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Methods of Cervical Cancer Screening in Developed and Developing Countries

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1. Abstract

1.1. Introduction

Cervical cancer (UCC) is the fourth most common cancer in women worldwide. Diagnostic and therapeutic evolutions in industrialized countries associated with an adequate policy of management by systematic screening have allowed a strong decrease in maternal morbimortality. The existence of effective programs to control UCC and the frequency of screening explain the observed difference in UCC mortality between DPs and SIDS.

1.2. Materials and Methods

We conducted a systematic review of the literature pertaining to screening practices in DPs and SIDS. A literature search was performed in the MEDLINE database of articles published between 2015 and 2019.

1.4. Results

The PubMed search retrieved 919 titles, of which 92 met the inclusion and exclusion criteria. Twelve articles were included from the references. The publications were of interest to different countries of the world, 48 articles related to European countries (22 countries), 20 related to African countries (12 countries), 22 related to Asian countries (13 countries), 17 related to North and Central American countries (8 countries), 5 related to South American countries (2 countries), and 5 articles related to Australia.

1.5. Discussion

The majority of the countries in our study used an organized screening program with an invitation system. The American [21], Canadian [22] and European [19] recommendations, as well as the WHO [6], recommend an interval of 3 years between two UFHs or two VIAs and an interval of 5 years in the case of screening by combined UFH and HPV test.

1.6. Conclusion

Our literature review has provided an update on different UCC screening strategies around the world, which offers an opportunity to learn from best practices and experiences in other countries.

2. Introduction

Cervical cancer (UCC) is the fourth most common cancer in women worldwide. In 2018, approximately 570,000 women were diagnosed with UCC worldwide which represents 6.6% of all female cancers, and approximately 311,000 women died from the disease. Furthermore, approximately 90% of UCC deaths occurred in low- and middle-income countries where mortality is 18 times higher compared to developed countries (DCs) [1]. In industrialized countries, diagnostic and therapeutic evolutions associated with an adequate management policy through systematic screening have allowed a strong decrease in mortality and morbidity where only 15% of UCC occur, with a decrease of 4% per year [2]. Most cases of UCC in developing countries (DC) are discovered in women in their mid-thirties, an age that is up to 15 years earlier than in women in developed countries [3]. In developed countries, 80% of detected cases are cured due to its early discovery. In developing countries, 80% of cervical cancers are incurable at the time of detection because it is too late. In fact, women present with a symptomatic tumor at an advanced stage (most often stage III and IV), where the 5-year survival rate is only 20%.

The existence of effective UCC control programs and the frequency of screening explain the observed difference in UCC mortality between PD and PEVD [4].

3. Materials and Methods

We conducted a systematic review of the literature pertaining to screening practices in DPs and SVDPs. A literature search was performed in the MEDLINE database of articles published between 2015 and 2019.

Inclusion criteria: articles evaluating screening modalities and/or describing methods of screening for UCC in the population of interest for screening in a given country.

Exclusion criteria:

Studies that focus on screening in a subpopulation.

Research that evaluated the performance of different screening methods, but focused more on test validity, efficacy, or safety

4. Results

The PubMed search retrieved 919 titles, of which 92 met the inclusion and exclusion criteria. Twelve articles were included from the references. Individual articles published between 2015 and 2019 were about screening actions or programs implemented between 1999 and 2019. The publications were of interest to different countries around the world, with 48 articles relating to European countries (22 countries), 20 relating to African countries (12 countries), 22 relating to Asian countries (13 countries), 17 relating to North and Central American countries (8 countries), 5 relating to South American countries (2 countries), and 5 articles relating to Australia. The table shows the number of countries mentioned in our study by continent and the number of corresponding articles.

In Europe, the majority of countries used two screening methods: cytology and HPV testing. Some Eastern European countries and France reported only cytology as a screening method. Both tests (cytology, HPV) were also used in almost all countries in North and Central America, with the exception of Canada, which performed only cytology. In Asia, the main screening test used was cytology. HPV testing was performed only in China and India. VIA was used in some countries such as Bangladesh, Mongolia, and India, and in poor settings in China.

In Africa, all articles mentioned the use of VIA. Cytology was only reported for some countries such as Cameroon, Nigeria and Zimbabwe. HPV testing was not mentioned in any of the articles for Africa. In Australia, HPV testing was introduced in 2017 as part of the renewal of the national screening program. The lowest minimum target population age (15 years) was reported in Zambia, Zimbabwe, and Mongolia. While the highest minimum target population age (35 years) was reported in China and Thailand. Four countries did not specify an age limit for participation in screening, Honduras, South Korea, and two European countries: Germany and the Czech Republic. The highest age limit (89 years) was found in the United States in a National Cancer Institute study of nearly 4.7 million women from 2010 to 2014. While the lowest cut-off age (49 years) was reported in Guinea, Ethiopia, Morocco and Zambia. The screening cut-off age was not recommended in either Japan or South Korea.

The screening interval in most of the countries in the study was between three and five years depending on the test used and the age range involved, with the exception of six countries. Germany and the Czech Republic adopted annual screening, Japan and South Korea recommended biennial screening, and Canada and the Dominican Republic opted for screening every 1 to 3 years. The level of screening coverage varied considerably between countries and sometimes within countries because of heterogeneity in the organizational strategies deployed, as well as economic disparity between geographic areas. According to the articles included, UCC screening was offered to women in a program described by the authors as organized in 72% of European countries. 82% of the European countries in our study had an invitation system, with physical invitation letters being the most common method, followed by telephone invitations. With the exception of three countries, African countries did not have national screening programs, and virtually no countries had a system of individual invitation of women in the target population. In North and Central America, two countries (25%) used an individual invitation method. In Canada, physical letters inviting women to be screened were the preferred method. Program staff in the Dominican Republic contacted participants by phone or in person to remind them about follow-up and appointments for results. In South America, in addition to letters and phone calls, health professionals called community health workers were also responsible for verbally inviting women who were attending health centers or going directly to their homes. In Asia, the letter-invitation system has been adopted by Hong Kong, Japan, and Mongolia. In China, trained interviewers are responsible for inviting women door-to-door. In India, women were invited from public places. In Australia, the government looked into the Letter of Invitation system with a reminder system in place.

Table 1: Nombre de pays et d'articles par continent.

Continent	Nombre de pays	Nombre d'articles
Europe	22	48
Afrique	12	20
Asie	12	22
Amérique du Nord et Centrale	8	17
Amérique du Sud	2	5
Australie	1	5

Table 2 : Méthode de dépistage du CCU dans les pays d'Europe.

Pays	Méthode du dépistage	Pays	Méthode du dépistage
Allemagne	Test cytologique, Test HPV	Estonie	Test cytologique
Angleterre	Test cytologique, Test HPV	France	Test cytologique
Belgique	Test cytologique, Test HPV	France-Guyane	Test cytologique
Danemark	Test cytologique, Test HPV	Lituanie	Test cytologique
Espagne	Test cytologique, Test HPV	Pologne	Test cytologique
Norvège	Test cytologique, Test HPV	Hongrie	Test cytologique
Finlande	Test cytologique, Test HPV	Roumanie	Test cytologique
Pays-Bas	Test cytologique, Test HPV	République tchèque	Test cytologique
Suède	Test cytologique, Test HPV		
Irlande	Test cytologique, Test HPV		
Islande	Test cytologique, Test HPV		
Italie	Test cytologique, Test HPV		
Turquie	Test cytologique, Test HPV		
Portugal	Test cytologique, Test HPV		

Table 3: Méthode de dépistage du CCU dans les pays d'Amérique du Nord et d'Amérique centrale

Pays	Méthode du dépistage
États-Unis	Test cytologique, Test HPV
Dominique	Test cytologique, Test HPV
Canada	Test cytologique
Îles du Pacifique US	Test HPV, IVA (triage)
Nicaragua	Test cytologique, Test HPV, IVA
Le Salvador	Test HPV
Honduras	Test HPV, IVA
Guatemala	Test HPV, IVA (triage)

In South America, cytology was the only test used.

Table 4: Méthode de dépistage du CCU dans les pays d'Amérique du Sud.

Pays	Méthode du dépistage
Brésil	Test cytologique
Chili	Test cytologique

In Asia, the main screening test used was cytology. HPV testing was performed only in China and India. VIA was used in some countries such as Bangladesh, Mongolia, and India, and in poor settings in China.

Table 5: Méthode de dépistage du CCU dans les pays d'Asie.

Pays	Méthode du dépistage
Corée	Test cytologique
Cambodge	Test cytologique
Hong Kong	Test cytologique
Émirats arabes unis	Test cytologique
Thaïlande	Test cytologique
Vietnam	Test cytologique
Japon	Test cytologique
Liban	Test cytologique
Inde	Test cytologique, Test HPV, IVA
Chine	Test cytologique, Test HPV, IVA
Mongolie	Test cytologique, IVA
Bangladesh	IVA

In Africa, all articles mentioned the use of VIA. Cytology was only reported for some countries such as Cameroon, Nigeria and Zimbabwe. HPV testing was not mentioned in any of the articles for Africa.

Table 6: Méthode de dépistage du CCU dans les pays d'Afrique.

Pays	Méthode du dépistage
Cameroun	IVA, IVL, Test cytologique
Nigeria	IVA, Test cytologique
Guinée	IVA, IVL
Congo	IVA, IVL
Zimbabwe	IVA, IVAC
Zambie	IVAC numérique
Ouganda	IVA
Rwanda	IVA
Maroc	IVA
Éthiopie	IVA
Tanzanie	IVA
Malawi	IVA

In Australia, HPV testing was introduced in 2017 as part of the renewal of the national screening program.

Table 7: Méthode de dépistage du CCU en Australie.

Pays	Méthode du dépistage
Australie	Test HPV avec génotypage partiel et triage réflexe par LBC

5. Discussion

The majority of countries in our study used an organized screening program with an invitation system. 16 European countries (72%), seven Asian countries (54%), six North and Central American countries (75%), two South American countries (100%) and three African countries (25%). However, there are significant variations in the organization of screening, screening methods, target age range and recommended screening interval, and payment strategies. Screening for UCC can be conducted in an opportunistic or organized manner. Opportunistic screening requires that women take the initiative to seek out the screening service, whereas in organized screening, women are invited by the organizer to perform a scheduled test. In the literature, a comparison of the trends in cancer incidence in different countries has led to the conclusion that organized screening is better than opportunistic screening. Therefore, the latest EU and WHO recommendations indicate that UCC screening should be offered to the general population in organized screening programs [5, 6]. For UCC screening programs to be considered organized, they must have the following characteristics: (1) clear policies specifying the target population, and specifying the type of screening tests and screening intervals; (2) public funding; (3) a system for inviting women for screening; (4) a team to oversee program implementation; and (5) structures to ensure quality improvement [7]. In addition, the SIDS that reported having an organized screening program did not meet the performance and quality indicators provided by WHO.

According to Louie et al, there are no screening programs for the early detection of precancerous lesions in sub-Saharan African countries. Most screening activities are carried out as pilot projects or scientific research that are discontinued after completion [8]. According to our systematic review of the literature, three methods are currently used for primary UCC screening: cytology, HPV testing and VIA/VILI. The most frequently used test is the cervical smear (conventional smear). This test is sometimes combined with HPV testing. However, most low- and middle-income countries lack the capacity to initiate and sustain quality cytology screening programs due to underdeveloped health services, several other priorities, lack of resources, and variable commitment to providing preventive health care; these programs have failed to reduce UCC mortality in some LICs and MICs where they exist [9,10]. VIA is the most widely evaluated alternative test in low-resource countries that allows a "see and treat" approach in a single visit. It is a point-of-care screening test in low-resource countries given the limited consumable and infrastructure requirements, the immediate results allowing for further testing and treatment in the same session, and the ease with which providers can be trained, despite variation in accuracy and reproducibility due to the subjective nature of the test; the realistic sensitivity and specificity of a single quality-assured VIA in detecting CIN2-3 lesions are approximately 50 and 85%, respectively [11]. HPV testing has high sensitivity but low specificity. Specificity is of increased importance in resource-limited settings, whether follow-up of a positive test is assessed or treated immediately. Additional costs are incurred when patients with a false-positive test are referred for an expensive test such as colposcopy. Similarly, when treatment is based on a screening test, low specificity of the test may lead to unnecessary treatment of a large number of patients. Several other studies confirm that HPV testing is feasible in low-resource settings and appears to be the best strategy for UCC in this setting [12-13]. A large-scale randomized trial in rural India showed that a single round of HPV testing could reduce UCC incidence and mortality by approximately 50%, whereas VIA and cytology-based approaches had little effect on these outcomes [14]. HPV DNA testing is recommended because of its sensitivity, which is better than that obtained by cytology or VIA [6,15], allowing longer screening intervals (minimum five years) and can be performed with self-collected vaginal samples [6]. When combined with Pap smears, HPV testing can achieve a sensitivity of nearly 100% and a specificity of 93% in women aged 30 years and older, with a negative predictive value of nearly 100% [16]. In addition, WHO recommends that, where resources permit, women aged 30-49 years should undergo validated tests that detect HPV in cervical or vaginal samples [6]

Over the past two decades, HPV testing has become an invaluable part of clinical guidelines for screening in several countries [17,18]. Nevertheless, to account for the relatively low specificity of the test and to avoid unnecessary follow-up or overtreatment of women with likely transient HPV infections, European guidelines recommend starting primary HPV testing after the age of 30 and up to 35 years [5,19]. However, in countries or regions where a primary cytology program is prevalent and effective, European recommendations allow the program to continue for 20-30 year olds, while initiating primary HPV testing for ages above 30 years [5,19].

Regarding the starting and ending ages of screening, we see that recommendations vary from one country to another, and even from one state or region to another. While current European recommendations emphasize the need to cover the 25-65 age range [20], many US organizations recommend starting screening around 18-21 years of age, because of the large proportion of young women who are already sexually active at that age and the difficulty for professionals to obtain information related to the sexual history of their patients. As for the age limit for screening, the U.S. Preventive Services Task Force (USPSTF) recommends that women over the age of 65 should not be screened if they have had a recent Pap smear (i.e., three consecutive negative Pap smears with no cytological abnormalities in the past 10 years) [21]. According to our systematic review of the literature, in resource-rich countries, patients are often screened for UCC every three to five years, depending on the test used and the age range involved. However, this frequency of screening is not feasible in most resource-limited settings. Decisions about the frequency of screening must therefore be made based on available resources. With regard to the age at which screening begins and ends, we see that recommendations vary from country to country, and even from state to state or region to region. While current European recommendations emphasize the need to cover the age range 25-65 years [20], many US organizations recommend starting screening around 18-21 years. According to our systematic review of the literature, in resource-rich countries, patients are often screened for UCC every three to five years, depending on the test used and the age range involved. However, this frequency of screening is not feasible in most resource-limited settings. Decisions regarding the frequency of screening must therefore be made based on available resources. The US [21], Canadian [22], European [19] and WHO [6] guidelines recommend an interval of 3 years between two UFHs or two VIAs and 5 years for combined UFH and HPV testing. Our literature review also described the invitation practices of population-based UCC screening programs worldwide. Physical invitation letters were the most common method, followed by telephone invitations. Invitation methods are part of the quality parameters of an organized screening program [5], which explains the fact that the majority of developed countries using organized screening programs resorted to the use of these methods. The method of invitation in a population-based screening program can have a direct impact on participation and screening coverage [23].

6. Conclusion

Guidelines for cancer screening differ from country to country, with some commonalities but also clear differences. Prevention of UCC has been largely achieved in developed countries; it will be necessary to use the tools and knowledge currently available to give women in low-resource settings the same opportunity to save lives. Therefore, pilot studies are needed, especially scientific research on program implementation, to inform feasible strategies and to evaluate national organized screening, testing, frequency, and age limits to estimate the benefits of such actions for our country.

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