

New challenges for cervical cancer

Cezary Wojtyła¹, Aneta Słabuszewska-Jóźwiak¹, Kinga Janik-Koncewicz², Witold A. Zatoński²

¹Centre of Postgraduate Medical Education, First Department of Obstetrics and Gynaecology, Warsaw, Poland

²Department of Cancer Control and Epidemiology, Maria Curie-Skłodowska Memorial Cancer Centre, Warsaw, Poland

ABSTRACT

One of the most common types of cancer found in women throughout the world is cancer of the cervix. Nationwide screening programmes, as commonly used in the developed world, have demonstrated significantly reduced rates of cervical cancer, thus in such cases leading to decreased mortality rates. In developing countries, indicators of cervical cancer are increasing. In Poland, as in other countries, we can observe a significant disproportion of its occurrence among different populations of women. During the first half of the 1990s, cervical cancer was the second most prevalent cancer in Poland. Since then its morbidity and mortality rates have gradually decreased. This trend has continued on from the second half of the 1980s, when the standardised morbidity rate decreased to 17.2/100,000 women. In 2010 this further decreased to 10.3/100,000 women. In the early seventies, the standardised mortality rate for cervical cancer in Poland was 9.2/100,000 women. At the moment, the cervical cancer mortality rate in Poland is 5.2/100,000 women. Nevertheless, we still observe higher rates of morbidity and mortality from cervical cancer compared to other developed countries. Following European Commission recommendations, Poland launched a nationwide programme for cytological screening in 2007. In 2009, 26.77% of women took part in the cervical screening programme. Data from subsequent years have not been published, but even if an upward trend is maintained within the first years of the programme, it seems that only around 1/3 of Polish women are covered. The low screening level is a major drawback in the attempt to reduce cervical cancer rates in Poland. We also do not have precise data on how many actual Pap tests are performed or on those women who have never had such tests done. It therefore seems necessary that such data be obtained to enable a high risk group of death from cervical cancer to be defined and appropriate countermeasures to be undertaken.

KEY WORDS: cervical cancer, cervical cytology, human papillomavirus (HPV), human papillomavirus vaccination, cancer prevention.

ADDRESS FOR CORRESPONDENCE: Cezary Wojtyła, First Department of Obstetrics and Gynaecology, Centre of Postgraduate Medical Education in Warsaw, 231 Czerniakowska St., 00-416 Warsaw, Poland, e-mail: czwo@op.pl

INTRODUCTION

One of the most common types of cancer found in women throughout the world is cancer of the cervix. The vast majority of such cases are diagnosed in developing countries where there are no efficient programmes for the early detection of precancerous changes [1]. However, countrywide screening programmes, as commonly used in the developed world, have demonstrated significantly reduced rates of cervical cancer, thus in such cases leading to decreased mortality rates. In

developing countries, indicators of cervical cancer are increasing [2]. When epidemiological data from prosperous countries are studied, significant disparities have been found. Women living in rural areas or those from low-income families tend to have the highest cervical cancer morbidity and mortality rates [2]. Defining those groups of women vulnerable to developing cervical cancer is currently a vital area for the prevention of this disease, which can now in fact be easily averted and early states indeed treated.

POLAND'S CONTRIBUTION TOWARDS ELUCIDATING CERVICAL CANCER AETIOLOGY

Nowadays, when the natural history of cervical cancer has become known, almost all cases and their precancerous changes are found to be due to a persistent infection with oncogenic types of human papillomavirus [2]. For many previous decades, however, the possible aetiology of this cancer was still being investigated. Likely causes which were then being considered included infectious agents transmitted sexually such as *Trichomonas vaginalis*, *Treponema pallidum*, *Neisseria gonorrhoeae*, *Mycoplasma hominis*, *Chlamydia trachomatis*, cytomegalovirus and herpes simplex virus (HSV) type 2 [3]. Nonetheless, until the early 1980s the causative factor remained unknown, but what had been determined were the risk factors, namely early sexual activity and many sexual partners [4], whereas protective factors were considered to be early marriage, bearing many children and a young age for having the first pregnancy [5].

In 1922, Lewandowsky and Lutz first described the disease characterized by the presence of various types of skin eruptions on exposed parts of the body which were likely to progress to skin cancer, now termed "papillary epithelial dysplasia" (*epidermodysplasia verruciformis*). Further studies by Lutz *et al.* [6] and Jabłonska *et al.* [7] had observed the phenomenon of autoinoculation (i.e. self-infection). Patients diagnosed with papillary epithelial dysplasia who had material from their nipple transferred to unrelated body areas developed warts within a few or several weeks. The breakthrough came when lesions were observed in two previously healthy women after having made skin contact with their brother's wart arising from papillary epithelial dysplasia. During the next few months, lesions were observed in both women. In two of the other siblings, where no such contacts had occurred, lesions were never seen. A diagnosis of invasive skin cancer was then later made in one of the women (Bowen's disease). Subsequent electron microscopy of

the lesion biopsy identified a virus from the papovavirus family. This work was performed by Jabłonska and her team [8], which thereby led to understanding the pathogenesis of not only some skin cancers but also cervical cancer. In today's taxonomy, the papovavirus family terminology has become obsolete, it being now divided into papillomaviruses and polyomaviruses. It is now known that the original virus observed by Jabłonska was in fact the human papillomavirus (HPV) [9].

In 1983, zur Hausen and Gissmann identified type 16 human papillomavirus in premalignant lesions of the reproductive system, whilst two years later they discovered viral genetic material in cervical cancer cells [10, 11]. Subsequent studies then revealed that nearly all cases of cervical cancer have a viral aetiology and that the causative agent, so long sought after, was the human papillomavirus [12].

FROM HPV INFECTION TO CERVICAL CANCER

The genetic material of the human papillomavirus is in the form of two DNA strands. Currently 12 oncogenic HPV virus types which may lead to the development of skin and cervical cancer are known; these are types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 [13]. It is only these types that are responsible for cancer and its development and which should be considered in screening tests and immunisation. The risk of developing invasive cervical cancer is not however equal in the above-mentioned types. The vast majority of cervical cancer cases are associated with the presence of type 16 HPV, which is the most potently carcinogenic and is linked to having the highest risk for developing higher grade cervical intraepithelial neoplasia (CIN III) [14]. The second viral type bearing a high risk of a precancerous change is type 18 HPV [14]. The area of the cervix where cancer develops is a transformation zone, with the glandular epithelium of the cervical canal being replaced by a flat epithelium. As mentioned above, the factor that initiates cervical cancer development is a persistent infection with oncogenic types of HPV. Although a significant majority of such an infections are transient, those that remain will, over time and without treatment, lead to progression of premalignant and cervical cancer. The increase in human papillomavirus infection rates differs for different populations and depends on when sexual activity starts [15]. The prevalence of HPV infection rapidly rises within the first years after sexual activity starts but then gradually falls with age. After about 5-15 years following sexual initiation, another crucial stage in the natural history of cervical cancer was observed. At this time, there were increasing rates of precancerous changes resulting from persistent HPV infection in some women. In subsequent years, invasive cancer rates then increased [1]. The prevalence of infection with human papillomavirus, the status of precancerous changes and cervical cancer is illustrated in Figure 1 [14]. Due to the long develop-

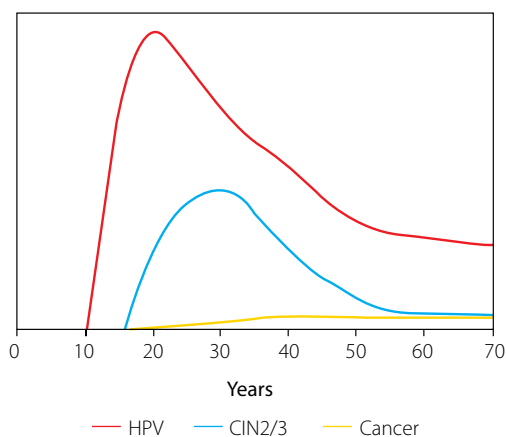


FIG. 1. Prevalence of infection with human papillomavirus, precancerous changes and cervical cancer according to age

ment time for invasive cancer, screening older women with newly diagnosed HPV is unnecessary. It is unclear whether becoming naturally infected with the human papillomavirus protects against any future reinfection. It seems that protection is afforded against reinfection in cases of the same virus type; however, it is probably not group specific and does not protect against reinfection with another type of HPV [13].

By far, most genital tract infections in women are asymptomatic and spontaneously resolve within 1-2 years. Sometimes however a persistent infection with oncogenic virus types can lead to the progression and development of invasive cervical cancer. A persistent infection by oncogenic human papillomavirus types is in fact a prerequisite for cancer to develop [12], which occurs in 5-10% of cases [13]. This infection may progress and lead to epithelial dysplasia of the cervix, this being classified upon histopathological examination as cervical intraepithelial neoplasia (CIN). The interval of time between exposure to HPV and the development of CIN, as identified by screening, lasts from several months to several years. By contrast, it takes 10 or more years to develop the invasive form of cancer. It is unknown why most women spontaneously achieve infection control, but in some, progression may occur. It is suspected that other factors are also involved, such as the patient's immune status, coinfection with other sexually transmitted pathogens (HSV, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*) and smoking [13].

The prevalence of HPV infection is highest in youngest women and decreases with age. Studies by Peto *et al.* [16] indicated that HPV is detected in 23% of women under the age of 25 years. Of these, the oncogenic type of virus was found in 83% of cases, with the type 16 HPV virus being detected in 47% of cases. In women aged over 40 years, the prevalence of any of the viral types was 4%. Those infected with the oncogenic virus type constituted almost 66% of cases, of which HPV 16 accounted for 49%. In women aged below 25 years, who gave any abnormal cytological test results, the prevalence of human papillomavirus was 68%, whilst in women aged above 40 years it was 36%.

A study conducted in Poland in the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology in cooperation with the International Agency for Research on Cancer [17] assessed the prevalence of HPV types for 834 healthy female subjects in Poland aged 18-59 years and in 88 women diagnosed with cervical cancer. Within the general group, HPV was found to be 16.6%, with those aged 25-34 years showing the highest levels at 24.2%. The prevalence of the highly oncogenic types of virus were 11.3%, with the most common type being HPV 16. However, in the cervical cancer group, nearly all had the highly oncogenic types of virus, of which the most frequently found was the HPV 16 type at 73%. In this group infections by more than

one virus were more rarely observed, compared to the general group of women.

In a study by Bosch *et al.* [18] on women diagnosed with cervical cancer, 1000 samples of tissue were histologically examined to determine the prevalence of the different types of HPV in the world. The sample tissues came from 22 countries, including Poland, which represented 10 of the 18 world regions. The Polish samples were provided by a team of experts from the Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology supervised by Professor Witold Zatonski. DNA from the HPV was identified in 93% of cases, and there were no significant variations found in the HPV types between the studied world regions. Almost half of the samples (49.9%) had the HPV 16 type, with HPV 18, 45 and 31 types being respectively found in 13.7%, 8.4% and 5.3% of cases. Indeed, HPV 16 was the most commonly found virus in all the studied countries, with the exception of Indonesia, where the HPV 18 type was most frequent. The HPV 16 type was also most often found in patients diagnosed with squamous cell carcinoma of the cervix, whereas type 18 predominated in cases of adenocarcinoma and squamous-glandular cancer.

A large majority of cytological results are benign. Those however requiring further diagnosis because of the risk of progression are due to atypical squamous cell epithelium of undetermined significance (ASC-US), atypical squamous cell epithelium without excluding HSIL (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) and squamous cell carcinoma of the cervix (SCC). In addition, distinctive atypical changes are apparent in glandular cells, i.e. atypical glandular epithelial cells (AGC), a non-invasive adenocarcinoma in situ (AIS) and adenocarcinoma of the cervix [18]. Additional information gained on human papillomavirus infection allows risk stratification for the developing precancerous changes as well as cervical cancer. The risk of developing CIN III lesions and more is lower in HPV-negative women with abnormal cytology than in women with abnormal cytology infected with HPV. This risk is greatest for developing adenocarcinoma, although it also remains raised for squamous cell carcinoma [19].

DIAGNOSIS AND PREVENTION OF CERVICAL CANCER

Understanding the natural history of cervical cancer has driven the development of effective programmes for its early detection and prevention. Screening tests allow us to specify a group of asymptomatic women who have an increased future risk of developing cervical cancer, to offer them appropriate treatment which is essential for its proper functioning. It should however be remembered that performing such a large-scale intervention on a healthy population may not only yield beneficial outcomes but may also lead to adverse ones. The great-

est advantage of implementing such undertakings is undoubtedly a reduction in women's morbidity and mortality through detecting precancerous changes at an early stage of development [19]. The challenge associated with these programmes is however in obtaining some false positive results leading to unnecessary interventions. Another challenge is false negative results, where such women bear a substantial risk of tumour progression with associated health damage. For both these reasons, it should be ensured that any programme for the early detection of precancerous changes is carried out in defined risk groups and aims to achieve coverage of such groups in their entirety [2].

Infections by the highly oncogenic types of HPV viruses are very common in young women; most are nevertheless eliminated without leaving behind any consequences. Cervical cancer usually develops slowly over 10-20 years. For this reason, such cancers are very rare before the age of 30 [2]. Screening before this age will detect many lesions within the cervical structure which never progress to cancer, but are responsible for a large proportion of false positive results [2]. In contrast, even a single screening of women aged between 30 and 49 years leads to a significant reduction in cancer mortality and is thus recommended for this age group. In women testing negative for cytology or in those where acetic acid is used, a re-examination is possible after 3-5 years. In contrast, women testing negative for HPV allows for a longer time interval between successive tests of at least 5 years [2]. Those women testing repeatedly negative or older women can have longer time periods between tests – even longer than 5 years [2].

Until recently, the only available programmes for the early detection of precancerous cervical changes were cytology testing. Today the alternatives are molecular detection of HPV or visualization using acetic acid. Viral screening permits detection of HPV DNA in highly oncogenic material taken from the vagina or cervix. HPV infections are common in young women, but a large proportion will become self-limiting, so it is not recommended that this testing be done in women below the age of 30 years. Whenever the high-oncogenic virus types are detected in older women, this may be evidence of persistent infection that could progress to cancer and is thus an indication for keeping this group under observation or for treating them accordingly [2]. The advantage of this method is that there is no need for internal investigation or visualisation of the cervix using a speculum. It is sufficient to sample material from the vagina, which can even be performed by the woman herself, and place the sample into a suitable test container. It should be noted that a positive result does not indicate a pathology of cervical epithelial cells; it is only a sign of infection by highly oncogenic types of HPV and thus requires further diagnosis [2]. Another type of test used in cervical screening is by speculum examination with 3-5% acetic

acid. It relies on colour changes to the cervix during acid retention. Early diagnosis of precancerous changes as well as more advanced ones can thus be accomplished. This test however does not allow the type of changes to be distinguished and requires some practical expertise from the analyst. Nonetheless, it is an inexpensive screening method [2].

The most popular screening test and one which is still mainly undertaken for screening programmes is the "Pap test" (smear test). This requires sampling of the transformation zone of the uterine cervix and then fixing the obtained smear onto a glass slide (Pap test) or placing the sample into a liquid – termed thin layer cytology or liquid-based cytology. The liquid medium increases the likelihood of obtaining a reliable result and additionally allows testing for HPV and other sexually transmitted microorganisms [2]. A well-structured programme, based on the Pap test, can thereby significantly reduce cervical cancer mortality in women. Obtaining a result, however, requires a range of actions that may affect its outcome, from the need to conduct gynaecological examination with a speculum, through appropriate sample fixation of the sample, to its transport to a laboratory for expert analysis by a qualified cytologist [2].

Irrespective of the method used, screening tests only allow the risk of developing cervical cancer to be determined, and require further diagnostic methods to permit a diagnosis to be made. These include colposcopy, biopsy and endocervical curettage. These then only allow women to be qualified for the most appropriate treatment and thereby for cervical cancer mortality to become reduced. It should be kept in mind that the success of programmes for early detection and diagnosis of cervical cancer depends not only on screening entire age groups of women *per se* but also on how efficiently diagnostic tests are performed together with applying the appropriate treatment [2].

VACCINATIONS

Determining the aetiological agent for cervical cancer has enabled the development of methods for primary prevention, namely vaccination. Currently there are two vaccines: a bivalent and a tetravalent one. The first contains the protein of the human papillomavirus type 16 and 18 and prevents the development of cervical cancer and rectal dependent HPV infection. The second vaccine includes a protein of the human papillomavirus type 16, 18, 8 and 11 and prevents also from developing genital warts [13]. Both are intended for people even before the first contact is made with the HPV virus, i.e. before sexual activity starts. The bivalent vaccine is aimed at girls aged 9-14 years and requires repeated doses of the vaccine at 0 and 6 months. The tetravalent vaccine is designed for girls and boys aged 9-13 years, also given at 0 and 6 months, or alternatively at 0, 2, and 6 months. If, however, it is to be given after 14 years of age, then a three-

dose scheme is recommended [13]. The immunological response to the vaccine is much stronger than that from naturally acquired infection [13]. Studies show that both types of vaccines are highly effective when used in the three-dose scheme for primary and persistent infection with the human papilloma virus and precancerous changes, such as average grade cervical intraepithelial neoplasia or higher (CIN II +) [2, 13]. Although both vaccines were originally intended for a three-dose scheme, it is now considered that the two-dose immunization regimen is equally effective [20]. It is also claimed that these vaccines show some cross-resistance with other virus types not used for their production [13]. Antibody levels produced by the vaccinated person peak shortly after the third vaccination dose and achieve a plateau about 2 years later, thenceforth remaining unchanged for at least 5 years [21]. For the bivalent vaccine, the effectiveness of the immune system against infection and development of cervical lesions resulting from human papillomavirus types 16 and 18 are respectively 8.4 and 9 years [13, 22]; for the tetravalent vaccine this time is 8 years [21]. These findings are for the three-dose vaccination schemes. Results for the two-dose scheme are still pending, but the first outcomes indicate a similar effectiveness [13]. Some vaccination efficacy studies are still being continued, but even now there is no evidence that the immune response has declined throughout 10 years after the immunisation schedule. There is therefore no need for any booster doses during this period [2]. Such vaccinations reduce the observed rates in changes of high-grade cervical lesions as well as precancerous changes in young women. With the tetravalent vaccine the rates of genital warts are also reduced [23].

Such vaccination in older women is unjustified. A significant proportion will already have had a human papillomavirus infection and therefore a corresponding immune response. There is also less likelihood of older women contracting a new infection, and thus the associated risk of developing cancer is likewise low as compared to young women [14]. As long as the immune response to HPV infection is not precisely known, it cannot be definitively concluded which women have suffered infection with the human papillomavirus, and which of them thus remain vulnerable to new infection and who may also benefit from the vaccination regimen [14].

MATERIAL AND METHODS

The present study is based on mortality data on cervical cancer in Poland between 1963 and 2010 derived from the database of the World Health Organization (WHO). The database contains information about the number of deaths by causes defined in the International Classification of Diseases (ICD), provided according to gender and in 5-year age groups. Data on Poland's changing population throughout 1963-2010, broken down by gender and a similar age group, were also taken from the same source. Details are described in the docu-

mentation, available on the WHO website (<http://www.who.int/whosis/mort/download/en/index.html>).

Data on cervical cancer rates in Poland between 1980 and 2010 were derived from the National Cancer Registry database. The Registry collects data obtained from reporting Cancer Card Documentation. Such cards are dispatched to provincial (voivodeship) cancer registries which gather data and perform analyses. These are then sent to the National Cancer Registry, to be verified, combined, and analysed comprehensively, and published annually since 1980.

The study analysed the number of cases and deaths due to cervical cancer in Poland, as specified in the seventh revision of the ICD number 171 (data from 1963 to 1968), in VIII (1969-1980) and IX (1981-1996) number 180 and X (1999-2010) code C53. Due to the doctors' strike during 1997-1998, data on cancer morbidity and mortality rates from this time were not available. Between these years, the graphical data were interpolated for the morbidity, whilst mortality data between 1996 to 1999 were averaged out.

The study was based on essential epidemiological indicators such as the absolute number of cases and deaths according to age as well as using direct methods to standardise age for analysing morbidity and mortality rates of cervical cancer in the age groups of 20-44, 45-64, 65 years and over (65+) and total (0+). As a standard population, we adopted a standard population of the world [4].

Analysis of the total cervical cancer mortality over time in Poland between 1970 and 2010 was performed by the Joinpoint Regression Program (<http://srab.cancer.gov/joinpoint/>). This software allowed the testing of whether the time trend factors or their changes within the studied time interval were statistically significant. The program performs fitting of linear models or a model consisting of several straight lines broken into the so-called joinpoints in which the observed trend becomes reversed and estimates are made of various annual percentage changes (APC) for these periods. The analysis starts by fitting a straight line to the data and then testing whether one or more of the joinpoints (up to 3) leads to a better data fit.

In an attempt to answer what socio-demographic factors could affect women to undergo screening for cervical cancer, two questions were included in a survey conducted every year on the prevalence of risk and protective factors for cancer within the Polish adult population. The survey was conducted at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology (COI) and TNS (Taylor Nelson Sofres) in Poland on 8-11 November 2012 on a representative population sample of 1000 subjects (including 523 women) aged 15 years and older. Those women participating were asked if they had ever had cytology tests done (defined as cervical swabbing in gynaecological surgery departments). If the reply was yes, then a second question was posed on how often such

testing had been performed, with the option of choosing one of the following four answers: every year, every 2-3 years; every 4-5 years; or at least every 5 years.

RESULTS

THE EPIDEMIOLOGICAL SITUATION IN POLAND AND THE WORLD

Up to the 1940s, uterine cancer, which at that time cervical cancer had been classified under, was the most common cause of death of women in the USA [24]. In the 1930s a steady and significant decrease in mortality had been observed in such USA cases. According to USA epidemiological data, this cancer is now currently the sixth leading cause of death of women, coming after cancers of the lung, breast, colon, pancreas and ovary [24]. The USA is however not the leading country for achieving the most spectacular decreases in morbidity and mortality from cancer. In fact it is Finland. This was one of the first countries to organise a screening programme for cervical cancer, which started in 1963 [25], when standardised mortality rates in women were 6.2/100,000. Introducing this national system for screening resulted in a sharp decline in morbidity and mortality for this condition. After 30 years, the standardised mortality rates had dropped by 80% [26]. Since then the level has been at 1/100,000 women, which is one of the lowest in the world [27].

Poland is a country with reported rates of cervical cancer morbidity and mortality that are among the highest in Europe. Although in the past 30 years the situation

has to a small extent improved, epidemiological findings are not satisfactory. In other countries that have successfully managed to implement effective programmes for the early detection of precancerous changes it was demonstrated that it is indeed possible to achieve full control over this type of cancer. During the first half of the 1990s, cervical cancer was the second most prevalent cancer among women in Poland. Since then its incidence has gradually decreased. In terms of mortality, cervical cancer was the fifth highest cancer among women in 2010 after breast, lung, colon and ovarian cancer (Fig. 2).

Cervical cancer morbidity rates in Poland have declined (Fig. 3). This trend has continued on from the second half of the 1980s, when the standardised morbidity rates had decreased to 17.2/100,000 women. In 2010, this further decreased to 10.3/100,000 women. Over the timeframe of the years studied, the largest decline in such rates occurred for the youngest women's age group of 20-44 years. Nevertheless, up until the 1980s, cervical cancer morbidity rates were on the increase for this age group. The highest morbidity rates were in fact observed in the early nineties (16.5/100,000 women), after which this adverse trend became reversed. The age group with the highest rates and the lowest decline in morbidity was that of women aged 45-64 years. In the latter half of the 1980s, the morbidity rate was 47.3/100,000 women, which subsequently decreased to 31.4/100,000 women in 2010. In a similar fashion, for the oldest group of women, an over forty percent reduction in morbidity rates occurred, with the level in 2010 down to 26.3/100,000

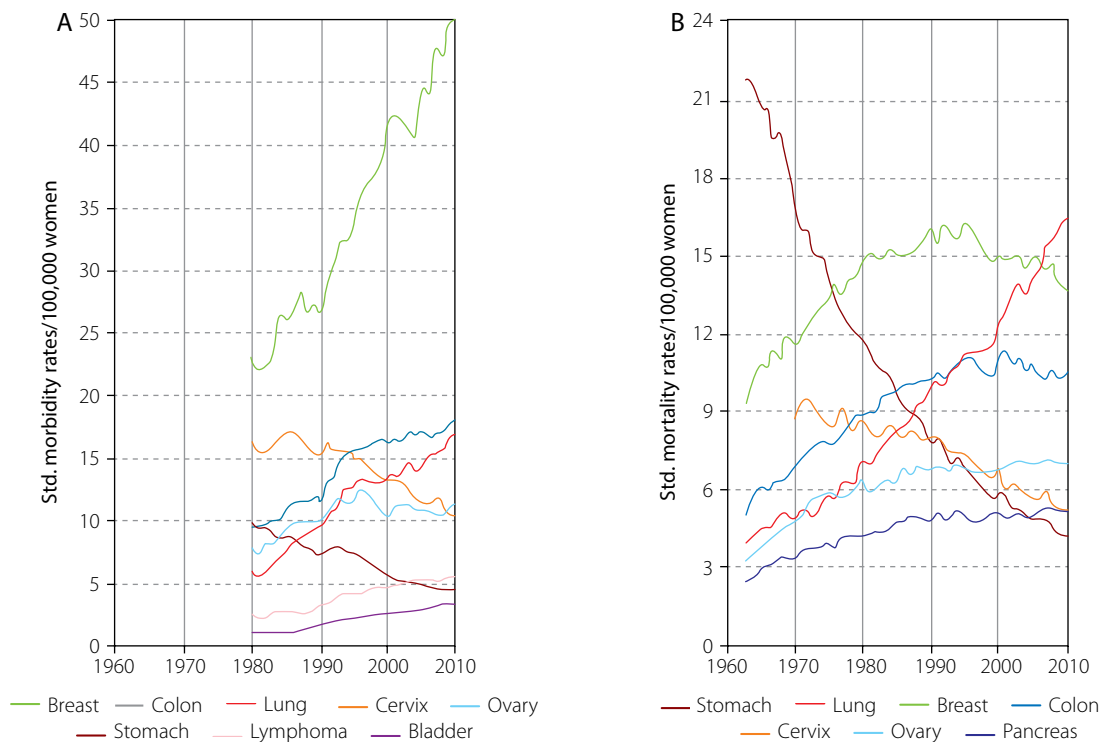


FIG. 2. Morbidity (A) and mortality (B) from cancer in Polish women, 1963-2010

women. These morbidity trends are shown in Figure 4 for the defined age groups.

In the early 1970s, the standardised mortality rate for cervical cancer in Poland was 9.2/100,000 women. Since then, reduced mortality rates have been observed, in similar fashion to morbidity rates. The annual percent change (APC) between 1970 and 1992 was 0.8%. After 1992, mortality declined rapidly by a percentage change of 2.2% annually. In 2010, the cervical cancer mortality rate in Poland was 5.2/100,000 women. Figure 5 shows the cervical cancer mortality in women between 1970 and 2010. When examining the age groups, significant differences were found. In women aged 20-44 years (Fig. 6) mortality rates remained relatively high up until the early 1990s, when they started to rapidly decline. In 2010, 300 fewer such deaths per annum were observed compared to 1991. For women aged 45-65 years (Fig. 7), there was a sharp rise in mortality up to the mid 1970s. Since then the standardized mortality rate has been steadily falling. By 2010 it was down to 15.9/100,000 women. In terms of absolute numbers, we continue to note, however, that the approximate figure of 900 deaths of women found in this age group is similar to the early 1990s. For the age group of 65 years and over (Fig. 8), a relatively stable mortality rate is apparent over a long period, which occurred following on from its rapid growth in the 1960s and 1970s. This mortality rate began falling only after 1990. However, this is a group which has the highest cervical cancer mortality rate, in 2010 being 21/100,000 women. In terms of absolute numbers for 2010, over 690 women in this age group died from the disease. The number of cervical cancer deaths in the overall Polish population of women in 2010 was 1,735,

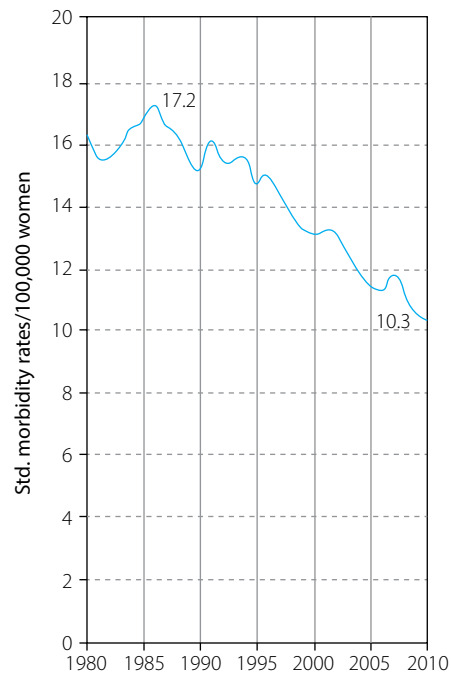


FIG. 3. Standardised morbidity rates for women suffering from cervical cancer in Poland during 1980-2010

which is 400 deaths less compared to 1991. The standardised mortality rates and absolute numbers of cervical cancer deaths recorded in the general population of Polish women between 1963 and 2010 are presented in Figure 9.

Upon analysing the socio-demographic factors affecting women's participation in cervical cancer screening, it was found that over a quarter (27%) of women aged 15 and above had never had a Pap test performed (Fig. 10);

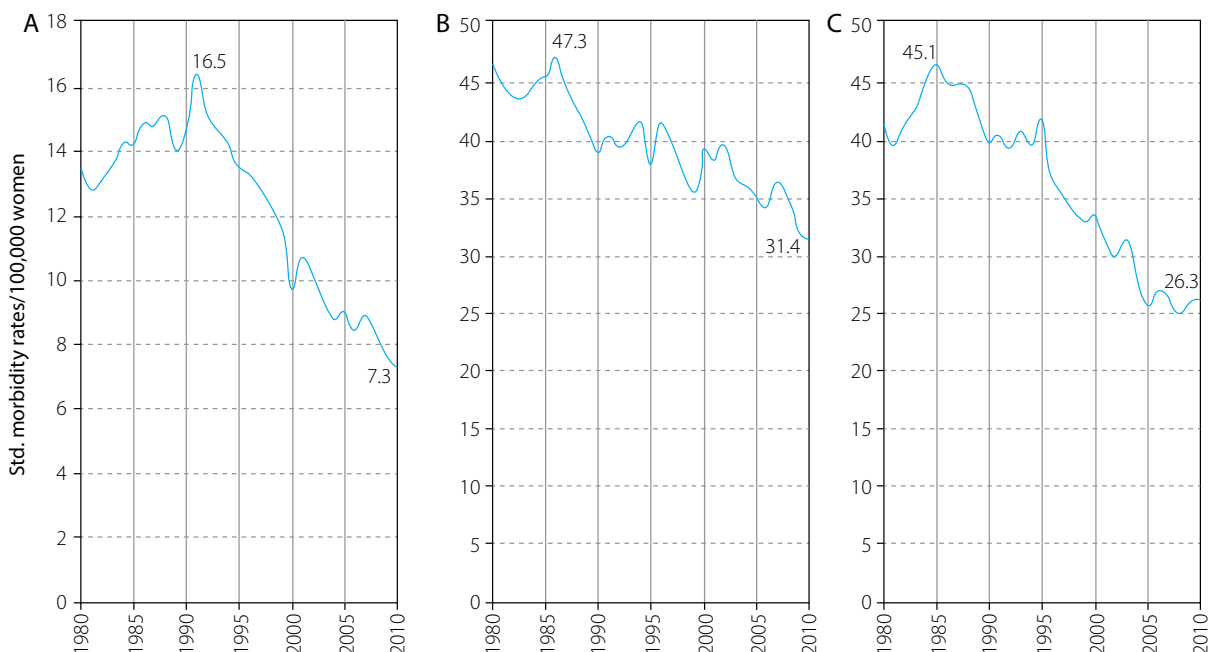


FIG. 4. Standardised morbidity rates for women suffering from cervical cancer in Poland according to age groups of 20-44 (A), 45-64 (B) and 65+ (C) during 1980-2010

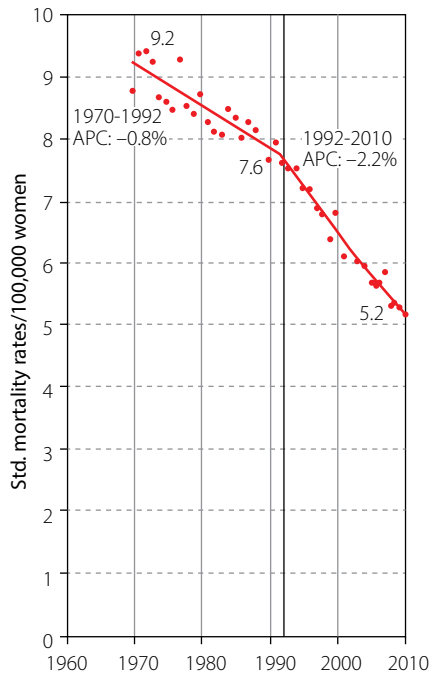


FIG. 5. Standardised mortality rates for cervical cancer in Polish women during 1970-2010

of these, the majority lived in rural areas. The larger the city lived in, the greater were the proportions of women who had performed the Pap test at least once during their lives (Fig. 11). The clearest factor differentiating the above group is however education. The largest group of women who had never performed the Pap test consisted

of those with primary and junior high school education (49%). For those possessing vocational, secondary and higher education, the numbers were respectively 25%, 24% and 14% (Fig. 12).

Due to the relatively small sample size (523 women) of this study performed by the COI and TNS, it can be considered to be a starting point for extended research projects targeted at elucidating the reasons why women’s participation in cytological screening is insufficient. Nevertheless, the above correlations suggest that a thorough educational and informational campaign on cervical cancer is required, especially one focused on women living in rural areas and those having a lower education. It appears that raising health awareness in these socio-demographic groups could help improve participation rates for screening. It should however be noted that 1/3 women with a higher education undergo cytology every year, and more than half (55%) do so every 2-3 years. According to the latest guidelines of the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP) and the American Society for Clinical Pathology (ASCP), it is sufficient that women aged 21-65 undergo such testing once every three years, and performing yearly cytology is not indicated.

PROGRAMME FOR PREVENTION AND EARLY DETECTION OF CERVICAL CANCER IN POLAND

Following European Commission recommendations, Poland launched a nationwide programme for cytological screening in 2007. Its target was the female

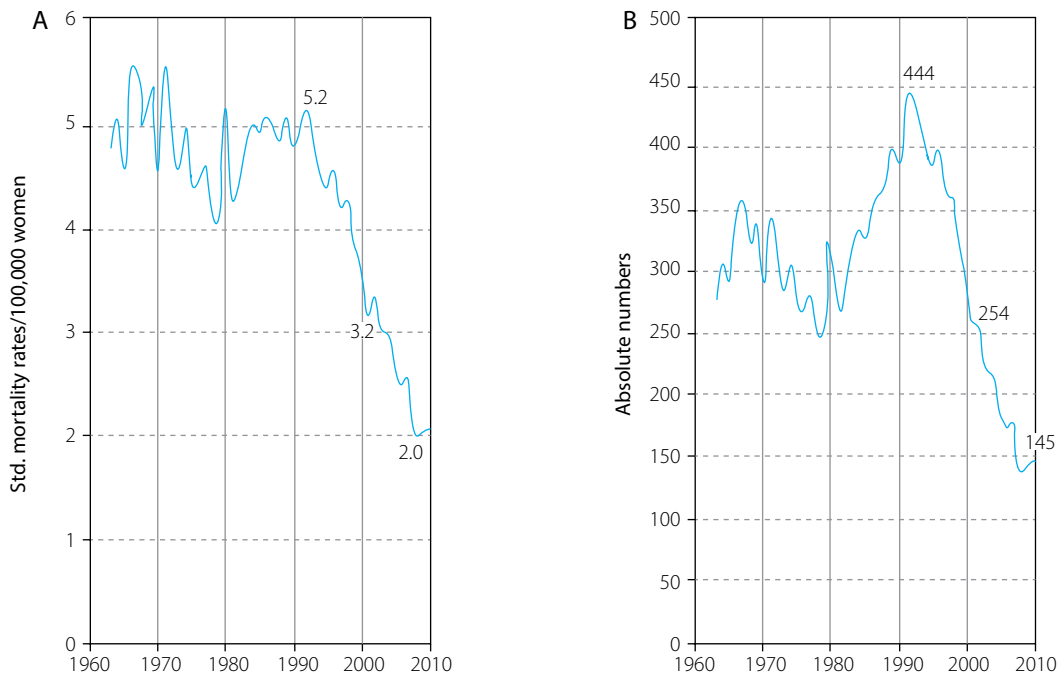


FIG. 6. Standardised mortality rates and absolute numbers of deaths due to cervical cancer in Polish women during 1963-2010 for those aged 20-44 years

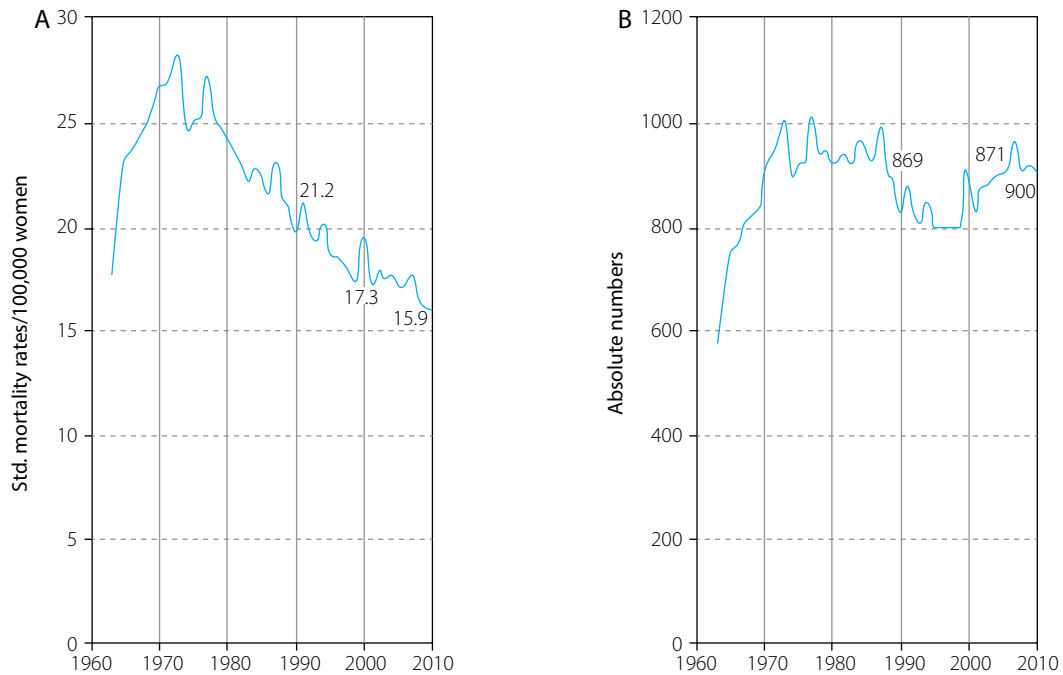


FIG. 7. Standardised mortality rates and absolute numbers of deaths due to cervical cancer in Polish women during 1963-2010 for those aged 45-60 years

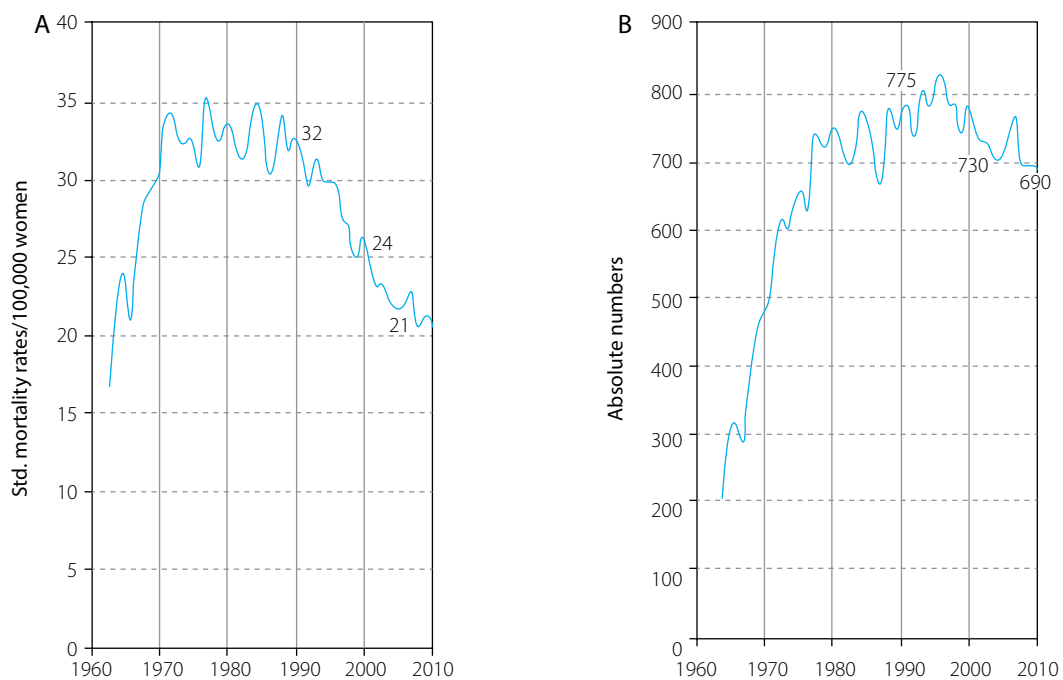


FIG. 8. Standardised mortality rates and absolute numbers of deaths due to cervical cancer in Polish women during 1963-2010 for those aged 65+ years

population, aged 25-59 years, insured by the National Health Fund (NFZ). Some women also undergo screening outside this programme, but receive financing from the NFZ, for example through Specialist Outpatients and Primary Health Care, whilst others undergo private gynaecological testing [28]; such data are not however recorded, and therefore it is difficult to assess the total number of women being so tested.

In 2009, 26.77% of women took part in the cervical screening programme [29]. Data from subsequent years have not been published, but even if an upward trend is maintained from the first years of the programme, it seems that only around 1/3 of Polish women are covered. It should nevertheless be remembered that these figures do not include Pap tests performed outside the programme, and therefore such estimates will be underval-

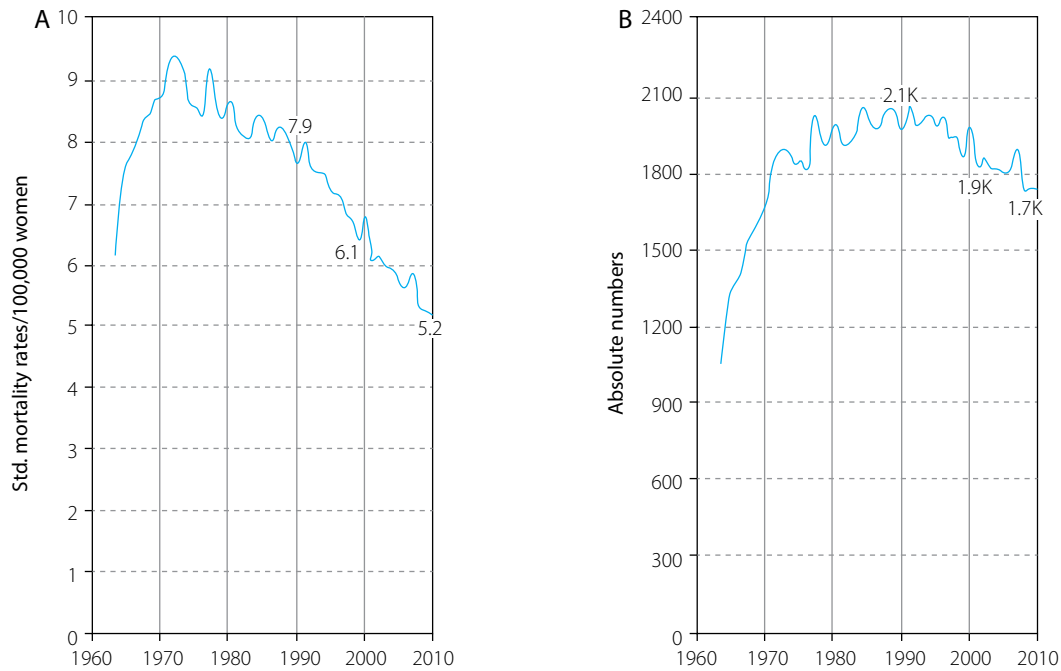


FIG. 9. Standardised mortality rates and absolute numbers of deaths due to cervical cancer in the overall Polish population during 1963-2010

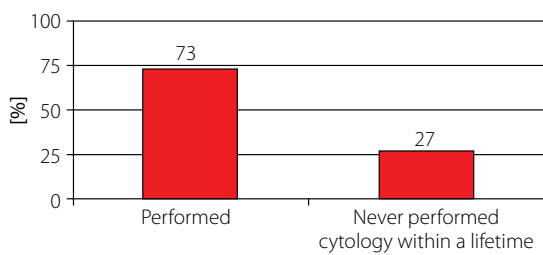


FIG. 10. Proportions of women never having undergone cytological testing

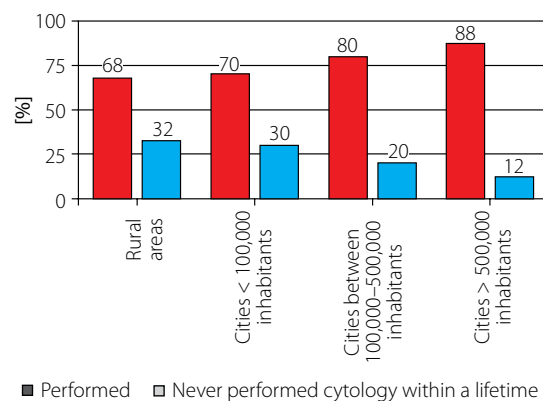


FIG. 11. Proportions of women who had undergone cytological testing according to place of residence

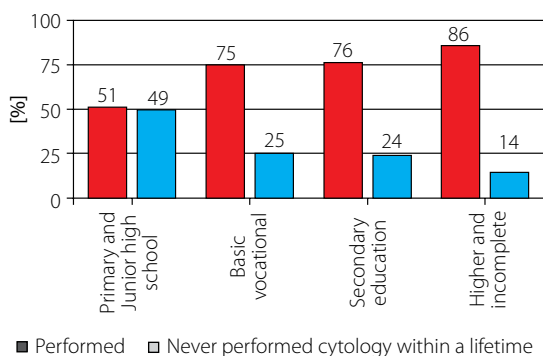


FIG. 12. Proportions of women who had undergone cytological testing according to education grade

ued. Despite full records being unavailable, such a proportion of women undergoing cytological screening is insufficient to obtain a satisfactory population impact. The low screening levels found in our study are a major drawback in the attempt to reduce cervical cancer rates

in Poland. We also do not have precise data on how many actual Pap tests are performed and on those women who have never had such tests done. It therefore seems necessary that these data be obtained to allow a high risk group of death from cervical cancer to be defined and appropriate countermeasures to be undertaken.

GLOBAL RECOMMENDATIONS FOR ORGANISING A PROGRAMME FOR THE PREVENTION AND EARLY DETECTION OF CERVICAL CANCER

An organised and comprehensive programme for prevention and the early detection of cervical cancer should include the three interdependent factors of primary prevention, secondary prevention and phase III prevention [2]. The principal aim of any prevention pro-

gramme is to eliminate the causative factor, which for cervical cancer is infection by the human papillomavirus. Interventions in primary prevention which are aimed at reducing the spread of HPV infection and which should be included in such a programme include ensuring that enough girls aged 9-13 years receive a full cycle of HPV vaccination and that boys and girls receive appropriate sex education, thus aiming to reduce the spread of sexually transmitted diseases, including HPV infection [2]. As part of the complex structured programme for preventing cervical cancer, the aim of secondary prevention is to minimise the morbidity and mortality rates. This includes suitably organising a network of clinics throughout the country to ensure that all patients aged 30-49 years have easy access to appropriate screening for the early detection of precancerous lesions and to provide appropriate treatment for women with known precancerous changes, before they progress. It should be borne in mind that the programme should also cover those women previously vaccinated who should be treated like the rest of the general female population in Poland [2]. As part of the phase III prevention, it is necessary to ensure that women with cervical cancer receive the required treatment so that mortality and any complications are reduced. Both monitoring and the evaluation of such programmes are equally important. By such means, a structured programme can permit drastic reductions in morbidity and mortality from cervical cancer to be achieved in some countries such as Finland [2].

There have been numerous studies in recent years on the molecular diagnosis of human papillomavirus. These have allowed new methods of screening for precancerous changes to be proposed. Both the World Health Organisation (WHO) [2] and recommendations from European organisations [30] point to the advantages of screening programmes for prevention and the early detection of cervical cancer based on virology rather than cytology. They advocate taking into account changes in existing screening programmes based on cytology to those based on virological investigation, but without running two programmes at the same time. Virological based screening should be started at 35 years (at least not earlier than 30 years) and finished at 60-65 years of age. The interval between successive virological testing, when a previous test was negative, should not be less than 5 years but may be extended to 10 years depending on the woman's age and previous test results, thus raising the chances of more women being covered by the programme [30]. Furthermore, samples for virology can be taken by the patients themselves without any third party involvement, which may also result in the programme covering more women who would otherwise have abstained because of cultural or societal reasons/restrictions. This method of sample collection, however, should remain as part of pilot studies that concern only those women not participating in screening [30].

HOW CAN POLAND'S PRESENT EPIDEMIOLOGICAL SITUATION BE IMPROVED?

High rates of morbidity and mortality from cervical cancer are still being observed in Poland. A significant number of women do not undergo screening. Nor is it known how many women (and how often) are tested outside screening programmes. Indeed, it is still not known how to reach those women not participating in cytology testing. This therefore requires that the current programme for prevention and early detection of cervical cancer be verified and modified. In accordance with the aforementioned recommendations, it seems that screening based on virology testing should indeed be adopted in our country, which is likely to lead to increased numbers of women covered by the programme. At the same time, introducing vaccination of girls aged 9-13 years should be considered under this programme. It is also necessary to identify those women who do not undergo screening and propose that they participate in pilot studies where they take their own samples. Another important aspect is additionally through education and information campaigns aimed at increasing the numbers of women screened. For such purposes, it appears necessary to reach the immediate social milieu of these women, not only through their families and partners, but also through primary care physicians, representatives of local authorities and church leaders. This would ensure that overall levels of people's health and wellbeing are raised regarding cervical cancer prevention, as well as building up such awareness for future generations.

DISCLOSURE

Authors report no conflict of interest.

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