ISRCTN71514910 https://doi.org/10.1186/ISRCTN71514910

Epidemiological analysis of human papillomavirus in western Kazakhstan in relation to HPV-attributable cervical pathology – social, clinical and genetic aspects

Submission date
03/12/2017

Recruitment status
No longer recruiting

Registration date
02/01/2018

Overall study status
Completed

Last Edited
24/02/2023

Condition category
Cancer

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
It's widely known that some types of Human Papillomavirus (HPV) lead to the development of cervical cancer. Researchers refer to especially dangerous types of the virus as high risk (HR-HPV). Due to the ability of HPV to constantly evolve, this HR-HPV group tends to extend. Many countries have developed national screening programmes to prevent cervical cancer. Such programmes were previously usually based on cytological (smear test) findings, but recently most advanced countries changed to HPV-oriented screening because of its effectiveness in early prevention of the disease. However, despite the increasing number of cervical cancer cases in Kazakhstan during recent decades, issues of the scope of HPV still remain unknown. Adopted by the government in 2008, the national screening programme based on cytological methods also needs to be revised firstly because of its ineffectiveness and in order to bring it to the current world standards. Thus, this study first aims to recruit women across the western region of Kazakhstan to reveal the real scope of HPV with detection of leading types and average viral load, and then compare women infected with HPV but not affected by cervical cancer vs. women with cervical cancer in order to find out the most significant risk factors of the disease. The second aim of the study, but not less important, is to assess the widely used screening methods, as such an evaluation has not been done yet. As mentioned above, overall two methods are running in Kazakhstan: a conventional method, mostly used in opportunistic screening, and a method adopted in 2013 that uses the South Korean CellScan technology. Data on HPV presence in smears referred to normal cytology will be collected. It is hoped that this will prove there is a need to change to a HPV-based method of cervical cancer screening, given its reliably proven effectiveness worldwide. The eventual goal of this study is to develop a package of measures to decrease the fast growing number of cervical cancer cases at least in the western region of the country.

Who can participate?
Women aged 18 to 60 who attend gynaecologists in PHC institutions of all types (state-sponsored, insurance and private clinics), and women with just (first time) diagnosed cervical cancer (no age limits)

What does the study involve?
Participants are asked to visit a researcher only one time. All participants (women from the general population and women with just diagnosed cervical cancer) fill in a questionnaire, undergo a smear test for HPV (two smears in those with cervical cancer), and two smears for cytology, after which a researcher performs a colposcopic examination (not indicated for women with cervical cancer in the developed stage).

What are the possible benefits and risks of participating?
There is no immediate direct benefit to those taking part, but there should be benefits to finding out their HPV status free of charge (unfortunately HPV tests are not provided free of charge in Kazakhstan), including their cytological status and colposcopic data. There are no risks of undergoing such an examination and filling in the questionnaire. To obtain the most truthful answers during the interview, the local staff is asked to come out from the office and the interviewees are guaranteed confidentiality of the information provided.

Where is the study run from?
The study is being run by the West Kazakhstan Marat Ospanov State Medical University and takes place in state-sponsored, insurance and some private PHC institutions, including regional oncological dispensaries, across the western region of Kazakhstan (four provinces – Aktobe, Uralsk, Atyrau, Mangystau)

When is the study starting and how long is it expected to run for?
April 2015 to December 2017

Who is funding the study?
Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
0115PK01224

Study information

Scientific Title
Epidemiological analysis of human papillomavirus in western Kazakhstan in relation to HPV-attributable cervical pathology – social, clinical and genetic aspects

Study objectives
Given the growing cervical cancer (CC) incidence rate in the western region of Kazakhstan, a high prevalence of HR-HPV types, along with insolvency of the basic screening tools and approaches are expected.

Rationale of this study: a high incidence of the CC (32.8 per 100,000 female population) is observed in the Republic of Kazakhstan in spite of the CC screening program, which was financially supported by the government, therefore this situation needs to be comprehensively evaluated in order to explore the shortcomings of the CC screening program and find solutions for this problem.

To achieve the goal and solve the problems posed in this work, a combined design was used that included 3 components: a survey and a cross-sectional study in the general female population of the Western region of Kazakhstan, and a cervical cancer case-control study, where women from the cross-sectional study of the same age infected with HPV but not affected by CC serve as a control for the CC cases.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West Kazakhstan Marat Ospanov State Medical University's Institutional Review Board, 10/09 /2014, Protocol No. 3

Study design
Survey, cross-sectional study and case-control study

Primary study design
Observational

Secondary study design
Cross sectional study

Study setting(s)
Hospital

Study type(s)
Screening

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Cervical cancer

Interventions
Overall, two large groups for comparison are provided by the cross-sectional study: HPV carriers vs. not HPV-infected subjects with consequent analysis of all aspects: data on risk factors obtained by the interview; cytological data compared in groups HPV carriers vs. not HPV-infected subjects with adequate analysis of HPV findings amongst normal cytology and further towards CIN-III. Data on different methods (LBC CellScan vs. conventional cytological method) are compared, involving all obtained histological findings and colposcopic data with accomplished biopsy when supposed CIN.

The cross-sectional study and survey amongst general female population aged 18-60 is conducted on the basis of medical institutions (outpatient clinics). For scope different categories of patients to achieve maximally representative sample and minimize possible bias, state, insurance and private medical organizations are included. Women are recruited from the general population living in the region of Western Kazakhstan - in cities of regional importance, small towns, suburbs and immediate neighborhoods.

For the case-control study, all consonants to participate in the study are selected amongst women with a newly diagnosed cervical cancer, on the basis of the regional oncologic dispensaries. Randomisation is not performed. The design of the CC case-control study also suggested conducting a survey to identify the role of the main risk factors for cervical cancer, a

similar taking of the material for HPV PCR-typing and for cytological testing using LBC and traditional methods (Romanovsky-Giemsa). Colposcopy was not performed when the advanced stages of cervical cancer.

The algorithm for women examining:
1. Compiling the patient's socio-behavioral profile by filling in a specially developed questionnaire, only after the signing of the Informed consent form (developed in two languages, optional). The questionnaire is developed in a semi-structured manner, with questions, mostly closed, to collect data reflecting the role of known risk factors in the development of cervical cancer.
2. Collection of material for PCR-typing of HPV and determination of viral load for each identified type.
Qualitative detection and quantification of human papillomavirus by PCR is performed with HPV Kvant-21 test systems (DNA-Technology LLC, Russia) using equipment: DT-prime4-M1 detection amplifier, serial number A5D409 LLC "DNA - Technology", software version V 7.6. Production of the company "DNA-technology" is certified (ISO 13485: 2012) and registered in the Republic of Kazakhstan (RK-MT-7-No. 013267 dated July 23, 2014).
Characteristics of the test systems used in the study:
Kit of HPV reagents Quantum-21 (the same production) is designed to identify, typing and quantifying the DNA of low-risk human papillomavirus (HPV 6, 11, 44) and possibly / potentially / high (HPV 16, 18, 26, 31, 33 , 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) carcinogenic risk.
3. Sampling of the smear for cytological examination by the methods of liquid (CellScan) and traditional cytology (Romanovsky-Giemsa coloring).
4. Colposcopic exam and entering information into the database.
The same algorithm is provided for the women with newly diagnosed cervical cancer enrolled for the case-control study. Besides, HPV L1 gene sequencing in the group of the women with newly diagnosed CC is covered by the CC case-control study.

Calculation of sample (N) for interview and cross-sectional study
In determining the sample, the following points mattered:
1. According to a pilot study of the West Kazakhstan University on HPV as of 2013-2014, N for HPV typing was 1098, with valid statistical results
2. From the republican statistical data as of 01/01/2014 the township female population (capitals of the provinces, suburbs and small towns) was taken from 4 provinces of Western Kazakhstan. In total, N according to calculations in the program SAS.9.3 (two-side type I error of p 0.05, CI 95%) was 1152, of which 417 in Aktobe, 253 in Uralsk, 237 in Atyrau and 245 in Mangystau.

The sample size for the CC case-control study was calculated using the formula, where $Z_{(\alpha)} = 1.96$ - critical values of the normal standard distribution for a given $\alpha = 0.05$; N - number of female population of the republic (6700000); $p = 0.048$ - incidence of cervical cancer; $q = 1-p = 0.952$; $\Delta = 0.05$ - sampling error. According to calculations, the sample size should be 64-67 people in each group (case/control).

In order to select a control group and find the dominant risk factors for cervical cancer, matching of those examined who infected with HPV but not affected by cervical cancer from the general population (cross-sectional study) has been performed. Matching was carried out at a scale of 1: 1 (71 vs. 70), i.e. for each case of the disease there was one case from the control group. Selection of the control group for the matching was made according to the age criterion, and also with the help of the random number generator, i.e. each infected person had equal chances to get into the control group

Since the type of research is cross-sectional, there is no further follow-up. All interventions in the group of general female population (N 1152 by calculations and 1166 eventually) and in the group of the women with first time diagnosed cervical cancer (N 64-67 by calculations and 71 eventually) are being conducted during the only visit.

Intervention Type
Other

Primary outcome measure
All outcomes measured at the single study visit:
1. Total HPV prevalence and in the each province of the region
2. Average viral load in HPV carriers, both in general population and in CC diseased
3. HPV leading types in general population and in CC diseased
4. % of women-carriers of HR-HPV genotypes in each age category
5. % and distribution of HPV different types in normal cytology
6. The most significant risk factors for the CC implementation
7. Probability of cervical cancer decrease (odds ratio)

Secondary outcome measures
All outcomes measured at the single study visit:
1. Results of comparison of two cytological methods operating in the region (amount of non-informative material by each method; degree of concordance with histological conclusions in each method; results of ROC analysis; Kappa statistics)
2. Colposcopic data – correlation between HPV viral load and points of the RCI (Reid colposcopic index)
3. Overall trend of CC morbidity in the region and in each age category
4. CC prognostic incidence for the nearest period
5. Detection of various HPV gene L1 isolates circulating in the region

Overall study start date
01/04/2015

Completion date
31/12/2017

Eligibility

Key inclusion criteria
Inclusion criteria for the cross-sectional study:
1. Age 18-60 years
2. Presence of pathology of the cervix of any degree of severity, including minimal, suitable for colposcopy
3. Resident of Western Kazakhstan of any ethnicity
4. Absence of vaccination in the anamnesis

Inclusion criteria for the case-control study:
1. All consonants to participate in the study were selected amongst women with a newly diagnosed cervical cancer
2. Any age
3. Any stage of the process
4. Histological verification of the diagnosis

Participant type(s)
Mixed

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
Female

Target number of participants
Cross-sectional study: 1152 (actual 1166); case-control study: 67 cases (actual 71) and 70 controls

Total final enrolment
1166

Key exclusion criteria
Exclusion criteria for the cross-sectional study:
1. Non-residents
2. Vaccinated
Note: HIV, 1 trimester pregnancy till 10-11 weeks are not exclusion criteria

Exclusion criteria for the case-control study:
1. Non-residents of Western Kazakhstan
2. Previous medical intervention - radiotherapy, chemotherapy, surgical treatment

Date of first enrolment
01/04/2015

Date of final enrolment
01/09/2017

Locations

Countries of recruitment
Kazakhstan

Study participating centre
West Kazakhstan Marat Ospanov State Medical University
Aktobe, 68, Maresyev Street
Aktobe
Kazakhstan
030019

Study participating centre
In Aktau: state outpatient clinic No. 1 (affixed register - 114000) and No. 2 (affixed register - 91649), as well as in the regional oncological dispensary, in the medical insurance company “Intertich”, and in the private clinic “Cha-Kur”
Aktau
Kazakhstan
130000

Study participating centre
In Atyrau: in the state outpatient clinic No. 1 (AR - 57186), No. 2 (AR-46000) and No. 7 (AR-35912), as well as in the regional oncological dispensary, in the medical insurance company "Intertich", in the private clinic "Dostar-med".
Atyrau
Kazakhstan
060000

Study participating centre
In Uralsk: on the basis of outpatient clinic No.1 (AR - 70412), No. 5 (AR - 46777), No. 6 (AR - 55704), as well as in the regional oncological dispensary. In the city of Aksai - on the basis of insurance clinics "Intertich" and "Medicare".
Uralsk
Kazakhstan
090000

Study participating centre
In Aktobe - on the basis of the clinical and diagnostic department of the Regional Perinatal Center, in the Medical Center of the University, in the private clinic "World of Women", in the medical insurance company "Intertich".
Aktobe
Kazakhstan
030000

Sponsor information

Organisation
Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan

Sponsor details

Astana city, 8, Mangilik Yel Street, the Ministries House, entrance 11, 10th floor
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Sponsor type
Government

Website
http://sc.edu.gov.kz/

ROR
https://ror.org/03pj6ge82

Funder(s)

Funder type
Government

Funder Name
Committee of Science of the Ministry of Education and Science of the Republic of Kazakhstan (Grant No. 2230/GF4)

Results and Publications

Publication and dissemination plan
Overall at least four large articles are expected to be published in peer-reviewed journals:
1. Description of the protocol of the cross-sectional study in BMC Women's Health journal
2. Description of the results on detection of the overall prevalence of the HR-HPV types in western Kazakhstan throughout the age groups
3. Report on the results of identification of the most significant risk factors responsible for high rate of the CC incidence in the region
4. Report of the results of the comparative analysis of the screening tools used in the country

Besides, elaboration and issue of the methodical recommendations "Management of the women with uterine cervical pathology in PHC institutions given the contemporary data about papillomavirus infection" is expected within the framework of the study.

Intention to publish date
01/07/2018

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Saule Balmagambetova (sau3567@gmail.com).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	30/11/2018		Yes	No
Basic results		04/01/2019	07/01/2019	No	No
Results article	results	29/04/2019		Yes	No
Results article	results	02/05/2019		Yes	No
Results article		20/11/2019	24/02/2023	Yes	No