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Cervical cancer – risk factors, prevention and diagnostic procedures in HPV infections and cervical carcinoma. Epidemiological analysis of morbidity and mortality in Poland and the world in 2012-2018

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Abstract

The following article is an analysis of current literature and the epidemiology of cervical cancer in Poland and the rest of the world over the 2012-2018 period. The analysis is based on reference articles and epidemiological reports from WHO – Cancer Mortality Database, The European Cancer Observatory, The Global Cancer Observatory (Globocan) and from the National Cancer Registry as well as statistical data on HPV vaccination based on the article “Szczepienia ochronne w Polsce”

from the Polish National Hygiene Institute (PZH). Additional information on HPV infections, clinical manifestation, diagnostic procedures, treatment and the state of HPV vaccination was sourced from publications found on databases such as: PubMed, Medline and Google Scholar.

Key words: cervical cancer, HPV infection, HPV prevention, HPV epidemiology, HPV vaccination

Introduction:

Cervical cancer is currently the fourth most common malignant cancer found in women globally in terms of morbidity and seventh most common carcinoma in the general global population. [7,8] The Pap test is available in all gynaecological doctor offices in Poland. Despite widespread prophylactic procedures (Pap tests) for the 25-59 y.o. age group and HPV vaccination, the current methodology does not grant satisfying levels of prevention against the development of advanced cervical cancer. Cervical cancer is most common in the underdeveloped and developing regions of the world, especially in East, Central and South Africa. [1-5] Over 1/5 of all yearly cervical carcinoma cases are diagnosed in India. [10] Annually, Poland accounts for 4, 000 reported cases of cervical cancer. [21]

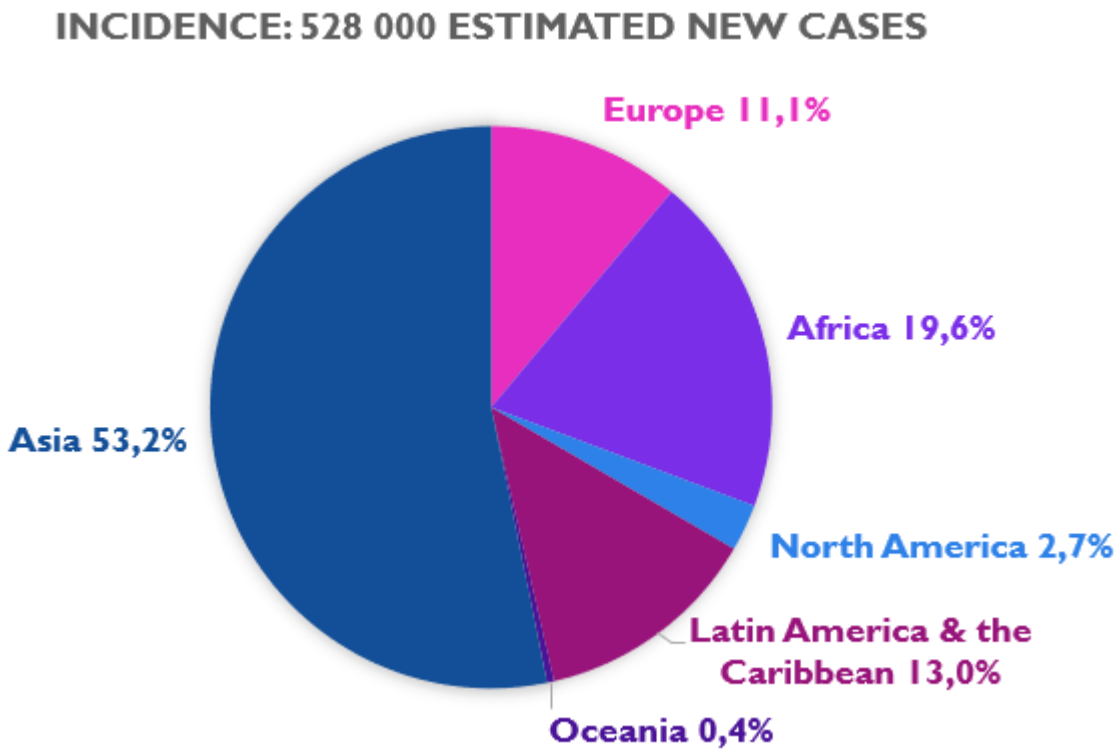

Figure 1. Estimated new cases of cervical cancer by region in 2012

Around 70% of cervical cancer cases are due to HPV infection. There are 200 types of Human Papilloma Virus of which the types 16, 18, 31 and 33 are the most carcinogenic. Globally, the most often detected HPV's in cases of cervical carcinoma are HPV16 (57%) and HPV18 (16%), other commonly detected HPV types include HPV58, 33, 45, 31, 52 and 35. [17] HPV infections are associated with the occurrence of cervical cancer in women, penile cancer in men, anal cancer and nasopharynx carcinoma in both sexes. Currently there are three types of vaccines available: bivalent, quadrivalent and 9-vanlent. The bivalent vaccine prevents HPV16 and HPV18 infection and should prevent the development of 75% of cervical carcinomas and 60% of malignant alterations in cervical tissue. The introduction of vaccines targeting additional types of high risk HPV's will improve prophylaxis against cervical carcinoma. [17] The prevention programs against HPV differ in different countries. The differences concern factors such as the targeted age group, types of vaccines and ways of financing. In Poland HPV vaccines are recommended however they are not refunded. There is a small group of countries where HPV vaccine is mandatory and is refunded. Women who vaccinate against HPV decrease the probability of cervical cancer development by 70%. The necessary actions to be taken in Poland include education and propagation of prevention methods against cervical cancer. The education of children and elders about HPV infection risk factors and sex-education may decrease the morbidity rate of cervical carcinoma in Poland [24, 25]

Epidemiology:

In Europe, in 2012 cervical cancer accounted or 3% of total new cases of cancer and 1% of deaths due to cancer in Europe. According to The European Cancer Observatory (ECO), the average number of new cases of cervical cancer in 2012 was up to 13,4 new cases/100 000 inhabitants/year. The average mortality rate for patients suffering from cervical cancer was 4,9 deaths/100 000 inhabitants/year. [6] In 2012, 53,2% of new cases globally and 53,6% of deaths due to cervical cancer come from Asia. [fig. 1] Reporting new cases is problematic due to the fact that some of the new cases as well as deaths due to CCU are coded as uterine cancer or partly unclassified uterine cancer. [1] Romania, Lithuania and Bulgaria have the highest morbidity rates of the European countries while the lowest morbidity rates are found in Finland, Switzerland and Malta. According to the data collected in 2012, the highest mortality rates due to CCU are found in Romania (14,2), Moldavia (10,3) and Serbia (10,3). The countries with the lowest mortality rates are Malta (1,1), Finland (1,4) and Switzerland (1,6).

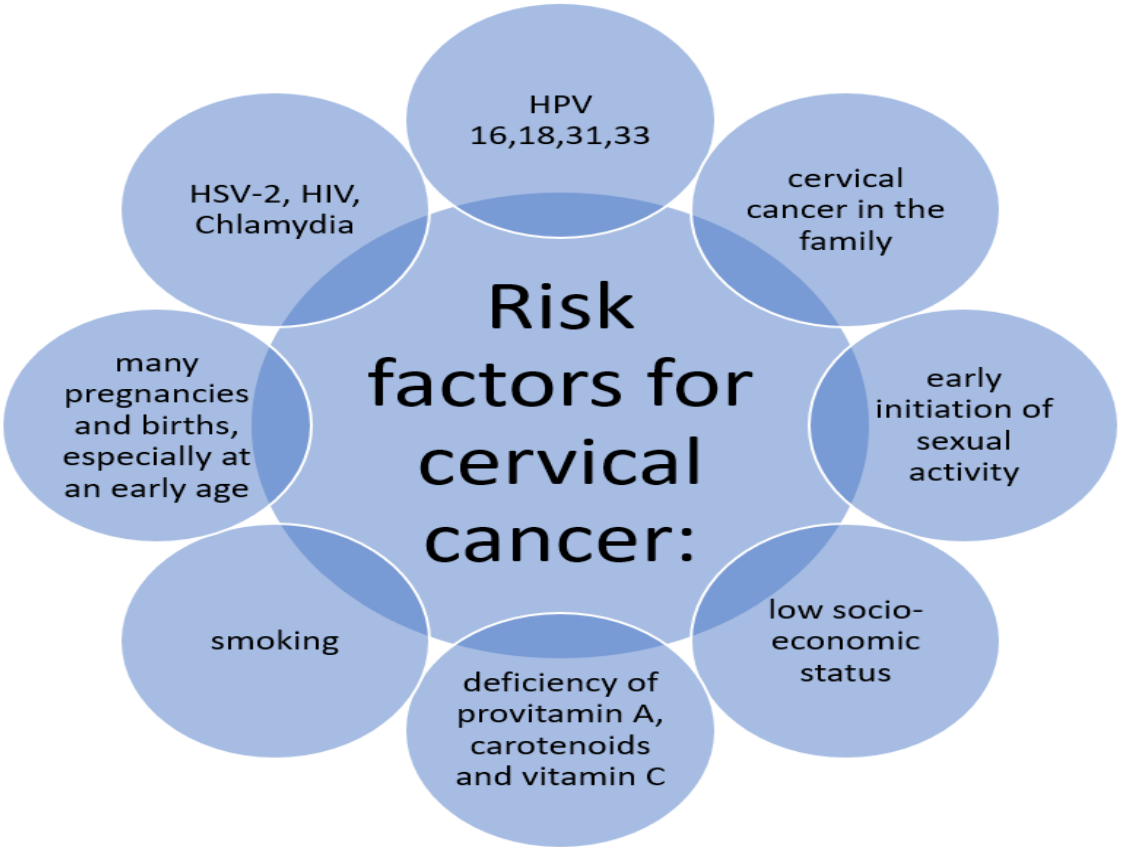

Figure 2. Risk factors for cervical cancer

According to Globocan 2018 data (The Global Cancer Data), cervical cancer made up 3,25% (569 847) of all new global cases of cancer and 3,15% (311 365) deaths due to cancer. [9] The International Agency for Research on Cancer (IARC) estimates that a fifth of men and a sith of women will have cancer during their lifetime and that one in eight men and one in eleven women will die due to cancer. The numbers are bad due to the aging of society and due to the lifestyle of people living in industrialized countries. In comparison to the data gathered in 2012, due to an increase in undertaking prophylactic actions and a change in social factors, the morbidity rates for cervical cancer have dropped in most regions accept for Subsaharan Africa (lack of screening tests and changing sexual behaviours such as a large number of sexual partners, young age of first intercourse, not using condoms, infections by Chlamydia and HSV-2 and HIV viruses which increases the risk of infection by HPV). [10,13, 18] [fig. 2]

Still the morbidity and mortality due to cancer are rising. 2018 data collected by IARC suggests that countries with a high Human Development Index (HDI) have a 2-3 times higher morbidity rates than countries with a low or moderate HDI. The numbers of the most popular cancers globally have changed as well.

Cervical cancer develops during reproductive age, adolescence, from the first pregnancy to menopause. There are multiple risk factors increasing the odds of developing cervical cancer. [22]

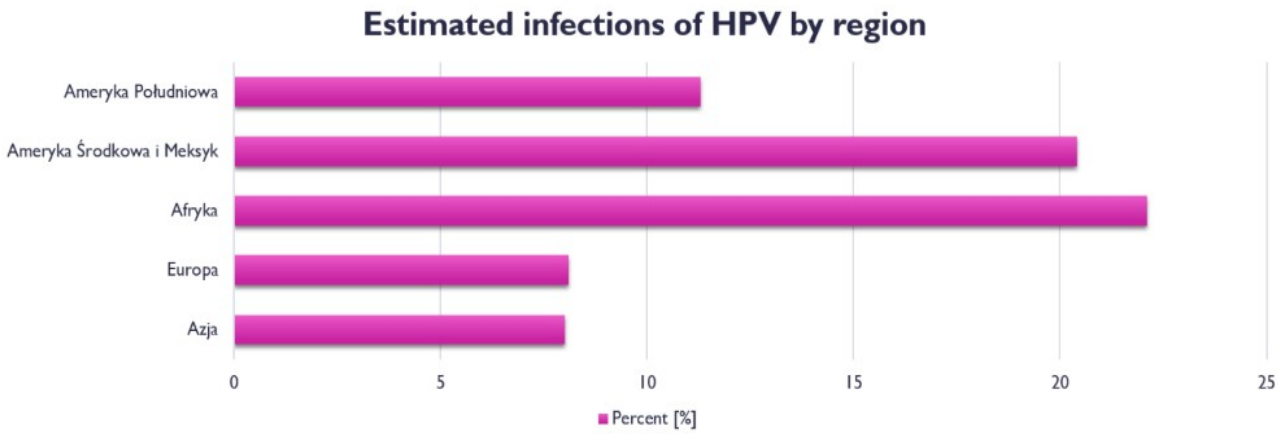

Figure 3. Estimated infections of HPV by region.

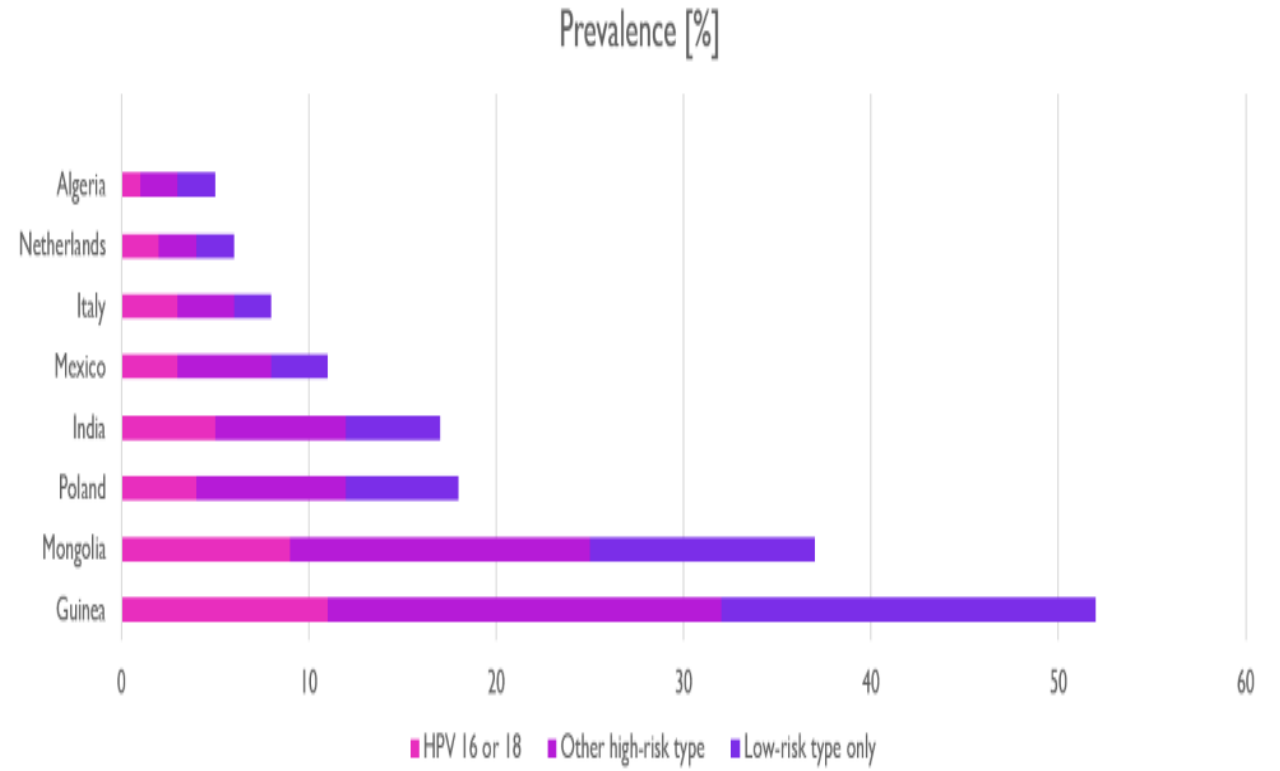

Figure 4. Age-adjusted prevalence (percentage) of cervical human papillomavirus (HPV) DNA in sexually active women aged 15–69 years in various countries

Invasive cervical cancer is preceded by three-stage cervical intraepithelial neoplasia (CIN) which develops into preinvasive cancer. Preinvasive cancer cells take up the entire thickness of the cervical epithelium without crossing the basement membrane. The stage of advancement of a microinvasive carcinoma depends on the depth and the area penetrated by the cancerous epithelial

cells. Early detection of cancerous changes is crucial, since CIN alone does not pose a risk to the patients' health. [12, 13] infection by HPV is very common for young women during their first decade of sexual activity, where 90% of new HPV infections subside during 6 to 18 months. Persistent infections and precancerous are detected in 10% of cases 5-10 years after infection by HPV. [15] Infections in old women last longer which suggest an increased risk of developing cervical cancer. [20] The incidence of cervical cancer after treating initial dysplasia is less than 1%, where mortality in this case I less than 0,5%. [12,13]

Globally, around 291 million women are infected by HPV, of which 32% are infected by the HPV16, HPV18 or both subtypes. The total incidence of HPV infections is at 10,4%, however it is higher amongst women younger than 25 y.o. (16,9%). Estimated infections of HPV by region included Africa (22,1%), Central America and Mexico (20,4%), North America (11,3%), Europe (8,1%) and Asia (8,0%). [fig. 3, 4]

Intraepithelial changes of low malignancy (CIN1) develop in middle aged women around 24-27 years old. Highly malignant changes develop in 35-47 year old women (CIN3). [16]

PIK3CA is the most common (31,3%) somatic mutation causing cervical cancer. The mutation Is associated with shorter survival time and is an unfavourable/disadvantageous prognostic factor. Other common mutations associated with cervical cancer are KRAS (8,8%) and EGFR (3,9%). [10]

85-90% of invasive cervical cancers, histologically are squamous epithelium carcinomas. Adenocarcinomas account for 10-15% of cervical cancers. Cervical cancer spreads by direct contact with other tissues, through lymphatic vessels and very rarely through the circulatory system. [19]

The situation in Poland:

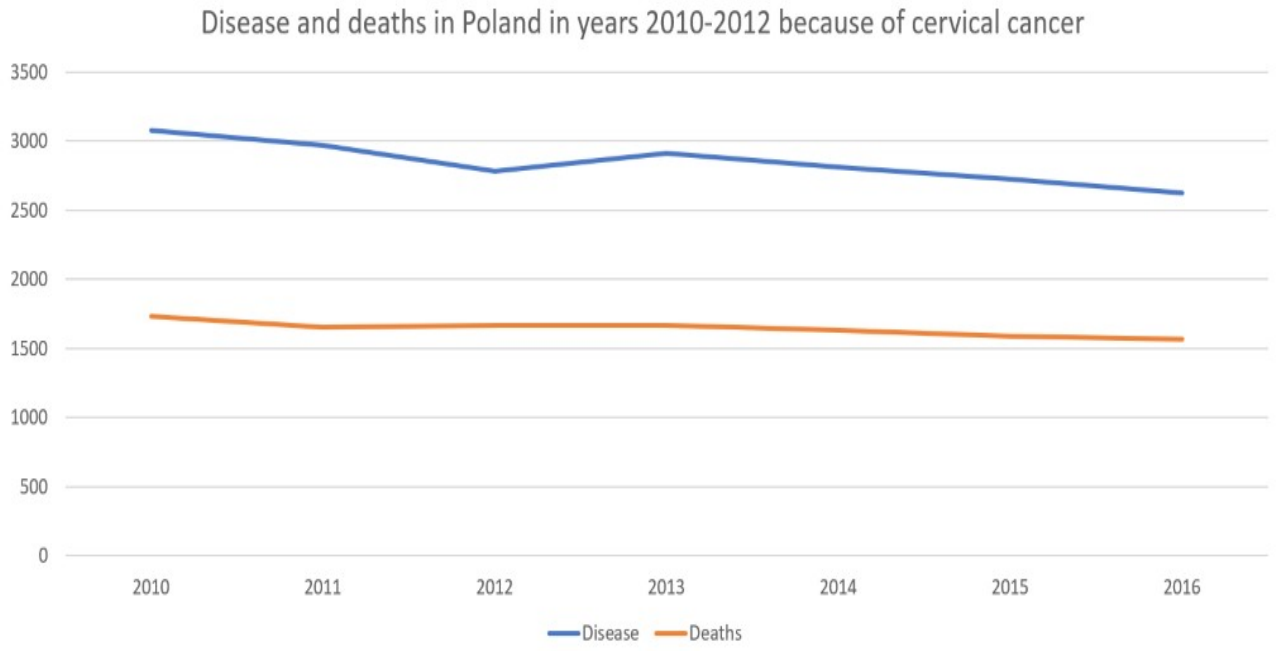

Figure 5. Disease and deaths in Poland in years 2010-2012 because of cervical cancer.

The incidence of cervical cancer in Poland is 15% higher and mortality rate due to cervical cancer is 70% higher than in other countries of the European Union. In 2017, Poland had 53% mortality due to CCU, while Germany had 31% and USA 37%. [24-26]

Analysing the data from the Polish National Cancer Registry a slow decrease in morbidity. Over the 2010-2016 period the number of new cases in Poland fell from 3078 to 2622 new cases/100 000 inhabitants. [fig.5]

Over the 2012-2016 period the pomorskie and lubuskie voivodships had the highest morbidity in Poland while świętokrzyskie and małopolskie voivodships presented the lowest morbidity. [28] [fig. 6]

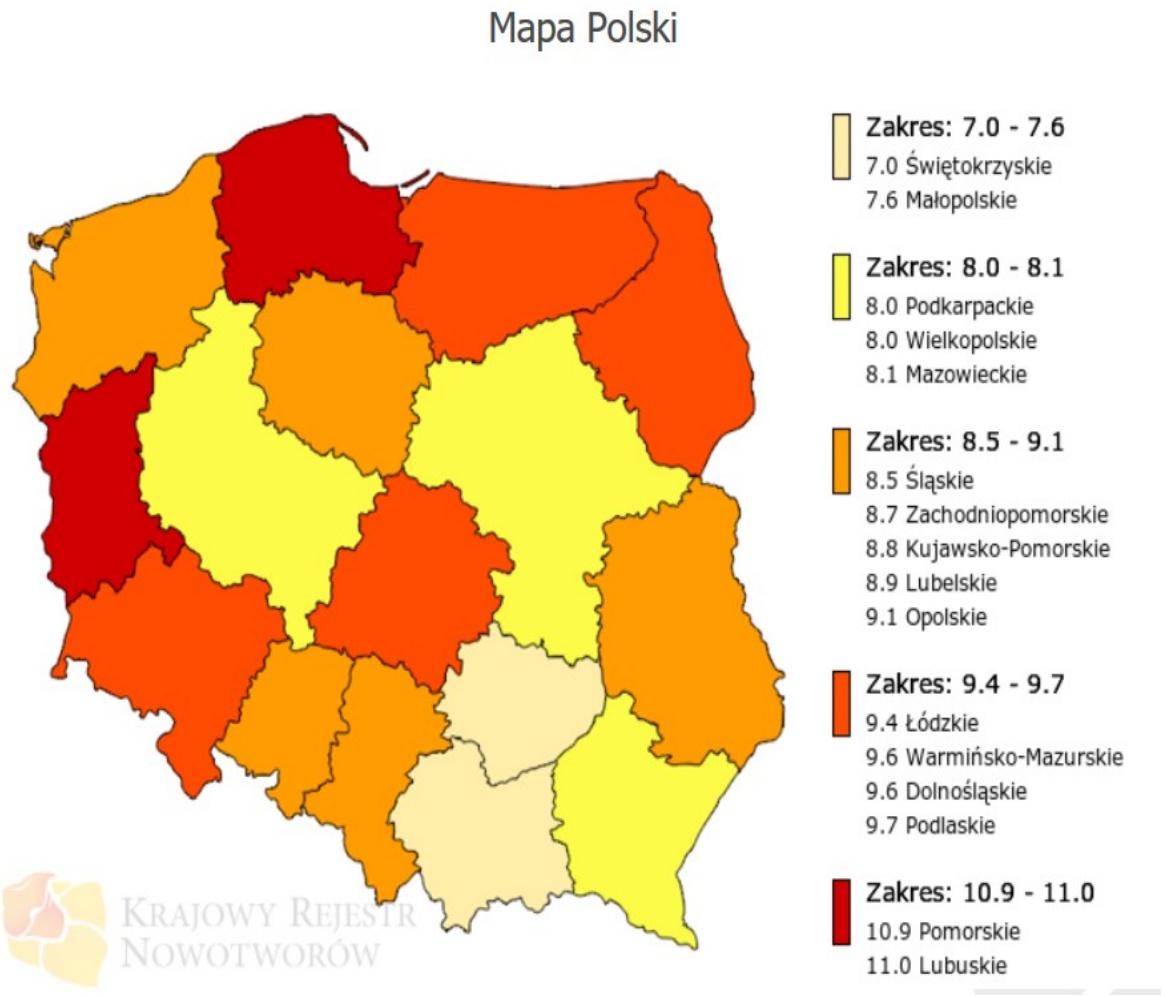

Figure 6. source: Krajowy Rejestr Nowotworów- National Cancer Registry - incidence map in Poland by region in 2012-2016 [28]

Clinical manifestation:
The symptoms of cervical cancer are nonspecific and their severity depends on the stage of illness advancement. Vagina discharge and bleeding from the birth canal are the most common causes of

gynaecological visits and can by symptoms of cancer however they can be associated with inflammation of the vagina or hormonal irregularities. Other unspecific symptoms of cervical cancer include lower abdomen, sacral area or acetabulofemoral joint pains. In late stages of cervical cancer, symptoms such as liver pain, dyspnoea and haemoptysis depend on the area of malignant infiltration or implantation of metastases during the metastatic faze.

Cervical cancer is classified according to the International Federation of Gynaecology and Obstetrics (FIGO). [30] Stage IA is a microscopic change. Stage IB is clinically visible and can be divided based on the size of the carcinoma into stage IB1 (≤4 cm) and IB2 (> 4 cm). In Stage II the cancer extends beyond the cervix though not to the pelvic sidewall or lower third of the vagina. In stage IIA upper 2/3 of the vagina is infiltrated by cancer cells without parametrial invasion. Stage IIA is divided into stage IIA1 and IIA2. In stage III the cancer has extended into the lower third of the vagina and cause kidney dysfunction. Stage III is divided into stage IIIA (tumour involves the lower third of the vagina without infiltrating the pelvic sidewall) and stage IIIB (extension into pelvic side wall or causing uropathy. Stage VI is the extension of the cancer beyond the true pelvis and distant metastases are present (stage IVB) or has involved the mucosa of the bladder and/or the rectum (stage IVA). [31] [Table 1]

Stage I	Carcinoma is strictlu confined to the cervix.
Stage IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
Stage IA_1	Measured stromal invasion <3mm in depth and <7mm in extension.
Stage IA_2	Measured stromal invasion >3mm in depth and not >5mm and extension <7mm.
Stage IB	Clinically visible lesions limited to the cervix or pre-clinical cancers >stage IA.
Stage IB_1	Clinically visible tumor <4 cm in greatest dimension.
Stage IB_2	Clinically visible tumor >4 cm in greatest dimension, parametril involvement, but not into side pelvic sidewall.
Stage II	Cancer extends beyond cervix though not to the pelvic sidewall or lower third of the vagina.
Stage IIA	Involves upper 2/3rd of vagina without parametrial invasion.
Stage IIA_1	Clinically visible tumor <4 cm in greatest dimension. Involvement of up to the upper two thirds of the vagina.
Stage IIA_2	Clinically visible tumor >4 cm in greatest dimension, but not into pelvic sidewall
Stage IIB	With parametral invasion, but not into the pelvic sidewall
Stage III	Cancer has extended into the pelvic sidewall. On rectal examination, there is no cancer free space between the tumour and the pelvic sidewall. The tumor involves the lower third of the vagina All cases with hydronephrosis or a non-functioning kidney are stage III cancers.
Stage IIIa	Tumor involves the lower third of the vagina with no extension to pelvic sidewall.
Stage IIIb	Extension to pelvic sidewall or causing obstructive uropathy, MR imaging findings that are suggestive of pelvic sidewall involvement include tumour within 3 mm of or abutment of the internal obturator, levator ani and pyriform muscles and the iliac vessel
Stage IV	Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum extension beyond pelvis or biopsy proven to involve the mucosa of the bladder or the rectum.
Stage IVa	Spread of the tumour into adjacent pelvis organs, extension beyond pelvis or rectal/bladder invasion.
Stage IVb	Distant organ spread.

Table 1. FIGO staging of cervical cancer (2009)

Course of treatment depends on the stage of the tumour, the presence and localization of metastases. Treatment for cervical carcinoma involves surgery, radiotherapy, radiochemotherapy and chemotherapy. [33]

Diagnostic procedure:

Diagnostic screening for cervical cancer include two tests: the Papanikolaou test and HPV test. The Papanikolaou test (Pap test) is used to assess the microscopic material gathered from the cervix in order to detect precancerous or cancerous processes in the cervix. The HPV test is used to detect HPV infection. In order to increase the diagnostic accuracy of the Pap test, the patient should avoid using local contraception, tampons or other intravaginal products for 48h before the test. There are multiple, available molecular tests for detecting HPV infections in tissue and cell samples, all of which work by tracing the virus DNA. For example the PCR method is both specific and sensitive. [13] According to American Society for Colposcopy and Cervical Pathology (ASCCP) in case of a patient with a positive test result for HPV DNA and a negative cytology (Pap test) result, both tests should be repeated after a 12 months or a more specific test should be performed for HPV16 or HPV18 DNA. If the same test results are collected (HPV+, cytology -) after 12 months, a prompt colposcopy should be performed. [32] The International Federation of Gynecology and Obstetrics (FIGO) recommend procedures such as colposcopy, biopsy, cervical conisation, cystoscopy and sigmoidoscopy to assess the stage of advancement of the tumour. Imaging procedures such as MRI, CT scans, PET/CTs may be useful in planning the course of therapy but are not necessary for determining the stage of advancement. [21, 31, 33]

According to the American Cancer Society regular screening using the Pap test should be performed every 3 years in all women 21 years old or older. The HPV test should be performed for women 21-29 years old in case the Pap test results are incorrect. Women aged 30-65 should be tested via Pap test and HPV test every 5 years. [13]. Cervical cancer prevention program in Poland is designed for women 25-59 years old who haven’t received screening tests in ≥3 years. For women with additional risk factors such as: receiving immunosuppressant’s, infected with HPV or HIV, the screening tests are performed every 12 months. Pap test (cytological test) is the most popular method of screening due to its low cost and high efficiency. Large scale screening is necessary. It is estimated that screening 75% of the population will result in a 25% decrease in mortality due to cervical cancer. [29]

Vaccination:

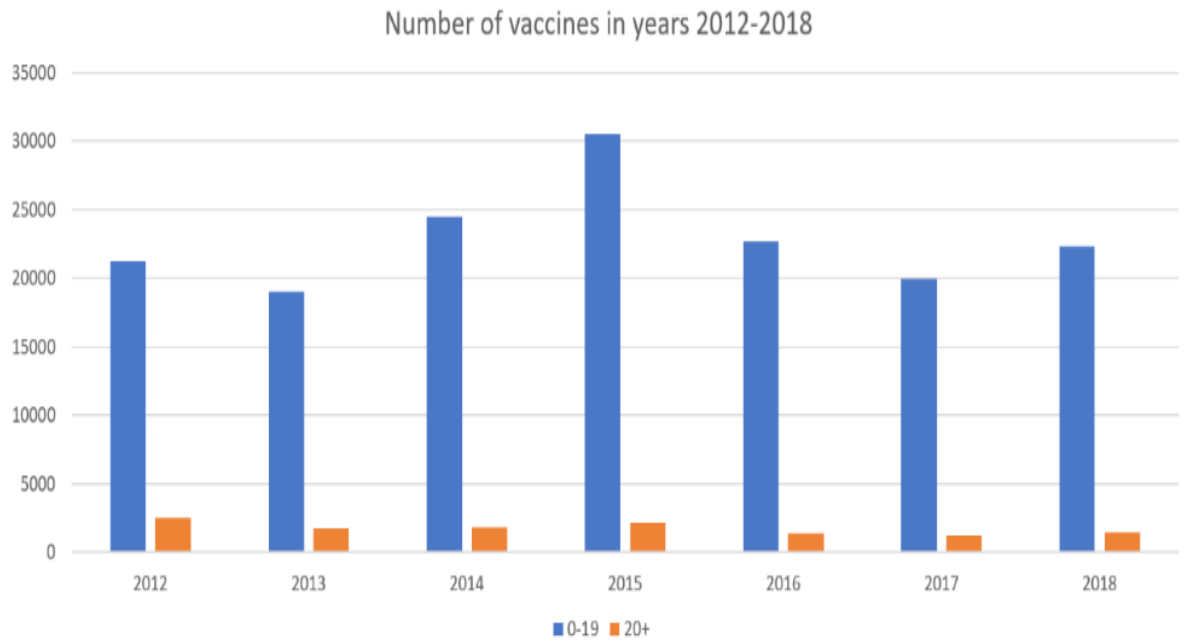

Figure 7. Number of vaccines in years 2012-2018 in Poland

There are three types of vaccines available: bivalent, quadrivalent and 9-vanlent. All vaccines are recombinant vaccines and do not contain the genetic material of HPV, they belong to the group of inactivated vaccines. [24] HPV vaccines contain L capsid protein assembled into virus-like proteins (VLP) which can activate neutralizing antibodies. [13] The vaccnies should prevent infection by HPV and diseases associated with HPV, they are not meant to treat active HPV infections. [16] HPV vaccination has a >90% efficiency in 15-26 year old women who haven't been infected with HPV. The estimated efficiency depends on the type of vaccine, investigated population, type of study and time of observation. [23] Tests with the quadrivalent vaccine (4vHPV) have shown efficiency close to 100% and successful prevention of HPV infection over a 5-6 year period. The creators of the vaccine are currently working on introducing improvements to the vaccine such as: extending the period of protection against HPV, increasing the efficiency of the vaccine for men and the induction of cross-reactive antibody or oncogenic types of HPV not present in the vaccines. [13] Despite the confirmed effectiveness of the HPV vaccine, parents in Poland are concerned about the negative side-effects of vaccination. The anti-vaccination movement has gained so much popularity that the members of the Polish Science Academy have expressed concerns about the number of vaccinated children in Poland dropping yearly. [24] [fig. 7] It is wort noting that the vaccine and its components, including the controversial use of tiomersal used as a preservative, are safe. The Committee on Epidemiology and Bioterrorism of the Sanitary and Epidemiological Council excludes any cause and effect relationship between vaccination and the rate of new cases of autism. [27] Over 90% of all HPV post-vaccination side effects are classified as mild. The most common side effects are: inching in the area of injection, subfebrile condition and mild fever. Reported side effects quickly disappeared. The remaining 10% of consisted of moderate side effects such as: nausea, head ache, fainting and pain in the area of injection.

The characteristic of the vaccines:

	2-valent	4-valent	9-valent
Trade name:	Cervarix	Silgard	Gardasil9
Registration date (USA):	Oct 2009 – girls	Jun 2006 – girls, Oct 2009 - boys	Dec 2014 – girls and boys
HPV types	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Recommended for:	Girsl 11-12 y.o. Women between 13 and 26 y.o. who have not undergone the whole vaccination cycle.	Girls and boys 11-12 y.o. Women between 13 and 26 y.o. who have not undergone the whole vaccination cycle; Men between 22 and 26 y.o. that are immunosupressed, homosexuals, bisexuals	Girls and boys 11-12 y.o. Women between 13 and 26 y.o. who have not undergone the whole vaccination cycle; Men between 22 and 26 y.o. that are immunosupressed, homosexuals, bisexuals
Administration	intramuscular	Intramuscular	intramuscular

Figure 8. The characteristic of the vaccines [24,26]

The first vaccines in Poland became available in pharmacies in 2008, shortly after they became available in the USA. In Poland, the HPV vaccine is an optional, payable and recommended vaccine, contrary to other countries such as the USA, Great Britain, Germany, Norway, France, Philippines and Malaysia where the vaccine is refunded by the government. The HPV vaccination scheme used in Poland consists of 3 doses of the vaccine (quadrivalent and the 9-valent vaccines are administered in a 0-2-6 month schedule, the bivalent vaccine is administered in months 0-1-6). [24] A completed vaccination scheme does not dismiss the necessity of regular screening for cervical cancer and the screening procedures should be continued according to the scheme recommended for one's age group. In the United States, the HPV vaccine is recommended to all 9-26 year old girls and women. [13]

Conclusion:

The increasing accessibility of a variety of sources concerning cervical cancer correlates with an increase in the frequency of gynaecological visits and cytological screenings attended by women. A successful decrease in morbidity and mortality due to HPV infections, which are the cause of cervical cancer and head and neck cancers may lead to the inclusion of HPV vaccination into the national vaccination program. Spreading awareness about the risk amongst young adults and parents, protecting their children through vaccination is necessary in order to achieve a decrease in morbidity and mortality due to cervical cancer.

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