ABSTRACT
Objective: to reflect on the precursors to cervical cancer and its risk factors. Method: reflective study based on literature review. Results: during the course of the study, initially the general characteristics of the uterus and precursor lesions for cancer of the uterine cervix, and methods used for diagnosis were initially addressed. Conclusion: based on the acquired knowledge, preventative measures directed to such patients can be adopted to improve the care in the referenced service, serving as a support for government and organizational policies. Despite all existing scientific and technological knowledge, such as the cancer colposcopy, HPV-DNA research and, more recently, vaccines against HPV, which allows the timely diagnosis and treatment, the main challenge, remains how to give people access to technology available to reduce morbidity and mortality from cervical cancer. Descriptors: The Cervix; Neoplasms of the Cervix; Risk Factors.

RESUMO
Objetivo: refletir sobre as lesões precursoras para o câncer do colo uterino e seus fatores de risco. Método: estudo reflexivo baseado em revisão de literatura. Resultados: ao longo do estudo foram abordadas inicialmente as características gerais do útero e lesões precursoras para o câncer de colo uterino, e posteriormente métodos utilizados para diagnóstico. Conclusão: com base no conhecimento adquirido, medidas preventivas direcionadas a essas pacientes poderão ser adotadas para aperfeiçoar o atendimento ao serviço referenciado, servindo de subsídios para políticas governamentais e organizacionais. Apesar de todo conhecimento científico e tecnológico existente, como a colpocitologia oncológica, a colposcopia, a pesquisa do DNA-HPV e, mais recentemente, as vacinas contra o HPV, que permite o diagnóstico e tratamento em tempo hábil, o principal desafio permanece em como dar às pessoas acesso à tecnologia disponível para reduzir a morbidade e a mortalidade por câncer do colo uterino. Descriptores: Colo do Útero; Neoplasmas do Cervix; Risco. Factors.

RESUMEN
Objetivo: reflexionar sobre los precursores de cáncer cervical y su riesgo factores. Metodología: estudio reflexivo basado en la revisión de la literatura. Resultados: durante el estudio fueron inicialmente dirigidas a las características generales de las lesiones del útero y precursor de cáncer de cuello uterino y métodos utilizados para el diagnóstico. Conclusion: se basa en los conocimientos adquiridos, pueden adoptarse medidas preventivas dirigidas a estos pacientes para mejorar la atención en el servicio de referencia, que sirve como soporte para las políticas del gobierno y de organización. A pesar de todos los conocimientos científicos y tecnológicos, como la colpocitologia cáncer, colposcopia, investigación de DNA de HPV y, más recientemente, las vacunas contra el VPH, que permite el diagnóstico oportuno y tratamiento, los restos del principal desafío cómo dárles acceso a la tecnología disponible para reducir la morbilidad y mortalidad de cáncer de cuello uterino. Descriptores: Cuello Uterino; Neoplasias del Cuello Uterino; Factores de Riesgo.
INTRODUCTION

Article drawn from the dissertation "epidemiological study of women with precursor lesions for cancer of the cervix in the region southwest of Mato Grosso" presented at Programa de Pós-Graduação em Ciências da Saúde, at the University of Brasília/UnB in 2011.

Cervical cancer is the second most common type of cancer among women, being on average 500,000 new cases per year in the world and 230 thousand deaths of women per year. It is considered a public health problem, although we know that, when diagnosed early, has great potential for prevention and cure. Its incidence is twice as large as in the least developed countries when compared to more developed countries, being the first cause of morbidity and mortality in some countries of South and East Africa, Central America and South-Central Asia.

In Brazil, the mortality from cancer of the cervix is high and previous year's statistics have shown significant growth. In 1979, the rate was 3.44/100,000; in 2000, 4.49/100,000 and, in 2008, was 19.1/100,000 women. The cervical cancer is a major public health problem, despite the efforts and the technological resources used in its prevention. This is one of the most relevant topics in the area of medical science, requiring research; they consider the reality and context of each region.

• THE uterus and precursor lesions

The uterus, an organ of the female reproductive system, is divided into body and neck. The cervix is coated with several layers of epithelial pavement cells, arranged in an orderly manner. The outer covering, called ectocervix is stratified squamous type, non-keratinized and the inner lining, simple columnar type, corresponding to the end cervical canal; is called the endocervix. The junction escamocolunar (JEC) is the name of the place where these two epithelia unite, focus 90% of cervical cancers. The riots in the stratification of this epithelium is called cervical intraepithelial neoplastic or precursors (NCI).

The concept of cervical intraepithelial neoplastic was suggested by Richardt, in 1967, to characterize and define the prognosis of cancer precursor lesions of the cervix. These lesions were referred to as cervical intraepithelial Neoplastic grade: 1 (NCI I), when the cluttering occurs in the basal layers of stratified epithelium; Cervical intraepithelial neoplastic grade 2 (NCI II), when the cluttering affects up to three-quarters of the thickness of the epithelium, preserving only the superficial layers; Cervical intraepithelial neoplastic grade 3 (NCI III), as the cluttering affects all layers of the epithelium.

Cervical cancer is a malignant disease, which develops in the epithelium of ecto and endocervix of the uterus and is characterized by disordered growth of cells that invade the tissue and organs. It begins with a precursor lesion, which progresses slowly until it reach the attacker, this time in which cells invade the cervical connective tissue, resulting in a situation where the cure is uncertain.

• Diagnostic methods

The examination of colpocitologia Oncology (CCO), developed in 1943 by Pap smear, consists in the analysis of cells from endocervix and ectocervix, extracted by scraping of the uterine cervix. The changes were initially classified as the sort of Smear. In 1988, a group of citopatologistas proposed the Bethesda classification system (1988) and, after modifications in this classification, the classification of Bethesda (2001), which is in force until the present day. This last classification groups changes HPV induced intraepithelial lesion 1:0 pm and NIC low-grade (LIEBG) and changes 2 and NIC 3:0 pm high-grade intraepithelial lesion (LIEAG).

It is the most widespread method for cervical cancer screening, widely used in the unified health system (SUS), given its easy implementation and low financial cost; must be started before the age of 21 and held annual intervals. After 30 years, women with three negative results can space the exams for every two or three years.

Although widely used, has limitations, such as insufficient cell sample, improper preparation of the blades, the absence of quality control laboratories of Cytology, improper interpretation of cytological findings and follow-up of women with inadequate smears changed. In addition to the errors pointed out, the high rate of women with cervicitis seeking medical assistance increases the number of false negative results. Studies conclude that CCO is not a diagnostic method, but a method that suggests any changes and, despite some disagreement between the cytological and histological results, identifying women with precursor lesions, since the sensitivity of the CCO is proportional to the severity of the lesions.

Population coverage by cancer colpocitologia regarded as the reference standard is 80% in women of 35 to 59 years. Despite the population coverage of Pap test have increased in recent decades; there has
been little reduction in mortality rates for cervical cancer, even in areas with satisfactory coverage.\textsuperscript{16}

Colposcopy, examination used to aid in the diagnosis of cancer of the cervix, consists in the inspection of the uterine cervix, vagina, vulva, perinea and perianal region, after the application of acetic acid solutions 3\%, 5\% and lugol's iodine, through the colposcopy, an optical device with lenses and filters, developed in 1924 by Hans Hinselmann. This method makes it possible to evaluate the epithelia of the lower genital tract and find the precursor lesions and cervical carcinoma.\textsuperscript{8} from its creation, various scholars presented terminologies for colposcopy classification.\textsuperscript{8,17}

The third method of diagnosis, histopathology, establishes the diagnosis of certainty of precursor lesions and/or cancer and is through biopsy, cone biopsy, endocervical curettage or excisional biopsy, the result being expressed by a nomenclature which allows histological quote correlation.\textsuperscript{8}

It should be noted that despite being considered a gold standard for the diagnosis of cancer of the uterine cervix, this method is subject to some variables, as appropriate local collection (most relevant), fragment size, conservation in formaldehyde, among others; However, the most relevant is the variability in the interpretation.

\section*{Human papiloma virus (HPV)and precursor lesions}

HPV is a DNA virus of the family \textit{Papillomaviridae} (formerly \textit{Papovaaviridae}), small, non-enveloped, with a diameter of 55nm, composed of capsid icosaédrico with 72 capsomeros. Infectious viral particles with the HPV genome can be found in the nuclei of infected cells of women with uterine cervix normal (extracromosomics). The precursor lesions and cervical cancer occur when the HPV genome becomes part of the host cell's chromosome, which is observed in some women with low-grade precursor lesions, most women of high-grade precursor lesions or cervical carcinoma with the uterus.\textsuperscript{18}

Human papilloma virus is the most common infectious agent worldwide\textsuperscript{19} preferably sexual transmission, and is considered one of the leading, if not the main risk factor for the development of cervical intraepithelial neoplastic and invasive carcinoma of the uterine cervix in over 90\% of cases.\textsuperscript{20}

Since HPV infects the human, body can interact in three ways: a): presence of visible injury clinic macroscopically, represented by Condyloma acuminate; b) subclinical: macroscopic lesions evident and not the diagnosis is suggested by the cancer colpocitologia, colposcopy, microcolposcopia or histology; c latent): the diagnosis is the detection of HPV DNA.\textsuperscript{21}

Cytological changes caused by HPV infection, when diagnosed in the first five years after the onset of sexual activity, have a lower risk of neoplastic progression.\textsuperscript{22}

However, persistent infections, regardless of age and with normal oncological colpocitologia test can predict high-grade cytological changes around 45 years.\textsuperscript{23}

\section*{Risk cofactors}

There is no doubt about the central role of HPV in cervical carcinogenesis,\textsuperscript{18} however, the literature has shown that in addition to the presence of HPV, interfere in the development and progression of intraepithelial lesions and cervical cancer virus type, the persistence of the infection and the association with other environmental cofactors (smoking, birth control and infection by human immunodeficiency virus), viral cofactors (certain types of HPV infection, viral load, coinfeciton with more than one HPV) and cofactors of the host (multiparity, immunological response and genetic predisposition).\textsuperscript{24}

Some cofactors of risk for HPV are associated with sexual activity, since, to result in infection, HPV need access the basal cells, access this possible due to micro-cracks in the lining, often produced during sex.\textsuperscript{25}

The cofactors in cervical carcinogenesis can act in three ways: they can influence the acquisition of HPV virus, can increase the persistence of HPV virus and may increase the risk of HPV infection to progress to precursor lesions and cancer of the uterine cervix.\textsuperscript{26}Will be described the following forward cofactors: age, number of partners, smoking, oral hormonal contraceptive, sexually transmitted diseases, HIV and immunosuppression and parity.

\section*{Age}

The HPV infection is more common in young, sexually active women\textsuperscript{9} with spontaneous regression after 36 months in 90\% of cases.\textsuperscript{27} only a small number of women, probably by immunological mechanisms, failure will present persistence of infection, resulting in atypical changes in cervical epithelium and evolving to malignant transformation.\textsuperscript{24}

Although the spontaneous elimination of the virus be frequent in younger women, even elimination capacity diminishes the higher the age of this women.\textsuperscript{26-27}
In a study to identify the risk factors for cervical cancer in women with HPV cervical lesions, observed that 57% of cases occurred in the age group between 18 and 38 years. Another study, found older than 30 years in 72% of your sample, with average age of 38.5 years. However, in case-control study that evaluates the risk factors for cervical intraepithelial neoplastic by cancer, HPV research colpocitologia by polymerase chain reaction (PCR), colposcopy and biopsy (when needed), no association was observed between the intraepithelial lesions and age group.

It is important to note that the interpretation of the results of studies that include young women is limited, because these women are less likely to present multiparity, smoking or use of birth control by.

- **Number of partners**

  Studies show that the higher the number, the greater the risk of acquiring HPV infection; However, having only one partner does not raise the possibility of acquiring HPV infection.

  A longitudinal study of HPV in women teens and young adults showed that, with each new partner per month, there is an increased risk of 10 times for HPV, reinforcing the hypothesis that most of the “new” infections in young women is predominantly due to exposure, instead of reactivation of latent infections in immunocompetent patients.

- **Smoking**

  The association between smoking and cervical neoplastic has been demonstrated since the Decade of 70 and is directly related to the age of onset, the exposure, the period and the frequency of cigarette consumption. Smoking is suspected of facilitating the acquisition or the persistence of HPV infection.

  Cigarette smoke emanates from substances with mutagenic effects and immunosuppressive. Nicotine and carcinogenic by-products of tobacco, cotidina, were found in the cervical mucus of women smokers and direct exposure to these substances seem to change the local immune response and damage the DNA of cervical epithelial cells.

  Certain authors through molecular biology methods observed in their study that the cervical HPV infection in women smokers lasted an average of 10.7 months, while the average length between women non-smokers was 8.5. The author collected the results correlated with the duration of smoking and the number of cigarettes consumed per day (dose-response) and showed that the tobacco use influence the natural history of HPV infection, since this factor favor’s the persistence of local infection by oncogenic types of HPV, contributing with the uterine cervical carcinogenesis.

  In case-control multicenter study, authors presented the relationship between smoking and the development of cervical carcinoma. Based on information obtained through interview and collecting material for HPV DNA research, found that women smokers, after control of HPV infection, a 1.6 times greater risk (95% CI 0.9 -2.9) of squamous carcinoma.

- **Oral hormonal contraceptive**

  With contraceptive purpose or replacement of endogenous steroid hormones deficit are widely used around the world. Many epidemiological studies have investigated the association between the use of combined oral contraceptives and cancer development however, there are controversies.

  Women using oral hormonal contraceptives are more likely to be exposed to HPV than those that use barrier methods or not has sex probably because contraceptives (ACOs) seem to interfere with effective HPV induced lesions of young women as they intensify the gene expression of HPV.

  One study noted that there is no risk or increased risk for cancer of the cervix in women using contraceptives for up to four years. However, the use of oral contraceptives for more than five years was significantly associated with cervical neoplastic, with fourfold increase for invasive cervical cancer (OR = 4, 95% CI 2.0 -8.0) and three times for the in situ carcinoma of the uterine cervix (OR = 3.4, 95% CI 2.1 -5.5).

  In the most recent meta-analysis of International Collaboration of Epidemiological Studies of Cervical Cancer were examined data from 24 studies around the world, including 16,573 women with cervical cancer and 35,509 healthy women. Among users of oral hormonal contraceptives, the risk of invasive cervical cancer increased with longer use. This risk decreased after the suspension of use: after ten or more years of suspension of the ACO, had returned to the same value of those who have never used.

  Thus, although the squamous cervical cancer is not considered hormone-dependent, studies also show that users of ACOs have time-dependent risk of developing it.
Although HPV is considered as the main Etiologic Agent of cervical cancer, some agents of other sexually transmitted infections, such as Cytomegalovirus, herpes simplex virus type 1 and 2, Chlamydia trachomatis and human immunodeficiency virus (HIV) can contribute to the development of squamous intraepithelial lesion and cervical cancer.¹⁸

Certain authors¹⁸ noted that HPV positive patients have a high risk of developing cervical lesions; however, those patients with CMV positive HPV positive did not have and concluded that the CMV acts as spectator, and not as a cofactor in cervical oncogenes. Other¹⁹ authors also studied the correlation of viral factors with cervical cancer and found that CMV is not involved directly in the oncogenic process, however, may increase the possibility of oncogenes or infect opportunistically cancer tissues.

Some studies have detected high levels of antibody to herpes simplex virus type 2 (HSV-2) in patients with cervical carcinoma, compared with patients without cancer, suggesting an interaction between HSV and HPV 16/18 in the etiology of cervical cancer.⁴⁰

Some¹¹ authors assessed the association between exposure to several Chlamydia trachomatis serotypes and the subsequent development of cervical squamous cell carcinoma and observed a statistically significant higher occurrence of carcinoma in women with serotype G; serotype 1 and serotype D, strengthening the evidence that there is a link between the past infection with Chlamydia trachomatis and cervical squamous cell carcinoma.

- HIV and immunosuppression

Immunosuppressed women, among them, the transplanted⁴² and infected with HIV,⁴³ in use of immunosuppressive drugs, are at increased risk of developing cancer and malignancies, cervical carcinoma, invasive.

Both conditions, HPV and HIV, contemplate the risk populations with similar demographic characteristics. However, the study shows that HPV infection and HIV's seropositivity are independent risk factors for lower genital tract pathology.⁴⁴ Other⁴⁵ authors suggest higher prevalence of intraepithelial neoplasms, besides injuries to a greater extent and greater in women with histological positive HIV serology. Low numbers of CD4 lymphocytes (< 200 cells/ml) are associated with HPV infection and development of intraepithelial neoplasms.

- Parity

Some authors¹⁸,⁴⁶ consider multiparity a cofactor of major risk, since there is twice the possibility of women who have four children being afflicted with cervical cancer, compared with those with no or one child. This risk is due to the permanence of the maintenance area in the exocervix or higher concentration of estrogen and progesterone hormone.⁴⁵ ²⁶ ⁴⁶ in multipara.

In their study, determined author⁴⁷ studying the Association of risk factors and cancer of the uterine cervix in HPV-positive women with and without cervical intraepithelial lesion of high degree, found that the high-grade lesions are directly proportional to the increased parity.

- Access to care

According to the program of attention to women's health (WOMAN INTEGRAL HEALTH ASSISTANCE PROGRAM) of the Ministry of health, the cancer colpocitologia tests are performed as spontaneous demand in primary health units. After the collection, the return to the delivery of results is scheduled for 30 days, average time recommended as ideal by governmental authorities of Brazil⁴⁸ for delivery.

The percentage of units that offer the BCC collection service is high, however, women who have change in the result of their gynecological preventive encounter difficulties in getting adequate treatment, which makes the disease reaches advanced stages, justifying the mortality rate found.⁴⁸

Given⁴⁹ study describes the difficulties of access and use of the SUS, identifying the access to the service of medium complexity as big difficult. On the other hand, the reference service professionals complain that many references are unnecessary, since they are cases, which could be dealt with by the unit referenced. Although the municipality organize a network of reference to more complex levels, there are flaws in ensuring compliance with users, compromising the integrality of attention to health.⁴⁸

Therefore, if they are performed early diagnosis and treatment of this pathology risks evolve are rare and the quality of life of women improves sharply.⁵⁰

Despite all existing scientific and technological knowledge, as the cancer colpocitologia, colposcopy, HPV-DNA research and, more recently, vaccines against HPV, which allows the timely diagnosis and treatment, the main challenge, remains how to give people access to technology available to reduce morbidity and mortality from cervical cancer.
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