Incidence, mortality and risk factors of cervical cancer in the world

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Abstract

Background: Cervical cancer imposes a huge global burden. To date, various studies have been conducted on the risk factors associated with cervical cancer. The aim of this study was to investigate the incidence, mortality, and geographical distribution of cervical cancer and its risk factors in the world.

Methods: A literature search was conducted using PubMed, Web of sciences, Scopus, and Google Scholar to search for studies published between 2000 and 2017. The keywords used included cervical cancer, cervix uteri cancer, risk factor, incidence, mortality, and a combination of these terms.

Results: The results of this study showed that the incidence of cervical cancer varies considerably between developed and developing countries. The findings of this study demonstrated that several factors including sexually transmitted infections, reproductive factors, hormonal influences, genetics and host factors are responsible for the incidence of cervical cancer. Conclusion: The results of this review study suggested that combination of biological, economic and health factors contributes to the incidence of cervical cancer. A large proportion cervical cancer can be prevented by prevention programs, lifestyle enhancement, smoking cessation, and timely and effective treatment of pre-cancerous lesions.

Keywords
Cervical cancer, Incidence, Mortality, Risk factors, World
Introduction

Cancer is currently the second leading cause of death, after heart disease, in the world (Torre et al., 2017), and this imposes a huge burden on societies (Cancer and Organization, 2016). Gynecological cancers are among the most common cancers in women. Cervical cancer is the most common type of gynecological cancer (Ferlay et al., 2015). Indeed, it is one of the major public health problems in the world and one of the top causes for disability-adjusted life-years (DALYs) (Fitzmaurice et al., 2015). Yet, cervical cancer is one of the most preventable cancers (Denny, 2012). Among women, it is a common cause of death, especially in women from less developed countries (Ferlay et al., 2015). However, from insight from research studies, the viral etiology of cervical cancer has become more well understood (Bosch and Muñoz, 2002). This cancer is among the most preventable cancers because of its slow progression, the presence of detectable lesions using cytology, and the introduction of effective treatments (Leyden et al., 2005).

In 2012, 528,000 new cases and 266,000 cases of death from cervical cancer were reported (Ferlay et al., 2015). Cervical cancer is a dynamic condition that has the highest incidence rate in young adults (Bruni et al., 2010). There has been a gradual decline in the incidence and mortality associated with cervical cancer worldwide. There has been a significant reduction in mortality associated with cervical cancer in developed countries as many cases are detected in a timely manner (Vaccarella et al., 2017). The results of several studies suggest that socioeconomic differences play an important role in the incidence, mortality and survival rate of cervical cancer (Akinyemiju et al., 2016; Ibfelt et al., 2013; Kim and Kang, 2016; Ueda et al., 2006). This is associated with a variety of factors, such as low access to screening (Leinonen et al., 2017), non-implementation of prevention programs (Chidyaonga-Maseko et al., 2015), ineffective and inadequate treatment, and poor sanitary conditions (Benard et al., 2008; Ganesan et al., 2015; Rossi et al., 2014).

Several epidemiological studies have revealed the role of various genetic factors in the incidence of cervical cancer (La Vecchia and Boccia, 2014; Roura et al., 2014; Silva et al., 2014). Among them are the infection of patients with one of the human papilloma virus (HPV) oncogene types; this factor is the most important etiological factor for induction of this cancer (Bosch and Muñoz, 2002; Plummer et al., 2016). Indeed, HPV is the most common sexually transmitted infection worldwide (Crosbie et al., 2013), and is strongly associated with cervical cancer. Over the past years, HPV testing (as a screening method) and vaccination were introduced for the prevention of cervical cancer (Heydari et al., 2017).

Identification of key risk factors continues to play an important role in the prevention of cervical cancer. To date, various studies have been conducted on the risk factors associated with cervical cancer (Durowade et al., 2012; Makuza et
The aim of this study was to investigate the incidence, mortality, and geographical distribution of cervical cancer and its risk factors in the world.

**Methods**

A literature search was conducted using PubMed, Web of sciences, Scopus, and Google Scholar to search for research studies published between 2000 and 2017. The keywords used included cervical cancer, cervix uteri cancer, risk factor, incidence, mortality, or a combination of these terms. The studies which clearly described the incidence and mortality rates of cervical cancer and/or related risk factors were included in our review study.

**Results**

**Incidence and mortality**

Cervical cancer is the fourth most common cancer in women and seventh most common cancer in general. In 2012, 528,000 new cases of cervical cancer were detected. There is a significant geographical difference in the incidence of cervical cancer. The majority of these cancers (about 85%) are found in less developed areas (Vaccarella et al., 2017). The incidence and mortality of cervical cancer were found to be the highest in sub-Saharan Africa, Southeast Asia, Latin America, the Caribbean, and Central and Eastern Europe. In Zimbabwe, Malawi, and Uganda, the prevalence of cervical cancer is more than twice as compared to other regions. The lowest prevalence was found in Western Asia (Torre et al., 2016). Five countries had the highest incidence of cervical cancer cases in 2012; they were India (122,844 cases), China (61,619), Indonesia (20,928), Brazil (18,503), and the Russian Federation (15,342) (Momenimovahed et al., 2017). It was reported, in 2012, that the age-standardized incidence of cervical cancer was 14 per 100,000 people worldwide, varying from 8.5 to 25.7 in countries with a high-to-low human development index. The incidence of cervical cancer shows a decreasing trend in most European and South American countries, North America and Oceania, and some Asian countries (such as Japan, China, and India) (Vaccarella et al., 2013). Indeed, the decrease of cervical cancer incidence varies across regions (Vaccarella et al., 2017).

Cervical cancer is the third leading cause of cancer death among low-income and middle-income countries. Although rare among high-income countries (Torre et al., 2016), there were still approximately 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of deaths from cancer in women. Approximately, 9 out of 10 cases of cervical cancer death occur in less developed regions. The mortality rate varies (up to 18-fold) between different regions of the world; it is less than 2 in 100,000 people in Western Asia, Western
Europe, and Australia/New Zealand, but over 20 per 100,000 people in Melanesia, and Middle and Eastern Africa (Vaccarella et al., 2017). A quarter of the deaths from cervical cancer occur in India. Women in many of the high incidence areas, including Africa, are less likely to be screened for cervical cancer and, therefore, are most at risk for developing invasive cervical cancer (De Sanjosé et al., 2007). According to Momenimovahed et al. (2017), the mean age-standardized mortality rate for cervical uterine cancer is 6.8 in 100,000 people (range varies from 2.7 in 100,000 people to 16.6 in 100,000 people) in countries with a high-to-low human development index (Momenimovahed et al., 2017).

There are important variables in the incidence and mortality of cervical cancer in different regions of the world. These variables that account for observed geographical differences include access to screening programs (that allow for early detection and timely treatment of pre-cancerous lesions), prevalence of HPV (Torre et al., 2016; Vaccarella et al., 2013), and effective prevention (such as vaccination against HPV) (Torre et al., 2016). In high-income countries where screening programs have been introduced and implemented over decades, the incidence of cancer has reduced by 4% annually and by a total of 70%. But the steady rate or even increased incidence of cervical cancer is still observed in countries with no screening, lack of quality screening, or low screening coverage (Torre et al., 2016). Socioeconomic differences among different countries play an important role in compliance with the screening programs (Monnat, 2014). Limited resources for implementing screening programs, lack of adequate knowledge, reduced access to health care (due to financial, physical or social constraints), and psychosocial stress all play an important role in screening and health promotion programs (Akinyemiju et al., 2016). As mentioned earlier, the differing prevalence of HPV is one of the most important factors for geographical variations in the incidence of cervical cancer. For instance, HPV is more prevalent in Africa and Latin America than it is in North America, Europe, and Asia (Bruni et al., 2010).

Vaccination against HPV has been introduced for many years to prevent and reduce the incidence of cervical cancer. However, there are several restrictions on using this effective method, with the most important being the cost of vaccination among developing countries (Gonçalves et al., 2014). Sex and reproductive factors as well as the quality of screening programs (laboratory and follow up) can also interfere with geographical differences (Vaccarella et al., 2013). Lack of accurate detection of lesions by cytology and lack of follow-up of abnormal cytology results are also responsible for high incidence of cervical cancer in less developed countries (Leyden et al., 2005).

Risk factors

Sexually transmitted infections (STI)

- HPV
The primary cause of pre-cancerous and cancerous cervical lesions is infection with a high-risk or oncogenic HPV types (Wardak, 2016). Most cases of cervical cancer occur as a result of infection with HPV 16 and 18. High-risk types, especially HPV 16, are found to be highly prevalent in human populations (Bruni et al., 2010). The infection is usually transmitted by sexual contact, causing squamous intraepithelial lesions. Most lesions disappear after 6 to 12 months due to immunological intervention. However, a small percentage of these lesions remain and can cause cancer (Zur Hausen, 2002).

The results of a meta-analysis showed that the highest prevalence of HPV occurs at the age of 25 years (De Sanjosé et al., 2007), which could be related to changes in sexual behavior (Crosbie et al., 2013). In a meta-analysis study, the bimodal distribution of cervical cancer in some regions has been studied. In this distribution, immediately after sexual intercourse, an outbreak of HPV can be observed, which is followed by a plateau at adult age; the second peak again is observed after 45 years of age (Bruni et al., 2010). Permanent infection with one of the high-risk types of HPV over time leads to the development of cervical intraepithelial neoplasia (CIN). The major mechanisms through which HPV contributes to carcinogenesis involve the activity of two viral oncoproteins, E6 and E7, which interfere with major tumor suppressor genes, P53 and retinoblastoma. In addition, E6 and E7 are associated with changes in host DNA and virus DNA methylation. Interactions of E6 and E7 with cellular proteins and DNA methylation modifications are associated with changes in key cellular pathways that regulate genetic integrity, cell adhesion, immune response, apoptosis, and cellular control (Galani and Christodoulou, 2009).

- **Chlamydia trachomatis**

In the study of Koskela et al., the results showed that previous infection with *C. trachomatis* contributes to an increased risk of cervical squamous cell carcinoma. In this study, *C. trachomatis* DNA was detected in 40% of invasive squamous cell carcinoma (Koskela et al., 2000). The results of a case-control study in 7 countries showed that serum antibodies of *C. trachomatis* are associated with a 1.8-fold increase in the risk of squamous cell carcinoma. This risk increases in women with higher antibody titers and in women under 55 years of age. *C. trachomatis* infection may increase the risk of squamous cell carcinoma by increasing host susceptibility to HPV or increasing HPV mediated effects. Inflammation that occurs as a result of chronic *C. trachomatis* infection can lead to the production of reactive oxygen species; hence, this can damage DNA and increase the risk of HPV-associated carcinogenesis. Furthermore, women with *C. trachomatis* may have a weakened ability to clear the HPV infection (Smith et al., 2004). *Chlamydia* can cause chronic inflammation, cervical hypertrophy, and squamous metaplasia. The metaplastic cells are the potential target cells for HPV. Therefore, as a result of infection with *Chlamydia*, apoptosis may be inhibited, there may be excessive expression of E6/E7 oncogenes, and cellular deformity may occur (Silva et al., 2014).

- **Human immunodeficiency virus (HIV)**
The risk of developing infection from high risk HPV types is higher in women with human immunodeficiency virus (HIV) (Ferenczy et al., 2003; Palefsky, 2007). The results of the studies on the relationship between HIV and cervical cancer suggested a higher rate of persistent HPV infection with multiple oncogene viruses (Mbulawa et al., 2010), more abnormal Papanicolau (Pap) smears, and higher incidence of CIN and invasive cervix carcinoma among people with HIV (Pantanowitz and Michelow, 2011).

- **Herpes simplex virus (HSV)**

There is relationship between HSV-2 antibodies in serum and invasive cervical cancer (or squamous cell carcinoma, adenocarcinoma, or adeno-squamous cervical carcinoma), as suggested by Smith et al. (Smith et al., 2002). However, these results have not been confirmed. For instance, a nested case control study by Lehtinen et al. concluded that HSV-2 does not play a role in the carcinogenesis of the cervix (Lehtinen et al., 2002).

**Reproductive and sexual factors**

- **Sexual partners**

An increased risk of cervical cancer is observed in people with multiple sexual partners (Castellsagué et al., 2003; Liu et al., 2015). This increase in risk is generally attributable to an increased risk of HPV infection. However, in the study by Liu et al., the risk of cancer was still high even after controlling for HPV infection. Therefore, other factors may contribute to the increased risk of cancer in people with multiple sexual partners (Liu et al., 2015). In the study by Edelson et al., sexual experience at older ages was suggested to be associated with lower age of diagnosis (Edelson et al., 2009). Also, early age at first intercourse is a risk factor for cervical cancer (Louie et al., 2009).

- **Parity**

Several studies have shown that full-term pregnancy increases the risk of invasive cervical cancer (Hildesheim et al., 2001; Kim et al., 2012; Muñoz et al., 2002). Moreover, high parity increases this risk of cancer in women (Muñoz et al., 2002). In a collaborative international epidemiological study of cervical cancer, a direct correlation was found between the risk of cervical cancer and parity; there was an inverse association between the risk of cervical cancer and the age of the mother at first pregnancy (González et al., 2006). Findings from the study by Hildesheim et al. are in agreement with the aforementioned study. Hildesheim et al. concluded that the risk of cervical cancer significantly increases with an increase in the number of deliveries (Hildesheim et al., 2001). In a cohort study with over 13 years of follow-up, delivery was the predictor of CIN 3. In this review study, too, delivery was observed to increase the risk of developing cervical cancer, especially among women with high risk HPV infection. In addition, no increase in pregnancy-associated risks was observed (Jensen et al., 2013).
**- Oral contraceptive (OC) pills**

The current and recent use of combined oral contraceptive (OC) methods is associated with an increased risk of cervical cancer (Hildesheim et al., 2001; Vanakankovit and Taneepanichskul, 2008). In an international collaborative epidemiological study of cervical cancer, the relative risk in current users increased with an increase in the duration of OC use. It has been reported that the use of OC method for 5 years or more can double the risk of cancer. However, there is a slight increase in the incidence of invasive cervical cancer in those who used only injectable progesterone for 5 years or more (Cancer, 2007).

In a multi-center case control study, among women who tested positive for HPV DNA, the risk of cervical cancer increased by 3 times if they have used OCP for 5 years or more. The results of this study showed that the risk of cancer does not depend on the first time use of OC pills (Moreno et al., 2002).

**Behavioral factors**

**- Smoking**

To date, various studies have shown that smoking is one of the most important risk factors for CIN 3 and invasive cervical cancer. There is a link between the history of smoking or current smoking, with cervical cancer (Fonseca-Moutinho, 2011; Hildesheim et al., 2001; Kim et al., 2012; Plummer et al., 2003). In a large cohort study, the risk of cancer was reduced by 50% among those who stopped smoking for 10 years when compared with those who continued to smoke. In this study, passive smoking was not associated with an increased risk of cervical cancer (Roura et al., 2014). Rather, the age of smoking is related to the incidence of cervical cancer. The results of the re-analysis of 23 epidemiological studies showed that the risk of squamous cell carcinoma of the cervix is related to cigarette smoking; with an increase in the number of cigarettes smoked there is a decrease in the age of smoking onset (González et al., 2006).

Smoking can increase the risk of cervical neoplasia through several mechanisms. One of the mechanisms is the local induction of immune suppression by tobacco metabolites. In addition, chemicals in cigarettes, such as nicotine and its metabolites, can cause DNA damage in squamous cells (Roura et al., 2014). Smoking can cause epigenetic changes in the epithelium of the cervix and contribute to the pathogenesis of neoplasia in the cervix and in many other parts of the body (Ma et al., 2011).

**- Obesity**

Obesity increases the risk of cervical carcinoma and is important in the incidence of cervical adenocarcinoma associated with hormonal risk factors (Lacey et al., 2003; Lee et al., 2013; Poorolajal and Jenabi, 2016). In a case control study, the risk of developing cervix adenocarcinoma in obese women with body mass
index (BMI ≥30) and overweight women (BMI ≥25) was 2-fold higher than for other women (Lacey et al., 2003).

Due to the conversion of androgen to estrogen in the peripheral adipose tissue, obesity (especially after menopause) is considered to be a marker of increased sex hormones levels (Lacey et al., 2003). In addition to the role of obesity in the pathogenesis of cervical adenocarcinoma through hormonal activity, obese women are less likely to seek screening for cervical cancer (Ludman et al., 2010; Wee et al., 2000). There are different reasons for lower screening rates in this group. For one, obese women have delays in receiving services due to their negative physical image, shame, reduced respect by health care providers, and lack of willingness to lose weight (Friedman et al., 2012). Besides, obesity can be a sign of non-compliance with health behaviors, such as cervical cancer screening. Also, illnesses associated with obesity may limit the implementation of prophylactic services. The technical problems of performing Pap smears in obese women (such as their anatomy and lack of adequate equipment) can impact their willingness to seek effective screening (Ferrante et al., 2010; Friedman et al., 2012). Finally, there tends to be less advice given from doctors to obese women during routine screening; this is another reason for the lower rate of cervical cancer screening in obese individuals (Maruthur et al., 2009).

**Nutritional and dietary factors**

Cervical cancer occurs through a series of events, including HPV infection, persistence of HPV, and HPV-related lesions and progression towards cervical cancer (Munoz et al., 2009). The role of nutritional factors in the pathogenesis of cervical cancer has been taken into great account in recent years and several studies have evaluated this topic, though conflicting results have been obtained (González et al., 2011; Labani et al., 2009; Siegel et al., 2010). In one study, increased concentrations of α- and γ-tocopherol and higher nutritional intake of green vegetables, or dark green and yellow fruits, were associated with a 50% decrease in CIN 3 (Tomita et al., 2010). Therefore, receiving a healthy and balanced diet leads to higher levels of antioxidants and, therefore, can play a role in cervical neoplasia. In the study by Ghosh et al. (2008), a significant correlation was observed between higher intake of vitamin C, folate, vitamin E, beta-carotene, vitamin A, lycopene, and vegetarian foods with cervical cancer (Ghosh et al., 2008).

There are potential biological mechanisms regarding the protective effects of the nutritional factors against cervical cancer. Vitamins C and E play a role in increasing the mucosal response to infection and protection against free radicals and oxidants. Vitamins C and E can inhibit the formation of DNA adducts that are induced by cigarettes. In addition, antioxidants can regulate immune responses and reduce viral replication and gene expression (González et al., 2011). A case control study conducted by Hernandez et al. showed that thiamine, riboflavin, folate and vitamin B12 may provide protection against pre-cancerous lesions of the cervix (Hernandez et al., 2003). A nested case-control
study showed that frequent consumption of antioxidant-rich fruits is associated with a reduction in the risk of developing squamous intraepithelial lesion (Siegel et al., 2010). A study in 2008 showed that plant-based diets may play a protective role in reducing the risk of cervical cancer (Ghosh et al., 2008). In a case control study, significant reduction was observed in serum levels of antioxidants (e.g. beta-carotene, lycopene, zeaxanthin, retinol, and α and γ tocopherol) in patients with CIN and cervical cancer (Cho et al., 2009).

Inflammatory disease

Several studies have investigated the role of inflammatory diseases in cervical cancer (Bernatsky et al., 2009; Kiss et al., 2010; Simon et al., 2015). The results of a population-based cohort study showed that women with rheumatoid arthritis and systemic lupus erythematosus are 1.5 times more likely to develop cervical dysplasia and cervical cancer (Kim et al., 2014). The results of a meta-analysis showed that there is a positive relationship between systemic lupus erythematosus and the risk of cervix neoplasia, and that these individuals are at greater risk for developing cervical cancer (Liu et al., 2010). For instance, in a research study by Al-Sherbeni et al., the rate of abnormal Pap smears was higher in patients with lupus (Al-Sherbeni et al., 2015).

It has been shown that the use of immunosuppressive agents, such as cyclophosphamide and azathioprine, may be associated with an increase in the incidence of cervical cancer in these individuals. On the other hand, the screening rate for cervical cancer is lower in people with lupus (Kiss et al., 2010).

Host factors

The role of host genetic sensitivity in the pathogenesis of cervical cancer has been investigated by several studies (Calhoun et al., 2002; Hildesheim and Wang, 2002; Rader, 2009). A case control study identified some of the host's genetic polymorphisms that may be associated with cervical cancer. Some polymorphisms were associated with cellular immune responses and/or antigenic processing (Calhoun et al., 2002). The results of a study by Wang et al. showed that host genetic variants may be responsible for determining the risk of cervical cancer pathogenesis in two important stages: the persistence of HPV and the progression of the disease (Wang et al., 2010). The findings of our review study also demonstrated a set of immune-deficiencies that are associated with carcinogenesis of HPV (Patel and Chiplunkar, 2009).

Prevention and vaccination

Understanding the role of HPV infection in cervical cancer has led to the development of immunogenic, safe and effective prophylactic vaccines (Crosbie et al., 2013). Vaccination against HPV has been available since 2006. These vaccines are available in many countries around the world, although vaccine coverage varies widely across different regions (Herrero et al., 2015). Sociocultural, health and political factors are the main barriers to the use of this
vaccine among low-income and less developed countries (Wigle et al., 2013). Currently, three types of vaccines are available.

- **Quadrivalent vaccine (Gardasil)**

  This vaccine consists of viral-like particles of L1 recombinant protein (major capsid protein) against HPV types 6, 11, 16 and 18 (Siddiqui and Perry, 2006).

- **Bivalent vaccine (Cervarix)**

  This vaccine contains viral-like particles of recombinant L1 capsid proteins against HPV types 16 and 18 (Monie et al., 2008).

- **Nonavalent vaccine**

  This vaccine was approved by the US Food and Drug Administration (FDA) in December 2014, and then approved by the European Medicine Agency in June 2015. This type of vaccine includes HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and has similar performance to the bivalent and quadrivalent vaccines for different targets. This type of vaccine provides nearly 90% protection against cervical cancer and about 90% protection against genital warts (Bonanni et al., 2017).

  These three types of vaccines primarily protect the individual against the HPV types present in the vaccine and provide only slight protection against other HPV types. These vaccines are recommended for women and men from the age of nine in two doses. For people over 15 years of age, three shots of the vaccine are usually given (Duclos, 2009).

**Conclusion**

The aim of this study was to understand the role of various risk factors in the incidence of cervical cancer and the burden associated with this cancer. The results of this study showed that the incidence of cervical cancer varies considerably between developed and developing countries. After the introduction of the Pap smear test and the use of prophylactic vaccines, the incidence of cervical cancer in the developed countries declined gradually. Significant differences in the incidence of cervical cancer among different countries can be attributed to the following factors: the existence, duration, and quality of screening programs; changes in the cervical cancer risk factors, especially those related to sexual behaviors that cause changes in exposure to HPV. Combination of biological, socio-economic and health factors contributes to the incidence of cervical cancer. A large proportion of cases of cervical cancer can be prevented by implementing prevention programs, lifestyle enhancement, smoking cessation and timely and effective treatment of pre-cancerous lesions.
Abbreviations

BMI: Body Mass Index
CIN: Cervical Intraepithelial Neoplasia
DALYs: Disability-Adjusted Life-Years
FDA: Food and Drug Administration
HIV: Human Immunodeficiency Virus
HPV: Human Papilloma Virus
HSV: Herpes Simplex Virus
ICC: Invasive Cervical Cancer
OC: Oral Contraceptive
STI: Sexually Transmitted Infections

Author Contribution

Zohre Momenimovahed: Literature review and data collection, drafted the first version and approved final version. Hamid Salehiniya: Literature review and writing the manuscript, drafted and edited the first version and approved final version.

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