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Results of a Survey Concerning Cervical Cancer Risk Factors among Women in Western Kazakhstan

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Abstract

During 2014–2017, a survey concerning risk factors for cervical cancer involving 1166 clinically healthy women and 65 having CaCx was conducted in Western Kazakhstan. Only 34.7% of interviewees constantly participated in state-sponsored screening program, while 37.3% ignored screening in free state-sponsored clinics. Favorable attitude toward vaccination stated 22.9% of the respondents, whereas 38.8% knew nothing, and 33.6% could not clarify their position in this issue. Education is a key factor for better perception of preventive measures—69.2% of the respondents with higher education are aware of vaccination ($p \leq 0.00001$, Cramer's V 0.18, χ^2 –23.1). Social profiles of HPV-infected and CaCx-diseased women differ significantly and, mainly, by standard of living and occupational status. The likelihood of the CaCx onset in Western Kazakhstan decreased by 14 times at relatively high standard of living (OR 0.0713, $p = 0.024$) and by 3.3 times provided at least irregular participation in screening (OR 0.3384, $p = 0.0304$). Overall, the findings are quite able to contribute to an understanding why women become affected by CaCx. Low standard of living due to lack of education, low attendance of screening, and low awareness on preventive measures—all these reasons are interacted and constitute a set of universal triggers for vulnerability toward CaCx.

Keywords: cervical cancer, human papillomavirus, awareness, vaccination, screening, risk factors, Kazakhstan

1. Introduction

For cervical cancer (CaCx), the number of diagnoses could “rise by at least 25% to over 700,000 by 2030, mainly in low- and middle-income countries,” said a statement from the Lancet [1]. Some sources mention areas of Western Asia as countries with the lowest CaCx rates [2], while just a few sources are available on the disease-related issues in borderline Central Asia, where Kazakhstan and some other post-Soviet states are located [3, 4]. Reportedly, the annual incidence rate of cervical cancer for Kazakhstan was calculated as 14.5 ± 0.3 with 8.0 ± 0.1 mortality

for the period 1999–2008 [5]. Data of the International Agency for Research on Cancer (IARC) on cervical cancer incidence in 2012 for the global network resource Cancer Today (formerly Globocan) indicated the highest incidence of CaCx in the Republic of Kazakhstan among borderline countries—29.4 per 100,000 of the female population standardized by age, while the corresponding index for the Russian Federation was 15.3, for Uzbekistan 13.5, and 7.5 for China, respectively [6]. Despite definite progress achieved, issues of cervical cancer prevention have still remained tense in the country. According to data of the ICO Information Centre on HPV and Cancer (the Catalan Institute of Oncology HPV center) as of December 23, 2015, there were 6.72 million women aged 15 years and older at risk of developing cervical cancer, and estimates indicated that every year 2789 women were diagnosed with cervical cancer and 982 died from the disease [7]. Morbidity, according to the ICO experts, has been roughly estimated 32.8 per every 100,000 women standardized by age, i.e., increased several times as many for the period less than a decade. Meanwhile, cervical cancer is a real object for early detection because of its belonging to a number of visual forms and can be largely prevented by both effective screening and vaccination [8].

A system of the cervical cancer screening has been implementing in our country since 2008, and in frames of this nationwide program, all women aged 30–70 years are subjected to mass cytological examination every 4 years. Age of women has been increased from 60 to 70 years, and the interval has been diminished from 4 to 5 years according to the latest regulation no. 995 as of December 25, 2017. With that, screening coverage (attendance), which had been about 72% for the first years upon implementation [3], i.e., in line with the WHO recommendations, then began to decline, reaching about 50% by the present time, as leading scientists of KazIOR (Kazakh Research Institute of Oncology and Radiology) recorded.

Furthermore, the other large problem is related to the CaCx screening routine in the country. To date, the majority of specialists in management of women with atypical cytological results are guided by the joint recommendations of the ACS (American Cancer Society), ASCCP (American Society for Colposcopy and Cervical Pathology), USPSTF (US Preventive Services Task Forces), and other leading institutions [9]. Regrettably, these recommendations still have not been adopted by the health policymakers in our country, despite the existing HTA (Health Technology Assessment) reports and leading experts' opinions confirming advantages of HPV-based screening in a co-testing way, i.e., collectively with cytology [10–14].

To implement worldwide-accepted screening in a co-testing way, any countries should first create their nationwide maps of HPV prevalence and type distribution, as HPV is an apparent causative factor for the CaCx development, and its various types differ by carcinogenic potential [15–19]. And meanwhile, data on HPV leading types across Kazakhstan still are limited with a few publications, and far not all the regions have been studied [20–23]. Currently, 14 types are referred to as the types of highly carcinogenic risk (HR-HPV) [24]. Listed researches on HPV prevalence reported high dissemination of HR-HPV types, within 25–28.3% across examined regions.

According to world's leading experts' opinion, only implementation of universal HPV vaccination with enhanced screening would maximally reduce the burden of cervical cancer in post-Soviet countries, albeit options for reducing the HPV-related disease burden are resource-dependent [4].

Revised in Melbourne (2014), the WHO tactics on the CaCx prevention has confirmed that HPV vaccination of girls aged 9–13 years still remains the primary principle of prevention [25].

High rates of cervical cancer along with wide dissemination of HR-HPV types in Kazakhstan entail the need to renew the state-scale program of universal

compulsory vaccination of adolescents. Successfully launched in Kazakhstan in 2013, a pilot vaccination program then was discontinued, largely due to the negative attitude of parents who were not yet ready to the challenges of modern world. However, further efforts are needed to overcome prejudices in primary prevention of cervical cancer. According to the estimates of specialists, stated in the press release of the Centers for Disease Control and Prevention (CDC), in the USA there was an impressive decrease in the prevalence of vaccine types of HPV by 56% in the group 14–19 years old for 7 years of the introduction of vaccination against cervical cancer in adolescent girls (2006–2013) [26]. Recommendations for vaccination are developed by the world's leading cancer institutes not only for girls but also for boys 11–12 years old. Effectiveness of vaccination now is convincingly proven and is no longer questioned [27].

Thus, a wide circle of issues on the CaCx prevention is to be solved in Kazakhstan in the nearest time, and specific information of the relatively targeted audience of these efforts would serve as a basis for positive changes in this direction.

2. Risk factors for HPV infection and cervical cancer development

According to WHO and CDC, the following conditions are considered the risk factors for the cervical cancer development:

- Inaccessibility of the screening program or rare participation in it.
- Persistent HPV infection.
- States causing immunosuppression, such as HIV, high-dose steroid use, etc.
- Lower genital tract neoplasia irrespective of the area: vulvar, vaginal, and anal.
- Increasing the number of sexual partners (increases risk of HPV acquisition) along with early age of sexual debut.
- Presence of sexually transmitted infections, such as *C. trachomatis* and possibly herpes simplex virus (HSV).
- Tobacco smoking (current and, to a lesser extent, past tobacco smoking) increases the risk of cervical squamous cell carcinoma.
- The use of birth control pills: long-term use increases the risk of cervical squamous cell carcinoma.
- More than three full-term pregnancies.

It is worthwhile to emphasize that the risk factors for HPV infection do not coincide in full with the risk factors for cervical cancer. Only persistent HPV infection constitutes fundamental condition for the CaCx development, while other mentioned risk factors such as smoking play a supporting role [13, 28].

To our knowledge, the peak incidence of HPV infection occurs in 20-year-olds, the peak incidence and detection of CIN-III is characteristic for the age group of 30-year-olds, and the peak incidence of cervical cancer occurs at the age of

40 years or more. According to estimates, cervical cancer can occur in about 3–5% of women with high-risk HPV infection unless secondary prevention (screening) implements [29].

3. Survey as an instrument to get information

Survey, being the most cost-effective and quick tool to recognize needs, intentions, and perception of the targeted audience, serves for specific purposes, but its design depends not only on the aims claimed but often on standard of living and concomitant features of the sample tested, such as educational level, availability and quality of healthcare, etc. One may observe quite noticeable differences in designing the surveys depending on economic status of the countries where those tools applied. Mostly, in high-income countries, more detailed surveys designed to reveal more complex context are used, due to relatively long practicing. For example, in Italy, surveys aimed for obtaining baseline data on risk factors have been widely practiced for at least 30 years [30]. Besides, in high-income countries, web-based survey, or computer-aided self-administered interviewing (CASI), appears to be frequently used, as well as applying mail and telephone surveys, due to providing better confidentiality for an individual, despite relatively low response rate (65% considered acceptable) [31–33]. Personal interviews usually are conducted upon facing “difficult cases,” i.e., where obtaining complex information is needed. Direct interviewing provides opportunities for best control, surveillance, and on-site verification. Meanwhile, direct interviewing, being a relatively expensive and time-consuming way to obtain data, nonetheless, applies more frequently in low-/middle-income countries, where there are many illiterate or low-educated people or in sites where sociocultural customs, different from western lifestyle, are practiced [34–36]. Overall, all these generalizations are quite arbitrary, as specialists choose a way of operating mostly based on purposes and capabilities of their research.

As to the models for questionnaire development, the two most cited and used approaches seem to be most popular, according to literature sources.

One of these approaches constitutes a conception of the Theory of Planned Behavior (TPB) as applied to the behavioral researches on cervical cancer issues [32, 37, 38]. According to the theory, the author Ajzen I. stated, “a more favourable attitude makes a person more attentive toward a recommendation made by significant others” [39].

The second approach refers to the Health Belief Model, on the basis of which Robert DeVellis developed guidelines summarized in his book *Scale Development*. Based on these guidelines, a principally new questionnaire, CPC-28, has been developed by Maria Teresa Urrutia and R. Hall [40]. The questionnaire includes six domains: “the barriers to take a Pap test,” “the cues to action,” “the severity,” “the need to have a Pap test,” “the susceptibility to cervical cancer,” and “the benefit” domain. CPC-28 has been used by many researchers as an example for development of their own questionnaires [41, 42].

These approaches suggest development of questionnaires aimed to reveal perception, intentions, beliefs, and possible attitudes of the individual tested. As applied toward HPV infection and cervical cancer issues, such models gave a lot to reveal prejudices relatively CaCx preventive measures—screening and vaccination—throughout almost all strata of the female population.

The following step in the questionnaire developing is testing for validation purposes, often including “pretest-test-retest” stages. Testing is the key factor for checking the tool’s validation and reliability. Usually, outer experts are involved to check the questionnaire. Field-testing in specially selected representative groups for

the trial interview purposes is combined with the testing of its internal consistency by Cronbach's alpha coefficient. During the trial interviews combined with Cronbach's alpha calculation, the amount of items may be changed. For example, in CPC-28 53 initial items then were decreased to 28, and other researchers reported cutting down their items from 69 to 26 in order to reach optimal Cronbach's alpha within 0.7 and higher [43]. It should be noted that when evaluating the survey specific results, it is not appropriate to rely on Cronbach's alpha index solely. Reliability of the interviewees' responses does not depend on Cronbach's alpha directly. In listed researches the number of items varies from 12 [36] to 26–29 [32, 40, 43] and up to 64–65 [41, 44].

A separate domain of surveys concerning CaCx is presented by studies addressing the issues of quality of life (QoL), information needs, sexuality, and other problems in patients with cervical cancer or its precursor, who had undergone the treatment [45–49].

Overall, creating an effective tool allows for obtaining a lot of valuable data for timely renewal of cervical cancer prevention strategies, including issues of selecting the most rational information sources for the targeted audience.

4. The survey on cervical cancer risk factors conducted in Western Kazakhstan: aims, methodology, and findings

Findings of the survey presented below are quite indicative and to a definite extent may reflect the current situation with awareness of the CaCx preventive measures not only in Kazakhstan alone but, in a broad sense, in post-Soviet Central Asian states.

General information about the country: the Republic of Kazakhstan is a leading state in Central Asia and refers to middle-income countries. The country ranks 9th in terms of territory in the world, 64th in terms of population, and 184th in terms of density (6.3 per sq. km). The population of the country as of January 1, 2016, is 17,417,673; the ratio of men and women is 48:52%. Share of the population aged 15–65 is 71%. The national composition of Kazakhs is 66.1%, Russians 21.5%, and other ethnic group. 12.4% (data are taken from the information source of the Agency of Statistics of the Republic of Kazakhstan). The western region is industrially developed and consists of four large provinces: Aktobe, West Kazakhstan, Mangystau, and Atyrau. All provinces are involved in oil industry, with the presence of atomic industry in Mangystau.

4.1 Aims, materials, and methods of the research

During 2014–2017 a multipurpose scientific project on HPV infection and cervical cancer issues was carried out across the region by the West Kazakhstan University's research team.

The interview constituted a part of the mentioned research and aimed to determine qualitatively and quantitatively a group at risk for possible cervical cancer development. Therefore, tasks of the survey were the following:

- Identifying women of general female population who are infected with HPV in order to allocate those who are exposed to the CaCx development risk factors
- Comparing women infected with HPV but not having CaCx and those diagnosed with cervical cancer by matching, to establish dominant risk factors in the region

Design and protocol of the study were approved by the University's Institutional Review Board (October 9, 2014). The work was carried out in accordance with the Helsinki Declaration principles. All participants who signed the informed consent form were fully informed on the objectives of this analysis.

4.1.1 General sample (clinically healthy women)

In determining the sample size for general female population, the following points mattered:

- According to a pilot study of the West Kazakhstan University on HPV as of 2014, N for HPV genotyping was 1098 with valid statistical results at the prevalence HR-HPV 26.04% ($p \leq 0.043$) [21].
- Statistical data on the number of urban female population living in western cities of regional importance and suburbs.

In total, N according to calculations (two-side type I error of $p \leq 0.05$, 95% CI) was counted 1152, of which 417 in Aktobe, 253 in Uralsk (West Kazakhstan), 237 in Atyrau, and 245 in Mangystau.

Data were collected in medical settings in cities of regional importance, including the nearest vicinities. To reach maximally possible scope of female population and avoid possible bias, all kinds of outpatient clinics were involved: state-sponsored, insurance, and private ones. Enrollment of women was held either during their routine visit to the gynecologist, by ads placed in the clinics lobby, or by the invitation of sentinel specialists. Inclusion criteria for general sample were the following: age 18–60+ years, resident of Western Kazakhstan of any ethnicity, and no vaccination history.

The exclusion criteria are nonresidents of Kazakhstan and vaccination history. HIV status and pregnancy of the first trimester were not exclusion criteria.

4.1.2 Cervical cancer sample

As to the sample size of the patients with CaCx first time diagnosed, the number of adult (18+) female population of the republic along with the incidence of cervical cancer in Kazakhstan equaled to 4.8% (data of the Agency on Statistics as of 2013) was applied in the formula:

$$N = \frac{p \times q \times Z_{\alpha}^2 \times N}{\Delta^2 \times N + p \times q \times Z_{\alpha}^2} \quad (1)$$

where Z_{α} (α) = 1.96 is the critical values of the normal standard distribution for a given $\alpha = 0.05$, N is the number of female population of the republic (6,700,000), $p = 0.048$ is the incidence of cervical cancer, $q = 1 - p = 0.952$, and $\Delta = 0.05$ is the sampling error.

According to calculations, the needed sample size was within 67–80.

All consonants to participate in the study were selected among women with first-time-diagnosed cancer across all regional oncology centers.

Inclusion criteria are any age, any stage of the cancer process, and histological verification of the diagnosis.

Exclusion criteria are nonresidents of the Western Kazakhstan and presence of the previous medical intervention—radiotherapy, chemotherapy, and surgical treatment.

Qualitative detection and quantification of human papillomavirus were performed in both samples by PCR real-time method based on the Russian test systems and equipment ("DNA-Technology" LLC, Russian Federation). Production of the company "DNA-Technology" was certified (ISO 13485: 2012).

4.1.3 Statistical processing

SPSS Statistics 20 software (IBM, Armonk, NY, USA) and the program Statistica 10 (Dell software, USA) were applied for calculations. For all tests a two-side type I error of $p = 0.05$ or less at 95% CI was assumed statistically significant. Nonparametric operational tests were used due to a priori missing a normal distribution. To identify the dominant risk factors for CaCx development, appropriate statistical tests were carried out: an analysis of the Pearson χ^2 contingency tables to identify significant links (with the definition of the Cramer's V criterion), analysis of the quantitative variables in two independent samples (Mann-Whitney test), and logistic regression analysis with odds ratio calculation (OR).

4.2 Questionnaire designing and survey conducting

4.2.1 Questionnaire designing

The questionnaire was developed in two languages, Kazakh and Russian (optional), in a semi-structured manner, with questions, mostly closed, to collect data reflecting a role of the most known risk factors in the development of CaCx.

Overall, the questionnaire included three conditional domains: the first one for collecting social/demographic information, such as age, ethnicity, education, occupation, and family (per capita) income of women who were being interviewed. This domain also included issues related to the number of pregnancies and the presence of cervical cancer in close relatives irrespective to the time period, at present or in the past (not in terms of hereditary, but to assess differences in perception). The conditional second part of the questionnaire concerned behavioral/social settings: attitude toward smoking, the number of sexual partners during life, age of sexual activity onset, and the method of contraception currently used, with focus on the birth control pills (BCPs). The third conditional domain included questions devoted to perception of the CaCx preventive measures: attendance of municipal PHC clinics (in terms of availability of state-sponsored free healthcare), screening activities, and attitude toward vaccination against cervical cancer. This part consisted of closed questions, to reveal the women's perception of nationwide measures, given a mentioned decreasing of the screening coverage and discontinuation of the pilot vaccination program in adolescents, started in 2013. As previously stated, adolescents' parents perceived the program mostly negatively.

As to the content of the questionnaire, models described in the literature were not applied when designing, since all available examples were intended for relatively homogeneous audience, whereas in this questionnaire, the list of questions was identical both for women from the general sample (i.e., clinically healthy) and women who were diagnosed with CaCx. Besides, another consideration was mattered. Such a study was the first in its kind in medical practice of the region and the country, and its response rate was unknown. So, it was decided to develop a light version of the tool consisting of 14 most important items. Eventually, this number of questions did not burden the participants and allowed the stated objectives of the survey to be solved.

4.2.2 Validation of the questionnaire

Validation of the questionnaire was performed through Cronbach’s alpha (α) calculation, and findings were summarized in **Table 1**.

The item “contraceptive use” knocked down the total row due to negative r (-0.06). When removing the item, a total Cronbach’s α increased from 0.53 (bad) to 0.58, i.e., eventually was recognized “doubtful.” Despite the fact that reliability properties of the questionnaire did not meet accepted requirements (α 0.07 and higher), it was decided not to modify the tool for increasing its internal consistency due to considerations described above. Preliminary testing and retest also were not performed.

Initial calculation for all items			Calculation upon deleting the item “contraception methods”		
Result for the scale, mean = 21.2652			Result for the scale, averaged = 19.7543		
Std. dev. = 4.07863			Std. dev. = 3,85,041		
N items, 14			N items, 13		
Alpha Cronbach, 0.452699			Alpha Cronbach, 0.567090		
Standardized alpha, 0.525177			Standardized alpha, 0.578369		
Mean interposition correlation, -0.080197			Mean interposition correlation, -0.096674		
Items	General position correl (r)	α upon removal	Items	General position correl (r)	α upon removal
Age	0.171210	0.430272	Age	0.254605	0.541922
Ethnicity	0.148982	0.441428	Ethnicity	0.146472	0.561391
Education	0.351550	0.376869	Education	0.364908	0.511785
Employment	0.370232	0.346615	Employment	0.396442	0.497283
Income	0.374762	0.378943	Income	0.420856	0.502972
Number of pregnancies	0.018588	0.464434	Number of pregnancies	0.021628	0.585372
Close relatives with CaCx	0.075294	0.451611	Close relatives with CaCx	0.087969	0.567689
Duration of sexual life	0.227343	0.415536	Duration of sexual life	0.301034	0.529433
Number of sexual partners	0.263014	0.414043	Number of sexual partners	0.290278	0.536063
Contraceptive use	-0.064162	0.568096	Contraceptive use	—	—
Smoking	0.155715	0.443014	Smoking	0.161773	0.561118
State PHC facilities attendance	0.281290	0.407147	State PHC facilities attendance	0.292777	0.533949
CaCx screening attendance	0.015578	0.471991	CaCx screening attendance	0.020295	0.595756
Vaccination awareness	0.161580	0.437350	Vaccination awareness	0.162059	0.558797

Table 1.
Results of Cronbach’s α calculation.

4.2.3 Allocation of interviewees according to the “per capita income”

Data for the “per capita income” item were taken from the website of the Statistics Committee of the Ministry of National Economy for the fourth quarter of 2014 (data on the standard of living, www.statgov.kz). The amount of the subsistence minimum determining the poverty line was within or slightly more than 100 USD (according to a currency rate).

Overall, three grades were allocated: from less than 100 USD per month up to 200 USD per capita (category of “poor”), from 200 USD up to 500 USD per capita (category of “satisfactory income”), and from 500 to 1000 USD and higher (the category of “relatively well-off people”). Allocation of the respondents in this questionnaire (“poor,” “satisfactory income,” “well-off”) was made based on statistical publications on the standard of living formed on the basis of a sample survey of households and posted on the website of the Statistics Agency of the Republic of Kazakhstan (“Monitoring of incomes and living standards of the population in the Republic of Kazakhstan”. Analytical notes of the Agency of the Republic of Kazakhstan on Statistics of the Department of Labor and Living Standards. Astana, 2011–2013). Based on the above information, it was decided to calculate per capita income within the twofold subsistence minimum amounting to 200 US dollars, as a threshold of a relatively satisfactory income, and revenue of 500–1000 USD as a threshold of a conditional “well-off income.”

4.2.4 Survey conducting

Direct interviews have been held on site by the research team without participation of the local staff for providing a better confidentiality of the information obtained. To motivate a better veracity, researchers allowed not to indicate a real name and provided relevant explanations on filling in the most “problematic” items—smoking, number of sexual partners, and income. At the same time, active assistance to interviewees when filling in the questionnaire was not permitted.

4.3 Results and discussion

A total of 1166 clinically healthy and 65 having CaCx women were interviewed across the region. A set of data on the survey across both samples, including descriptive statistics, is presented in **Table 2**.

Some obtained data have been cross-checked through the available sources. Information on such indicators as the age of sexual debut, number of pregnancies, specific gravity of smokers, and number of women who use BCPs has been presented in the mentioned report on Kazakhstan by the ICO group on monitoring cervical cancer [7]:

- Average age of sexual debut in women in the Republic of Kazakhstan—20.7 (20.8 in the present survey)
- Average number of pregnancies—2.7 (3.0 in the present survey)
- Total number of women applying birth control pills—7.1% (4.8% in the present survey)
- Total number of smoking women—9.5% (10.8% in the present survey)

Parameters (the questionnaire items)	Cronbach's α for each item	Detailing	General sample, N 1166	CaCx sample, N 65	Notes
Age categories	0.54	18–29	37.7%	1.5%	
		30–39	34.0%	21.9%	
		40–49	17.8%	34.4%	
		50–60+	10.5%	42.2%	
Average age of the interviewees					
General sample: 34.5 \pm 9.9 (31.2;36.1, 95% CI) Range 16.0–63.0 M 33.0 (27.0–41.0 by 25/75 quartile)			CaCx sample: 49.0 \pm 12.4 (45.9;52.1, 95% CI) Range 28.0–80.0 M 47.5 (40.0–58.5 by 25/75 quartile)		
Ethnicity	0.56	“Asian”	85.3%	79.7%	Representatives of Turkic-speaking people
		“European”	13.6%	20.3%	Representatives of the Slavic diasporas, Germans
		Other (mostly Caucasus ethnic groups)	1.1%	—	Azerbaijanis, Dagestanis, Koreans, etc.
Education level	0.51	School education	31.4%	65.6%	
		Professional college	22.9%	17.2%	
		Higher education (university)	45.7%	17.2%	
Employment	0.50	Not occupied	33.6%	48.4%	Unemployed, housewives, retired
		Low-skilled labor	13.7%	26.5%	
		Medium-sized proficiency sector	20.7%	9.4%	
		Highly-skilled occupations	32.0%	15.6%	
Monthly income per capita	0.50	From less than 100 USD and up to 200 USD	40.1%	50.0%	Category of “poor” people
		From 200 USD up to 500 USD	39.4%	46.9%	Category of “satisfactory income”
		From 500 to 1000 USD and >	20.5%	3.1%	Category of relatively well-off people
Total number of pregnancies	0.59	None	10.7%	3.1%	This refers to childbirth, abortion, ectopic pregnancy
		1–2	36.1%	25.0%	
		3 and more	53.2%	71.9%	
Average number of pregnancies in the history					
General sample*: 3.0 \pm 2.2; range 0–16; M 3.0 (2.8–4.4 by 25/75 quartile)			CaCx sample: 4.5 \pm 3.3; range 0–14; M 4.0 (2.0–6.0 by 25/75 quartile)		

Parameters (the questionnaire items)	Cronbach's α for each item	Detailing	General sample, N 1166	CaCx sample, N 65	Notes
Presence of close relatives with CaCx	0.57	Yes	5.1%	9.4%	Irrespective to the time period: at present or in the past
		No	94.9%	90.6%	
Age of onset of sexual activity					
General sample*: 20.8 \pm 3.4 Range 13.0–45.0 M 20.0 (18.0–22.0 by 25/75 quartile)		CaCx sample: 20.3 \pm 2.3 (19.4;20.8, 95% CI) Range 19.0–21.0 M 20.0 (15.0–27.0, 25/75 quartile)			
Lasting of sexual life	0.53	0–10 years	47.2%	3.1%	Regardless the marriage or relationship lasting
		11–20 years	29.9%	31.3%	
		20+ years	22.9%	65.6%	
Average lasting of sexual life					
General sample: 13.5 \pm 9.2; range 1.0–45.0 M 12.0 (6.0–20.0)		CaCx sample: 26.5 \pm 10.8 (23.3;29.7, CI 95%) M 22.0 (7.0–59.0)			
Number of sexual partners during life	0.54	1 partner	64.7%	60.9%	Regardless of the relationship lasting
		2–5 partners	28.2%	28.1%	
		6 and more	7.1%	10.8%	
Average number of sexual partners during life					
General sample: 2.2 \pm 2.9 (1.9;2.7, CI 95%); range 1–30			CaCx sample: 3.0 \pm 3.4 (2.1;3.9, CI 95%); range 1–15		
Current application of contraceptive methods (at the time of interview)*	—	I do not apply	43.8%	89.0%	Only the age category \leq 49 years old was considered
		Birth control pills*	4.8%	—	
		IUD (intrauterine device)	12.4%	4.7%	
		Condoms	23.0%	6.3%	
		Other (tubal ligation, calendar method, coitus interruptus)	16.1%	—	
Attitude toward smoking*	0.56	I smoke (smoked)	10.8%	9.4%	Regardless of the smoking lasting
		I do not smoke	89.2%	90.6%	
Attendance of municipal PHC facilities (outpatient clinics at the place of residence)	0.53	I visit constantly	40.7%	31.3%	
		I visit sometimes, irregularly	46.3%	39.0%	
		I do not visit, as I attend only private clinics	13.0%	29.7%	
Participation in the nationwide screening program for cervical cancer (in state-sponsored clinics)	0.60	I participate constantly	34.7%	39.0%	Age category < 30 years old was not considered as not included in the screening routine
		I participate irregularly (missed the last/	28.0%	15.6%	

Parameters (the questionnaire items)	Cronbach's α for each item	Detailing	General sample, N 1166	CaCx sample, N 65	Notes
Awareness of vaccination against cervical cancer	0.58	previous examination)			
		I do not participate (ignore, as I attend gynecologists in private clinics only	37.3%	45.3%	
		I know nothing about vaccination	38.8%	60.9%	
		I have heard about vaccination, but do not know how to percept	33.6%	25.0%	
		I welcome vaccination against cervical cancer	22.9%	10.9%	
		I am set against vaccination/I consider it unnecessary/dangerous	4.7%	3.1%	

**An asterisk indicates some indicators of general sample, for which there are republic-wide data from other sources.*

Table 2.
Total data for both samples across the region with inclusion of descriptive statistics.

In another authoritative source [50], published in the framework of the UNICEF international research and summarizing data of the Republic of Kazakhstan on many medical and social indicators, the share of women 15–24 years old who had sexual intercourses with the “unofficial partner/partners” (promiscuity) during the last year was 16.6%, while the proportion of smoking women aged 15–49 years—8.4%.

Overall, data from these authoritative sources in fact coincided with those obtained in the present work, which to a definite extent might indicate reliability of the information provided by participants of the interview.

4.3.1 Social profile of women infected with HPV in the western region of Kazakhstan

A total of 25% of women from the general sample in frames of the present research appeared to be infected either with HR-HPV types or with non-HR types (22.3; 27.7 CI 95%, $p = 0.05$), N 291. One of the tasks of the present study was to compare those infected with HPV with those who are not infected in order to identify links between the risk for HPV infection and social/behavioral parameters. Results of the analysis are presented in **Table 3**.

This analysis made it possible to outline the social profile of women infected with HPV in the western region of the country. These are women with satisfactory financial status (monthly per capita income 200–500 USD), occupied with highly skilled work, who had up to five sexual partners and more than three pregnancies in

№.	Parameter or potential risk factor	Achieved level of significance, p-value (≤ 0.05)	Cramer's V value	Maximum contribution to the final statistics, Pearson's χ^2
1	Age	0.062	0.09	—
2	Ethnicity	0.78	0.03	—
3	Education	0.4	0.05	—
4	Employment	0.002	0.11	χ^2 —18.03 9.1% out of 25.0% HPV-infected are representatives of highly skilled occupations
5	Level of per capita income	0.00007	0.13	χ^2 —19.1 12.1% out of 25.0%—a group with an income of 200–500 USD per month per capita (“satisfactory income”)
6	Number of pregnancies	<0.00001	0.14	χ^2 —24.0 11.2% out of 25.0% had three and more pregnancies
7	Presence of close relatives with CaCx	0.52	0.02	—
8	Sexual life duration/age of onset of sexual activity	0.062	0.07	—
9	Number of sexual partners	<0.00001	0.16	χ^2 —30.7 23.5% out of 25.0% had up to five partners
10	Application of birth control pills	0.33	Phi 0.00096	—
11	Smoking	0.47	0.02	—
12	Municipal outpatient clinic attendance	0.46	0.02	—
13	Participation in screening program	0.19	0.05	—
14	Awareness of vaccination	0.54	0.03	—

Table 3.
Analysis of the links between HPV infection and social/behavioral parameters.

their history. These women constitute a group at risk for further development of the process, i.e., persistent infection and possible invasive cancer. Increasing awareness of CaCx prevention among young women should rank first in making policy concerning CaCx issues.

4.3.2 Relationship between the level of education and perception of CaCx preventive measures

Further analysis has been performed with the aim of clarifying the relationship between the level of education and perception of preventive measures for cervical cancer. As mentioned before, attendance of state (municipal) PHC facilities implies accessibility and sufficiency of a national free healthcare. In a broad sense, opportunity to attend state-sponsored free outpatient clinics is also to be considered as a prevention of socially significant diseases.

In the general sample (**Table 1**), only 13% of respondents indicated that they do not visit state-sponsored clinics at the place of residence, while among respondents with higher education, this indicator has increased up to 35.1% ($p \leq 0.00001$; Cramer's V 0.14; χ^2 -23.1). Only 62.7% of interviewees (34.7% constantly and 28.0% sometimes) respond to an invitation to visit free screening in state (municipal) facilities, and 37.3% of respondents do not attend free screening program at all, preferring either opportunistic screening in private physicians or not undergoing Pap test at all. Among the educated subjects, this indicator has increased up to 51.3% ($p = 0.002$, Cramer's V 0.1, χ^2 -18.1). Among respondents in the general sample, 40.7% regularly visit the state PHC facilities, but only 34.7% of all interviewees treat toward screening activities responsibly.

More than two-thirds (69.2%) of subjects with higher education are aware of vaccination against cervical cancer ($p \leq 0.00001$, Cramer's V 0.18, χ^2 -23.1), whereas in the total sample, this figure amounted to 56.5% (33.6% have heard, but cannot clarify their attitude—positive or negative, 22.9% are aware and welcome).

Ideally, close to 100% of educated subjects of this research had to welcome mass screening and nationwide immunization program against cervical cancer. For example, according to a large-scale survey conducted in Brazil ($n = 54,000$), a high correlation was found between the level of education/standard of living and the attendance of mammography and cytology (Pap test): up to 70–80% of educated interviewees constantly visited screening events— $r = 0.52$ and $r = 0.66$, respectively [51]. In general, Kazakhstan belongs to a group of countries with high Human Development Index (HDI). According to the results of HDI evaluation in 2016 [52] when these data were collected, our country ranked 56th in the international rating between Belarus and Malaysia.

Given the relatively high HDI of the country with a large stratum of enlightened women, the findings suggest that measures for primary (vaccination) and secondary (screening) prevention of cervical cancer are insufficient and do not meet the needs of population, especially of its educated part. The same applies to situation with municipal PHC facility attendance (35.1% of educated subjects avoid visit and 51.3% of them avoid free screening there). In this context, relatively low attendance found in the present survey in educated population can be indicative of unsatisfactory quality of services, which eventually may result in bringing down a prestige of the national healthcare.

4.3.3 Overall awareness of CaCx preventive measures: role of information sources

Overall awareness of the broad circle of the issues on CaCx prevention varies depending on the countries, age groups, and education level. Though 71–78% adults aged 50–70 in England knew that the main aim of the screening programs was to catch cancer early, but only 18% of them were aware that cervical screening is primarily preventive [53]. The low level of Pap screening awareness was found among the students in South Korea [32], about 65% female Saudi teachers were considered less-knowledgeable about CaCx risk factors [33], only 13% of interviewed Uyghur women heard about vaccine against CaCx [34], and 30.1% of female students in Poland were unaware of vaccination as a prevention method [44]. In the present research, the obtained data on awareness of vaccination in general sample are approximately similar with the mentioned: 38.8% knew nothing about vaccines against cervical cancer, while 33.6% heard, but could not decide how to percept it. These findings evidence a deficit of information apprehensible for a majority of female population.

A trend, to a definite extent confirming the mentioned TPV model, according to which most of people in issues of health are guided by opinion of significant others

showing to them more favorable attitude (close relatives, etc.), might be traced in findings of the present survey. A group of interviewees which collided with cervical cancer in their families were analyzed in order to compare their awareness with a baseline level in general sample. Among relatives of women who fell ill or died from cervical cancer, the awareness of vaccination has reached 76.8% ($p = 0.01$, $\phi 0.1$, $\chi^2 - 6.0$), i.e., even higher than in the stratum of highly educated interviewees (69.2%), which implied that a part of them purposefully had sought information regarding prevention/treatment of CaCx. These findings involve the issues on information sources. According to the mentioned survey conducted across the country's households [50], a share of women aged 15–24 which use the Internet (social networks, messengers) is 94.6%, while the proportion of women aged 15–49 years, at least once a week consuming mass media (newspapers, magazines, radio, TV), is only 16.1%. Results of this research concerning preferences in information seeking in young women would be worth to arrange CaCx prevention awareness campaign via the Internet across the country.

4.4 Cervical cancer-diseased women in the western region of Kazakhstan: likelihood of the disease onset

A total of 65 women aged in average 49.0 ± 12.4 diseased with CaCx (just diagnosed and not yet undergoing treatment) have been interviewed during a survey. Overall description of this sample has been summarized in **Table 1**. What is the most inherent to them comparing to the general sample: most of them (65.6%) have just school education (compulsory for all population in Kazakhstan) vs. 31.4% in the general sample, the share of the employed in highly skilled occupations is 15.4 vs. 32% in the general sample, only 3.1% of them refer to a “relatively well-off” in terms of income, a part of them never visited municipal PHC facilities (31.3%) vs. 13% in the general sample, and they never heard about vaccination (60.9%) vs. 38.8% of clinically healthy women, respectively.

In order to reveal the dominant risk factors for cervical cancer and select a control group, matching was conducted among those infected with HPV but not affected with cervical cancer and those having CaCx. Matching was carried out in proportion 1:1 (65 vs. 65), i.e., for each case of the disease, there was one case from the control group. Selection of the control group for matching was made according to the age criterion and also with the help of the random number generator, i.e., each HPV-infected had equal chances to get into the control group. Thus, 65 respondents from HPV-infected group were randomly selected for analysis to identify risk factors.

An analysis of the Pearson χ^2 contingency tables to identify significant links (including the Cramer's V criterion) is shown in **Table 4**.

Table 5 presents results of the Mann-Whitney test, detailing the analysis of quantitative variables.

Thus, social profile of women with CaCx was defined: they are mostly aged 50–60 + years old, in overwhelming majority infected with HPV 16, poorly educated, unemployed, mostly living within the poverty line, with lasting of sexual life over 20 years, not participating in the screening program, and not aware of the cervical cancer prevention measures (vaccination). A large number of pregnancies and high level of viral load also mattered in their profile.

To assess the likelihood of the disease onset, a logistic regression model was developed. As a “positive effect,” the onset of the disease was accepted, and as a “negative effect”—the absence of cervical cancer. The logistic regression was performed by the “forward” method, provided that the variables were introduced, if $p < 0.05$, and removed, if $p > 0.1$. The sample size was 130 cases, where 65 (50%)

№.	Qualitative parameter or potential risk factor	Achieved level of p-value (≤ 0.05)	Cramer's V criterion	Maximum contribution to the summary statistics, Pearson's χ^2
1	Age	0.003	0.29	11.3—age 50–60+
2	Ethnicity	0.5	0.09	1.19
3	Education	0.00075	0.33	14.4—poorly educated
4	Employment (occupation)	0.00053	0.37	17.6—not employed (unemployed, housewives, retired)
5	The level of per capita income	0.001	0.33	13.6—low income
6	Number of pregnancies	0.23	0.15	2.9
7	Presence of close relatives with CaCx	0.13	0.13—phi	2.2
8	Sexual life duration	0.007	0.28	9.9—over 20 years
9	Number of sexual partners	0.19	0.16	3.3
10	Methods of contraception	0.32	0.007	0.0009
11	Smoking	0.97	0.002	0.0007
12	Attendance of the state clinics	0.09	0.19	4.8
13	Participation in screening program	0.006	0.28	10.2—not participating in screening program
14	Awareness of vaccination	0.026	0.27	9.2—not aware of vaccination
15	Type of HPV*	0.00007	0.35—phi	15.9–72.6% of women with CaCx are infected with typ. 16

* For other genotypes of HPV p-value 0.05 has not been revealed.

Table 4.
Results of contingency table analysis.

were positive and 65 (50%) were negative ones. The logistic regression model was evaluated through the Nagelkerke R^2 (0.3881, $p < 0.0001$) and recognized “working.” Coefficients, standard errors, and a chance, including the odds ratio (OR), have been calculated by commonly accepted methods, and the risk group for CaCx begins at a value >40 . Results are summarized in **Table 6**.

Thus, likelihood of the disease onset:

- Decreases by 14 times at a per capita income level of 500–1000 USD + (category of relatively well-off)
- Increases by 0.9 times with the lasting of sexual life over 20 years
- Increases by 0.16 times provided lack of attendance in the state (municipal) clinics
- Decreases by 3.3 times provided at least irregular participation in screening for cervical cancer

Calculation of the morbidity prognosis based on OR in both groups (HPV-infected but not affected with CaCx and having CaCx) was performed.

Variables	U Mann-Whitney test							
	Criteria are significant at the level of $p < .05000$							
	Summary rank CaCx	Summary rank control	U	Z	p-Level	Z correct.	p-Level	Two-sided exact p
Age	4931.5	3453.5	1308.5	3.63184	0.000281	3.63469	0.000278	0.000233
Age of onset of sexual activity	3845.0	4540.0	1765.0	-1.48147	0.138482	-1.49867	0.133960	0.138856
Number of partners	4049.5	4335.5	1969.5	-0.51816	0.604346	-0.56433	0.572531	0.603861
Duration of sexual life (exposure)	4955.0	3430.0	1285.0	3.74254	0.000182	3.74551	0.000180	0.000148
Number of pregnancies	4595.0	3790.0	1645.0	2.04674	0.040685	2.06837	0.038606	0.040401
Viral load level	4785.0	3600.0	1455.0	2.94174	0.003264	2.94231	0.003258	0.003057

Table 5.
Results of the Mann-Whitney test.

Variables	Coefficient	Std. error	Wald	p	OR	95% CI
Income per capita 500–1000 USD + (3)	−2.64144	0.86882	9.2432	0.0024	0.0713	0.0130–0.3912
Sexual life lasting >20 years (3)	0.083917	0.023797	12.4349	0.0004	1.0875	1.0380–1.1395
Attendance of state clinics (lack of attendance) (3)	1.80433	0.63020	8.1974	0.0042	6.0759	1.7667–20.8954
Participation in screening (irregular) (2)	−1.08362	0.50041	4.6892	0.0304	0.3384	0.1269–0.9023
Constant	−1.69108	0.58494	8.3581	0.0038		

Table 6.
Calculation of a chance and OR for the disease onset.

Overall, prognosis is justified for 73.9% infected with HPV, but not affected by cervical cancer and for 70.3% for women having CaCx (correctly predicted cases—72.09%, at a cutoff value of $p = 0.5$).

4.5 What was learned from a survey on cervical cancer risk factors in Western Kazakhstan

Based on the data collected in 1166 clinically healthy women, of them 291 (25%) infected with HPV, and 65 women having cervical cancer, one may conclude that the main reason for a chance of the CaCx onset is a low understanding on what are the measures of preventing CaCx.

Only 34.7% of interviewees constantly participate in nationwide screening program, while 37.3% fully ignore nationwide screening in free state-sponsored PHC facilities. Favorable attitude toward vaccination against cervical cancer stated 22.9% of respondents, whereas 38.8% knew nothing, and the rest 33.6% could not clarify their position in this issue.

Education is a key factor for better perception of preventive measures—more than two-thirds of respondents with higher education are aware of vaccination against cervical cancer ($p \leq 0.00001$, Cramer’s V 0.18, χ^2 –23.1).

And meanwhile, the same stratum of educated women mostly negatively treats to state-sponsored PHC facilities, avoiding visit (35.1 vs. 13.0% in the general sample, $p \leq 0.00001$, Cramer’s V 0.14, χ^2 –23.1). Moreover, 51.3% of educated women avoid nationwide free screening in state PHC facilities ($p = 0.002$; Cramer’s V 0.1; χ^2 –18.1). This fact evidences insufficient quality of medical care in state-sponsored clinics.

Lack of relevant information on the CaCx in interviewees who had close relatives with CaCx made them seek and eventually reach a higher awareness level concerning preventive measures—76.8% vs. 56.5 in the general sample ($p = 0.01$, phi 0.1, χ^2 –6.0). These findings evidence a deficit of information apprehensible for a majority of the female population.

Though a more number of sexual partners contributed to the risk of being infected with HPV ($p \leq 0.00001$, Cramer’s V 0.16, χ^2 –30.7), but this factor played no role in the risk of CaCx development. Overall, social profiles of HPV-infected and CaCx-affected women differ significantly and, mainly, by standard of living and occupational status.

Social profile of women having CaCx is mostly aged 50–60 + years old, in overwhelming majority infected with HPV 16 (72.6% of them), poorly educated, unemployed, mostly living within the poverty line, with the sexual life lasting over 20 years, not participating in the screening program, and not aware of the cervical

cancer prevention measures (vaccination). A large number of pregnancies and high level of HPV viral load also mattered in their profile.

The likelihood of the CaCx onset under conditions of Western Kazakhstan decreases by 14 times at relatively high standard of living, income not less 500 USD per capita (OR 0.0713, $p = 0.024$) and decreases by 3.3 times provided at least irregular participation in screening for cervical cancer (OR 0.3384, $p = 0.0304$).

Overall, the findings suggest that measures for primary (vaccination) and secondary (screening) prevention of cervical cancer are insufficient and do not meet the needs of the population, especially of its educated part.

5. General conclusion

Findings obtained in this first survey arranged in Kazakhstan are quite generalizable for post-Soviet Central Asian states and, to a lesser extent, for the overwhelming majority of Asian developing countries with high incidence of CaCx. These findings are quite able to contribute to an understanding why women become diseased with CaCx. Low standard of living due to lack of education, low attendance of screening, and low awareness on preventive measures, all these reasons, are interacted and constitute a set of universal triggers for vulnerability toward CaCx.

Kazakhstan is not an exclusion within a wide range of middle-income countries, which need drastic changes in approach to prevent cervical cancer and in revision of a set of applied measures. Population-based surveys, being a very effective tool for studying needs of the targeted audience, should serve as the first step toward diagnostically optimal and cost-effective updated nationwide program for the CaCx prevention.

Elaboration and implementation of a new program should focus on a significant increase of awareness in female population on cervical cancer consequences and a role of HPV infection as a causative factor.

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Conflict of interest

All authors declare that they have no competing interests.

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