rate and levels of awareness about its prevention among different population groups** *Human health and ecology* 2014, **February (2):** :25-30.

94. MV V: **Level of knowledge about cervical cancer and it's prevention among senior medical students of National medical university od Belarus.** . *Scientific aspirations* 2013, **5**(May:):120.

95. Borovikova OI KI, Borovikov IO, Nikogda YV: **Awareness of cervical cancer in Krasnodar. Modern problems of science and education.** . 2014, **6**(June):80-82.

96. Haesebaert J, Lutringer-Magnin D, Kalecinski J, Barone G, Jacquard AC, Regnier V, Leocmach Y, Vanhems P, Chauvin F, Lasset C: **French women's knowledge of and attitudes towards cervical cancer prevention and the acceptability of HPV vaccination among those with 14 - 18 year old daughters: a quantitative-qualitative study**. *BMC Public Health* 2012, **12**:1034.

97. Lima EG, de Lima DB, Miranda CA, de Sena Pereira VS, de Azevedo JC, de Araujo JM, de Medeiros Fernandes TA, de Azevedo PR, Fernandes JV: **Knowledge about HPV and Screening of Cervical Cancer among Women from the Metropolitan Region of Natal, Brazil**. *ISRN Obstet Gynecol* 2013, **2013**:930479.

98. **2010 All-Russian Population Census.** [[http://www.gks.ru/free_doc/new_site/perepis2010/croc/perepis_itogi1612.htm]]

99. **The sanitary and epidemiological welfare of the population in Arkhangelsk region in 2016** [http://29.rospotrebnadzor.ru/c/document_library/get_file?uuid=dd26a6f3-1d10-4a71-a917-42e6e773e54f&groupId=10156]

100. Vaktskjold A, Lebedintseva JA, Korotov DS, Tkatsjov AV, Podjakova TS, Lund E: **Cancer incidence in Arkhangelskaja Oblast in northwestern Russia. The Arkhangelsk Cancer Registry**. *BMC Cancer* 2005, **5**:82.

101. **On the improvement of the system of the State Cancer Registry** [http://docs.cntd.ru/document/902136492]

102. Marlow LA, Zimet GD, McCaffery KJ, Ostini R, Waller J: **Knowledge of human papillomavirus (HPV) and HPV vaccination: an international comparison**. *Vaccine* 2013, **31**(5):763-769.

103. Waller J, Ostini R, Marlow LA, McCaffery K, Zimet G: **Validation of a measure of knowledge about human papillomavirus (HPV) using item response theory and classical test theory**. *Prev Med* 2013, **56**(1):35-40.

104. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, Prey M, Raab S, Sherman M, Wilbur D, Wright T, Jr. *et al*: **The 2001 Bethesda System: terminology for reporting results of cervical cytology**. *JAMA* 2002, **287**(16):2114-2119.

105. **The International Cancer Survival Standard (ICSS) weights for cervical cancer** [https://seer.cancer.gov/stdpopulations/survival.html]

106. Dane FC, Parish DC: **Ethical issues in registry research: in-hospital resuscitation as a case study**. *J Empir Res Hum Res Ethics* 2006, **1**(4):69-76.

107. Muir CS, Demaret E, Boyle P: **The cancer registry in cancer control: an overview**. *IARC Sci Publ* 1985(66):13-26.

108. A V: **The quality and use of two health registries in Russia**. *International Journal of Circumpolar Health*, **65**(3):274-276.

109. Registries IAoC: 2017.

110. Freitas-Junior R, Soares LR, Barrios CH: **Cancer survival: [corrected] the CONCORD-2 study**. *Lancet* 2015, **386**(9992):428-429.

111. Nowakowski A, Cybulski M, Buda I, Janosz I, Olszak-Wasik K, Bodzek P, Sliwczynski A, Teter Z, Olejek A, Baranowski W: **Cervical Cancer Histology, Staging and Survival before and after Implementation of Organised Cervical Screening Programme in Poland**. *PLoS One* 2016, **11**(5):e0155849.
112. Landy R, Birke H, Castanon A, Sasieni P: **Benefits and harms of cervical screening from age 20 years compared with screening from age 25 years**. *Br J Cancer* 2014, **110**(7):1841-1846.
113. Coughlin SS, Thompson TD, Hall HI, Logan P, Uhler RJ: **Breast and cervical carcinoma screening practices among women in rural and nonrural areas of the United States, 1998-1999**. *Cancer* 2002, **94**(11):2801-2812.
114. Liff JM, Chow WH, Greenberg RS: **Rural-urban differences in stage at diagnosis. Possible relationship to cancer screening**. *Cancer* 1991, **67**(5):1454-1459.
115. Elnicki DM, Morris DK, Shockcor WT: **Patient-perceived barriers to preventive health care among indigent, rural Appalachian patients**. *Arch Intern Med* 1995, **155**(4):421-424.
116. Blair SL, Sadler GR, Bristol R, Summers C, Tahar Z, Saltzstein SL: **Early cancer detection among rural and urban Californians**. *BMC Public Health* 2006, **6**:194.
117. [http://www.ach.gov.ru/press_center/news/21297]
118. Kovchur PI, Bakhidze EV: **[Effectiveness of the model used for screening and early diagnosis of cervical cancer in Karelia]**. *Vopr Onkol* 2014, **60**(3):298-305.
119. Force USPST: **Screening for cervical cancer: recommendations and rationale**. *Am J Nurs* 2003, **103**(11):101-102, 105-106, 108-109.
120. Dickman PW, Hakulinen T, Luostarinen T, Pukkala E, Sankila R, Soderman B, Teppo L: **Survival of cancer patients in Finland 1955-1994**. *Acta Oncol* 1999, **38 Suppl 12**:1-103.
121. Maklecova SA RT: **Papilloma virus: opportunities for combined treatment**. *StatusPraesens* 2015, **1**(24):73-78.
122. Kataeva OA RS: **Cervicology, HPV,screening** *StatusPraesens* 2014, **4**(21):19-25.
123. Capogrosso P, Ventimiglia E, Matloob R, Colicchia M, Serino A, Castagna G, Clementi MC, La Croce G, Capitanio U, Gandaglia G *et al*: **Awareness and knowledge of human papillomavirus-related diseases are still dramatically insufficient in the era of high-coverage vaccination programs**. *World J Urol* 2015, **33**(6):873-880.
124. Williams MU, Carr MM, Goldenberg D: **Public awareness of human papillomavirus as a causative factor for oropharyngeal cancer**. *Otolaryngol Head Neck Surg* 2015, **152**(6):1029-1034.
125. Tiro JA MH, Kobrin S, Chollette V: **What do women in the U.S. know about human papillomavirus and cervical cancer?** *Cancer Epidemiol Biomarkers Prev* 2007, **16**(2):288-294.
126. Holcomb B, Bailey JM, Crawford K, Ruffin MTt: **Adults' knowledge and behaviors related to human papillomavirus infection**. *J Am Board Fam Pract* 2004, **17**(1):26-31.
127. Kharkova OA, Krettek A, Grjibovski AM, Nieboer E, Odland JO: **Prevalence of smoking before and during pregnancy and changes in this habit during pregnancy in Northwest Russia: a Murmansk county birth registry study**. *Reprod Health* 2016, **13**:18.
128. Kahn JA, Zimet GD, Bernstein DI, Riedesel JM, Lan D, Huang B, Rosenthal SL: **Pediatricians' intention to administer human papillomavirus vaccine: the role of**

practice characteristics, knowledge, and attitudes**. *J Adolesc Health* 2005, **37**(6):502-510.

129. Shipitsyna E, Zolotoverkhaya E, Kuevda D, Nasonova V, Romanyuk T, Khachaturyan A, Orlova O, Abashova E, Kostyuchek I, Shipulina O *et al*: **Prevalence of high-risk human papillomavirus types and cervical squamous intraepithelial lesions in women over 30 years of age in St. Petersburg, Russia**. *Cancer Epidemiol* 2011, **35**(2):160-164.

130. Syrjanen S, Shabalova I, Petrovichev N, Kozachenko V, Zakharova T, Pajanidi J, Podistov J, Chemeris G, Sozaeva L, Lipova E *et al*: **Sexual habits and human papillomavirus infection among females in three New Independent States of the former Soviet Union**. *Sex Transm Dis* 2003, **30**(9):680-684.

131. Kjaer SK, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME, Walboomers JM, Meijer CJ: **Determinants for genital human papillomavirus (HPV) infection in 1000 randomly chosen young Danish women with normal Pap smear: are there different risk profiles for oncogenic and nononcogenic HPV types?** *Cancer Epidemiol Biomarkers Prev* 1997, **6**(10):799-805.

132. Chan PK, Chang AR, Cheung JL, Chan DP, Xu LY, Tang NL, Cheng AF: **Determinants of cervical human papillomavirus infection: differences between high- and low-oncogenic risk types**. *J Infect Dis* 2002, **185**(1):28-35.

133. Munoz N, Kato I, Bosch FX, Eluf-Neto J, De Sanjose S, Ascunce N, Gili M, Izarzugaza I, Viladiu P, Tormo MJ *et al*: **Risk factors for HPV DNA detection in middle-aged women**. *Sex Transm Dis* 1996, **23**(6):504-510.

134. Chichareon S, Herrero R, Munoz N, Bosch FX, Jacobs MV, Deacon J, Santamaria M, Chongsuvivatwong V, Meijer CJ, Walboomers JM: **Risk factors for cervical cancer in Thailand: a case-control study**. *J Natl Cancer Inst* 1998, **90**(1):50-57.

135. Poppe WA, Ide PS, Drijkoningen MP, Lauweryns JM, Van Assche FA: **Tobacco smoking impairs the local immunosurveillance in the uterine cervix. An immunohistochemical study**. *Gynecol Obstet Invest* 1995, **39**(1):34-38.

136. Lazcano-Ponce E, Herrero R, Munoz N, Cruz A, Shah KV, Alonso P, Hernandez P, Salmeron J, Hernandez M: **Epidemiology of HPV infection among Mexican women with normal cervical cytology**. *Int J Cancer* 2001, **91**(3):412-420.

137. Peyton CL, Gravitt PE, Hunt WC, Hundley RS, Zhao M, Apple RJ, Wheeler CM: **Determinants of genital human papillomavirus detection in a US population**. *J Infect Dis* 2001, **183**(11):1554-1564.

138. Burchell AN, Winer RL, de Sanjose S, Franco EL: **Chapter 6: Epidemiology and transmission dynamics of genital HPV infection**. *Vaccine* 2006, **24 Suppl 3**:S3/52-61.

139. Greenberg J, Magder L, Aral S: **Age at first coitus. A marker for risky sexual behavior in women**. *Sex Transm Dis* 1992, **19**(6):331-334.

140. Nnko S, Boerma JT, Urassa M, Mwaluko G, Zaba B: **Secretive females or swaggering males? An assessment of the quality of sexual partnership reporting in rural Tanzania**. *Soc Sci Med* 2004, **59**(2):299-310.

141. Wellings K, Collumbien M, Slaymaker E, Singh S, Hodges Z, Patel D, Bajos N: **Sexual behaviour in context: a global perspective**. *Lancet* 2006, **368**(9548):1706-1728.

142. Manhart LE, Koutsky LA: **Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis**. *Sex Transm Dis* 2002, **29**(11):725-735.

143. Potter LB, Anderson JE: **Patterns of condom use and sexual behavior among never-married women**. *Sex Transm Dis* 1993, **20**(4):201-208.
144. Jama Shai N, Jewkes R, Levin J, Dunkle K, Nduna M: **Factors associated with consistent condom use among rural young women in South Africa**. *AIDS Care* 2010, **22**(11):1379-1385.
145. Vaccarella S, Herrero R, Dai M, Snijders PJ, Meijer CJ, Thomas JO, Hoang Anh PT, Ferreccio C, Matos E, Posso H *et al*: **Reproductive factors, oral contraceptive use, and human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys**. *Cancer Epidemiol Biomarkers Prev* 2006, **15**(11):2148-2153.
146. Peng Y, Wang, X., Feng, H., Yan, G.: **Is oral contraceptive use associated with an increased risk of cervical cancer? An evidence‐based meta‐analysis.** *J Obstet Gynaecol Res* 2017, **43**:913‐922.
147. Mitrani-Rosenbaum S, Tsvieli R, Tur-Kaspa R: **Oestrogen stimulates differential transcription of human papillomavirus type 16 in SiHa cervical carcinoma cells**. *J Gen Virol* 1989, **70 (Pt 8)**:2227-2232.
148. Mittal R, Tsutsumi K, Pater A, Pater MM: **Human papillomavirus type 16 expression in cervical keratinocytes: role of progesterone and glucocorticoid hormones**. *Obstet Gynecol* 1993, **81**(1):5-12.
149. **"On the improvement of obstetric and gynecological care in outpatient clinics".** [http://www.med-pravo.ru/PRICMZ/PricMZ2003/50/50_2-1.html]
150. **On the Approval of the Procedure for the provision of medical assistance in the field of obstetrics and gynecology** [https://www.rosminzdrav.ru/documents/9154-prikaz-ministerstva-zdravoohraneniya-rossiyskoy-federatsii-ot-1-noyabrya-2012-g-572n-ob-utverzhdenii-poryadka-okazaniya-meditsinskoy-pomoschi-po-profilyu-akusherstvo-i-ginekologiya-za-isklyucheniem-ispolzovaniya-vspomogatelnyh-reproduktivnyh-tehnologiy]

Paper 1

Article

Do Cervical Cancer Patients Diagnosed with Opportunistic Screening Live Longer? An Arkhangelsk Cancer Registry Study

Elena E. Roik [1,2,*], Evert Nieboer [3], Olga A. Kharkova [1,2], Andrej M. Grjibovski [2,4], Vitaly A. Postoev [2] and **Jon Ø. Odland [1]**

[1] Department of Community Medicine, Faculty of Health Sciences, UiT—The Arctic University of Norway, Tromsø N-9037, Norway; olga.a.kharkova@uit.no (O.A.K.); jon.oyvind.odland@uit.no (J.Ø.O.)
[2] International School of Public Health, Northern State Medical University, Arkhangelsk 163000, Russia; andrej.grjibovski@gmail.com (A.M.G.); vipostoev@yandex.ru (V.A.P.)
[3] Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON L8S 4L4, Canada; nieboere@mcmaster.ca
[4] Department of Preventive Medicine, International Kazakh -Turkish University, Turkestan 050040, Kazakhstan
* Correspondence: roik.elena@gmail.com; Tel.: +7-906-284-08-44

Abstract: The aim of the current study was to compare cervical cancer (CC) patients diagnosed with and without screening in terms of: (i) sociodemographic and clinical characteristics; (ii) factors associated with survival; and (iii), and levels of risk. A registry-based study was conducted using data from the Arkhangelsk Cancer Registry. It included women with newly diagnosed malignant neoplasm of the uterine cervix during the period of 1 January 2005 to 11 November 2016 (N = 1548). The Kaplan-Meier method, the log-rank test, and Cox regression were applied. Most participants who were diagnosed by screening were at stage I and died less frequently from CC than those diagnosed without screening. The latter group was also diagnosed with CC at a younger age and died younger. Younger individuals and urban residents diagnosed with stage I and II, squamous cell carcinoma had longer survival times. Cox regression modeling indicated that the hazard ratio for death among women with CC diagnosed without screening was 1.61 (unadjusted) and 1.37 (adjusted). CC diagnosed by screening, cancer stage, patient residence, histological tumor type, and age at diagnosis were independent prognostic variables of longer survival time with CC. Diagnosis of CC made within a screening program improved survival.

Keywords: screening; cervical cancer; uterine; survival; Arkhangelsk Cancer Registry; Russia

1. Introduction

Cervical cancer (CC) ranks as the second-to-third most frequent cancer in women worldwide with an estimate of 528,000 cases in 2015 [1,2]. In 2015, about 266,000 women died from this preventable disease [1]. The incidence and death rates are substantially higher in low- and middle-income countries due to limited access to preventive measures [2]. In Russia, CC ranks as the fifth leading cause of female cancer with an estimate of about 15,342 new cases diagnosed annually [3]. Its crude incidence rate in Russia is generally lower than in Arkhangelsk region (21.27 versus 24.25 in 2015) [4]. The Arkhangelsk region is the biggest Arctic region in Europe and its Gross Regional Product (GRP) places it as a middle-income region in the Russian Federation [5].

The objectives of CC screening are to detect precancerous lesions and early stage cancer, thereby avoiding new cancer cases and the development of advanced stages and deaths from them [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 [6,7]. The introduction of screening appears to have improved survival [8]. Opportunistic screening (i.e., screening on demand) can also decrease CC rates, but usually to a smaller extent [9,10]. This approach tends to cover younger women, thereby often missing those at highest risk [11], and success depends strongly on attendance rate. Generally speaking, non-participation in screening is associated with a lower level of education [11–13], single status [12,14], smoking [12], and thus a low awareness level is likely [15,16]. Ethnicity [17], psychological barriers [18], and residence (urban/rural residence) are other factors that have been shown to be associated with participation rates in screening programs [19].

Canada and the United States have been regarded as leaders in cervical cancer screening. Most of the research on the implementation of screening has taken place in US settings, where it is predominantly opportunistic. In Canada, a combination of opportunistic and organized approaches is used [20,21]. The latest recommendations by the European Union (EU) state that cancer screening programs should only be offered on a population basis in an organized fashion, and must include quality control protocols at all levels [22]. National and World Health Organization (WHO) guidelines that describe how to start and organize a screening program are available [23]. There is wide variation in the structure of CC screening programs, and this reflects the resources available [19]. Cancer-screening programs in the Nordic countries have been successful in decreasing incidence and mortality rates. Finland was the first country to have success in organized screening of CC. Its implementation has resulted in rapid decreases in the invasive CC incidence and mortality rates. It also has generated a change in the staging and histological distribution of CC in that country [24].

In spite of existing screening methods, CC continues to be a major public health problem in the Russian Federation [25]. The incidence and mortality rates of CC in Russia are generally high and show little tendency to decrease [25]. Cytological screening for this cancer was introduced in the Soviet Union in 1964 [26]. Until 2003 the screening was opportunistic, and was based on conventional cytology stained by the Romanovski-Gimse method with Ayre's spatula as the tissue sample-taking instrument. In 2003, the Ministry of Health of the Russian Federation issued order No. 50, which delineates the preferred CC screening procedure [27]. The order states that cytological testing for CC should be started at the age of 18 with no upper age limit, is to be performed annually, and should be combined with a gynecological examination. The cytobrush is the preferred instrument for acquiring samples, when possible. In 2012 the Ministry of Health of the Russian Federation issued a new order (No. 572n), which included standards for medical care in the field of obstetrics and gynecology [28]. This order did not specify instructions on screening, its frequency, a recommended age of initiation, nor specific tissue sampling instruments and staining methods. Its focus was on the International Classification of Disease (ICD) cancer codes. There is no national screening registry in Russia, nor guidelines for the management of women with cervical pathology. Currently, Human papilloma virus (HPV) testing and vaccination are available on demand for a fee, but are not included in the national vaccine calendar. The Romanovski-Gimse staining method is still widely used in the region. It was in this context that a regional cancer registry was set up in Arkhangelsk, Northwest Russia.

Information on survival is recognized as an important indicator in cancer control activities [29]. Survival analyses provide important information for public health authorities in evaluating treatment access and its effectiveness. We employed data from the Arkhangelsk Cancer Registry (ACR) to compare CC patients diagnosed with and without screening in terms of: (i) sociodemographic and clinical characteristics; (ii) factors associated with survival; and (iii) calculated hazard ratios.

2. Materials and Methods

2.1. Study Setting, Design, and Sample Size

The Arkhangelsk Region (AR) is located in the northwestern part of the Russian Federation. It covers an area of 589,900 square km and had a population of 1,174,078 on 1 January 2016 [5]. The ACR is a joint effort of the University of Tromsø (Norway) and the Arkhangelsk Regional Oncological

Hospital, and was established in 1999. Our data include all cases of cervical cancer registered during the period of 1 January 2005 to 11 November 2016. Electronic registration of cancer cases within the ACR consists of three databases. The ACR contains the following information: date of birth, sex, ethnicity, maternal occupation, date of diagnosis, ICD-9 and -10 codes, histological tumor type, morphology code, stage, tumor, node and metastasis (TNM) stage, method of cancer diagnosis, how the tumor was revealed, type of treatment and its result, the occurrence of cancer metastases, and cancer recurrence. Additional details about its content and implementation have been described previously [30]. Data quality control exercises of the ACR were conducted twice, specifically in November 2003 and May 2003, and the quality of the registered information was accepted as suitable for epidemiological studies [30]. According to the Russian legislation (order No. 135, issued by the Russian Ministry of Health on 19 April 1999), every newly diagnosed cancer has to be reported by physicians to an oncological hospital within three days using a prescribed form. Three trained individuals entered the received data into the Cancer Registry database. Since 2000, a computer program was installed to monitor the accuracy of the entered data [30].

A total of 1940 CC cases were registered in the ACR for the designated period. The inclusion criterion was the presence of a newly diagnosed malignant neoplasm of the uterine cervix. The study sample included 1548 cases, with 371 being excluded due to repeated consultations (cancer recurrences), and 21 were lost to follow-up.

2.2. Data Collection

Age at the time of diagnosis and of death were presented as continuous variables (in years). For the purpose of the survival analyses, we used the International Cancer Survival Standard (ICSS) weights for CC, with age at diagnosis divided into five groups: 15–44 years, 45–54 years, 55–64 years, 65–74 years, and over 75 years [31]. Vital status by the end of each year was categorized as: (i) death from CC; (ii) death from other reasons; and (iii) alive. Survival time was calculated in months, with the day of diagnosis as the initial date. For patients whose underlying cause of death was CC, the final date was that at death. Deaths from other causes were also recorded in the ACR, including its date of death. For patients who did not die, the final date of the study period was 11 November 2016. Stage-specific survival analysis was carried out for each stage separately. Furthermore, data for stages I and II were combined to yield an early cancer variable, and that for stages III and IV were combined for advanced cancers. This was done because of the small number of observations.

Based on medical records, the ACR contained information on CC diagnostic methods (whether with or without screening), cancer location and stage, year-end vital status, histological type of tumor, age at diagnosis, date of birth, and date of death (if applicable). Residence was defined as urban or rural. Diagnosed with screening means that the diagnosis was made during a regular health check or when consulting a gynecologist for a condition not related to symptomatic patient care. Regular health checks are usually done over the non-selected population, i.e., people belonging to different age groups, residences, and occupations. They routinely include testing for cervical cancer (cytological sampling). A diagnosis made without screening indicates that the patient was symptomatic for CC. The most common symptoms are copious foul-smelling vaginal discharge, abnormal bleeding or inter-menstrual bleeding, postcoital bleeding, postmenopausal bleeding, or backache. In both settings the cervical cytology was performed similarly in the diagnostic process. Cancer stage at diagnosis was in accordance with the guidelines of the International Federation of Gynecology and Obstetrics (FIGO). Patients with an in situ cancer were not included in the registry, nor in the survival analyses. Histologic subtypes were classified according to the International Classification of Disease for Oncology, 2nd ed. (ICD-02). For purpose of analysis, histopathological types were grouped as squamous cell carcinomas (codes 8050–8078, 8083–8084); adenocarcinomas (8140–8141, 8190–8211, 8230–8231, 8260–8263, 8310, 8380, 8382–8384, 8440–8490, 8570–8574, 8576), and other/unspecified malignant neoplasms (8010–8380, 8382–8576, 8010–8035, 8800–8811,8830, 8840–8921, 8990–8991, 9040–9044, 9120–9133, 9150, 9540–9581, 8000–8005).

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2.3. Data Analysis

We used the Pearson's chi-squared test to analyze categorical variables. The *t*-test was used to compare continuous variables, the Kaplan-Meier method approach was applied in the determination of CC mean survival times and related graphics, the log-rank method was used for the comparison of accumulated survival curves, and the Cox proportional risk model was employed for the calculation of hazard ratios (HRs) for the independent study variables. The latter were adjusted for age, cancer stage and histology, residence, and year of diagnosis. The statistical analyses were carried out using SPSS version 24 (SPSS Inc., Chicago, IL, USA).

2.4. Ethical Considerations

This study was granted ethical approval by the Ethical Committee of Northern State Medical University, Arkhangelsk, Russia (Этический комитет Северного Государственного Медицинского Университета), Report Number 01/02/2017 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.

This study was based on a retrospective review of the Arkhangelsk Cancer Registry (ACR) de-identified records. Informed consent for this study was not obtained because our study database does not contain personal information and the project was not interventional. The cancer reporting is specified in the Russian legislation. Related specifics have been described by Vaktskjold et al. [30].

3. Results

There were 1940 cases of confirmed and registered primary invasive cancers of the cervix. Among these, 1548 records matched the selection criteria and represent the study sample. Most of the cases were diagnosed at stage I, squamous cell carcinoma was the predominant histological form, and one third of deaths were due to CC (see Table 1). Residence, age at diagnosis, cancer stage, tumor histology, and the number of deaths among those diagnosed with the screening are also reported in this table. Most participants who were diagnosed by screening were at stage I ($p < 0.001$), and died less frequently from CC ($p < 0.001$) than those diagnosed without screening. The latter group was also diagnosed with CC at a younger age ($p = 0.013$) and died younger ($p = 0.002$). Compared to women with CC diagnosed by screening, tumor histology and residence did not differ for those diagnosed without screening (Table 1).

The Kaplan-Meier survival curves for the study period are provided in Figure 1 and illustrate a significant difference in survival time between the two groups ($p = 0.001$). The 5- and 10-year survival was about 60% among CC patients diagnosed without screening and more than 70% for those diagnosed with it. In Figure 2, the Kaplan-Meier curves are depicted by initial staging. Five-year survival was about 97% for stage I, 64% for stage II, 38% for stage III, and 19% for stage IV.

In stage-specific analyses, we observed significant difference in survival for those diagnosed with screening compared to those diagnosed without only for stage II ($p = 0.052$); while for stage I $p = 0.379$, for stage III $p = 0.495$, and for stage IV $p = 0.789$.

As illustrated in Figure 3a,b, women diagnosed with CC with screening in the early stages (I and II) of this disease survived longer when compared to those diagnosed without it. However, for the advanced stages (III and IV), we did not find such a difference.

The sociodemographic and clinical variables for the unadjusted survival functions are provided in Table 2.

Table 1. Sociodemographic characteristics and clinical variables of women with different types of cervical cancer diagnostics.

Variables	N (%)	No Screening	Screening	P [1]
		N = 1285	N = 263	
Age at Diagnosis (years) [2]*: Mean (SD)*	48.5 (15.2)	48.1 (15.1)	50.6 (15.7)	0.013
Residence:				
urban	1122 (72.5)	941 (73.2)	181 (68.8)	0.145
rural	426 (27.5)	344 (26.8)	82 (31.2)	
Stages:				
I	606 (39.1)	471 (36.7)	135 (51.3)	
II	404 (26.1)	349 (27.2)	55 (20.9)	<0.001
III	352 (22.7)	314 (24.4)	38 (14.4)	
IV	186 (12.0)	151 (11.7)	35 (13.4)	
Histological tumor type:				
squamous cell	1292 (83.5)	1072 (83.4)	220 (83.7)	
carcinoma	141 (9.1)	116 (9.0)	15 (9.5)	0.829
adenocarcinoma unspecified/other	94 (6.1)	78 (6.1)	16 (6.1)	
uknown	21 (1.4)	19 (1.5)	2 (0.7)	
Vital status:				
alive	969 (62.6)	773 (60.2)	196 (74.5)	
died from cervical cancer	514 (33.2)	455 (35.4)	59 (22.4)	<0.001
died from other causes	65 (4.2)	57 (4.4)	8 (3.0)	
Age of death (years) [2]*: Mean (SD)*	54.2 (16.5)	53.5 (16.3)	60.3 (17.3)	0.002

[1] Chi-square test; [2] *t*-test.

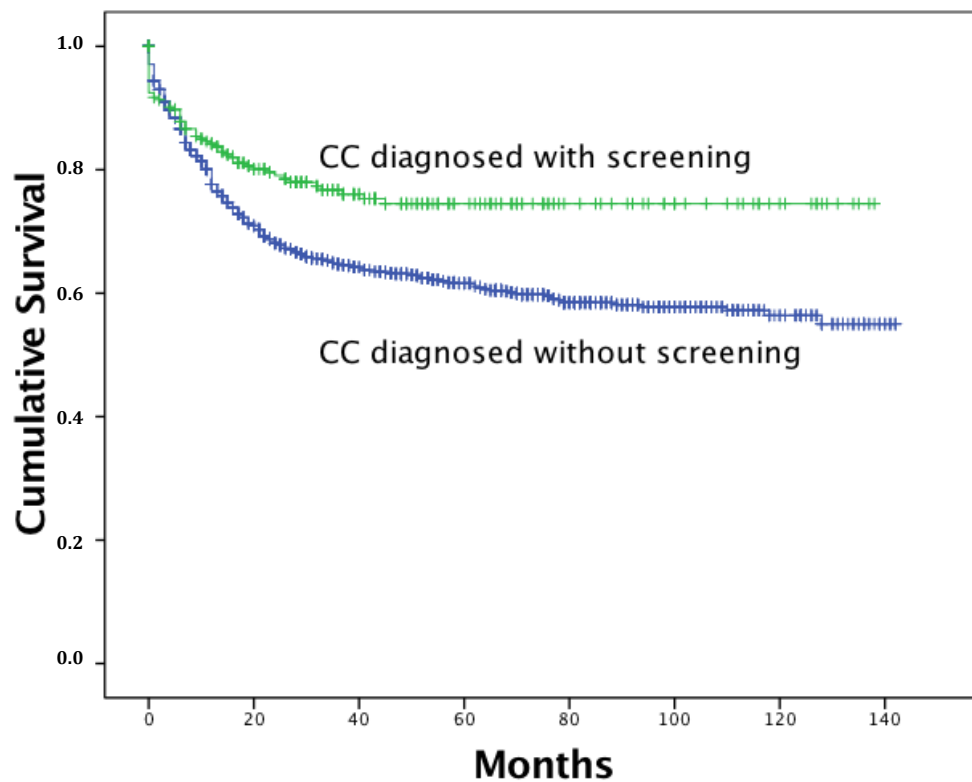**Figure 1.** Survival curve for women with cervical cancer and registered in the Arkhangelsk Cancer Registry (ACR).

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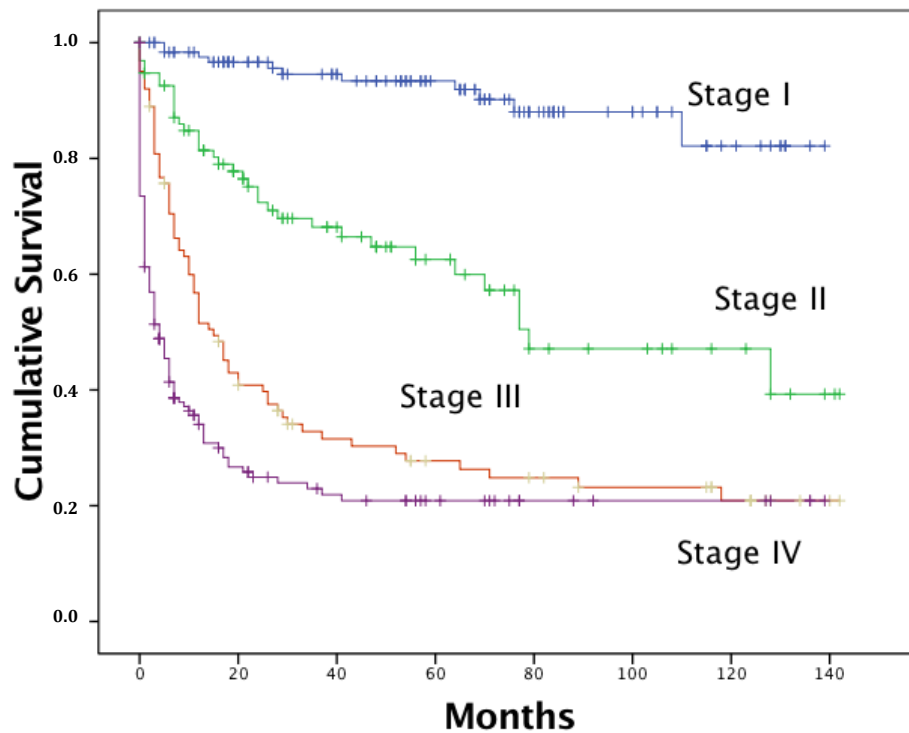
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Figure 2. Survival curve for women with different stages of cervical cancer registered in the ACR.

At the end of the follow-up, 59 (22.5%) and 455 (35.4%) of women, respectively with CC diagnosed with and without screening, had died. Younger aged, urban residents diagnosed with stage I and II, squamous cell carcinoma 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) and 1.37 (adjusted) (Table 3).
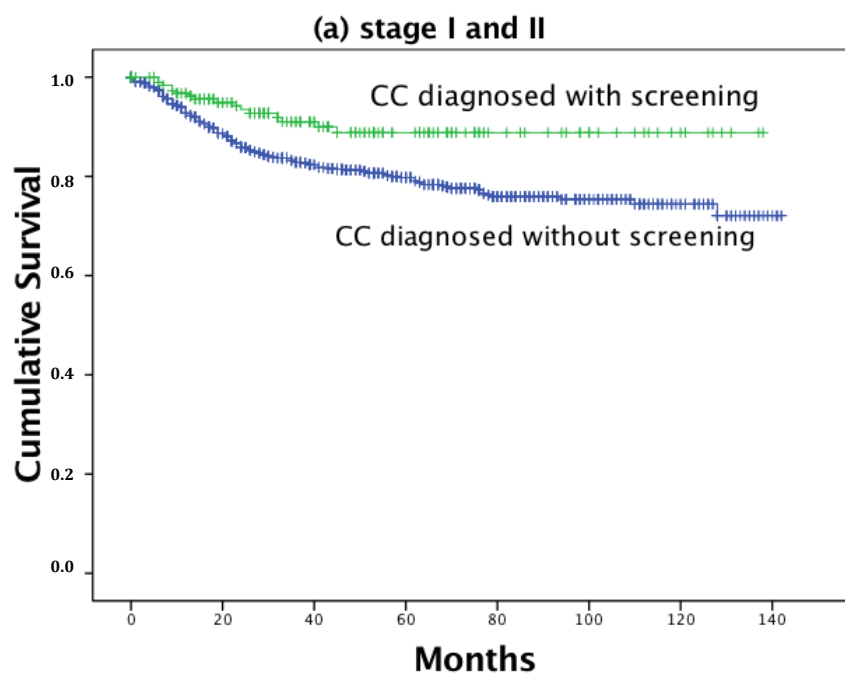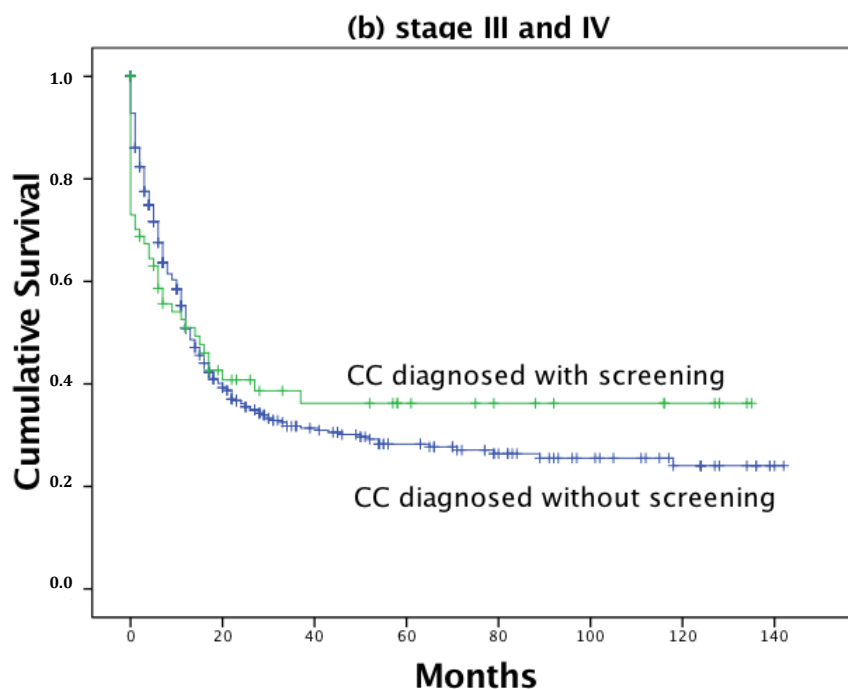

Figure 3. *Cont.*

Figure 3. Stage-specific survival curves for women diagnosed with different types of CC (whether with or without screening) and registered in the ACR: (**a**) stages I and II (*p* = 0.003); (**b**) stages II and III (*p* = 0.890).

Table 2. Number of deaths, mean survival time and its 95% confidence lower limits (LL) and upper limits (UL) estimated by the Kaplan-Meier method, and the results of the log-rank test (*p*-value) for the study variables in women with cervical cancer.

	N	Deaths	Mean Survival Time (Months)			Log-Rank *p*-Value
			Mean	**95% LL**	**95% UL**	
Cervical cancer (CC) diagnosed by screening:						0.001
no	1285	455	89.7	85.9	93.4	
yes	263	59	105.8	98.5	113.0	
Age in years:						<0.001
15–44	746	202	101.7	97.0	106.4	
44–54	314	99	94.1	86.5	101.7	
55–64	244	93	80.6	71.2	90.0	
65–74	158	60	82.8	72.2	93.1	
75 and more	107	60	53.4	40.7	66.0	
Stage:						<0.001
I	606	36	132.5	129.5	135.5	
II	404	135	92.2	85.6	98.9	
III	352	203	55.7	48.5	62.9	
IV	186	140	30.7	22.4	39.0	
Residence:						0.018
urban	1122	358	95.0	91.0	98.9	
rural	426	156	85.9	78.9	92.8	
Histological tumor type:						<0.001
squamous cell carcinoma	1292	390	97.1	93.4	100.7	
adenocarcinoma	141	66	67.7	55.2	80.2	
unspecified/other	94	42	73.6	59.8	87.5	
unknown	21	16	31.6	11.3	51.8	

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Table 3. Hazard ratio (Cox model, crude and adjusted), with the respective lower and upper 95% confidence limits (LL and UL) in women with cervical cancer.

	Crude			Adjusted [1]		
	HR	**95% CI**	***p*-Level**	**HR**	**95% CI**	***p*-Level**
Cervical cancer diagnosed by screening:						
no	1.61	1.22–2.10	0.001	1.37	1.04–1.80	0.027
yes	1.00			1.00		

[1] Adjusted for age, cancer stage and histology, residence, and year of diagnosis.

4. Discussion

4.1. Main Findings

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

4.2. Data Interpretation and Comparisons with Previous Studies

The observed mean age at diagnosis of CC was 48.5 years, which is comparable to values reported by others. For example, in a British study [32] the median age at diagnosis for CC approached 50 years. Screening ages between the late 40s to middle 60s appear to be most common. Our findings of a significant difference in the mean age of CC cases diagnosed with and without screening (48.1 and 50.6 years, respectively) is consistent with that observed in a Swedish study [33]. The latter showed a slight increase in the mean age at diagnosis for all stages after the introduction of screening. By contrast, others report no significant differences in the median age at diagnosis [32,34,35]. The age of screening initiation varies from country to country. In the Russian Federation, national screening protocols are regulated by the Ministry of Health Orders No. 50 and 808, which specify that CC screening should be started at the age of 18, or at initiation of sexual activity with no upper age limit. Initiation of screening at an early age can lead to overestimation of CC risk. Landy et al. concluded that screening from age 20 years on would lead to over-treatment and over-testing, while having little impact on CC prevention [36].

Our data show that residence was not associated with CC diagnosis made with or without screening. By contrast, lower participation rates in CC screening have been reported for rural areas of the USA [37]. Rural residents would appear to have a higher risk of late cancer detection due to barriers that include: lack of convenient access to or availability of preventive health services (including early detection screening) [38–40] and a lack of awareness and knowledge about the existence of screening programs [41,42]. On the other hand, for cancers diagnosed at late stages, the absence of significant associations between rural/urban residence and survival [43] have been reported [44].

The fraction of the participants with a positive CC diagnosis decreased across the four CC stages, namely: 39.1% (I), 26.1% (II), 22.7% (III), and 12.0% (IV). At stage I, the percent of CC cases diagnosed with screening was higher compared to those without (51.3 versus 36.7%). This is consistent with the findings of Hellman et al. [33], who reported an increase in stage I to more than 50% of all CC cases. Several studies presented opposite results. For example, Nowakowski et al. [34] reported that advanced stages of CC dominated in a cervical screening program in Poland. In the present study, women diagnosed with CC with screening (stages I and II) had longer survival compared to those diagnosed without screening. However, for the advanced stages we did not find this difference. This may be partly explained by the speedier examination of those diagnosed with

screening. Usually, women diagnosed without screening have to wait for a colposcopy and biopsy appointment, which could take up to six months.

After the collapse of the Soviet Union, the number of primary healthcare centers and number of medical workers has decreased in Russia, and in about 17,500 municipalities there is no health infrastructure. Moreover, 35% of settlements are not covered by public transport and ambulance services are often not available [45]. The latter may be one possible explanation for the low level of participation in CC screening programs. Several factors determine the participation in preventive measures for CC: (i) at the system level, there is underfunding; (ii) at the provider level, suitable screening intervals are not recommended, nor is treatment/follow-up carried out in a timely manner; and (iii) at the individual level, women often face lack of transportation/childcare, impeding clinical visits, and have insufficient knowledge about screening. A 2010 Norwegian study illustrated the importance of such knowledge, including awareness of screening intervals and CC risk factors for enhancing public participation [14]. Sporadic screening or lack of communication among healthcare professionals that lead to misunderstanding between cytologists and gynecologists might have been responsible, as well as low screening coverage (on average 43–45%, with a range of 11.5–61.9% in 2009 and 23.6–24.6% in 2001–2007). Furthermore, low attendance rates across a region due to the low awareness of women about the risk of CC might contribute as well [46,47]. Lack of training in smear sampling and usage of old instruments have also been identified as possible reasons for screening failure in a region [48], as well as demographic changes in population size and distribution by age and sex [25]. It has been reported that one fifth of the patients diagnosed with CC in the Republic of Karelia died within the first year of the disease [46].

Squamous cell carcinoma was the predominant histological type and accounted for more than 80% of all CC cases, of which 9.1% were adenocarcinoma. During the 1950s and 1960s worldwide, nearly 95% of all invasive CCs were squamous cell carcinomas, followed by adenocarcinomas (5%) [49,50]. Most recently, the squamous type accounted for approximately 75% of CC, whereas adenocarcinomas contributed 25% [51]. This change is likely due to the introduction of screening [32] with cytological testing as the primary screening tool [49,52]. The difficulty of anatomic accessibility has been suggested as one of the main causes for the low detection rates and the diagnosis of late stage adenocarcinomas [53]. Therefore, one of the methods suggested for improving early detection of adenocarcinoma is to use a combination of cytology and testing for high-risk HPV types [52]. The healthcare system availability, wide use of contraceptive pills, and changes in smoking habits and in sexual behavior increased awareness of CC risk all appear to have contributed to the changes in CC distribution by age, stage, and histopathology [33].

Our study group of women diagnosed with CC with screening had higher 5-year survival times than those who were diagnosed without screening. Worldwide, the 5-year survival from CC varies widely from <50% to >70%, although in most countries it has increased somewhat during the last 10 years. The highest 5-year survival reported occurred in the Nordic countries (78%), while the lowest was registered in Malta (44%) [54]. According to the American Cancer Society (ACS) in 2010, the overall 5-year survival in the USA was 72% [55]. While the 5-year survival for our stage I patients concurs with that reported by the ACS (≤93%), for the other three stages they were lower than their values of ≤63% (stage II), ≤35% (stage III), and around 15% (stage IV) [55].

Age as a prognostic factor for survival can be confounded by age-dependent factors, since the prevalence of other diseases (e.g., hypertension and cardiovascular diseases) may mitigate receiving optimal treatment or a favorable result from it [56]. Survival up to 87% for women aged less than 30 years and 45.5% for those older than 70 years is typical [56]. In the EUROCARE-3 study, the relative survival in the age group 15–44 years at diagnosis was more than two-fold higher when compared to the group of women aged 75 or more (74% and 34%, respectively at 5 years). Our findings closely match the latter (Table 2).

According to the International Agency for Research on Cancer (IARC) [35], the CC stage at diagnosis is generally the most important factor in the survival of cancer patients [56,57]. In our

study, women with late-stage CC had substantially lower survival rates, even less than 5 years after first CC diagnosis (Figure 2). Improvement in survival is often used as an indicator of successful screening. In Finland, the implementation of screening for cervical cancer resulted in a slight decrease in survival [58]. The latter was attributed to a growing proportion of cases of advanced cancers in women not attending screening. However, most counties in the study that showed improvements in survival of CC had adequate diagnostic and treatment procedures and screening programs in place.

4.3. Limitations and Strengths

To the best of the authors' knowledge, this study is first in Russia to use the cancer registry data to assess the effectiveness of CC screening and patient survival. Our analysis is limited by the lack of data on socioeconomic status, smoking, use of oral contraception, parity, and cases of carcinoma or adenocarcinoma in situ—the precursors of invasive CC. The results of the cytological screening were not available and could not be included in the analysis. Information about HPV type-specific infection that would have helped to quantify its role in the development of specific histologic CC subtypes was also not available. Therefore, our study might have been biased by over-diagnosis. The appearance of the latter is common in early detection programs [59]. Another related and common phenomenon in screening programs is healthy-volunteer bias, because individuals willing to participate in screening may be of a higher socioeconomic group, have easier access to healthcare, and follow the health providers' recommendations more precisely. Consequently, those who participated in screening may have lower mortality rates and longer survival than the total population at risk [56]. Lead-time bias may also have been an issue. Early diagnosis by screening may not improve survival and could enhance a patient's anxiety as she needs to live longer with the knowledge of having CC. To avoid this, more sensitive screening tools have to be designed and used to ensure that the diagnosis can be made at the pre-cancer stage.

5. Conclusions

Our study demonstrates that death from CC was 37% higher when the diagnosis was made without opportunistic screening when compared to those diagnosed with screening after adjustment for cancer stage, patient residence, histological tumor type, age at diagnosis, and by year. The hazard rates for death among women with CC diagnosed without screening were also significantly higher compared to those diagnosed with it. Diagnosis of CC made within our screening program further prolonged survival. Exploring women's awareness about existing CC screening programs should be considered in efforts to enhance participation rates. In terms of generalizability, our results may well apply to other regions of Russia because of the similarity of CC screening programs to that described.

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References

1. Bruni, L.; Barrionuevo-Rosas, L.; Albero, G.; Serrano, B.; Mena, M.; Gómez, D.; Muñoz, J.; Bosch, F.X.; de Sanjosé, S. *Human Papillomavirus and Related Diseases in the World*; Summary Report 2015-04-08; ICO Information Centre on HPV and Cancer (HPV Information Centre): Barcelona, Spain. Available online: http://www.hpvcentre.net/statistics/reports/XWX.pdf (accessed on 15 January 2017).

2. World Health Organisation. Media Centre. Human Papillomavirus (HPV) and Cervical Cancer. Fact sheet No. 380. Reviewed March 2015. Available online: http://www.who.int/mediacentre/factsheets/fs380/en/ (accessed on 15 January 2017).

3. Bruni, L.; Barrionuevo-Rosas, L.; Albero, G.; Serrano, B.; Mena, M.; Gómez, D.; Muñoz, J.; Bosch, F.X.; de Sanjosé, S. *Human Papillomavirus and Related Diseases in Russian Federation*; Summary Report 2017-07-27; ICO Information Centre on HPV and Cancer (HPV Information Centre): Barcelona, Spain. Available online: http://www.hpvcentre.net/statistics/reports/RUS.pdf (accessed on 18 September 2017).

4. Petrova, G.V.; Kaprin, A.D.; Gretzova, O.P.; Starisky, V.V. *Malignant Neoplasms in Russia. Overview of Statistical Data 2015*; Moscow Research Oncological Institute named after P.A. Herzen: Moscow, Russia, 2016. Available online: http://www.oncology.ru/service/statistics/malignant_tumors/2015.pdf (accessed on 18 September 2017). (In Russian)

5. Territorial Office of the Federal State Statistics Service of the Arkhangelsk Region. Available online: http://arhangelskstat.gks.ru/wps/wcm/connect/rosstat_ts/arhangelskstat/ru/statistics/population/ (accessed on 10 January 2017).

6. Hakama, M.; Räsänen-Virtanen, U. Effect of a mass screening program on the risk of cervical cancer. *Am. J. Epidemiol.* **1976**, *103*, 512–517. [CrossRef] [PubMed]

7. Laärä, E.; Day, N.; Hakama, M. Trends in mortality from cervical cancer in the Nordic countries: Association with organised screening programmes. *Lancet* **1987**, *329*, 1247–1249. [CrossRef]

8. Klint, A.; Tryggvadottir, L.; Bray, F.; Gislum, M.; Hakulinen, T.; Storm, H.H.; Engholm, G. Trends in the survival of patients diagnosed with cancer in female genital organs in the Nordic countries 1964–2003 followed up to the end of 2006. *Acta Oncol.* **2010**, *49*, 632–643. [CrossRef] [PubMed]

9. Lynge, E.; Madsen, M.; Engholm, G. Effect of organised screening on incidence and mortality of cervical cancer in Denmark. *Cancer Res.* **1989**, *49*, 2157–2160. [PubMed]

10. Nieminen, P.; Kallio, M.; Anttila, A.; Hakama, M. Organised versus spontaneous Pap-smear screening for cervical cancer: A case control study. *Int. J. Cancer* **1999**, *83*, 55–58. [CrossRef]

11. Coleman, D.; Day, N.E.; Douglas, G.; Farmery, E.; Lynge, E.; Philip, J.; Segnan, N. European guidelines for quality assurance in cervical cancer screening. *Eur. J. Cancer* **1993**, *29A* (Suppl. 4), S1–S38. [PubMed]

12. Seidel, D.; Becker, N.; Rohrmann, S.; Nimptsch, K.; Linseisen, J. Socio-demographic characteristics of participation in the opportunistic German cervical cancer screening programme: Results from the EPIC-Heidelberg cohort. *J. Cancer Res. Clin. Oncol.* **2009**, *135*, 533–541. [CrossRef] [PubMed]

13. Ronco, G.; Senore, C.; Giordano, L.; Quadrino, S.; Ponti, A.; Segnan, N. Who does Pap-test? The effect of one call program on coverage and determinants of compliance. *Epidemiol. Prev.* **1994**, *18*, 218–223. [PubMed]

14. Hansen, B.T.; Hukkelberg, S.S.; Haldorsen, T.; Eriksen, T.; Skare, G.B.; Nygard, M. Factors associated with non-attendance, opportunistic attendance and reminded attendance to cervical screening in an organized screening program: A cross-sectional study of 12,058 Norwegian women. *BMC Public Health* **2011**, *11*, 264. [CrossRef] [PubMed]

15. Harper, D.M.; Nieminen, P.; Paavonen, J.; Lehtinen, M. Cervical cancer incidence can increase despite HPV vaccination. Correspondence. *Lancet Infect. Dis.* **2010**, *10*, 594–595. [CrossRef]

16. Van der Aa, M.A.; Pukkala, E.; Coebergh, J.W.; Anttila, A.; Siesling, S. Mass screening programmes and trends in cervical cancer in Finland and The Netherlands. *Int. J. Cancer* **2008**, *122*, 1854–1858. [CrossRef] [PubMed]

17. Moser, K.; Patnick, J.; Beral, V. Inequalities in reported use of breast and cervical screening in Great Britain: Analysis of cross sectional survey data. *Br. Med. J.* **2009**, *338*, b2025. [CrossRef] [PubMed]

18. Azerkan, F.; Widmark, C.; Sparen, P.; Weiderpass, E.; Tillgren, P.; Faxelid, E. When Life Got in the Way: How Danish and Norwegian Immigrant Women in Sweden Reason about Cervical Screening and Why They Postpone Attendance. *PLoS ONE* **2015**, *10*, e0107624. [CrossRef] [PubMed]

19. Webb, R.; Richardson, J.; Esmail, A.; Pickles, A. Uptake for cervical screening by ethnicity and place-of-birth: A population-based cross-sectional study. *J. Public Health* **2004**, *26*, 293–296. [CrossRef] [PubMed]

20. Canadian Cancer Society. Screening for Cervical Cancer. Available online: http://www.cancer.ca/en/prevention-and-screening/early-detection-and-screening/screening/screening-for-cervical-cancer/?region=on (accessed on 10 November 2017).

21. Saraiya, M.; Steben, M.; Watson, M.; Markowitz, L. Evolution of cervical cancer screening and prevention in United States and Canada: Implications for public health practitioners and clinicians. *Prev. Med.* **2013**, *57*, 426–433. [CrossRef] [PubMed]

22. The Council of the European Union Council recommendation of 2 December 2003 on cancer screening. *Off. J. Eur. Union* **2003**, *878*, 34–38. Available online: https://ec.europa.eu/jrc/sites/jrcsh/files/2_December_2003%20cancer%20screening.pdf (accessed on 18 September 2017).

23. World Health Organization. Guidelines for Screening and Treatment of Precancerous Lesions for Cervical Cancer Prevention. 2013. Available online: http://apps.who.int/iris/bitstream/10665/94830/1/9789241548694_eng.pdf (accessed on 10 November 2017).

24. Hinkula, M.; Pukkala, E.; Kyyronen, P.; Laukkanen, P.; Koskela, P.; Paavonen, J.; Lehtinen, M.; Kauppila, A. A population based study on the risk of cervical cancer and cervical intraepithelial neoplasia among grand multiparious women in Finland. *Br. J. Cancer* **2004**, *90*, 1025–1029. [CrossRef] [PubMed]

25. Petrova, G.V.; Kaprin, A.D.; Gretzova, O.P.; Starisky, V.V. *Malignant Neoplasms in Russia. Overview of Statistical Data 1993–2013*; Moscow Research Oncological Institute named after P.A. Herzen: Moscow, Russia, 2015. (In Russian)

26. Novik, V.I. Screening for cervical cancer. *J. Pract Oncol.* **2010**, *11*, 66–72. (In Russian)

27. Order of the Ministry of Health of the Russian Federation of 10.02.2003 No. 50. On the Improvement of Obstetric and Gynecological Care in Outpatient Clinics. Available online: http://www.med-pravo.ru/PRICMZ/PricMZ2003/50/50_2--1.html (accessed on 18 September 2017).

28. Order of the Ministry of Health of the Russian Federation of 1 November 2012 No. 572n. On the Approval of the Procedure for the Provision of Medical Assistance in the Field of Obstetrics and Gynecology. Available online: https://www.rosminzdrav.ru/documents/9154-prikaz-ministerstva-zdravoohraneniya-rossiyskoy-federatsii-ot-1-noyabrya-2012-g-572n-ob-utverzhdenii-poryadka-okazaniya-meditsinskoy-pomoschi-po-profilyu-akusherstvo-i-ginekologiya-za-isklyucheniem-ispolzovaniya-vspomogatelnyh-reproduktivnyh-tehnologiy (accessed on 18 September 2017).

29. National Cancer Control Programs. *Policies and Managerial Guidelines*; WHO: Geneva, Switzerland, 2002. Available online: http://www.who.int/cancer/media/en/408.pdf (accessed on 10 January 2017).

30. Vaktskjold, A.; Lebedintseva, J.A.; Korotov, D.S.; Tkatsjov, A.V.; Podjakova, T.S.; Lund, E. Cancer incidence in Arkhangelskaja Oblast in northwestern Russia. The Arkhangelsk Cancer Registry. *BMC Cancer* **2005**, *5*, 82. [CrossRef] [PubMed]

31. National Cancer Institute. The International Cancer Survival Standard (ICSS) Weights for Cervical Cancer. Available online: https://seer.cancer.gov/stdpopulations/survival.html (accessed on 18 September 2017).

32. Sasieni, P.; Castanon, A.; Cuzick, J. Effectiveness of cervical screening with age: Population based case-control study of prospectively recorded data. *BMJ* **2009**, *339*, b2968. [CrossRef] [PubMed]

33. Hellman, K.; Hellstrom, A.C.; Pettersson, B.F. Uterine cervix cancer treatment at Radiumhemmet: 90 years' experience. Time trends of age, stage, and histopathology distribution. *Cancer Med.* **2014**, *3*, 284–292. [CrossRef] [PubMed]

34. Nowakowski, A.; Cybulski, M.; Buda, I.; Janosz, I.; Olszak-Wasik, K.; Bodzek, P.; Sliwczynski, A.; Teter, Z.; Olejek, A.; Baranowski, W. Cervical Cancer Histology, Staging and Survival before and after Implementation of Organised Cervical Screening Programme in Poland. *PLoS ONE* **2016**, *11*, e0155849. [CrossRef] [PubMed]

35. IARC Working Group on Cervical Cancer Screening. Screening for squamous cervical cancer—The duration of low risk following negative results in cervical cytology test: Introduction. *Br. Med. J.* **1986**, *292*, 659–664.

36. Landy, R.; Birke, H.; Castanon, A.; Sasieni, P. Benefits and harms of cervical screening from age 20 years compared with screening from age 25 years. *Br. J. Cancer* **2014**, *110*, 1841–1846. [CrossRef] [PubMed]

37. Coughlin, S.S.; Thompson, T.D.; Hall, H.I.; Logan, P.; Uhler, R.J. Breast and cervical carcinoma screening practices among women in rural and nonrural areas of the United States, 1998–1999. *Cancer* **2002**, *94*, 2801–2812. [CrossRef] [PubMed]

38. Liff, J.M.; Chow, W.H.; Greenberg, R.S. Rural-urban differences in stage at diagnosis. Possible relationship to cancer screening. *Cancer* **1991**, *67*, 1454–1459. [CrossRef]

39. Wang, F.; McLafferty, S.; Escamilla, V.; Luo, L. Late-Stage Breast Cancer Diagnosis and Health Care Access in Illinois. *Prof. Geogr.* **2008**, *60*, 54–69. [CrossRef] [PubMed]

40. Jemal, A.; Ward, E.; Wu, X.; Martin, H.J.; McLaughlin, C.C.; Thun, M.J. Geographic patterns of prostate cancer mortality and variations in access to medical care in the United States. *Cancer Epidemiol. Prev. Biomark.* **2005**, *14*, 590–595.

41. Elnicki, D.M.; Morris, D.K.; Shockcor, W.T. Patient-perceived barriers to preventive health care among indigent, rural Appalachian patients. *Arch. Intern. Med.* **1995**, *155*, 421–424. [CrossRef] [PubMed]

42. Fazio, L.; Cotterchio, M.; Manno, M.; McLaughlin, J.; Gallinger, S. Association between colonic screening, subject characteristics, and stage of colorectal cancer. *Am. J. Gastroenterol.* **2005**, *100*, 2531–2539. [CrossRef] [PubMed]

43. Blair, S.L.; Sadler, G.R.; Bristol, R.; Summers, C.; Tahar, Z.; Saltzstein, S.L. Early cancer detection among rural and urban Californians. *BMC Public Health* **2006**, *6*, 194. [CrossRef] [PubMed]

44. Shugarman, L.R.; Sorbero, M.E.; Tian, H.; Jain, A.K.; Ashwood, J.S. An exploration of urban and rural differences in lung cancer survival among medicare beneficiaries. *Am. J. Public Health* **2008**, *98*, 1280–1287. [CrossRef] [PubMed]

45. Accounts Chamber of Russian Federation. Press-Centre Release, 13 April 2015. Available online: http://www.ach.gov.ru/press_center/news/21297 (accessed on 17 January 2017). (In Russian)

46. Bakhlaev, I.E.; Kovchur, P.I.; Mikhetko, A.A.; Kurmyshkina, O.V.; Nilva, S.E. Cervical cancer in Karelia. *Vestnik ROINC Imeni Blokhina* **2011**, *22*, 22–29. (In Russian)

47. Bakhlaev, I.E.; Kovchur, P.I. Prevention of cancer of the cervix uteri at an antenatal clinic. *Tumors Womens Reprod. Syst.* **2009**, *3–4*, 94–98. (In Russian)

48. Bakhlaev, I.E.; Kovchur, P.I.; Mikhetko, A.A.; Nilva, S.E. Epidemiologic features and cytological screening of cervical cancer in Karelia. *Vliyanie Ecologii na Vnutrennie Bolezni* **2010**, *1*, 1757–1761. (In Russian)

49. Smith, H.O.; Tiffany, M.F.; Qualls, C.R.; Key, C.R. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—A 24-year population-based study. *Gynecol. Oncol.* **2000**, *78*, 97–105. [CrossRef] [PubMed]

50. Vinh-Hung, V.; Bourgain, C.; Vlastos, G.; Cserni, G.; De Ridder, M.; Storme, G.; Vlastos, A.T. Prognostic value of histopathology and trends in cervical cancer: A SEER population study. *BMC Cancer* **2007**, *7*, 164. [CrossRef] [PubMed]

51. Vizcaino, A.P.; Moreno, V.; Bosch, F.X.; Munoz, N.; Barros-Dios, X.M.; Borras, J.; Parkin, D.M. International trends in incidence of cervical cancer: II. Squamous-cell carcinoma. *Int. J. Cancer* **2000**, *86*, 429–435. [CrossRef]

52. Mathew, A.; George, P.S. Trends in incidence and mortality rates of squamous cell carcinoma and adenocarcinoma of cervix-worldwide. *Asian Pac. J. Cancer Prev.* **2009**, *10*, 645–650. [PubMed]

53. U.S. Preventive Services Task Force. Screening for cervical cancer: Recommendations and rationale. *Am. J. Nurs.* **2003**, *103*, 101–109.

54. OECD Health Statistics. Available online: http://www.oecd.org/els/health-systems/health-data.htm (accessed on 10 January 2017).

55. American Cancer Society. *Cancer Facts and Figures*; American Cancer Society: Atlanta, GA, USA, 2010. Available online: https://www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/survival.html (accessed on 10 January 2017).

56. Kosary, C.L. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: An analysis of 1973–87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. *Semin. Surg. Oncol.* **1994**, *10*, 31–46. [CrossRef] [PubMed]

57. Perez, C.A.; Grigsby, P.W.; Nene, S.M.; Camel, H.M.; Galakatos, A.; Kao, M.S.; Lockett, M.A. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. *Cancer* **1992**, *69*, 2796–2806. [CrossRef]

58. Dickman, P.W.; Hakulinen, T.; Luostarinen, T.; Pukkala, E.; Sankila, R.; Sodermam, B.; Teppo, L. Survival of cancer patients in Finland 1955–1994. *Acta Oncol.* **1999**, *38*, 1–103. [CrossRef] [PubMed]

59. Kramer, B.S.; Croswell, J.M. Cancer screening: The clash of science and intuition. *Annu. Rev. Med.* **2009**, *60*, 125–137. [CrossRef] [PubMed]

Paper 2

Knowledge about human papillomavirus and prevention of cervical cancer among women of Arkhangelsk, Northwest Russia

Elena E. Roik[1,2]*, Ekaterina E. Sharashova[1], Evert Nieboer[3], Olga A. Kharkova[1,2], Vitaly A. Postoev[2], Jon Ø. Odland[1]

1 Department of Community Medicine, Faculty of Health Sciences, UiT—The Arctic University of Norway, Tromsø, Norway, **2** International School of Public Health, Northern State Medical University, Arkhangelsk, Russia, **3** McMaster University, Department of Biochemistry and Biomedical Sciences, Hamilton, ON, Canada

* elena.e.roik@uit.no

Abstract

Background

Knowledge about cervical cancer (CC) risk factors and benefits of CC prevention motivates women to participate in its screening. However, several studies show that there is a significant knowledge deficit worldwide about human papillomavirus (HPV). The current study explores the level of knowledge about HPV and CC prevention in the context of sociodemographic and behavioral characteristics of women who visited an antenatal clinic in Arkhangelsk, Russia.

Methods

This cross-sectional study was conducted in the city of Arkhangelsk, which seats the administrative center of Arkhangelsk County, Northwest Russia. It included women who consulted a gynecologist for any reason between January 1, 2015 and April 30, 2015, were residents of Arkhangelsk, 25 to 65 years of age and sexually active (N = 300). Student's t-test for continuous variables and Pearson's χ^2 test for categorical variables were used in the comparisons of women grouped as having either poor or sufficient knowledge. Linear regression analysis was also employed.

Results

The level of knowledge about HPV and CC prevention was associated with education, parity, age of initiating of intercourse, and sources of information. After adjustment, women with university education were more likely to have higher knowledge about HPV and CC prevention compared to those with lower education.

Conclusions

We observed that most participants had a sufficient level of knowledge. Educational gaps were identified that potentially could be used to tailor interventions in CC prevention.

Introduction

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infection in both women and men worldwide and more than 100 HPV types are known [1]. They are classified as non-oncogenic (low-risk HPVs) and oncogenic (high-risk HPVs). Most such infections are transient, and more prevalent among young adults subsequent to engaging initiation in sexual activity. The most important risk factor for cervical cancer (CC) is persistent infection with high-risk HPV types [2, 3].

CC is the fourth most common cancer affecting women worldwide, with estimates of 527 624 new cases and 265 572 deaths in 2012 [4]. The highest incidence is observed in low and middle-income countries, in which CC is a major cause of cancer-related deaths. In Russia, the crude incidence of CC was 20.0 per 100 000 women in 2012 [5]. CC affects women aged 15 years and older, and its risk gradually increases with age, peaking between 45–49 years. CC is ranked as the second most common female cancer in the 15–44 year group [5]. Its incidence and mortality can be reduced by early detection of pre-invasive lesions because they respond to treatment. Cervical cytology is the most common method employed in CC screening worldwide [6]. In low and middle-income countries, many women are not screened nor followed-up regularly [7]. Low coverage, poor participation and follow-up, as well as lack of quality control measures constitute possible reasons for ineffective CC screening [8].

Knowledge about CC risk factors and benefits of its prevention motivate women to participate in screening [8]. However, several studies indicate that there is a significant HPV knowledge deficit worldwide [9–14]. Lima et al. [15] demonstrated that HPV knowledge level was associated with age, education, marital status, household income and pregnancies. Older women had higher knowledge scores compared to younger women. Moreover, women with a high school or higher education, married or with a partner, middle or high income, and previously pregnant exhibited better knowledge about HPV [15]. Hanisch et al. [8] did not find an association between HPV knowledge level and marital status, whereas age and education were associated with it.

HPV-related knowledge has been explored and described in countries worldwide [9–14], although little is known about the situation in Russia. This study aims to address this gap. We examine associations between knowledge of HPV and CC prevention and sociodemographic and behavioral characteristics of women who visited an antenatal clinic in Arkhangelsk, Russia.

Materials and methods

Study design, setting, participants and data collection

This cross-sectional study was conducted in the city of Arkhangelsk that seats the administrative center of Arkhangelsk County in Northwest Russia. On January 1, 2015, Arkhangelsk city had a population of 350 982 [16]. Enrolment was conducted during the period January 1, 2015 to April 30, 2015 at the *Samoylova* Clinical Maternity Hospital, which serves as an antenatal clinic for all Arkhangelsk city districts.

A sample size of 300 with an HPV prevalence of 10% was calculated to satisfy the condition $(1-\beta) \geq 0.80$ at $\alpha = 0.05$. Women who came to a gynecologist for any reason, were sexually active residents of Archangelsk and aged 25 to 65 years were invited to participate in the study. Since there are no national guidelines that regulate the cervical screening age in Russia, we adopted that of the United Kingdom NHC Cervical Screening Programme (NHSCSP). The latter recommends that routine screening be conducted during the 25–65 age interval [17]. Of the 350 women invited, 300 (86%) agreed to participate and signed the consent form. All

participants completed a questionnaire (S1 Questionnaire and S2 Questionnaire). The questionnaire was designed to reflect both our study objectives and published studies, including reports by pertinent international health care agencies [18–21]. We aimed to incorporate questions that reflected current knowledge about HPV and cervical cancer prevention. Questions were formulated in such a way as to facilitate clear answers, and for some more than one response was allowed. Care was taken to ensure that the questionnaire was not too long in order to facilitate its completion while in a gynecologist's waiting room. Prior to use, the questions were read by randomly selected women, both educated and those not receiving education beyond the basic level, to make sure that the questions were understood by all. Accordingly, appropriate adjustments were made. The questions used in the statistical analyses are provided as Supporting Information (S1 Questionnaire and S2 Questionnaire).

The questionnaire sought information about the participants' knowledge about HPV and CC prevention (through 14 pertinent questions), as well as specific details about their sociodemographic status (age, education, marital status, parity, smoking) and their sexual behavior characteristics (age of initiating of intercourse, history of sexually transmitted infections, contraception, history of cervical cytology by the Papanicolau (Pap) test and related abnormal findings and their management). All the questions were accompanied by several possible answers to choose from. For the questions on knowledge about HPV and CC prevention, only one answer could be keyed in as correct.

Variables

Participants' knowledge about HPV and CC prevention was used as both a discrete variable (number of correct answers from 0 to 14) and a binary variable. For the latter, we considered having at least 50% of the questions answered correctly (7–14 out of the 14 questions) as a sufficient level of knowledge, and less than 50% of the questions answered correctly (6 or less out of the 14 questions) as a poor level. Sources of knowledge about HPV and CC prevention included TV/media, physician, or other (including family and friends). The frequency of screening for CC was categorized as once in: six months, a year (national recommendations), and in 3–5 years. The last screening the participants received was categorized into four intervals: less than 3 years ago, more than 3 years ago, never, and do not know.

Age as a variable was considered as both continues (years) and categorical (25–44 or ≥ 45 years). Education was categorized as university level or less than university level. Women were divided into three groups based on their marital status: married, cohabiting, or single (including divorced or widowed). Parity was classified as 0, 1, or ≥ 2 deliveries. Smoking was designated as yes or no (ever and never smokers).

Age of initiating intercourse was used as a continuous (years) and a categorical variable (≤17, 18–21, and > 21 years) and the number of lifetime sexual partners was recorded as three and less or more than three. History of sexually transmitted infections was categorized into ever had or never had, and contraception into four categories (use of condoms, combined oral contraceptive pill, an intrauterine device, or none).

Data analysis

Histogram was used to describe the distribution of HPV and CC prevention knowledge (used as a discrete variable) among the study participants. Means and standard deviations for age of the participants and the age of intercourse initiation, and proportions for other sociodemographic and sexual behavior categories were calculated for each of the poor and sufficient levels of knowledge. This statistical comparison between the two levels of knowledge groups was

carried out using the independent Student's t-test for continuous variables and Pearson's χ^2 test for categorical variables.

We used linear regression analysis to estimate possible associations between the level of knowledge about HPV and CC prevention (when used as a discrete variable) and sociodemographic and sexual behavior characteristics. Crude and mutually adjusted regression coefficients were calculated with 95% confidence intervals. The p-value <0.05 was considered to be statistically significant. The analysis was carried out using SPSS version 24 (SPSS Inc., Chicago, IL).

Ethical considerations

All study participants provided written informed consent. The research was approved by the Research Ethics Committee of Northern State Medical University of Arkhangelsk, Northwest Russia Report Number 01/02-17 obtained on 01/03/2017; and the Norwegian Regional Committee for Medical and Health Research Ethics (RECNorth), Tromsø, Norway, Registered Report Number 2014/1670.

Results

Characteristics of study participants

The mean age of the study participants was 35.8 (9.0) years. Out of 300 participants, 163 (54.3%) had university education, 166 (55.3%) were married and 72 (24%) were cohabiting, 123 (41.0%) had one delivery, and 116 (38.7%) had two or more deliveries; and the prevalence of smoking among the participants was 13%. Almost half of the women (45.3%) reported to ever have had sexually transmitted infection. The mean age of initiating intercourse was 18.3 (2.5) years, and 50.3% reported use of contraception. Condom use was the most common method of contraception (38.3%), with 6.7% indicating the use of combined oral contraceptive pills and 5.3% intrauterine devices.

Knowledge about human papillomavirus and cervical cancer prevention

Fig 1 demonstrates that the number of correct answers was distributed normally among the study participants. Mean number of correct answers was 8.5 (2.2), median was 9.0, and first and third quartiles were 7.0 and 10.0 respectively.

The 14 questions used to estimate women's knowledge about HPV and CC prevention, the answer keys, and number of women who answered correctly for each of the 14 questions are presented in Table 1.

Of the 300 responders, 74.7% understood the role of having multiple sexual partners as a risk factor of CC, and 67% were generally aware of the prevalence of HPV and sexually active people will likely contract HPV in their lifetime. However, only 35.7% of the women knew about the existence of a vaccine against HPV, and only 9.7% understood that one ought to have follow-up screening after vaccination. Moreover, 79.3% of the study participants answered incorrectly that having had HPV vaccine prevents the development of CC, and most (90%) answered incorrectly that most HPV types clear up on their own.

Out of all participants, 37.1% had undertaken screening (cytological smear from cervix, or Pap test) less than three years ago; 7.0% more than three years ago; 38.0% never had a Pap test; and 17.7% did not know. Among those who knew that screening can detect CC in its early stages, 48.5% had this test less than three years ago; 8.6% more than 3 years ago; 29.3% never had a Pap test; and 13.6% did not know (p < 0.001).
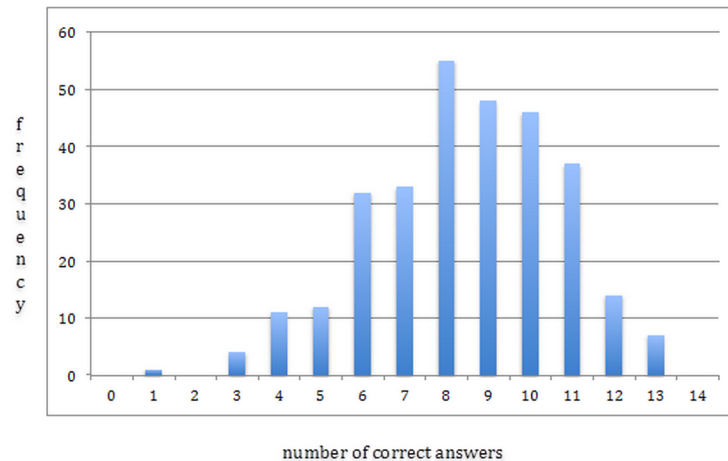
Fig 1. A histogram of the number of correct answers to the 14 questions about human papillomavirus (HPV) and cervical cancer prevention among women of women of Arkhangelsk (n = 300).

About one third of the study participants reported that their doctor was the main source of information about HPV and CC prevention. Others mentioned TV/media (53.3%) and other sources of information (12.7%).

Table 1. The 14 questions on knowledge about human papillomavirus (HPV), cervical cancer and its prevention; the answer keys; and the number of women who answered correctly (n = 300).

Questionnaire item	The answer keys	Number (%) of women who answered correctly
1. Have you ever heard of HPV?	yes	190 (63.3)
2. HPV is very common in women.	true	246 (81.8)
3. HPV can be passed on during vaginal sexual intercourse.	true	186 (62.0)
4. The chance of getting HPV increases with number of sexual partners.	true	224 (74.7)
5. What is the main hazard of HPV for female?	causes cervical cancer	247 (82.3)
6. Most HPV types can cleared up on their own.	true	30 (10.0)
7. A person usually does not have symptoms when infected with HPV.	true	160 (53.3)
8. Most sexually active women will never get HPV during their life.	false	202 (67.3)
9. According to Russian legislation, how often should routine screening for cervical cancer be done?	once in a year	178 (59.3)
10. Cytological smear (Pap test) can detect changes that can lead to cancer if left untreated.	true	190 (66.3)
11. HPV vaccine can prevent cervical cancer.	true	107 (35.7)
12. HPV vaccine is most effective if given to individuals who have never had sex.	true	262 (87.3)
13. Someone who has undergone HPV vaccination cannot develop cervical cancer.	false	62 (20.7)
14. Women who have undergone HPV vaccination do not need a Pap test later in their life.	false	29 (9.7)

Associations between the level of knowledge about human papillomavirus, cervical cancer prevention and other personal characteristics

Of the 300 participants, 20.0% had a poor level of knowledge about HPV and CC prevention and 80.0% had sufficient knowledge. Selected characteristics of the study participants stratified by their level of knowledge about HPV and CC prevention are provided in Table 2.

Women in both groups were of comparable age (in their mid-thirties). The level of knowledge about HPV and CC prevention was associated with education (p = 0.049), parity (p = 0.049), age of initiating of intercourse (p = 0.014), and source of information about HPV and CC prevention (p = 0.006) (Table 2). More specifically, women with a university education, those who had an early sexual debut, had two or more children, and/or whose physician was the primary source of information had higher levels of knowledge about HPV and CC prevention. The primary source of information about CC and its prevention was the mass media (more than 50%). Interestingly, women with adequate understanding had their physician as a source of information more frequently than those with a poor knowledge level. Moreover, the latter group received the information from their social surroundings more often compared to those with sufficient level (p = 0.005). Conversely, women with lower educational levels, nulliparous women, late sexual debut, and other sources of information on HPV and CC prevention were less informed. 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 evident.

Table 3 summarizes results of crude and adjusted linear regression with the knowledge about HPV and CC prevention score as the dependent variable and other characteristics as predictors.

Crude differences in the number of correct answers on the 14 questions about HPV and CC prevention was significant between the educational levels, and were even more pronounced after adjustment. Women with university education were more likely to have higher knowledge about HPV and CC prevention compared to women with lower educational level. Having two or more deliveries was associated with having more questions on HPV and CC prevention answered correctly when compared to nulliparous women. However, this difference was not statistically significant after adjustment. In the crude and adjusted linear regression models age, marital status, smoking, age of initiating of intercourse, number of partners and history of sexually transmitted infections were not associated with the number of correct answers to the 14 questions about HPV and CC prevention.

Discussion

Our study demonstrates that majority of women in Arkhangelsk had sufficient level of knowledge about HPV and CC prevention, and this was associated with level of education, parity, age of initiating of intercourse, and source of information about HPV and CC prevention. After adjustment, women with university level of education were more likely to have a higher score of correct answers on knowledge about HPV and CC prevention compared to less educated women.

Interpretation of the results and comparison with other studies

The level of knowledge and awareness about HPV and CC prevention has been suggested to be important in the development of positive approaches toward CC prevention [8]. Our results show that most of the women in our sample knew the potential consequences of having an

Table 2. Sociodemographic and sexual behavior characteristics according to the two levels of knowledge about human papillomavirus (HPV) and cervical cancer prevention in women of Arkhangelsk (n = 300).

Variable	Level of knowledge[1,2]		P value[3]
	Poor (n = 60)	Sufficient (n = 240)	
Age, years	34.7 (7.8)	36.1 (9.2)	0.288
Age			0.335
25–44 years	53 (88.3)	199 (83.3)	
≥45 years	7 (11.7)	40 (16.7)	
Education			0.049
University	26 (43.3)	138 (57.5)	
Other	34 (56.7)	102 (42.5)	
Marital status			0.245
Married	29 (48.3)	137 (57.1)	
Cohabiting	17 (28.3)	45 (18.8)	
Single	14 (23.4)	58 (24.2)	
Parity			0.049
0 deliveries	14 (23.3)	47 (19.6)	
1 delivery	31 (51.7)	92 (38.3)	
≥ 2 deliveries	15 (25.0)	101 (42.1)	
Smoking			
Yes	7 (11.7)	32 (13.3)	0.731
No	53 (88.3)	208 (86.7)	
Age of initiating of intercourse, years	17.7 (1.7)	18.4 (2.7)	0.014
Age of initiating of intercourse			0.145
<17 years	28 (46.7)	89 (37.1)	
18–21 years	30 (50.0)	126 (52.5)	
≥22 years	2 (3.3)	25 (10.4)	
Number of partners			0.224
1–3	28 (46.7)	133 (55.4)	
>3	32 (53.3)	107 (44.6)	
Sexually transmitted infections			0.985
Never	33 (55.0)	131 (54.6)	
Ever	27 (45.0)	109 (45.4)	
Contraception			0.547
Condoms	25 (41.7)	90 (37.5)	
Combined oral contraceptive pill	3 (5.0)	17 (7.1)	
Intrauterine device	5 (8.3)	11 (4.6)	
No contraception	27 (45.0)	122 (50.8)	
Source of information			0.006
TV/media	33 (55.0)	127 (52.9)	0.773
Doctor	13 (21.7)	89 (37.1)	0.024
Social surrounding (family, friends)	14 (23.3)	24 (10.0)	0.005

[1]Number (%) for categorical variables and means (standard deviations) for continuous variables are presented according to the two levels of knowledge about HPV and cervical cancer prevention.

[2]Sufficient level of knowledge about HPV and CC prevention was defined as having at least 50% of the questions answered correctly (≥ 7 of the 14 questions). Poor level of knowledge was defined as having less than 50% of the questions answered correctly (< 7 of the 14 questions).

[3]Independent Student's t-test for continuous and Chi-square test for categorical variables.

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Table 3. Associations between the number of correct answers to the 14 questions about human papillomavirus (HPV) and cervical cancer prevention and sociodemographic and sexual behavior characteristics of the study participants (n = 300).

Variables	Univariable[1]		Multivariable[1,2]	
	B	**p-value**	**B**	**p-value**
Age				
≥45 years	0.57	0.108	0.40	0.329
25–44 years	reference		reference	
Education				
University	0.56	0.029	0.65	0.021
Other	reference		reference	
Marital status				
Cohabiting	-0.70	0.038	-0.32	0.379
Single	-0.30	0.341	0.04	0.903
Married	reference		reference	
Parity				
1 delivery	0.17	0.623	0.21	0.628
≥2 deliveries	0.88	0.012	0.79	0.071
0 deliveries	reference		reference	
Smoking				
Yes	0.17	0.649	-0.18	0.665
No	reference		reference	
Age of initiating of intercourse				
≥22 years	0.89	0.062	0.62	0.214
18–21 years	0.24	0.385	0.11	0.700
<17 years	reference		reference	
History of sexually transmitted infections				
Ever had	0.11	0.662	0.27	0303
Never had	reference		reference	

[1]Linear regression analysis was conducted with number of correct answers to the 14 questions on knowledge about HPV and screening of cervical cancer as the dependent variable and other variables in the table as independent variables (the regression coefficients B and p-values are indicated).

[2]Regression coefficients were mutually adjusted for all variables in the table. $R^2 = 0.063$, F = 1.939, df = 10, p = 0.040

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HPV infection. Several studies report opposite results and demonstrate a significant deficit in HPV knowledge among women worldwide [8, 9, 11, 12, 15].

While many participants in our study were aware of the sexual transmission of HPV, gaps in knowledge about symptoms and treatment of HPV infection were nevertheless evident. Although HPV is one of the most common sexually transmitted infections, it is transient and thus women tend not to seek treatment. Our findings demonstrate that close to 90% of women think that HPV should be treated. This result can be partly explained by the misinformation provided by some health care professionals and pharmaceutical companies that detection of HPV requires antiviral treatment. The HPV test is commercially and widely available in Russia. Another possible explanation is a wide use of colposcopy in Russia, while the number of educational courses and amount of literature on how to perform this procedure correctly is limited [22, 23]. This can lead to an over-diagnosis of cervical lesions. Lack of guidelines and training among doctors are mentioned as pertinent factors of over diagnosis and over treatment of cervix [23].

Women in our study have exhibited good knowledge about CC risk factors. Our study also shows that knowledge about the latter and CC screening is of great importance. Thus those

women who were aware that the Pap test is used for CC screening took this test more often than women who did not. However, our analysis also reveals that there was insufficient knowledge about HPV vaccination (in terms of the development of CC and need of Pap test). Although the HPV vaccine is the most effective way to prevent HPV infection, it is not widely available in Russia as it is not yet included in the Russian official vaccination program. These findings highlight a great importance of educational efforts in CC prevention.

We found no association between the level of knowledge about HPV and CC prevention and age. An earlier study reported that younger women had a higher level of knowledge of HPV and CC prevention [24]. Younger populations [24] specify that Internet and other mass media constitute their main source of pertinent information. Educating older women may facilitate their participation in CC screening, and this would help to reveal the presence of CC at earlier stages and thereby reduce the CC burden. Indeed, Williams et al. [25] report that most of the respondents with higher HPV knowledge received this information in school. This suggests that HPV education might best occur at early ages, such as in school settings or even earlier.

With respect to age, all women in our study were at risk of getting HPV infection and thus developing CC. Clearly, they constitute an age group to whom preventive measures such as CC screening must be directed. However, Tiro et al. [26] showed that older and less educated women would benefit from improved awareness of HPV and CC prevention. Our findings reinforce this, as university educational level was independently associated with a higher level of knowledge about HPV and CC prevention [8, 24]. Smoking which is a known risk factor for CC was not associated with the level of knowledge in our study [26, 27]. The relatively low smoking rate (12–13%) among our study subjects is likely the reason. A recent study in the Murmansk region of North-west Russia for the period 2006–2011 reports that the prevalence of smoking among delivering women was 25.2% prior to pregnancy [28]. Differences in age and education level might have contributed to this two-fold difference.

Risky behavior — specifically early age of intercourse initiation and high number of sexual partners — is generally accepted as increasing the risk of HPV infection [29]. We found no association between number of sexual partners and level of their knowledge about HPV and CC prevention, although individuals in our knowledge sufficient group were slightly older (p = 0.014). Interestingly, an earlier USA study indicated that neither age of intercourse initiation nor number of lifetime sexual partners were associated with knowledge scores [27].

We observed no association between the level of HPV and CC knowledge and history of sexually transmitted infections. Even though women with such history had to seek a physician about their infection, they had not received information about HPV or had forgotten it. This suggests that clinicians need to pay more attention to women's education about HPV and HPV associated cancers, as well as other sexually transmitted infections. Neither was there an association with the type of contraception. Moreover, every second woman did not use contraception at all. One of possible explanations could be that they are more concerned about being infected with chlamydia or gonorrhea than with HPV. In doing so, they may have underestimated the seriousness of an HPV infection and as a consequence fail to seek help.

Interestingly the level of HPV and CC prevention knowledge was associated with source of information. Sufficient level of knowledge was more common among those who reported having a doctor as the primary source of information. Despite the fact that more than half of the study participants received knowledge about CC and its prevention from media and TV, there was no difference in the knowledge level in this context. Since there was a difference for physicians as the information source, we conclude that they could provide more precise and accurate knowledge about CC and its prevention. Consequently for the proper implementation and acceptability of cervical cancer screening, physicians need to provide more education on

the importance of routine screening for cervical cancer prevention. In addition, educational campaigns for women are needed, since social surrounding also constitutes a source of information that leads to a poor level of knowledge.

Holcomb et al. [27] also observed this, although sexual behavior of those with higher level of knowledge did not differ from others in their study. Interestingly, Tiro et al. [26] state that women who did not trust any source of information about health were less likely to report HPV awareness.

Several Russian studies and those conducted in former Soviet Union countries have evaluated level of knowledge about HPV and CC among specific groups, such as medical students and health professionals [11, 12, 13]. All these investigations demonstrate a relatively low level of knowledge about HPV among the participants. Kahn et al. [30] describes a similar situation among USA pediatricians. These various findings indicate that educational efforts in relation to HPV infection have not been widespread. Even though scientific knowledge about HPV is on the increase (especially in terms of virus detection), a need for an increase in knowledge about HPV and CC prevention prevails in both the general population and health professionals.

Limitations and strengths

Our study has several potential limitations. In spite of a relatively high response rate (86%), bias due to non-participation remains a possibility. Taking into account that this is a cross-sectional study and all the information was self-reported, recall bias may have occurred. Moreover, the data were collected at an antenatal health care center, and therefore a built-in selection bias may have occurred. It is possible, for example, that individuals who participated in the survey were more health conscious and curious about HPV than women in the general population. It is also important to mention that our study sample might have over represented frequent users of the health care system, and thus under represented those who live in remote and poorer regions of Arkhangelsk with less access to health care services. If true, the knowledge about HPV and CC prevention would probably be lower than what we assessed. Because of the cross-sectional nature of the study, the associations observed between the level of knowledge about HPV and CC prevention and selected behavioral characteristics cannot be interpreted as causal.

To our knowledge, this is the first study in Russia aiming to assess knowledge about HPV and CC prevention and associations between level of this knowledge and a range of sociodemographic and sexual behavioral characteristics among women. Our study population was comprised of women in the age group at risk of HPV infection, and therefore constituted the target group for CC screening and prevention.

Conclusion

Our study provides detailed information on knowledge about HPV and CC screening among women of Arkhangelsk, Northwest Russia. We observed that most participants had a sufficient level of knowledge. Women with a university level of education displayed the highest knowledge scores about HPV and CC prevention. Health care professionals as the primary source of information are well positioned to improve women's knowledge about HPV and CC screening, including promotion of preventive measures. However, a large proportion of participants did not know that most HPV types clear up on their own, that HPV vaccination does not avoid the development of CC nor replaces the need for a Pap test later in life. Consequently, there is need to improve knowledge about the role of CC screening and HPV vaccination in CC prevention among women of Arkhangelsk. These educational gaps might be used to tailor

interventions in CC prevention. Consequently, ongoing educational campaigns that emphasize the role of HPV in CC development and importance of regular screening and HPV vaccination are recommended.

Supporting information

S1 Questionnaire. Questionnaire assessing knowledge of HPV and CC prevention and sociodemographic and behavioral characteristics of women. In Russian.
(DOC)

S2 Questionnaire. Questionnaire assessing knowledge of HPV and CC prevention and sociodemographic and behavioral characteristics of women. In English.
(DOCX)

Author Contributions

Conceptualization: Elena E. Roik.

Formal analysis: Elena E. Roik, Olga A. Kharkova.

Investigation: Elena E. Roik.

Methodology: Elena E. Roik, Ekaterina E. Sharashova, Olga A. Kharkova, Vitaly A. Postoev, Jon Ø. Odland.

Project administration: Elena E. Roik.

Supervision: Jon Ø. Odland.

Writing – original draft: Elena E. Roik.

Writing – review & editing: Ekaterina E. Sharashova, Evert Nieboer, Olga A. Kharkova, Vitaly A. Postoev, Jon Ø. Odland.

References

1. Center for disease control and prevention. Manual for the surveillance of vaccine-preventable disease. Chapter 5: Human papillomavirus (HPV) Available online: http://www.cdc.gov/vaccines/pubs/surv-manual/chpt05-hpv.html

2. Ho GY, Burk RD, Klein S, Kadish AS, Chang CJ et al. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. J Natl Cancer Inst 1995; 87:1365–71. PMID: 7658497

3. Schiffman M, Kjaer SK. Natural history of anogenital human papillomavirus infection and neoplasia. J Natl Cancer Inst Monogr 2003; 31:14–9.

4. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 2015–04–08 [updated 2015 December 15]. Available from: http://www.hpvcentre.net/statistics/reports/XWX.pdf

5. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S et al. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Russian Federation. Summary Report 2016–02–26 [updated 2016 June 15]. Available from: http://www.hpvcentre.net/statistics/reports/XWX.pdf

6. Kobayashi D, Takahashi O, Hikosaka C, Okubo T, Fukui T Optimal cervical cytology mass screening interval for cervical cancer. Arch Gynecol Obstet. 2013 Mar; 287(3):549–54. Epub 2012 Oct 11. https://doi.org/10.1007/s00404-012-2588-8 PMID: 23053319

7. Aniebue PN, Aniebue UU Awareness and practice of cervical cancer screening among female undergraduate students in a Nigerian university. J Cancer Educ. 2010 Mar; 25(1):106–8. https://doi.org/10.1007/s13187-009-0023-z PMID: 20082175

8. Hanisch R, Gustat J, Hagensee ME, Baena A, Salazar JE, Castro MV et al. Knowledge of Pap screening and human papillomavirus among women attending clinics in Medellín, Colombia. Int J Gynecol

Cancer. 2008 Sep-Oct; 18(5):1020–6. Epub 2007 Nov 16. https://doi.org/10.1111/j.1525-1438.2007.01131.x PMID: 18021221

9. Moreira ED, Oliveira BG, Ferraz FM, Costa S, Costa Filho JO, Karic G. Knowledge and attitudes about human papillomavirus, Pap smears, and cervical cancer among young women in Brazil: implications for health education and prevention. Int J Gynecol Cancer. 2006 Mar-Apr; 16(2):599–603. https://doi.org/10.1111/j.1525-1438.2006.00377.x PMID: 16681732

10. Massad LS, Evans CT, Wilson TE, Goderre JL, Hessol NA, Henry D et al. Knowledge of cervical cancer prevention and human papillomavirus among women with HIV. Gynecol Oncol. 2010 Apr, 117(1): 70–76 https://doi.org/10.1016/j.ygyno.2009.12.030 PMID: 20106513

11. Volchenko A.N. Dynamics of cervical cancer incidence rate and levels of awareness about its prevention among different population groups Human health and ecology. 2014 February (2): 25–30.

12. Voloshin M.V. Level of knowledge about cervical cancer and it's prevention among senior medical students of National medical university od Belarus. Scientific aspirations 2013 May (5): 120.

13. Borovikova O.I., Kucenko I.I. Borovikov I.O., Nikogda Y. V. Awareness of cervical cancer in Krasnodar. Modern problems of science and education. 2012 June: 80–82.

14. Haesebaert J, Lutringer-Magnin D, Kalecinski J, Barone G, Jacquard AC, Regnier V, et al. French women's knowledge of and attitudes towards cervical cancer prevention and the acceptability of HPV vaccination among those with 14–18 year old daughters: a quantitative-qualitative study. BMC Public Health 2012 Nov 27; 12:1034. https://doi.org/10.1186/1471-2458-12-1034 PMID: 23186288

15. Lima EG, de Lima DB, Miranda CA, de Sena Pereira VS, de Azevedo JC, de Araulo JM, de Medeiros Fernandes TA, de Azevedo PR, Fernandes JV Knowledge about HPV and Screening of Cervical Cancer among Women from the Metropolitan Region of Natal, Brazil. ISRN Obstet Gynecol. 2013 Mar 31; 2013:930479. Print 2013. https://doi.org/10.1155/2013/930479 PMID: 23606981

16. Territorial office of the federal state statistics service of the Arkhangelsk region. Available from: http://arhangelskstat.gks.ru/

17. The United Kingdom NHC cervical screening program https://www.bsccp.org.uk/assets/file/uploads/resources/NHSCSP_20_Colposcopy_and_Programme_Management_(3rd_Edition)_(2).pdf

18. Marlow LA, Zimet GD, McCaffery KJ, Ostini R, Waller J. Knowledge of human papillomavirus (HPV) and HPV vaccination: an international comparison. Vaccine. 2013; 31(5): 763–9. https://doi.org/10.1016/j.vaccine.2012.11.083 PMID: 23246310.

19. Waller J, Ostini R, Marlow LA, McCaffery K, Zimet G. Validation of a measure of knowledge about human papillomavirus (HPV) using item response theory and classical test theory. Prev Med. 2013; 56 (1):35–40. https://doi.org/10.1016/j.ypmed.2012.10.028 PMID: 23142106.

20. World Health Organization. Human papillomavirus (HPV) and cervical cancer. Fact sheet. Available online: http://www.who.int/mediacentre/factsheets/fs380/en/

21. Center for disease control and prevention. Human papillomavirus (HPV). Questions and answers. Available online: https://www.cdc.gov/hpv/parents/questions-answers.html

22. Maklecova SA, Rabinkina TS Papilloma virus: opportunities for combined treatment. StatusPraesens 2015; 1(24):73–78

23. Kataeva OA, Rogovskaya SI Cervicology, HPV,screening StatusPraesens 2014; 4(21): 19–25

24. Capogrosso P, Ventimiglia E, Matloob R, Colicchia M, Serino A, Castagna G et al.: Awareness and knowledge of human papillomavirus-related diseases are still dramatically insufficient in the era of high-coverage vaccination programs. World J Urol 2015, 33(6):873–880. https://doi.org/10.1007/s00345-014-1379-1 PMID: 25179010

25. Williams MU, Carr MM, Goldenberg D: Public awareness of human papillomavirus as a causative factor for oropharyngeal cancer. Otolaryngol Head Neck Surg 2015, 152(6):1029–1034. https://doi.org/10.1177/0194599815577781 PMID: 25820579

26. Tiro JA, Meissner HI, Kobrin S, Chollette V: What do women in the U.S. know about human papillomavirus and cervical cancer? Cancer Epidemiol Biomarkers Prev 2007, 16(2):288–294. https://doi.org/10.1158/1055-9965.EPI-06-0756 PMID: 17267388

27. Holcomb B, Bailey JM, Crawford K, Ruffin MT: Adults' knowledge and behaviors related to human papillomavirus infection. J Am Board Fam Pract 2004, 17(1):26–31. PMID: 15014049

28. Kharkova OA, Krettek A, Grjibovski AM, Nieboer E, Odland JO: Prevalence of smoking before and during pregnancy and changes in this habit during pregnancy in Northwest Russia: a Murmansk county birth registry. Reprod Health. 2016 Mar 8; 13:18. https://doi.org/10.1186/s12978-016-0144-x PMID: 26952100

29. Kjaer SK, Dahl C, Engholm G, Bock JE, Lynge E, Jensen OM: Case-control study of risk factors for cervical neoplasia in Denmark. II. Role of sexual activity, reproductive factors, and venereal infections. Cancer Causes Control 1992, 3(4):339–348. PMID: 1617121

30. Kahn JA, Zimet GD, Bernstein DI, Riedesel JM, Lan D, Huang B et al. Pediatricians' intention to administer human papillomavirus vaccine: the role of practice characteristics, knowledge, and attitudes. J Adolesc Health. 2005; 37:502–510. https://doi.org/10.1016/j.jadohealth.2005.07.014 PMID: 16310128

Paper 3

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RESEARCH ARTICLE

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Sociodemographic characteristics, sexual behaviour and knowledge about cervical cancer prevention as risk factors for high-risk human papillomavirus infection in Arkhangelsk, North-West Russia

Elena Roik [a,b], Ekaterina Sharashova [a], Olga Kharkova [a,b], Evert Nieboer [c], Vitaly Postoev [b] and Jon Ø. Odland [a,d]

[a]Department of Community Medicine, Faculty of Health Sciences, UiT – The Arctic University of Norway, Tromsø, Norway; [b]International School of Public Health, Northern State Medical University, Arkhangelsk, Russia; [c]Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON, Canada; [d]Department of Public Health and Nursing, Faculty of Medicine and Health Sciences, The Norwegian University of Science and Technology (NTNU), Trondheim, Norway

ABSTRACT

While sociodemographic predictors of cervical cancer (CC) are well understood, predictors of high-risk (HR) human papillomavirus (HPV) infection have not been fully elucidated. This study explored the HR-HPV infection positivity in relation to sociodemographic, sexual behavior characteristics and knowledge about HPV and CC prevention among women who visited the Arkhangelsk clinical maternity hospital named after Samoylova, Russia. This cross-sectional study was conducted in the city of Arkhangelsk, Northwest Russia. Women who consulted a gynecologist for any reason between 1 January 2015 and 30 April 2015 were residents of Arkhangelsk, 25–65 years of age were included. The Mann–Whitney and Pearson's χ^2 tests were used. To determine the HR-HPV status, we used the Amplisens HPV-DNA test. We used a questionnaire to collect the information on sociodemographic factors. Logistic regression was applied. The prevalence of HR-HPV infection was 16.7% (n = 50). HR-HPV infection was more prevalent in younger women, cohabiting, nulliparae, smokers, having had over three sexual partners and early age of sexual debut. The odds of having a positive HR-HPV status increased by 25% with an annual decrease in the age of sexual debut. Moreover women with one child or more were less likely to have positive HR-HPV status.

Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide. Most sexually active individuals of both sexes will acquire it at some points in their lives [1–3]. HPV genotypes are classified as high-risk (HR) and low-risk based on their ability to cause cervical cancer (CC) [4]. The presence and persistence of high-risk human papillomavirus infection (HR-HPV) infection is a key etiological factor in the development of carcinoma of the cervix and accounts for approximately 4.8% of all cancers [5]. CC accounts for 7.5% of all female cancers [6]. It therefore significantly affects morbidity and mortality risks worldwide [5]. CC has been termed "a disease of disparity". Within the European Union the highest CC mortality is seen in countries with the lowest screening programmes participation rates [7]. High participation in screening programmes employing the Papanicolaou test (cytology-based) and subsequent treatment of precancerous lesions has effectively reduced the CC mortality [8,9]. Nevertheless, CC is considered a major public health issue in Sweden, This country has the 9th lowest CC mortality rate in the EU, high participation rate and screening programme in place since 1967 [7,10,11]. In addition, HPV is also associated with increased risk of head and neck, vaginal, vulvar, penile and anal cancers [11,12]. However, the prevalence of HPV in Russia remains unknown or is controversial [13].

CC is the fourth most common female malignancy worldwide with estimates of 528 000 of new cases and 266 000 deaths in 2012 [6]. Most of the cases arise from countries with low-income or middle-income economies, where preventive resources are limited [14]. According to the report of International Agency for Research on Cancer, CC is the second most frequent cancer among women aged 15–44 years in Russia [15]. It is estimated that 64.5 million Russian women aged 15 years and older are at risk of developing this cancer, and 15 342 women are diagnosed with CC, and 7 371 women die from the disease every year [15].

Women positive for HR-HPV DNA have an increased risk of developing CC. HPV infection is the most important but not the only risk factor for CC. Many epidemiological studies have so far focused on the role of co-factors associated with the cancer development and progression [1]. While sociodemographic predictors of CC are well understood, those of HR-HPV infection have not been. Epidemiological chain of infection involves both women and men [16,17]. Both men and women at the same time could be carriers without symptoms, transmitters and the ones who experience active infection [18].

Predictors of HPV may differ from those of CC because the development of the latter is influenced by many variables, including co-factors involved in carcinogenesis and adherence to screening guidelines [16,19,20]. Several studies reported an association between HPV positivity and lifetime number of sexual partners [16,19,21]. On the other hand, the influence of age at sexual debut and condom use on the risk of being HPV positive is questionable [20,22,23]. Other potential risk factors for cervical HPV infection include tobacco smoking [24], nulliparity [25,26], and use of oral contraceptives [25]. Geographic and cultural variations in the sexual behaviour of women and their partners have also been reported to be strongly associated with HPV acquisition [19,27].

Representative information about HR-HPV infection in relation to different sociodemographic and sexual behaviour characteristics have not been available in Russia. Such data may be useful in designing effective preventive public health strategies to reduce CC and related mortality.

Aims

(i) To estimate prevalence of HR-HPV infection in women who visited Arkhangelsk clinical maternity hospital named after Samoylova in Arkhangelsk, Russia; (ii) to identify sociodemographic characteristics and sexual behaviour associated with HR-HPV status; and (iii) to assess a possible association between the HR-HPV status and knowledge about HPV and CC prevention.

Materials and methods

Study design, setting, participants and data collection

This cross-sectional study was conducted between 1 January and 30 April 2015 in the city of Arkhangelsk, which is the administrative centre of Arkhangelsk County in Northwest Russia. In 2015 the population of Arkhangelsk was 351 488, of whom 194 765 were

females, while 109 096 were in the 25–65 age group [28].

Women who were residents of Arkhangelsk, aged 25 to 65 years and consulted a gynaecologist for any reason at the Samoylova Clinical Maternity hospital were recruited. Since there are no national guidelines that regulate the cervical screening age in Russia, we adopted that of the UK NHC Cervical Screening Programme (NHSCSP). The latter recommends that routine screening be conducted during the 25–65 age interval [29]. A sample size of 300 with an HPV prevalence of 10% was calculated to satisfy the condition (1 − $β$) ≥ 0.80 at $α$ = 0.05. The final analytical sample was 300, which constitutes 86% of women recruited.

All participants completed a questionnaire entitled "HPV and CC Related Factors Questionnaire" which sought information on the participants' knowledge about HPV and CC prevention and as described previously [30] included 14 questions pertaining to: sociodemographic characteristics (age, education, marital status, parity, smoking) and sexual behaviour characteristics (age of sexual debut, history of sexually transmitted infections, contraception, history of the papanicolaou test (the Pap test) and related abnormal findings and their management).

At enrolment, women underwent a pelvic examination with collection of cervical specimens for cervical cytology and for HR-HPV DNA genotyping. The cervical smears were collected with a cervical cytobrush and were transported to the laboratory and stored in a buffer solution. Liquid-based cytology (LBC) (SurePath Technology; TruePath Imaging Inc, Burlington, NC) samples were sent to the central laboratory for cytological diagnosis, HPV detection and genotyping (Central Research Institute of Epidemiology "Rospotrebnadzor", Moscow, Russia). Pap smears were prepared and reviewed by the study pathologist who was not aware of the HPV results. Abnormalities were reported according to the Bethesda System 2001 [31]. Smears were classified as normal, atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) or carcinoma. Women with ASCUS and negative HPV test were recommended to repeat both tests in 6 months. Women with other abnormal cytological findings and/or positive HPV test were referred to colposcopy and histologic confirmation.

HPV positivity was determined using an HPV DNA test (AmpliSens® HPV HCR screen-titre-FRT PCR kit, InterLabService, Moscow, Russia), which is an *in vitro* nucleic acid amplification test for qualitative and quantitative detection in biological materials of DNA of HPV of high carcinogenic risk (HCR). This test is able to

detect DNA of HR-HPV of the four phylogenetic groups, namely A7 (HPV types: 18, 39, 45, and 59), and A9 (HPV types: 16, 31, 33, 35, 52, and 58), A5 (HPV type 51) and A6 (HPV type 56). The analytical sensitivity was 1×10^3 copies/ml. An endogenous internal control was present in all our HPV kits, which allowed an assessment of the control stages of PCR (DNA isolation and amplification) and an evaluation of sample quality and storage adequacies. When epithelial swab quality was not sufficient (i.e. insufficient number of epithelial cells in the clinical sample), the signal of β-globin gene was significantly lower. This β-globin based Internal Control protocol significantly reduces false negative results caused by a poor clinical sample quality. Samples were considered to be positive with an HPV-DNA threshold of 1pg/ml, which is recommended by the USA Food and Drug Administration (US FDA). Automated results were confirmed with blind manual readings undertaken by experienced laboratory personnel.

Variables

For the analyses, women were grouped based on their 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 at sexual debut (in years) was used as a continuous variable, and the number of lifetime sexual partners was recorded as 3 or less and more than 3. History of sexually transmitted infections was categorised into ever-had or never-had. Smoking was designated as yes or no (ever and never smokers). Contraception was categorised into use of condoms (yes and no) and use of combined oral contraceptive pill for over 5 years (yes and no). Participants' knowledge about HPV and CC prevention was used as both a discrete variable (number of correct answers from 0 to 14) and a binary variable. We considered having at least 50% of the questions answered correctly (7 out of 14) as a sufficient level of knowledge, and less than 50% of the questions answered correctly (6 or less out of the 14 questions) as a poor.

HR-HPV infection was used as a binary variable (being positive or negative for any type of HR-HPV) and were categorised into the four groups HR-HPV infection types mentioned, as well a mixed group that included HR-HPV types from both group A9 and group A7.

Data analyses

The proportion of HR-HPV types are described and displayed graphically in Figure 1. Sexual debut and number of correct answers were presented as the median with the first and third quartiles. All the other variables were shown as numbers and percentages. Statistical comparison between women with and without HR-HPV infection was carried out using the Mann–Whitney U test for continuous variables and Pearson's χ^2 test for categorical variables.

We used logistic regression analysis to estimate possible associations between the HR-HPV status as the outcome and age, parity, age at sexual debut and number of sexual partners as predictors. We tested for linear trends by entering ordinal variables as continuous in the regression analyses. As we aimed to explore risk factors that are causally related to the outcome these predictors were chosen based on the previous knowledge taking into account the cross-sectional design of the study and excluding potential mediators. Crude and adjusted odds ratios (ORs) were calculated with 95% confidence intervals (95% CIs). The value of $p < 0.05$ was considered to be statistically significant. The statistical analyses were carried out using SPSS version 24 (SPSS Inc., Chicago, IL, USA).

Ethical approval was obtained from the Research Ethics Committee of the 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 a written informed consent.

Results

HPV prevalence

Of the 300 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 and then group A7 (Figure 1). Multiple infections were detected in 14% ($n = 7$). Around 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% ($n = 2$) were assigned as having atypical squamous cell undetermined significance (ASCUS) changes in the smear.

Associations between sociodemographic characteristics, sexual behaviour and knowledge about HPV and cervical cancer prevention and the high-risk HPV infection

Women aged 25–29 years ($p = 0.013$), those cohabiting ($p = 0.011$), being nulliparae ($p = 0.009$), smokers ($p = 0.011$) and having more than three sexual partners
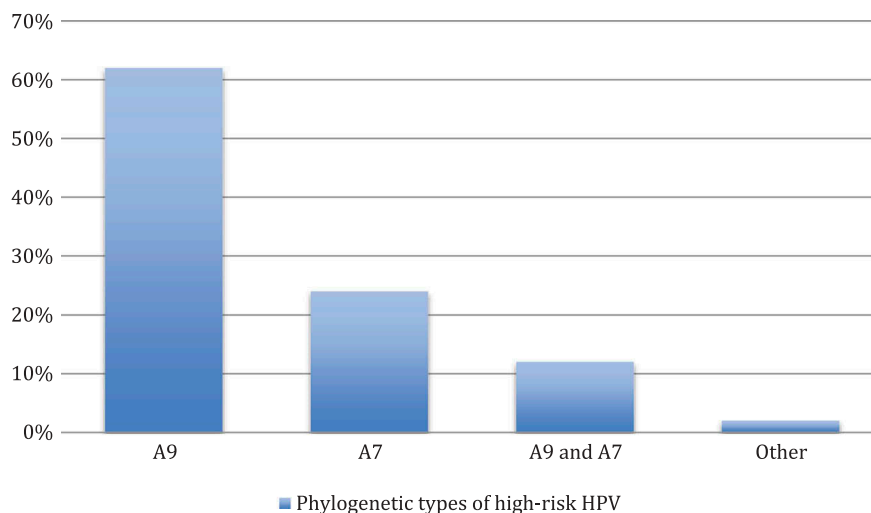
Figure 1. Distribution of the phylogenetic types of high-risk HPV in women who visited Arkhangelsk Clinical Maternity Hospital, Russia (*n* = 50).

Footnote: Phylogenetic types of high-risk HPV (in per cent): A7 (HPV types 18, 39, 45, and 59); A9 (HPV types 16, 31, 33, 35, 52, and 58); and other: A5 (HPV type 51) and A6 (HPV type 56).

(*p* = 0.034) were more prevalent to have positive HRH PV status rather than negative (Table 1). Moreover, women with a positive HR-HPV status had sexual debut at earlier age than women with a negative HR-HPV status (*p* = 0.001). The prevalence of positive and negative HR-HPV infections did not differ in women with different educational levels, those with previous abortions, hormonal contraceptive use, condom use and history of sexually transmitted infections (Table 1).

Regardless of their HR-HPV status, the study participants answered correctly more frequently to the following questions/statements: "The chance of getting HPV increases with number of sexual partners"; "What is the main hazard of HPV for female"; and "HPV vaccine is most effective if given to individuals who have never had sex" (Table 2). The statement "Most HPV types can clear up on their own if left untreated" was the most poorly answered. We found no difference in the numbers of correct answers between women with positive and negative HPV status (Table 2). The prevalence of poor knowledge was not significantly different for participants with positive and negative HPV status (28.0% versus 18.4% *p* = 0.121, respectively).

Factors associated with positive HPV status

In the crude analyses, risk of being positive for HR-HPV infection increased gradually with being younger and with lower parity: *p*-values for linear were 0.012 and 0.007, respectively (Table 3). Odds of having 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 presented in Table 3, associations with age and the number of sexual partners were no longer significant.

Discussion

To the best of our knowledge, this study is the first in Russia to explore potential risk factors and knowledge about HPV and CC prevention in relation to HR-HPV infection. In addition to young age, a lifetime number of more than 3 sexual partners, nulliparity, cohabiting, smoking and having earlier age at sexual debut were associated with HR-HPV status. The independent risk factors for positive cervical HR-HPV infection among women aged 25–65 years consulting gynaecologists in the Samoylova Clinical Maternity hospital were early age at sexual debut and nulliparity.

The observed prevalence of HR-HPV infection in our study was 16.7%, which is higher than the worldwide prevalence of HPV infection in women without cervical abnormalities of 11–12% [5,32]. Higher prevalence rates have been reported in the Caribbean (35.4%), sub-Saharan African (24%) and Eastern European (21%), while those reported for North America (4.7%) and Western Asia (1.7%) were lower compared to our estimate [5]. The estimates of HR-HPV prevalence vary between the regions, and this could in part be due to different ages of the study populations, use of different methods of HPV detection, different screening

Table 1. Associations between sociodemographic and sexual behaviour characteristics and HPV status in women who visited Arkhangelsk Clinical Maternity Hospital named after Samoylova, Russia.

Characteristics	HPV status, n (%)		P-value
	Negative n = 250	Positive n = 50	
Age			0.031
25–29	58 (23.2)	20 (40)	
30–39	123 (49.2)	22 (44)	
≥ 40	69 (27.6)	8 (16)	
Marital status			0.029
Married	145 (58)	21 (42)	
Cohabitation	45 (18)	17 (34)	
Single	60 (24)	12 (24)	
Parity			0.018
0	44 (17.6)	17 (34)	
1	103 (41.2)	20 (40)	
≥ 2	103 (41.2)	13 (26)	
Education			0.108
University	142 (56.8)	22 (44)	
Other	109 (43.2)	28 (56)	
Lifetime number of sexual partners			0.034
1–3	141 (56.4)	20 (40)	
> 3	109 (43.6)	30 (60)	
Abortion			0.570
Yes	129 (51.6)	28 (56)	
No	121 (48.4)	22 (44)	
Age at sexual debut, years			0.001
Me (Q1–Q3)	18 (17–19)	17 (16–18)	
Condom use			0.836
Yes	129 (51.6)	25 (50)	
No	121 (48.4)	25 (50)	
Sexually transmitted infections			0.468
Never had	129 (55.6)	25 (50)	
Ever had	111 (44.4)	25 (50)	
Smoking status			0.011
Yes	27 (10.8)	12 (24.0)	
No	223 (89.2)	38 (76.0)	

The value of $p < 0.05$ was considered to be statistically significant.

Table 2. Associations between knowledge about HPV and cervical cancer prevention and HPV status in women who visited Arkhangelsk Clinical Maternity Hospital named after Samoylova, Russia (n = 300).

Questions about HPV and cervical cancer prevention	HPV status, n (%)[a]		P-value
	Negative n = 250	Positive n = 50	
1. Have you ever heard of HPV?	156 (62.4)	34 (68.0)	0.453
2. Most HPV types can cleared up on their own.	23 (9.2)	7 (14.0)	0.302
3. HPV is very common in women.	205 (82.0)	38 (76.0)	0.324
4. The chance of getting HPV increases with number of sexual partners.	187 (74.8)	37 (74.0)	0.905
5. What is the main hazard of HPV for female?	206 (82.4)	41 (82.0)	0.946
6. A person usually does not have symptoms when infected with HPV.	118 (47.2)	22 (44.0)	0.679
7. Most sexually active women will never get HPV during their life.	165 (66.0)	37 (74.0)	0.271
8. According to Russian legislation, how often should routine screening for cervical cancer be done?	151 (60.4)	27 (54.0)	0.400
9. Cytological smear (Pap test) can detect changes that can lead to cancer if left untreated.	164 (65.6)	35 (70.0)	0.548
10. HPV vaccine can prevent cervical cancer.	94 (37.6)	13 (26.0)	0.118
11. HPV vaccine is most effective if given to individuals who have never had sex.	219 (87.6)	43 (86.0)	0.756
12. Someone who has undergone HPV vaccination cannot develop cervical cancer.	199 (79.6)	39 (78.0)	0.799
13. Women who have undergone HPV vaccination do not need a Pap test later in their life.	26 (10.4)	3 (6.0)	0.336
14. HPV can be passed on during vaginal sexual intercourse.	155 (62.0)	31 (62.0)	1.000
Numbers of correct answer, scores, Me (Q1–Q3)[b]	8 (7–10)	9 (6–10)	0.716
Level of knowledge[c]:			0.121
sufficient	204 (81.6)	36 (72.0)	
poor	46 (18.4)	14 (28.0)	

[a]Number (%) of women who answered correctly for each of the 14 questions.
[b]Median (first and third quartiles) number of correct answers (from 0 to 14).
[c]Number (%) of women who had sufficient (from 7 to 14 correct answers to the 14 questions) or insufficient (< 7 correct answers) knowledge about HPV and cervical cancer prevention.
The value of $p < 0.05$ was considered to be statistically significant.

Table 3. Risk factors for positive high-risk HPV status among women who visited Arkhangelsk Clinical Maternity Hospital named after Samoylova, Russia ($n = 300$).

Variable	Crude			Adjusted*		
	OR	95% CI	P for linear trend	OR	95% CI	P for linear trend
Age			0.012			0.437
25–29	1.00	Reference		1.00	Reference	
30–39	0.52	0.26–1.02		0.67	0.32–1.42	
≥ 40	0.33	0.14–0.82		0.72	0.26–1.98	
Parity			0.007			0.035
0	1.00	Reference		1.00	Reference	
1	0.50	0.24–1.05		0.47	0.21–1.03	
≥ 2	0.33	0.15–0.73		0.38	0.16–0.93	
Sexual partner						
1–3	1.00	Reference		1.00	Reference	
> 3	1.94	1.04–3.60		1.65	0.85–3.24	
Sexual debut						
Years	0.77	0.65–0.91		0.80	0.67–0.96	

*Method – Enter, $R^2 = 0.117$, $x^2 = 21.576$, $p = 0.001$.
Homer–Lemeshow test: $x^2 = 8.5$, $p = 0.385$.
The value of $p < 0.05$ was considered to be statistically significant.

programme implemented or variation in study designs and exposure to HPV risk factors [32].

The prevalence of HPV among women in Russia has been poorly documented and is restricted primarily to studies conducted in Saint-Petersburg, where HR-HPV positivity of 13% ($n = 107$) has been reported [33]. A cohort study of women at risks for HPV infection in three independent states of the former Soviet Union suggested an overall HPV prevalence of 33.4% [34]. Differences in the prevalence estimates within Russia may be partly explained by the disparity in the study populations. Age is one of the major determinants of the HPV infection prevalence. In our study group, younger aged women (age groups 25–29 and 30–39) tended to have an HPV positive status more often than those aged 40 years or older. These findings are in accordance with other studies that show that HPV infection steeply decreases with age [20,22]. In general, the younger a population is, the higher the prevalence of HPV infection. It has been suggested that most HR-HPV infections in young women are transient and often involve sexual contacts with new partners, and that persistent infections occur in a small proportion of women [20].

One possible explanation for our observation that cohabiting is associated with HPV infection could be that the time since last exposure to HPV is longer in married women than in singles. Also sexual activity in single people tends to be sporadic [35]. Nevertheless, there is a growing prevalence of sex outside marriage, and thus marriage status does not reliably safeguard sexual-health status [35–37].

We found an association between HR-HPV infection and reproductive factors. There was a negative linear trend observed for parity. That is consistent with a study of Munoz et al. [38] where parity was a protective factor for positive HPV status. The latter could be explained by prenatal hormonal changes in the transformation zone that contribute to HPV resistance during sexual intercourse [39]. Study from Colombia showed that high parity increases the risk of squamous-cell carcinoma of the cervix among HPV-positive women [40].

Despite the relatively low smoking rate (13%) among our study subjects, we found that positive HPV status was associated with cigarette smoking. A recent study from the Murmansk region of North-West Russia reports that the prevalence of smoking among women was 25.2% during 2006–2011 [41]. Differences in the time frame, age and education level between the study populations might have contributed to the discrepancy. Although smoking is associated with an increased risk of CC [42], its effect on HPV infection is mixed. Poppe et al. [43] found that smoking potentially increased the risk of HPV infection through a local impairment of cell-mediated immunity, although the magnitude of the effect was small. While some studies report an increased risk of HPV infection among smokers [22], others found a reduced risk [44].

Our observation that age at sexual debut and number of lifetime sexual partners are associated with positive HPV status is consistent with previous studies [19–22]. Age at sexual debut appears to have declined over time [45]. Most young women and men become sexually active during their teenage years and generally do so unsafely [35]. Little knowledge and lack of access to contraceptive related services explain the low use and high rates of ineffective use. Greenberg et al. [46] have demonstrated that early age at first sexual intercourse in a female population was associated with risky

behaviours, such as multiple sexual partners, intravenous drug-use, higher likelihood of having sexually transmitted diseases. Others have demonstrated that risky behaviours including multiple sexual partners and frequency of vaginal intercourse are associated with HPV infection, particularly by the high oncogenic risk types. Of these, a positive association with the number of sexual partners has most consistently been reported [20–22]. Multiple lifetime sexual partners has been shown to increase the risk of being HPV-DNA positive [19,40]. However, women tend to underreport the number of lifetime sexual partners [22,35,36].

Our findings indicate that condom use was not associated with HPV status. Munoz et al. [22] showed that condoms most likely prevent HPV infection, although the evidence of their effectiveness against other sexually transmitted diseases is mixed. Manhart et al. [23] in their meta-analyses showed that there was no consistent evidence that condom use reduces the risk of becoming HPV-DNA positive. Authors suggest that while condoms may not prevent HPV infection, they may protect against genital warts and CC [23]. Underestimation of the potential protective effect of condom use is possible, as very few women used it consistently [47,48].

Long-term use of oral contraceptives could be a cofactor that increases the risk of cervical carcinoma [25]. Previous studies indicate that compared to never-users, patients who used oral contraceptives for less than 5 years did not have an increased risk of CC [49,50]. However its use for over 5 years resulted in higher risks of CC [25,26]. Almost 30 years ago it was hypothesised that oestrogen and other hormones are capable of reactivating HPV or increase its viral expression [51,52]. However this relation is not likely to be causal. Contraceptive users may generally differ from nonusers in other aspects than sexual behaviour.

Despite the sufficient level of knowledge about HPV and CC prevention among our study participants, it yielded no apparent protection against positive HPV status. Neither was there a difference with education level. Women with sufficient level of knowledge about HPV and CC prevention had the same positive HPV status as those with a poor level. One possible explanation could be that the mode of communication between women and their healthcare providers was that scientific information was shared in a matter-of-fact manner, with no or little attention to a problem's complexity or the context of a patient's understanding of a health issue. It may well be necessary to re-conceptualise the education of healthcare workers to include a better understanding of STDs and HPV infection.

There remains little doubt that women who were positive for HPV can be distinguished from those who were HPV negative by a number of characteristics in their reproductive health, their sexual behaviour and preferences. However, many of the sociodemographic characteristic as well as variables used to measure sexual behaviour are closely interrelated and could be potential confounders and/or mediators in multivariable analysis. Moreover, total exposure to some of the potential risk factors, such as for example marital status and smoking, could not be measured properly due to cross-sectional design of the study. In relation to this, it was difficult to build a regression model that would be the best to explore potential independent risk factors. We found that age at sexual debut and parity, but not age or the lifetime number of sexual partners were independent predictors for cervical HR-HPV infection.

Limitations

Our study has several potential limitations related to cross-sectional design. Our study used non-probabilistic sampling and this is why it cannot be generalised. Despite the fact that we excluded the younger age group (< 25 years old), it has been shown that initiation of screening at an early age can lead to an overestimation of CC risk [53]. All survey data based on self-reports are susceptible to bias. Sexual behaviour might suffer more than other variables because of social desirability bias — the tendency for participants to respond according to social expectations of what is acceptable. Our study's cross-sectional design has the risk of reporting bias, particularly in the context of variables that address aspects of sexual behaviour, such as age at sexual debut and lifetime number of sexual partners. Many surveys find that women tend to under-report the number of sexual partners [35–37]. Thus selection bias might have occurred in our study. It is possible that study participants were more health conscious in terms of HPV and CC than women in the general population.

The cross-sectional study design is limited in revealing a causal relationship between HR-HPV positivity and selected sociodemographic and sexual characteristics. It measures prevalence and does not reflect any temporal influence. Moreover, changes in social attitudes may have affected the results of the survey since what is being captured could in part reflect a change in behaviour itself. Furthermore, our study results cannot be generalised. We can extrapolate our data only to women who have visited gynaecologists for any reason in the Arkhangelsk Clinical Maternity Hospital named after Samoylova.

Conclusion

The observed prevalence of HR-HPV is comparable to estimates mentioned in previous studies. We have established that women in the HR-HPV positive group differed from the HR-HPV negative group by age, marital status, parity, age at sexual debut, number of sexual partners and cigarette smoking. Women with early age at sexual debut and those nulliparous have had a higher risk of having a positive HR-HPV status. Our results reinforce the importance of sexual behaviour educational programmes for women and healthcare providers in the prevention of HR-HPV infections. There is no universal approach or a single intervention that would work everywhere, as regional and local social contexts can contribute to risky sexual practices. Surveys of cervical HPV prevalence and related risk factors can help to increase general understanding and provide a basis for the design and establishment of educational programmes and their assessment.

Disclosure statement

Competing interests

The authors declare that they have no competing interests.

Availability of supporting data

According to the Russian Federal Law №152 from 27th of July 2006 "Personal data" "cross-border data transfer may be prohibited or restricted in order to protect constitutional rights of the Russian citizens".

However, it allows attaching the dataset from corresponding author on the basis of properly submitted requests.

Consent for publication

Not applicable.

ORCID

Elena Roik http://orcid.org/0000-0001-7226-2198
Ekaterina Sharashova http://orcid.org/0000-0001-9412-2065
Olga Kharkova http://orcid.org/0000-0002-3130-2920
Evert Nieboer http://orcid.org/0000-0001-5165-2832
Vitaly Postoev http://orcid.org/0000-0003-4982-4169
Jon Ø. Odland http://orcid.org/0000-0002-2756-0732

References

[1] Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol. 2005;32(Suppl 1): S16–24.

[2] Human Papillomavirus (HPV) Statistics. Available from: https://www.cdc.gov/std/hpv/stats.htm

[3] 6 Reasons to Get HPV Vaccine for Your Child. Available from: https://www.cdc.gov/hpv/infographics/vacc-six-reasons.html

[4] Munoz N, Bosch FX, de Sanjose S, et al. International agency for research on cancer multicenter cervical cancer study G: epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518–527.

[5] Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. Vaccine. 2012;30(Suppl 5):F12–23.

[6] Globocan. Cervical Cancer Estimated Incidence, Mortality and Prevalence Worldwide in; 2012. Available from: http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp

[7] Altobelli E, Lattanzi A. Cervical carcinoma in the European Union: an update on disease burden, screening program state of activation, and coverage as of March 2014. Int J Gynecol Cancer. 2015;25(3):474–483.

[8] Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the USA, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin. 2017;67(2):100–121.

[9] Davis M, Feldman S. Making Sense of Cervical Cancer Screening Guidelines and Recommendations. Curr Treat Options Oncol. 2015;16(12):55.

[10] Elfstrom KM, Arnheim-Dahlstrom L, von Karsa L, et al. Cervical cancer screening in Europe: quality assurance and organisation of programmes. Eur J Cancer. 2015;51 (8):950–968.

[11] Ostensson E, Silfverschiold M, Greiff L, et al. The economic burden of human papillomavirus-related precancers and cancers in Sweden. PLoS One. 2017;12(6): e0179520.

[12] Parkin DM, Bray F. Chapter 2: the burden of HPV-related cancers. Vaccine. 2006;24(Suppl 3):S3/11–25.

[13] Aad G, Abajyan T, Abbott B, et al. Measurement of top quark polarization in top-antitop events from proton-proton collisions at radicals=7 TeV using the ATLAS detector. Phys Rev Lett. 2013;111(23):232002.

[14] Jones SB. Cancer in the developing world: a call to action. BMJ. 1999;319(7208):505–508.

[15] Bruni LB-RL, Albero G, Serrano B et al.: Human papillomavirus and related diseases in russian federation. Summary Report; 2017.

[16] Kjaer SK, Chackerian B, van den Brule AJ, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). Cancer Epidemiol Biomarkers Prev. 2001;10 (2):101–106.

[17] Castellsague X, Bosch FX, Munoz N, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. N Engl J Med. 2002;346 (15):1105–1112.

[18] Castellsague X, Bosch FX, Munoz N. The male role in cervical cancer. Salud Publica Mex. 2003;45(Suppl 3): S345–353.

[19] Vaccarella S, Franceschi S, Herrero R, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. Cancer Epidemiol Biomarkers Prev. 2006;15 (2):326–333.

[20] Chan PK, Chang AR, Cheung JL, et al. Determinants of cervical human papillomavirus infection: differences between high- and low-oncogenic risk types. J Infect Dis. 2002;185(1):28–35.

[21] Peyton CL, Gravitt PE, Hunt WC, et al. Determinants of genital human papillomavirus detection in a US population. J Infect Dis. 2001;183(11):1554–1564.

[22] Kjaer SK, van den Brule AJ, Bock JE, et al. Determinants for genital human papillomavirus (HPV) infection in 1000 randomly chosen young Danish women with normal Pap smear: are there different risk profiles for oncogenic and nononcogenic HPV types? Cancer Epidemiol Biomarkers Prev. 1997;6(10):799–805.

[23] Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. Sex Transm Dis. 2002;29(11):725–735.

[24] Vaccarella S, Herrero R, Snijders PJ, et al. Smoking and human papillomavirus infection: pooled analysis of the International Agency for Research on Cancer HPV Prevalence Surveys. Int J Epidemiol. 2008;37(3):536–546.

[25] Vaccarella S, Herrero R, Dai M, et al. Reproductive factors, oral contraceptive use, and human papillomavirus infection: pooled analysis of the IARC HPV prevalence surveys. Cancer Epidemiol Biomarkers Prev. 2006;15(11):2148–2153.

[26] Munoz N, Franceschi S, Bosetti C, et al. International agency for research on cancer. multicentric cervical cancer study G: role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet. 2002;359(9312):1093–1101.

[27] Bosch FX, Munoz N, de Sanjose S, et al. Importance of human papillomavirus endemicity in the incidence of cervical cancer: an extension of the hypothesis on sexual behavior. Cancer Epidemiol Biomarkers Prev. 1994;3(5):375–379.

[28] Territorial office of the federal state statistics service of the Arkhangelsk region. Available from: http://arhangelsk stat.gks.ru/wps/wcm/connect/rosstat_ts/arhangelskstat/ ru/statistics/population/

[29] The UK NHC cervical screening program. Available from: https://www.bsccp.org.uk/assets/file/uploads/resources/ NHSCSP_20_Colposcopy_and_Programme_ Management_(3rd_Edition)_(2).pdf

[30] Roik EE, Sharashova EE, Nieboer E, et al. Knowledge about human papillomavirus and prevention of cervical cancer among women of Arkhangelsk, Northwest Russia. PLoS One. 2017;12(12):e0189534.

[31] Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287(16):2114–2119.

[32] Bruni L, Diaz M, Castellsagué X, et al. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 2010;202(12):1789–1799.

[33] Shipitsyna E, Zolotoverkhaya E, Kuevda D, et al. Prevalence of high-risk human papillomavirus types and cervical squamous intraepithelial lesions in women over 30 years of age in St. Petersburg, Russia. Cancer Epidemiol. 2011;35(2):160–164.

[34] Syrjanen S, Shabalova I, Petrovichev N, et al. Sexual habits and human papillomavirus infection among females in three New Independent States of the former Soviet Union. Sex Transm Dis. 2003;30(9):680–684.

[35] Wellings K, Collumbien M, Slaymaker E, et al. Sexual behaviour in context: a global perspective. Lancet. 2006;368(9548):1706–1728.

[36] Nnko S, Boerma JT, Urassa M, et al. Secretive females or swaggering males? An assessment of the quality of sexual partnership reporting in rural Tanzania. Soc Sci Med. 2004;59(2):299–310.

[37] Curtis SL, Sutherland EG. Measuring sexual behaviour in the era of HIV/AIDS: the experience of Demographic and Health Surveys and similar enquiries. Sex Transm Infect. 2004;80(Suppl 2):ii22–27.

[38] Munoz N, Mendez F, Posso H, et al. Instituto Nacional de Cancerologia HPVSG: incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. J Infect Dis. 2004;190(12):2077–2087.

[39] Louie KS, de Sanjose S, Diaz M, et al. Early age at first sexual intercourse and early pregnancy are risk factors for cervical cancer in developing countries. Br J Cancer. 2009;100(7):1191–1197.

[40] Munoz N, Kato I, Bosch FX, et al. Risk factors for HPV DNA detection in middle-aged women. Sex Transm Dis. 1996;23 (6):504–510.

[41] Kharkova OA, Krettek A, Grjibovski AM, et al. Prevalence of smoking before and during pregnancy and changes in this habit during pregnancy in Northwest Russia: a Murmansk county birth registry study. Reprod Health. 2016;13: 18.

[42] Chichareon S, Herrero R, Munoz N, et al. Risk factors for cervical cancer in Thailand: a case-control study. J Natl Cancer Inst. 1998;90(1):50–57.

[43] Poppe WA, Ide PS, Drijkoningen MP, et al. Tobacco smoking impairs the local immunosurveillance in the uterine cervix. An immunohistochemical study. Gynecol Obstet Invest. 1995;39(1):34–38.

[44] Lazcano-Ponce E, Herrero R, Munoz N, et al. Epidemiology of HPV infection among Mexican women with normal cervical cytology. Int J Cancer. 2001;91(3):412–420.

[45] Burchell AN, Winer RL, de Sanjose S, et al. Chapter 6: epidemiology and transmission dynamics of genital HPV infection. Vaccine. 2006;24(Suppl 3):S3/52–61.

[46] Greenberg J, Magder L, Aral S. Age at first coitus. A marker for risky sexual behavior in women. Sex Transm Dis. 1992;19(6):331–334.

[47] Potter LB, Anderson JE. Patterns of condom use and sexual behavior among never-married women. Sex Transm Dis. 1993;20(4):201–208.

[48] Jama Shai N, Jewkes R, Levin J, et al. Factors associated with consistent condom use among rural

young women in South Africa. AIDS Care. 2010;22
(11):1379–1385.

[49] Peng Y, Wang X, Feng H, et al. Is oral contraceptive use
associated with an increased risk of cervical cancer? An
evidence-based meta-analysis. J Obstet Gynaecol Res.
2017;43::913–922.

[50] Moreno V, Bosch FX, Munoz N, et al. International Agency
for Research on Cancer. Multicentric Cervical Cancer
Study G: effect of oral contraceptives on risk of cervical
cancer in women with human papillomavirus infection:
the IARC multicentric case-control study. Lancet.
2002;359(9312):1085–1092.

[51] Mitrani-Rosenbaum S, Tsvieli R, Tur-Kaspa R. Oestrogen
stimulates differential transcription of human papilloma-
virus type 16 in SiHa cervical carcinoma cells. J Gen Virol.
1989;70(Pt 8):2227–2232.

[52] Mittal R, Tsutsumi K, Pater A, et al. Human papillomavirus
type 16 expression in cervical keratinocytes: role of proges-
terone and glucocorticoid hormones. Obstet Gynecol.
1993;81(1):5–12.

[53] Landy R, Birke H, Castanon A, et al. Benefits and harms
of cervical screening from age 20 years compared with
screening from age 25 years. Br J Cancer. 2014;110
(7):1841–1846.

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
     - ○ Количество родов_____
     - ○ Количество абортов_____
     - ○ 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
     - ○ Гормональные контрацептивные препараты
     - ○ Презерватив
     - ○ Внутриматочная спираль
     - ○ 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