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Developing a risk factor assessment tool for the cytological changes towards cervical cancer in pap test and the Regression Model of its determinants in Iran

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Developing a risk factor assessment tool for the cytological changes towards cervical cancer in the Pap test and the Regression Model of its determinants in Iran

ABSTRACT

INTRODUCTION: Despite mostly considered a preventable disease, cervical cancer after breast cancer, is the second most common cancer among women around the world and the leading women's cancer in the developing countries. Cervical cancer is a unique kind of cancer in human being because of having a long incubation period and the fact that we know its main cause (HPV) so the cancer can be prevented. In order to identify high risk patients, have a suitable and rapid action and also to reduce some medical expenses the present study was conducted based on two objectives: 1) Developing a risk factors assessment tool for the cytological changes towards cervical cancer in pap test, 2) To compare the risk factors and clinical manifestations in women with and without atypical cytological findings in Pap test and develop the regression model of its determinants in Iran.

METHODS: According to the aims this study was performed in 2 phases. 1) A methodological study to develop the research tool, 2) A case-control study with a total of 201 subjects chosing by convenience method who were eligible according to the research criteria. The subjects were assigned in two groups: 51 women in case group with, and 150 women in control group without atypical cytological findings in their Pap test. Research environment were clinics of gynecology and oncology affiliated with the Hamadan University of Medical Sciences, Hamadan, Iran. For data analysis we used Mean, Standard Deviation, Chi-Square Test, Odds Ratio and Logistic Regression Models.

RESULTS: Result for the first Phase of the research led to create a tool entitled: "A risk factors assessment tool for the cytological changes towards cervical cancer in the Pap test". It is a standardized questionnaire (CVR=94.39, CVI=96.01) with 50 questions which can be used by other researchers in their related projects and also by the midwives and physicians in face with their patients. This is a unique tool and has two subscales including risk factors and clinical manifestations. Results for The second phase of this research are provided in 14 tables. According to the logistic regression in this study the age ($p>0.05$, OR= 1.08), age at the menarche ($p>0.05$, OR=0.75), number of deliveries ($p>0.05$, OR=1.44), BMI ($p>0.05$, OR=2.598) and the use of protection (condom) ($p>0.05$, OR=0.023) are determinants for

cytological findings in Pap test. Having unhealthy cervix (including: Chronic cervicitis, Erosion/ Laceration, and Hypertrophied cervix) in case group was significantly higher than that of control group (X^2= 47.166, df=1, P< .001). Most of the subjects in case group had done the current pap test due to a medical prescription while in control group it was performed as a routine check up and Chi-Square test showed that there is a significant difference between two groups related to this variable (p< .001). Painful sex, Low abdominal pain, Pelvic pain and Low back pain are the clinical manifestations that in case group were significantly higher than that of control group (P<.001).

CONCLUSION: We strongly recommend this risk factors assessment tool to be considered and applied in all the clinics that are open to women because of the gynecological problems. It can help the physicians to predict the patients' health situation in order to have a suitable and quick action. To save most lives, both prevention and early detection should be covered totally by public health insurance especially in low income people. Available facilities should be entirely used to enhance women's knowledge and awareness about cervical cancer, risk factors, and also about its main cause: HPV. Women's health care professionals, media, press and any printed matters can have an operational and effective role about it.

Lo sviluppo di uno strumento di valutazione fattore di rischio per i cambiamenti citologici verso il cancro cervicale nel Pap test e il modello di regressione delle sue determinanti in Iran

ASTRATTO

INTRODUZIONE: Nonostante lo più considerata una malattia prevenibile, il cancro cervicale dopo il cancro al seno, è il secondo tumore più comune tra le donne di tutto il mondo e il cancro delle donne leader nei paesi in via di sviluppo. Il cancro cervicale è un unico tipo di cancro negli esseri umani a causa di avere un lungo periodo di incubazione e il fatto che conosciamo la causa principale (HPV), in modo che il cancro può essere prevenuto. Al fine di identificare i pazienti ad alto rischio, hanno un'azione adeguata e rapida e anche per ridurre alcune spese mediche del presente studio è stato condotto sulla base di due obiettivi: 1) Lo sviluppo di uno strumento di valutazione dei fattori di rischio per i cambiamenti citologici verso il cancro cervicale nel pap test , 2) Per confrontare i fattori di rischio e manifestazioni cliniche nelle donne con e senza risultati citologici atipici in Pap test e sviluppare il modello di regressione delle sue determinanti in Iran.

METODI: Secondo gli scopi di questo studio è stato eseguito in 2 fasi. 1) uno studio metodologico per sviluppare lo strumento di ricerca, 2) uno studio caso-controllo con un totale di 201 soggetti chosing dal metodo comodo che erano ammissibili in base ai criteri di ricerca. I soggetti sono stati assegnati in due gruppi: 51 donne nel gruppo di caso con, e 150 donne nel gruppo di controllo senza risultati citologici atipiche nel loro Pap test. ambiente di ricerca sono stati ambulatori di ginecologia e oncologia affiliati con l'Università di Scienze Mediche Hamadan, Hamadan, in Iran. Per l'analisi dei dati abbiamo usato media, la deviazione standard, test chi-quadro, odds ratio e di regressione logistica modelli.

RISULTATI: Risultato per la prima fase della ricerca ha portato a creare uno strumento dal titolo: "Uno strumento di valutazione dei fattori di rischio per i cambiamenti citologici verso il cancro cervicale nel Pap test". Si tratta di un questionario standardizzato (CVR = 94.39, CVI = 96.01) con 50 domande che possono essere utilizzati da altri ricercatori nei loro progetti correlati e anche dalle ostetriche e medici a faccia con i loro pazienti. Questo è uno strumento unico e ha due sottoscale tra fattori di rischio e manifestazioni cliniche. Risultati per la seconda fase di questa ricerca sono forniti in 14 tavoli. Secondo la regressione logistica in

questo studio l'età (p> 0.05, OR = 1.08), età al menarca (p> 0.05, OR = 0.75), numero di consegne (p> 0.05, OR = 1.44), indice di massa corporea (p > 0.05, OR = 2.598) e l'uso di protezione (preservativo) (p> 0.05, OR = 0.023) sono determinanti per i risultati citologici in Pap test. Avendo cervice malsano (tra cui: cervicite cronica, Erosione / lacerazione, e Ipertrofico cervice) nel gruppo dei casi è risultata significativamente più alta di quella del gruppo di controllo (X2 = 47,166, df = 1, p <.001). La maggior parte dei soggetti nel gruppo caso avevano fatto il pap test corrente a causa di una prescrizione medica, mentre nel gruppo di controllo è stato eseguito come una routine check-up e test chi-quadrato ha dimostrato che vi è una differenza significativa tra due gruppi relativi a questa variabile (p <.001). sesso doloroso, dolore addominale, dolore pelvico e mal di schiena bassa sono le manifestazioni cliniche che nel gruppo dei casi erano significativamente superiore a quella del gruppo di controllo (P <.001).

CONCLUSIONE: Si consiglia vivamente di questo strumento di valutazione dei fattori di rischio da considerare e applicato in tutte le cliniche che sono aperti alle donne a causa dei problemi ginecologici. Può aiutare i medici prevedere situazione salute dei pazienti al fine di avere un'azione adeguata e rapida. Per salvare la maggior parte delle vite, sia la prevenzione e la diagnosi precoce dovrebbero essere coperti totalmente da assicurazione sanitaria pubblica soprattutto nelle persone a basso reddito. servizi disponibili devono essere interamente utilizzati per migliorare la conoscenza e la consapevolezza delle donne sul cancro cervicale, i fattori di rischio, e anche la sua causa principale: HPV. femminile operatori sanitari, i media, stampa ed eventuali materiali stampati possono avere un ruolo operativo ed efficace su di esso.

Chapter 1

Introduction

The topics discussed in this chapter are including: cervical cancer statistic, etiology, about the disease, objectives, the necessity of conducting the present research, prevention, early detection: Pap test, Risk factors, the first aim and the second aim.

CERVICAL CANCER STATISTIC

Despite mostly considered a preventable disease, cervical cancer after breast cancer, is the second most common cancer among women around the world and the leading women's cancer in the developing countries[1, 2].

Based on the studies, invasive cervical cancer is listed as the third most common cancer in women and the fourth leading cause of cancer death in women worldwide [3-7].

Although cervical cancer is 13%-15% of all the females' cancers globally, it accounts for 20%-30% of that in Asia and it is a major cause of death in women living in the developing countries [5, 8, 9]. The disease has a very rough distribution; more than 85% of cases can be found in poor countries including: sub-Saharan Africa, Central America, South-Central Asia, and Melanesia[5, 7]. However cervical cancer remains a leading cause of morbidity and mortality in women worldwide[10, 11].

According to the World Health Organization (WHO) the additional cases of cervical cancer, only in Ghana, will be over 5000 with at least 3300 deaths every year by 2025[12].

Cervical cancer is responsible for over 275,000 female deaths each year, with more than 500,000 new diagnoses across the globe annually. India, lonely, accounts for over a quarter of cases occurring in low- and middle-income countries. In Turkey, 560 women die of cervical cancer per year. Other parts with the highest incidence rates are parts of Africa and South America, whilst lowest rates are seen in Europe, Western Asia and North America [2, 13, 14].

So the cervical cancer is still a serious disease for women worldwide. particularly in those countries with rare screening and lack of high-quality treatment or unaffordable treatment, health outcomes for women with cancer are poor [15].

Cervical cancer is around 1.6% of all recently diagnosed cancers amongst Italian women [16]. This cancer as a cause of morbidity and mortality, leading to just about 3500 new cases and 1000 deaths annually in Italy. In order to early detection, a widely funded national screening program actively offering Pap-smear testing every 3 years to women aged 25–64 years, covers around 40% of the target population with large geographical variability in this country. However most of Italian women experience Pap-smears in the private clinics and the screening program covers 73% of women aged 25–64 years through both the public and the private health sectors [17].

Compared to only 1.7 in North America, age standardized rates of cervical cancer mortality in East Africa are 25.3 per 100,000. Even within countries with low cervical cancer mortality, cancer risk is significantly affected by deprivation and ethnicity. In the USA, African-American women are twice likely to die from cervical cancer when compared to non-Hispanic white women, whilst States in the Deep South experience higher mortality rates than Northern States. In the UK also, the most vulnerable sectors of society consistently show an increased burden of disease [1].

During the past 20 years a decline has been observed in cervical cancer incidence and deaths in the developed world but, unfortunately, there has not been a significant change in the same key indicators in developing countries. For example, cervical cancer is the most common cancer among women in Ghana and is the cause of 16% of death due to the cancer in this country[12].

In Iran the incidence and mortality rate of cervical cancer are 2.4% and 1.6% respectively and cervical cancer was diagnosed in 4.1% of women living only in Tehran (2012) , the capital city of Iran [18, 19].

In this country, cancer as the third leading cause of the death and the second most important group of chronic non-communicable diseases is one of the main public health problems faced by Iran's health care system. [20, 21].

Although most of cervical cancers in the population are diagnosed in advanced stage of the disease, there is no organized cervical screening program in Iran and some other developing countries. Generally speaking, referring to the Pap smear is not desirable in poor countries.

Women undergo the Pap smear screening test by chance for example when they visit a doctor for gynecological symptoms or the other health problems. In Iran, Pap smear screening is not well covered by private or public insurance. As a result, only a small percentage of women with high socioeconomic status undergo regular screening [19, 22, 23].

According to Khorasanizadeh: "the cervical cancer incidence rates observed in Iran are similar to rates reported from other Muslim countries in the Middle East, including Saudi Arabia (2.1 per 100,000), Egypt (1.6 per 100,000), Syria (2 per 100,000), Iraq (3.1 per 100,000), Bahrain (3.6 per 100,000), Turkey (4.2 per 100,000) and Afghanistan (6.6 per 100,000)" [22]. Although the cervical cancer incidence rate is low in Iran, the mortality to incidence ratio (M/I) was over 44%, which is similar to the ratios reported from Saudi Arabia (43%) and Libya (62%). A high M/I ratio means that the disease is diagnosed in relatively advanced stages so the prognosis of cervical cancer is poor [22, 24].

Cervical cancer is the third most common cancer among American women after uterine and ovarian cancers. Based on the statistics provided by the cancer record of the American Cancer Society (ACS), the prevalence of the cervical cancer is 6-7% per 100, 000 women, in the US. [20].

Cervical cancer with 528,000 cases reported in 2012 leading to 266,000 deaths, is a globally significant subject in Medicine. It affects women's mind, body, and family leading to a change in the their entire lives [20, 25].

The socioeconomic feature of this cancer is highlighted by the fact that in 2012, about 87 % of cervical cancer deaths happened in poor countries. India, alone, accounted for 25% of cervical cancer deaths in 2012 [25].

The load of cervical cancer is very high in South America also and it is considered as the second most common cause of cancer among women in this part of the world. The incidence of this cancer in south America was four times and the mortality was five times higher than that in North America, in 2008 [26].

The most affected region is Sub-Saharan Africa accounting for 80% of the new cases and 85% of the mortality from cervical cancer around the world [27, 28].

In a few words, in countries with well-established screening programs, the incidences of cervical cancer have been decreased about 70-90%. Inversely, in developing countries because of low access to screening services the incidence of cervical cancer continues to exist at high levels [28].

ETIOLOGY:

The most significant scientific discoveries related to cervical cancer during the past 30 years, which can open exciting new possibilities for controlling this disease, is the causal relation between Human Papillomavirus (HPV) infection and the cervical cancer. Harald zur Hausen and his colleagues found that HPV- 16 can be detected in cervical cancer tissues and their findings led to prevent 70–80% of cervical cancers nowadays [1, 29, 30].

An estimated 5% of human cancers are caused by human papillomavirus, which is a non-enveloped, encapsulated, double-stranded DNA, and most of these cancers are of the cervix[31].

The WHO has also recognized cervical cancer to be completely related to human papillomavirus oncogenic genotypes infection. It is estimated that more than 50% of women catch high risk HPV genotypes during their sexual lifetime. More than 90% of HPV infection at any age can be removed spontaneously in 6–18 months, but if it continues the precancerous lesions may follow. Type 16 is by far the likeliest to persist and cause CIN3 and cervical cancer. Fortunately, the progression of HPV infection to cervical cancer occurs over an extended period of time [13, 17, 29].

Now it has been well established that 99.7% of cervical cancer cases are linked to persisting HPV infection, a common virus which is sexually transmitted [28, 29, 32].

Human papillomavirus is a branch of the papillomavirus family, with diverse range of hosts in both animals and human. The family has a taxonomy which is based on genome sequence homology, biological function, and pathological outcomes. There are more than 100 types of human papillomavirus have been known, 13 of them are responsible for cervical, anogenital and oropharyngeal cancers [21, 29] . Genetic and epigenetic characteristics of HPV infection

have a significant role in cancer progression as well [21]. Recent studies revealed that 76% of cervical cancer patients are positive for HPV infection and HPV causes 70% of cases of cervical cancer. Few infections are persistant and progress to pre-cancer and cervical intraepithelial neoplasia grade 3 (CIN3). The most commonly detected HPV types are HPV 16 (56% of all types), HPV 18 (15% of all types) and HPV 31 (10% types). According to these findings, the prevalence of HPV in the general Iranian female population is 7% [22, 33, 34]. The various types of HPV are also responsible for some other forms of cancer such as oropharyngeal, anal, penile, vulvar and vaginal cancers so the vaccination can make a milestone in cancer prevention [35]. The two most common high-risk subset of HPV strains are HPV-16 and -18 that are found and in 60–78% of cervical squamous cell carcinomas and 72–94% of adenocarcinomas.[13]. According to Crosbie, "anal cancer caused by HPV is rare in the general population of both sexes (<2 cases per 100, 000 people) but it is 20-times more common in men who have sex with men. Other cancers attributed to human papillomavirus infection include those of the vagina (70%), penis (50%), vulva (43%), and oropharynx (26%)" [29].

ABOUT THE DISEASE

Cervical intraepithelial neoplasia (CIN) most often arises in an area of metaplasia in the transformation zone at the advancing squamocolumnar junction (SCJ) [36]. "Metaplasia advances from the original SCJ inward, toward the external os and over the columnar villi, to establish the transformation zone" [37]. "CIN is most likely to begin either during menarche or after pregnancy, when metaplasia is most active; after menopause, metaplasia is less active and a woman has a lower risk of developing CIN" [38].

Cervical intraepithelial neoplasia (Mild dysplasia= CIN1) is a histopathological sign of HPV infection, CIN2 (Moderate dysplasia) includes a heterogeneous group of lesions that have different potential to progress to cancer, and CIN3 (Sever dysplasia) represents the most clinically relevant lesions and is the best endpoint for cervical cancer in screening and vaccination trials [29, 39].

"Untreated, most CIN 1 and some CIN 2 lesions spontaneously regress; nevertheless, CIN refers to a lesion that may progress to invasive carcinoma. This term is equivalent to the term dysplasia, which means abnormal maturation; consequently, proliferating metaplasia without atypical mitotic activity should not be called dysplasia. Squamous metaplasia should not be diagnosed as dysplasia (or CIN) because it does not progress to invasive cancer. More than 90% of CIN is attributed to human papillomavirus (HPV) infection" [38].

Crosbie found that "The probability of clearance of HPV depends on the duration of infection; longer persistence reduces the probability of clearance. Human papillomavirus infections detected in women aged older than 30 years persist for longer than those in younger women because they are more likely to be persistent infections of long duration." [29].

"HPVs are belonging to the viral family of Papovaviridae. HPVs are small viruses with a size up to 60 nm in diameter encompass a capsid with icosahedral structure but these viruses miss envelop within their viral structure. The lack of envelope may lead to occurrence of resistant HPVs against antiviral agents"[40].

According to Crosbie (2013) "Human papillomavirus infects only epithelial cells and depends on the differentiation pathway of epithelial cells to complete its lifecycle human papillomavirus infects cells in the basal layer of the epithelium, probably via micro abrasions in the epithelial surface. It capitalizes on the lateral extension of basal cells that accompanies wound healing to gain entry to the cell. Infectious internalization takes several hours, after which viral DNA is released from the capsid and transported into the nucleus as free genetic material or extra chromosomal episomes. Early gene expression is tightly controlled in the basal epithelial cells with substantial amplifi cation of viral DNA. Replication occurs only in suprabasal, differentiating cells that are destined for maturity and senescence, and as thus do not naturally express the replicative machinery that the virus depends on for survival. To circumvent this problem, human papillomavirus encodes two proteins (E6 and E7) which together promote cellular proliferation, prolong cell-cycle progression, and prevent apoptosis. The cell becomes permissive for viral replication and hundreds or even thousands of human papillomavirus genomes are generated within a single cell. The capsid proteins L1 and L2 are expressed in the most superficial layers of the epithelium, where viral assembly takes place, and finally, new infectious viral particles (virions) are shed from the epithelial surface. The

papillomavirus lifecycle takes 2–3 weeks, the time necessary for a cervical cell to migrate from the basal to most superficial layers of the epithelium, mature, undergo senescence, and die"[29].

Haghshenas et al (2013) wrote that "HPVs infect cutaneous and mucosal epithelial cells of the anogenital tract, which can lead to a variety of diseases with a range of severities. The mildest form of HPV disease is low grade intraepithelial neoplasia (CIN-I). These lesions can persist and progress to high grade disease (CIN-III) and invasive cervical cancer. HPVs are also found in cancers of the tonsils, anus, penis and cancer of neck. High-risk HPV 16 and 18 are found with the highest frequencies in cervical cancer and account for approximately two thirds of all cervical carcinomas worldwide, with HPV-16 occurring most frequently. It has been demonstrated that the presence of even minimal amounts of HPV DNA is associated with an increased risk in the development of cervical cancer" [41].

Based on Berek (2012) "Potentially premalignant squamous lesions fall into three categories: (i) atypical squamous cells (ASC), (ii) low-grade squamous intraepithelial lesions (LSIL), and (iii) high-grade squamous intraepithelial lesions (HSIL). The ASC category is subdivided into two categories: those of unknown significance (ASC-US) and those in which high-grade lesions must be excluded (ASC-H). The LSIL category includes CIN 1 (mild dysplasia) and the changes of HPV, termed koilocytotic atypia. The HSIL category includes CIN 2 and CIN3 (moderate dysplasia, severe dysplasia, and carcinoma in situ). The spontaneous regression rate of biopsy-proven CIN 1 is 60% to 85% in prospective studies. The regressions typically occur within a 2-year follow-up with cytology and colposcopy. For LSIL that persists longer than 2 years, the choice of treatment is optional. Expectant management is still appropriate in some patients, and ablative therapies, including cryotherapy and laser ablation, are acceptable treatment modalities. When a cytologic specimen suggests the presence of HSIL, colposcopy and directed biopsy should be performed. Although high grade CIN can be treated with a variety of techniques, the preferred treatment for CIN 2 or 3 in nonadolescent patients is loop electrosurgical excision procedure (LEEP). Atypical endocervical cells pose a risk for adenocarcinoma in situ (AIS), which must be considered a precursor of adenocarcinoma. After sampling to rule out invasive disease, vaginal intraepithelial neoplasia (VAIN 3 lesions can be treated with laser or outpatient excisional therapy. Patients with vaginal intraepithelial neoplasia (VAIN 1 and most VAIN 2 and HPV infection) do not require treatment. These

lesions are multifocal and often regress, but may recur after ablative therapy. Vulvar intraepithelial neoplasia, grade 3 (VIN 3), is treated by simple excision, laser ablation, or superficial (partial) vulvectomy, with or without splitthickness skin grafting. Excision of small foci of disease produces excellent results, and although multifocal or extensive lesions may be difficult to treat by this approach, it offers the most cosmetic result. VIN 1 or 2 is generally associated with dystrophic changes or HPV and can be managed expectantly. Intraepithelial disease frequently occurs in the cervix, vagina, and vulva, and it may coexist in these areas. The cause and epidemiologic basis are common to all three locations, and treatment typically is ablative, excisional, and conservative. Early diagnosis and management are essential to prevent disease from progressing to invasive cancer" [38].

RISK FACTORS

For the first time, the term "risk factor" was used by Dr. William B. Kannel (1961) in an article in Annals of Internal Medicine[42]. According to WHO risk factor defines as: "any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury" [43].

Along with the occurrence of certain genotypes of HPV the risk of cervical cancer has increased. So, the existence of these kind of genotypes demonstrate an important risk factor for the progress of cervical cancer [41].

In this regard Turkistani and et al wrote that "rates are also related to marital status higher in married women than in singles and higher in widow or divorced women than in married. The epidemiologic features associated with cancer of the cervix in women are low socioeconomic status, early age at the first intercourse, and multiple sexual partners, besides other risk factors such as age, ethnicity, multiparity, cigarette smoking and extend use of oral contraceptives, point to a venereal pattern of etiology". Oral contraceptives may contribute to the increase in risk through an interaction with HPV infection [44].

As another associated factors with ccervical cancer is nonattending in regular screening program. "A longitudinal study on the basis of cytological Pap smear tests in the federal state

of Mecklenburg-Western Pomerania showed that more than 50 percent of women with invasive cervical cancer diagnosis had not attended screening in the 5 years preceding the diagnosis, and another 30 percent had attended irregularly. The study impressively demonstrates the link between nonattendance at screening and developing invasive cervical cancer" [35].

Some other obstacles have also been discussed in this regard. "Health care access and socioeconomic barriers may also limit overall screening coverage and contribute to disparities among population subgroups. A woman's ability and decision to receive screening may depend on her knowledge about Pap smears, health care access, socioeconomic status, and educational levels" [26].

Some studies suggest that women of higher socioeconomic status attend screening more regularly than women of lower socioeconomic status. The role of fear or anxiety is controversial. While most studies consider fear to be a barrier for screening attendance, others suggest that anxiety is predictive of higher screening attendance. Knowledge of cervical cancer and human papillomavirus (HPV) tends to be low overall, as various studies have shown. Infection with HPV is the main risk factor for developing cervical cancer [35].

The persistent role of socioeconomics and family structure has been mentioned to have a persistent role in screening programs attending and subsequently prevention of cervical cancer as well [11].

The only clear risk factors for persistence and progression of human papillomavirus are immunodeficiency and the human papillomavirus type, although sexual and reproductive factors, recent oral contraceptive use, smoking, and Chlamydia trachomatis infection have also been implicated. There is also a large fall in high-risk human papilloma virus infection with the age. 40% in those who are 20–24 years and 7% in 50–54 years old [29].

Other mentioned major risk factors for cervical cancer are having many sexual partners and cigarette smoking. Both are strongly related to socioeconomic status and ethnicity [45].

EARLY DETECTION: PAP TEST

Cervical cancer is a unique kind of cancer in human being because of having a long incubation period and the fact that we know its main cause so the cancer can be prevented [5, 46] and the lowest incidence and mortality rates are recorded in countries where screening is available to women.[7].

The morbidity and mortality rates of cervical cancer are very high so detection of cancer in its early stages in combination with appropriate treatment has been a significant factor in cancer control in recent decades [47].

The main aim of conducting Cervical screening is to prevent invasive cervical carcinoma by detecting and treating cervical intraepithelial neoplasia (CIN2 and CIN3) which are known as its precursors [48, 49].

There are several routine diagnostic methods including cytological (Pap smear), histopathological and some conventional Polymerase Chain Reaction (PCR), Visual inspection with acetic acid (VIA) which have been proposed as screening method for cervical cancer [28, 40, 50].

Despite its low sensitivity, the Pap test, which has introduced to the world of medicine in 1941, is one of the most successful cancer screening tests of all time. Pap test has made a dramatically decrease in invasive cervical cancer incidence and mortality rates in countries with high-quality and broad-coverage screening programs [51, 52].

Cervical cancer is less common in the Western world due to fully accessible Pap test. For example in Canada: the incidence of invasive cervical cancer has decreased from 0.02% in 1970 to its current rate of 0.008% / 100,000 populations. Studies indicate that about 54% of women with invasive cervical cancer have never been screened or have not been screened regularly before diagnosis. [4, 19, 28].

In developed countries 75% of women are screened for cervical cancer, typically by Pap smears and more recently HPV test, compared with just 5% in developing countries [6]. According to the studies the risk of cervical cancer with just one negative Pap test reduce to 45% and with 9 negative tests during lifetime reduce to 1% [46]. Therefore we can consider

Pap test as a life saving tool which can detect changes inside the cells of the cervix before cancer develops [53].

In most of the countries prevention efforts mainly focused on Pap smears. [26]. In the screening guideline, women who are between 25 to 49 years old are invited for the Pap test every 3 years and women who are 50 to 64 years old are invited every 5 years. women are asked to make an appointment for a Pap test with their general practitioner or Midwife by the written invitations [45].

Liquid-based, thin layer preparation of cervical cytology specimens is the recent modification in technique. Terminology for reporting cervical cytology was standardized by the Bethesda System in 1988 which has been revised several times and the current system was developed in 2001 [52].

Data from randomized trials have consistently shown that women with a prior negative HPV test have a lower risk of developing grade-3 cervical intraepithelial neoplasia (CIN) and invasive cervical cancer compared with women with a prior normal Pap smear. HPV testing can be done on a vaginal sample taken by the women themselves, which might offer opportunities to reach those who are reluctant to undergo gynaecological examinations [54]. HPV testing is more sensitive, but less specific than Pap test for detecting cervical intraepithelial neoplasia (CIN). Considering that in younger women HPV screening leads to overdiagnosis of regressive CIN2, using Pap test remains more desirable [55].

Regarding to the words above, new cervical cancer screening guidelines released separately by the United States Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS) recommend against routine yearly testing [56] as follow :

Definitions for screening guideline [56]

GRADE	DEFINITIONS
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C	Note: The following statement is undergoing revision. Clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

Clinical Summary of U.S. Preventive Services Task Force Recommendation [56]

Population	Women ages 21 to 65	Women ages 30 to 65	Women younger than age 21	Women older than age 65 who have had adequate prior screening and are not high risk	Women after hysterectomy with removal of the cervix and with no history of high grade pre cancer or cervical cancer	Women younger than age 30
Recommendation	Screen with cytology (Pap smear) every 3 years. Grade: A	Screen with cytology every 3 years or co-testing (cytology/HPV testing) every 5 years. Grade: A	Do not screen. Grade: D	Do not screen. Grade: D	Do not screen. Grade: D	Do not screen with HPV testing (alone or with cytology). Grade: D

Screening for Cervical Cancer: Clinical Summary of U.S. Preventive Services Task Force Recommendation [57]

Risk Assessment	HPV infection is associated with nearly all cases of cervical cancer. Other factors that put a woman at increased risk of cervical cancer include HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer.					
Screening Tests	Screening women ages 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms. Screening with cytology more often than every 3 years confers little additional benefit, with large increases in harms. HPV testing combined with cytology (co-testing) every 5 years in women ages 30 to 65 years offers a comparable balance of benefits and harms, and is therefore a reasonable alternative for women in this age group who would prefer to extend the screening interval.					
Timing of Screening	Screening earlier than age 21 years, regardless of sexual history, leads to more harms than benefits. Clinicians and patients should base the decision to end screening on whether the patient meets the criteria for adequate prior testing and appropriate follow-up, per established guidelines.					
Interventions	Screening aims to identify high-grade precancerous cervical lesions to prevent development of cervical cancer and early-stage asymptomatic invasive cervical cancer. High-grade lesions may be treated with ablative and excisional therapies, including cryotherapy, laser ablation, loop excision, and cold knife conization. Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemoradiation.					
Balance of Harms and Benefits	The benefits of screening with cytology every 3 years substantially outweigh the harms.	The benefits of screening with cotesting (cytology/HPV testing) every 5 years outweigh the harms.	The harms of screening earlier than age 21 years outweigh the benefits.	The benefits of screening after age 65 years do not outweigh the potential harms.	The harms of screening after hysterectomy outweigh the benefits.	The potential harms of screening with HPV testing (alone or with cytology) outweigh the potential benefits.

REPORT MODALITY OF THE PAP SLIDES ACCORDING TO THE 2001 BETHESDA SYSTEM [58]:

Specimen Adequacy

A. Satisfactory for evaluation (note presence / absence of endocervical. The Transformation zone component)
B. Unsatisfactory for evaluation (specify reason)

    1. Specimen rejected / not processed (specify reason)
    2. Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of Specific reason

General Categorization (Optional)

- Negative for intraepithelial Lesions or Malignancy
- Epithelial cell abnormality
- Others

Interpretation / Result

Negative for intraepithelial Lesions or Malignancy

Organisms

- ***Trichomonas vaginalis***
- Fungal organisms morphologically consistent with ***Candida species***
- Shift in flora suggestive of bacterial vaginosis.
- Bacteria morphologically consistent with ***Actinomyces species***
- Cellular changes consistent with herpes simplex virus

Other non neoplastic findings (Optional to report; list not comprehensive)

- Reactive cellular changes associated with Inflammation (includes typical repair)
- Radiation

Intrauterine contraceptive device

- Glandular cells status post-hysterectomy
- Atrophy

Epithelial Cell Abnormalities

a. Squamous cell

i. Atypical squamous cells (ASC)
   - of undetermined significance (ASC-US)
   - Cannot exclude HSIL (ASC-H)

ii. Low grade squamous intraepithelial lesion (LSIL)
   - Encompassing: human papillomavirus / mild dysplasia/ cervical intraepithelial neoplasia (CIN)

iii. High grade squamous intraepithelial lesion (HSIL)
   - Encompassing: moderate and severe dysplasia, carcinoma in situ: (CIN2 and CIN 3)

iv. Squamous cell carcinoma

Glandular cell

v. Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified)

vi. Atypical glandular cells, favour neoplastic (specify endocervical or not otherwise specified)

vii. Endocervical adenocarcinoma in situ (AIS)

viii. Adenocarcinoma

b. Other (List not comprehensive)

- Endometrical cells in a woman > 40 y of age.

GUIDELINES FOR THE MANAGEMENT OF ABNORMAL PAP TEST ACCORDING TO AMERICAN SOCIETY FOR COLPOSCOPY AND CERVICAL PATHOLOGY (ASCCP) (Fig. 1-8) [59]

1. Unsatisfactory results: Cytology results are unsatisfactory for 1% or less across all preparation types. Pap tests can be rendered unsatisfactory by obscuring blood, inflammation, or other processes. Unsatisfactory cytology arise largely from insufficient squamous cells due to different reasons such as lubricant contamination [60].

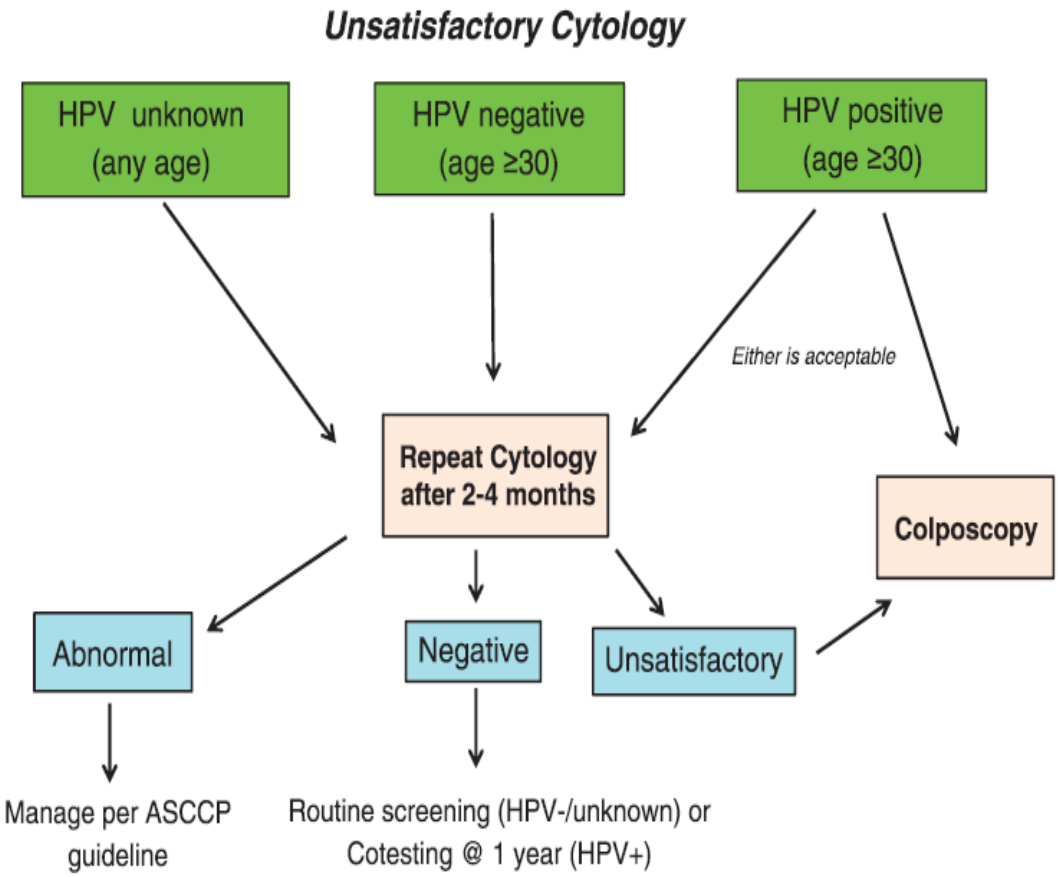

Figure 1: Management of unsatisfactory cervix [59]

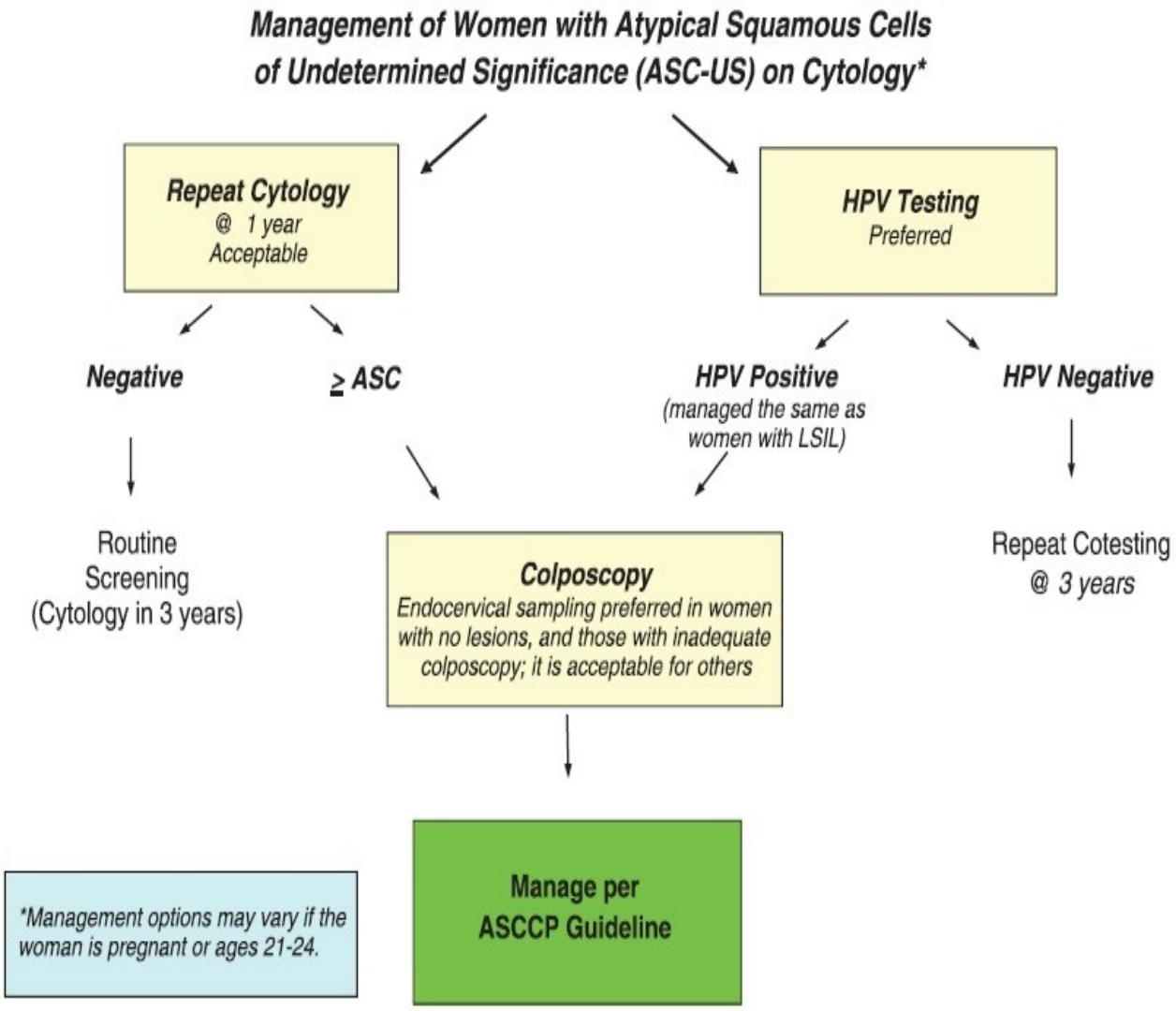

Figure 2: Management of women with ASC-US [59]

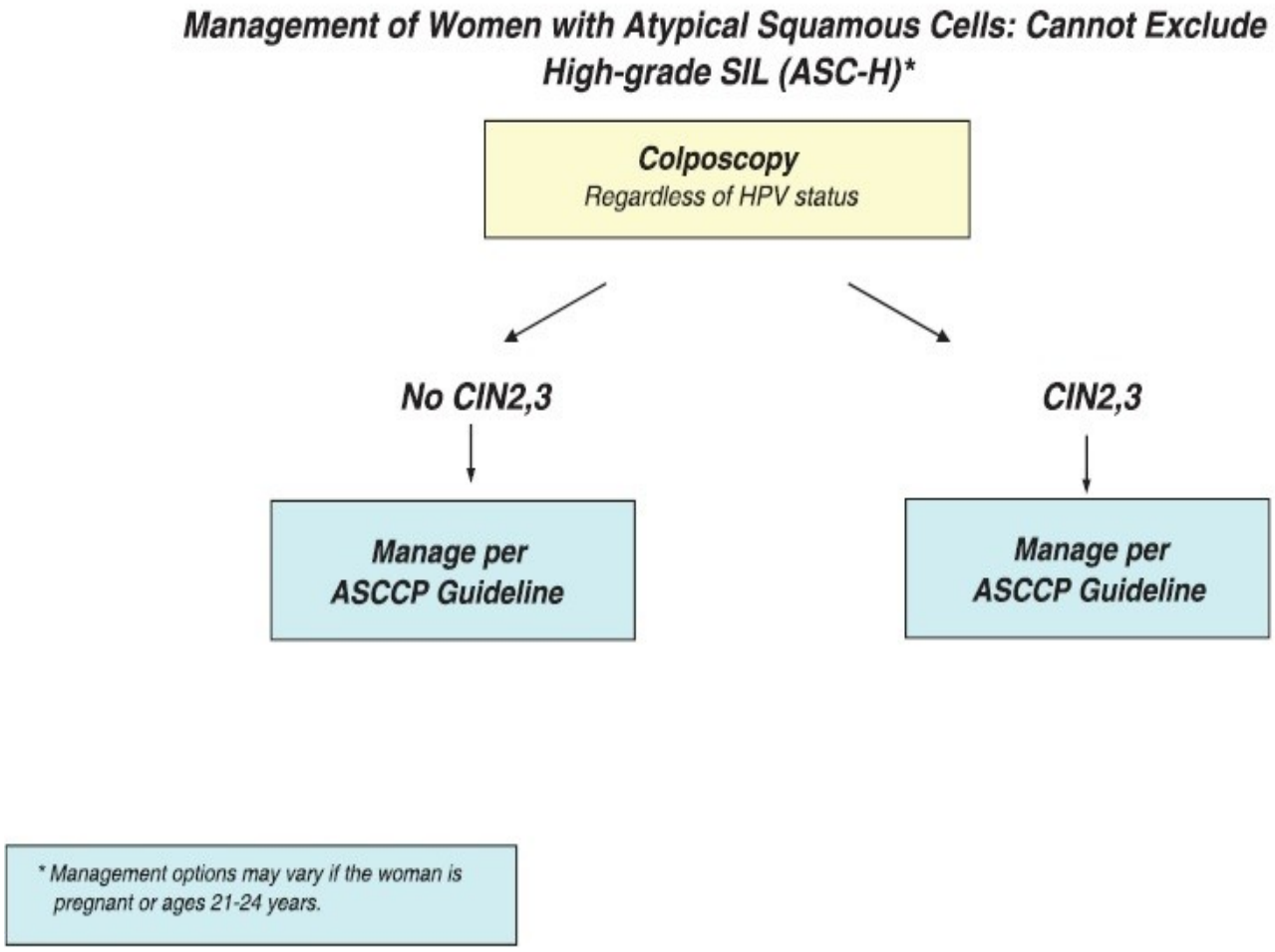

Figure 3: Management of women with ASC-H [59]

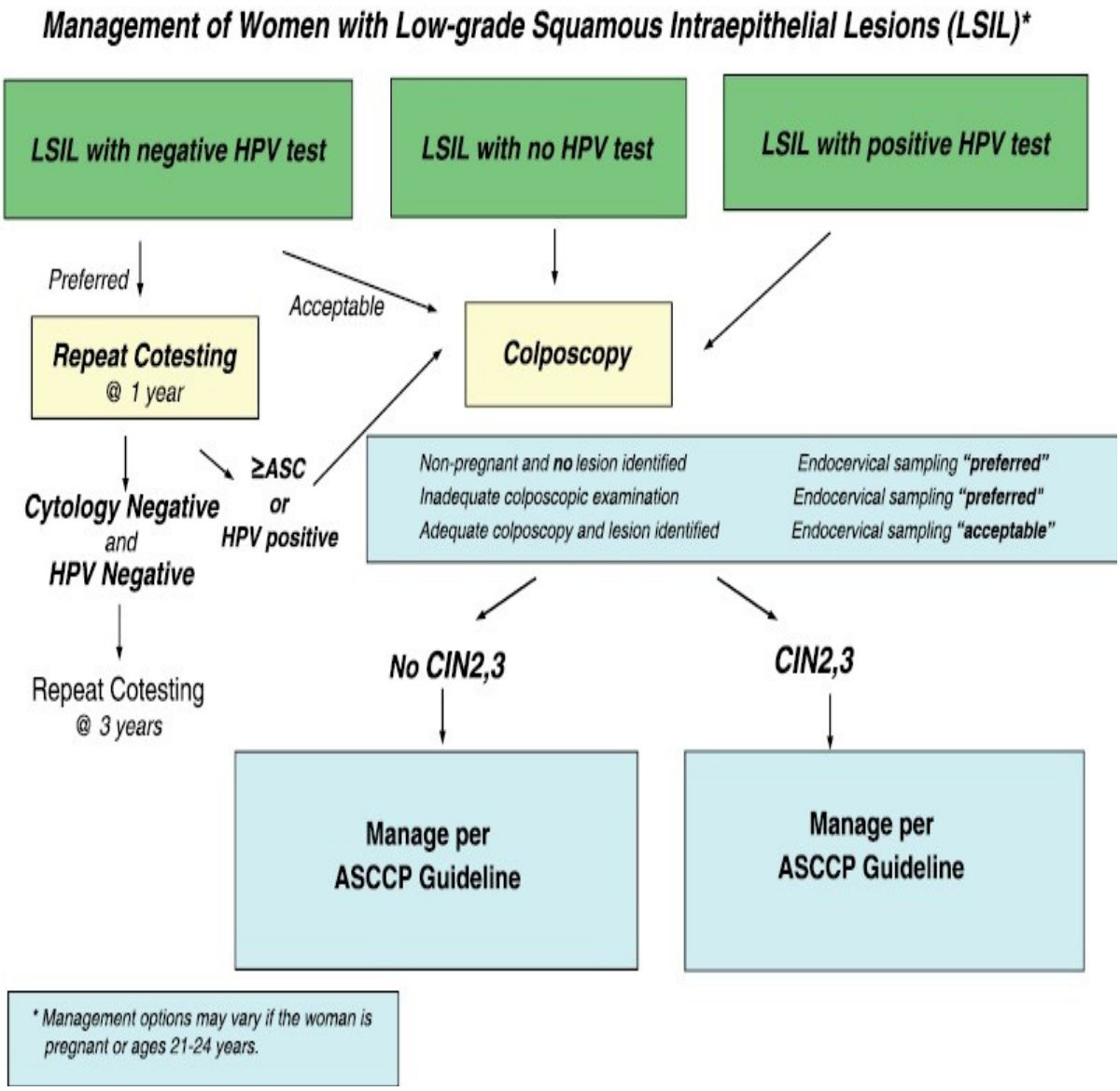

Figure 4: Management of women with LSIL [59]

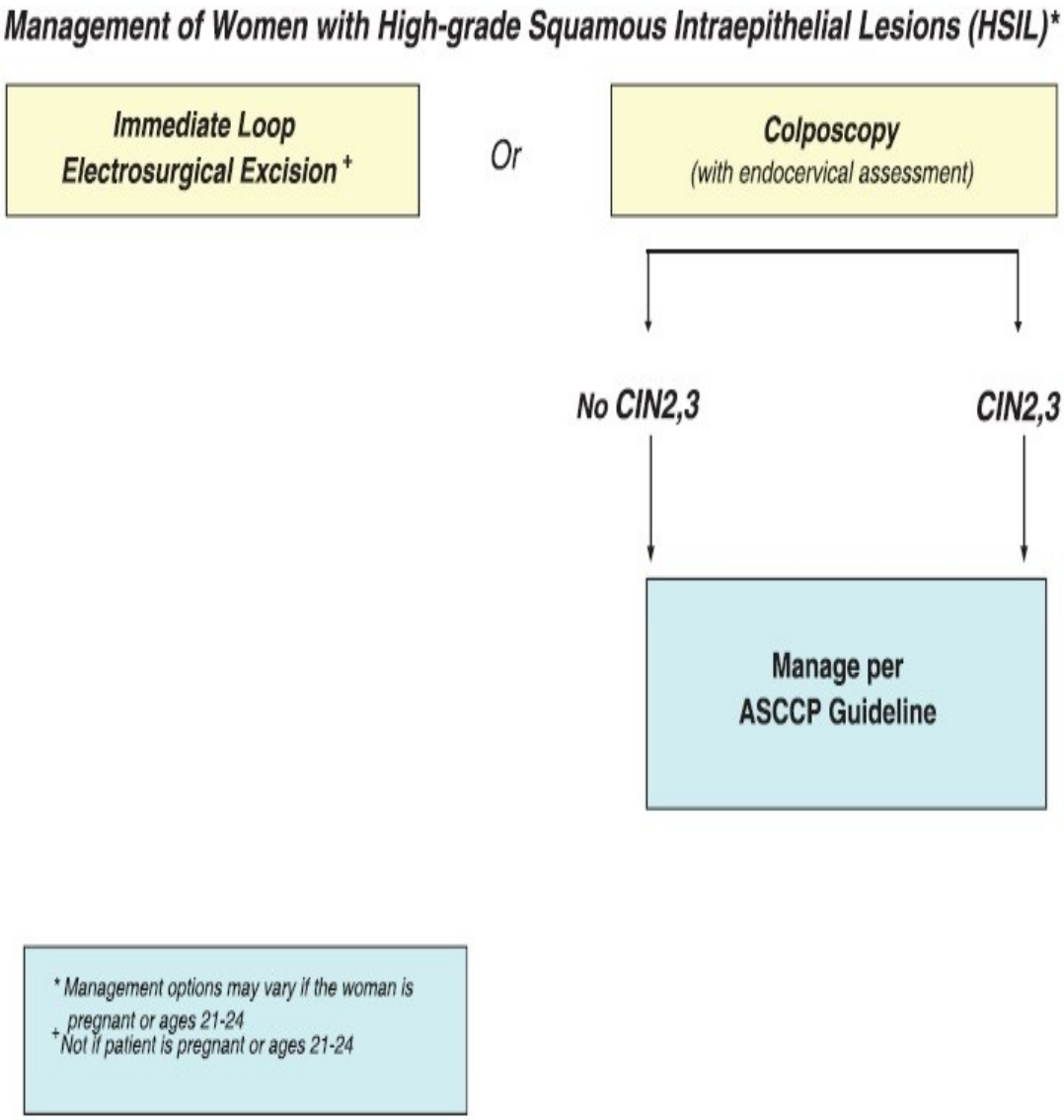

Figure 5: Management of women with HSIL [59]

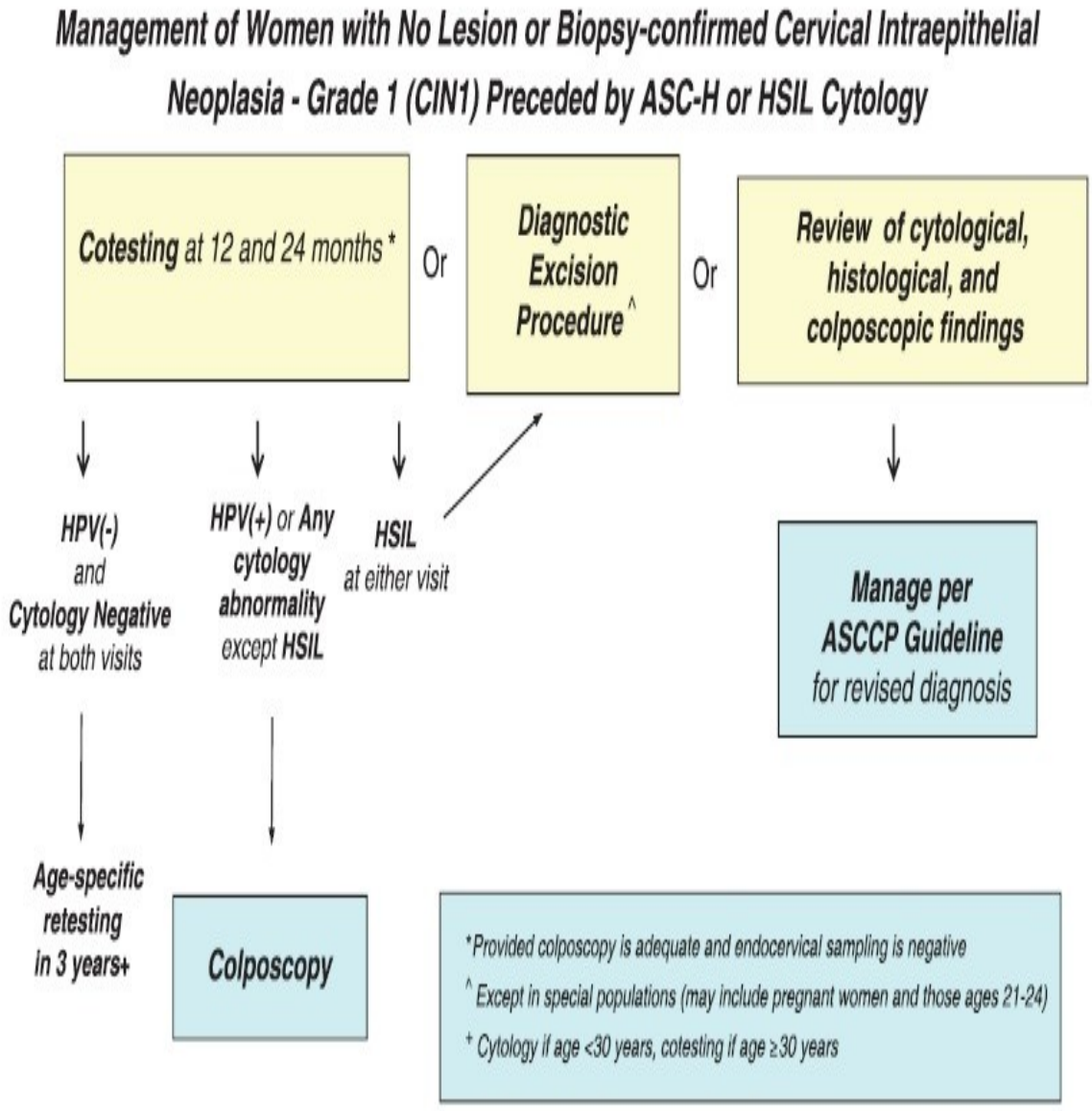

Figure 6: Management of women with CIN1[59]

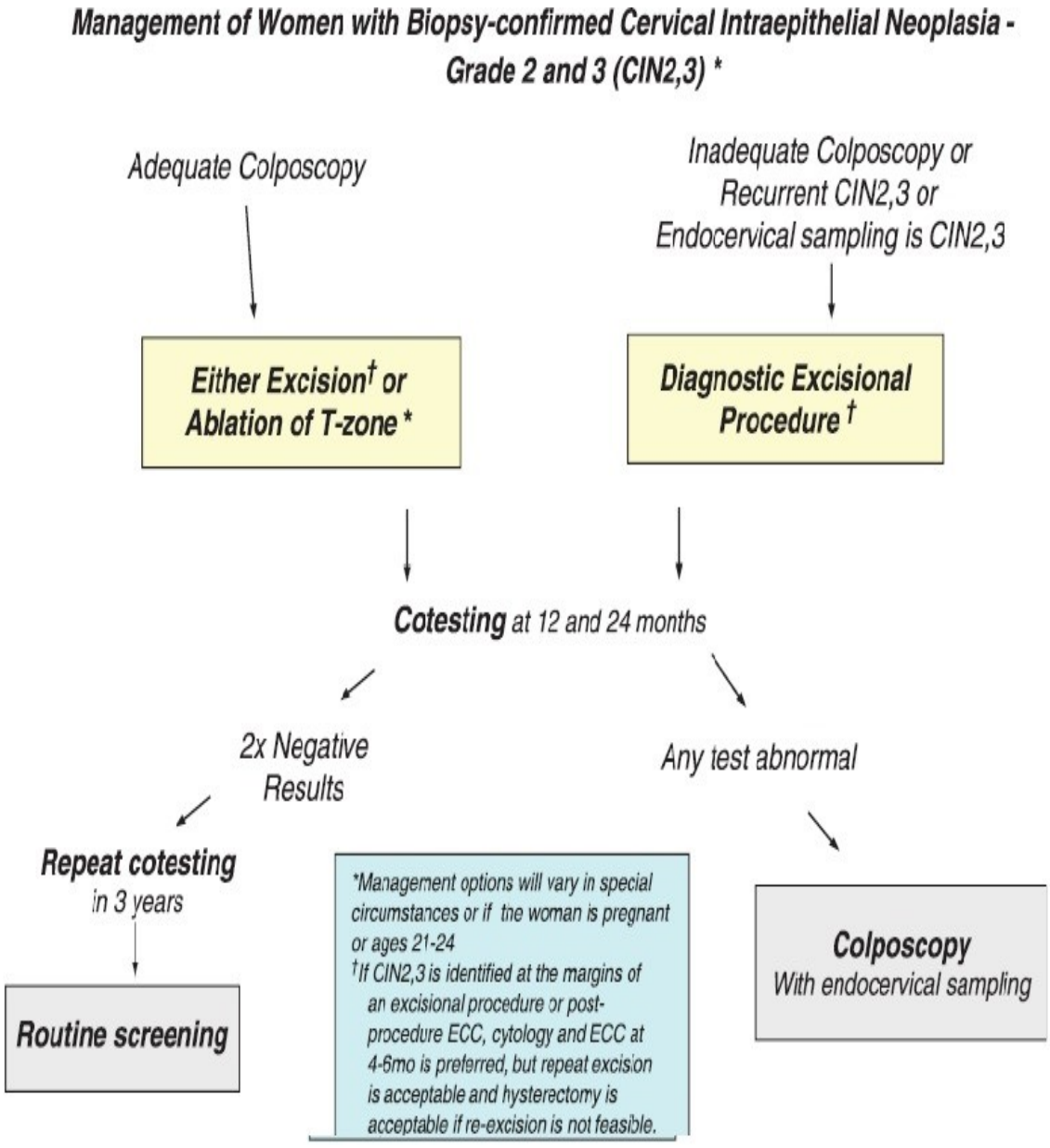

Figure 7: Management of women with CIN2, 3 [59]

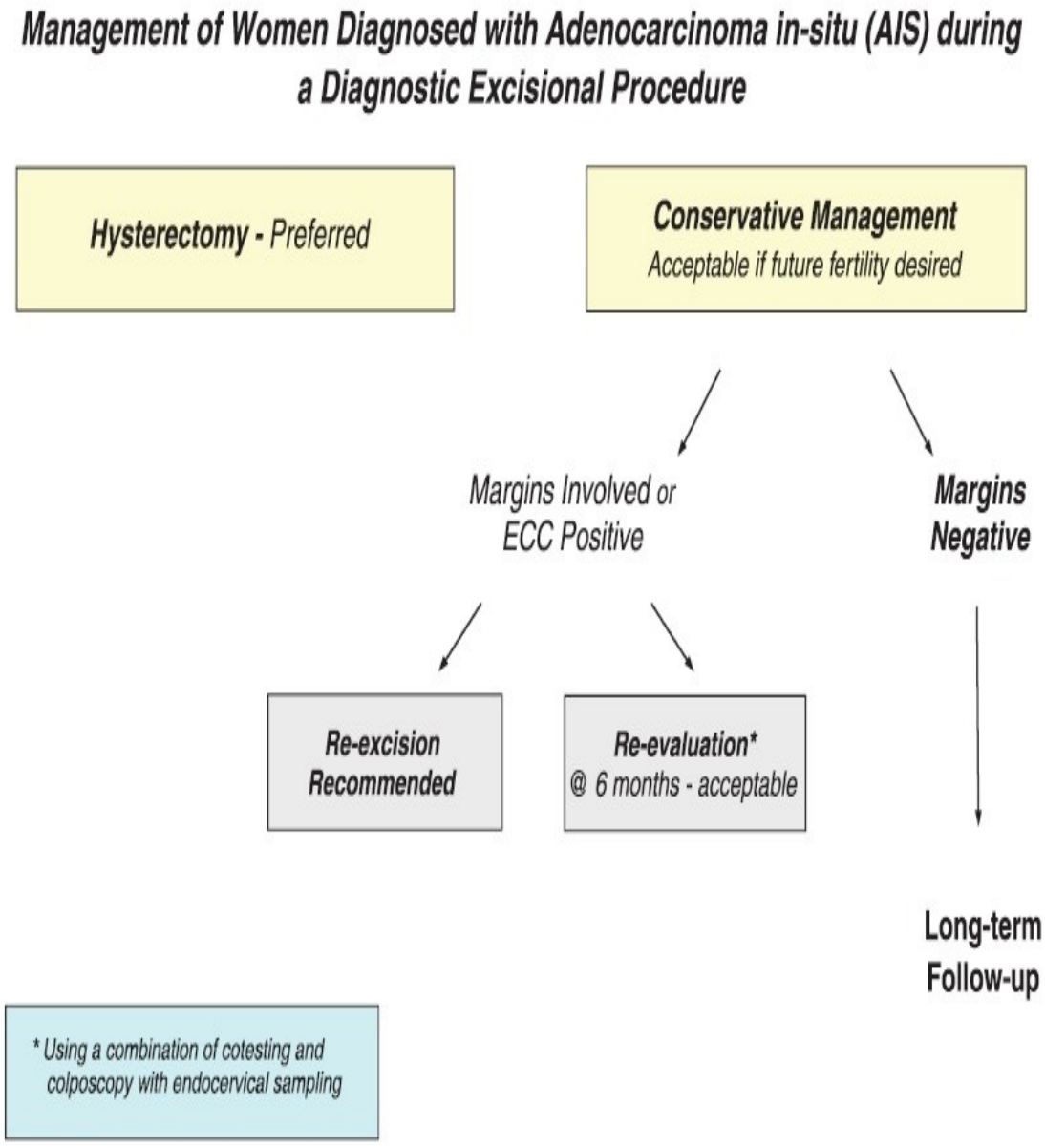

Figure 6: Management of women with AIS [59]
(ECC=Endocervical Curetage)

PREVENTION

Despite the successful screening program, in the current 28 Member States of the European Union (EU), approximately 34,000 new cases of cervical cancer and 13,000 deaths due to the disease occur annually. From those 3000 women are diagnosed with cervical cancer and about 900 women die of the disease each year only in the UK [45, 61]. So it seems that using of an effective prevention method is necessary.

"Following discovery of papillomavirus as the cause of cervical cancer, an enormous worldwide effort involving epidemiologists, molecular biologists, vaccinologists, and clinicians culminating in the development of effective prophylactic vaccines for human papillomavirus, which have the means to prevent 70–80% of cervical cancer" [29].

After introducing of HPV vaccines, for the first time in the history of medicine the prevention of the major cause of a cancer turned into a possibility even before its onset. Regarding the point that the vaccines are most effective in HPV negative women, young girls are the first target group, with the aim of vaccinating before starting sexual activity and as avoiding such potential infections [15, 35].

Finally, two distinct vaccines were evaluated, **Gardasil** a quadrivalent vaccine containing virus-like particles (VLPs) of types 6, 11, 16 and 18 and **Cervarix**, a bivalent vaccine containing VLPs of types 16 and 18. Evidence suggests these vaccines provide nearly 100% protections for these strains. Moreover, Cervarix appears to provide cross protection against other oncogenic strains such as HPV 31, 33 and 45. Gardasil also demonstrated a strong protection against genital warts as well [13, 62, 63].

HPV vaccination against the virus types causing cervical cancer has been officially recommended for girls aged 12–17 since 2007. But it is strongly emphasized that annual screening attendance is necessary despite vaccination because of the residual risk of becoming infected with other potentially carcinogenic HPV types not covered by the vaccine and because of the possibility of having been infected with the high-risk HPV types prior to vaccination [35, 45, 64]. Cervical cancer-related deaths could be reduced up to 76% With a comprehensive vaccination program [13].

A substantial reduction in CIN2+ have been shown in countries with high vaccination coverage and catch-up programs for both older persons and young women within five years of implementation **[65, 66].**

Moreover, vaccination programs have the potential to be very cost-effective in both the poorest, as well as high income countries, although this will be dependent on equitable vaccine pricing. By 2010, 18 European countries had instituted HPV vaccination programs, though these tended to be in the countries that already had the lowest cervical cancer mortalities and not in developing countries [13].

"Vaccine efficacy in patients who had not previously had HPV infection was 98%. As expected, efficacy was lower (44%), for women who had had an active human papillomavirus 16 or 18 infection at baseline or had previous exposure to human papillomavirus based on the presence of human papillomavirus antibodies to vaccine-related human papillomavirus types at baseline"[29].

It is estimated that 80% vaccine coverage will lead to a 63% decline in cervical cancer occurrence in 20–29 year old women by 2025 [45]. Using a vaccine to prevent a malignancy is a comparatively new concept so awareness and education will be very important in the implementation of this strategy [1].

THE NECESSITY OF CONDUCTING THE PRESENT RESEARCH

There is no enough information currently about the prevalence of, or risk factors for, HPV infection in Muslim countries in the Middle East, where sexual manners differ from many other world populations [67].

Although cytological screening has started in developing countries, the adoption of pap smear as a screening approach in the developing world has been found to be a low screening and limit progress against the burden of cervical cancer due to the lack of trained cytologists, laboratories and inefficient health systems for evaluation and follow-up of the test results [26, 28].

In this regard, the World Health Organization predicts that new cases of cancer increase from 11.3 million in 2007 to 15.5 million in 2030. Moreover nearly two thirds of the cancer cases predicted for 2050 will occur in developing countries [19].

Developing statistical models that estimate the probability of developing cancer over a defined period of time will help clinicians identify individuals at higher risk of specific cancers, allowing for earlier or more frequent screening and counseling of behavioral changes to decrease the risks. These types of models also will be useful for designing future chemoprevention and screening intervention trials in individuals at high risk of specific cancers in the general population [68].

Studies have already showed that there are lots of factors which can affect cytological findings in Pap smear such as age [69], race [70], smoking [71] etc, but there is not any research has been performed to show the severity of these impacts to this extent, especially in Iran.

One of the main objectives of the present study is to develop a risk factors assessment tool for the cytological changes in Pap test. It could be an effective help for researchers conducting clinical or educational interventions in this area through providing a standard solution to match the case and control groups. It can also be used in gynecological clinics by physicians and health care givers in face with their clients in order to approch an early diagnosis and treatment.

In the present study the researcher plans to obtain a regression model of the determinants for results of Pap smears including cervical cancer as well. “Regression is one of the methods used to determine the effects of one variable on another one. Regression models are used to predict one variable from one or more other variables. Regression models enable the scientist, with a powerful tool, to predict the present or future events by the information. The scientist employs these models either because it is less expensive in terms of time and/or money to collect the information to make the predictions than to collect the information about the event itself, or more likely, because the event to be predicted will occur in some future time” [72].

The regression modle obtained in this study can help the physicians to predict their patients' health situation in order to have a suitable and quick action. In addition, the regression model

obtained from this study could be a good guide to determine the priority for pathological checks and will be effective in reducing the medical expenses as well.

OBJECTIVES

The present research was conducted based on the two following objectives.

THE FIRST OBJECTIVE: Develop a risk factors and clinical manifestations assessment tool for the cytological changes towards cervical cancer in Pap test

The specific objectives:

1) To identify the full content domain and items generation through the extend review of related articles
2) To provide the primary draft of the research tool
3) To assess the validity & reliability
4) To develop the final research tool

THE SECOND OBJECTIVE: Compare the risk factors and clinical manifestations between women with (Case group) and without (Control group) atypical cytological findings in Pap test and develop the regression model of its determinants in Iran.

The specific objectives:

1) To compare the demographic characteristics between the subjects in the case and control groups
2) To compare the health history between the subjects in the case and control groups
3) To compare the clinical manifestations between the subjects in the case and control groups
4) To provide the regression model of the cytological findings determinants in Pap test for the research population

Chapter 2

Literature Review

THE FOLLOWING STUDIES HAVE BEEN USED TO MAKE THE RESEARCH TOOL.

Montgomery and Smith conducted a research entitled: "Human Papillomavirus and Cervical Cancer Knowledge, Health Beliefs, and Preventive Practices in 2 Age Cohorts: A Comparison Study", in 2012. The objective of this study was to evaluate and compare the HPV and cervical cancer knowledge, health beliefs, and preventive practices in women in 2 age groups: 19 to 26 and 40 to 70. "This study used a cross-sectional, descriptive design". A convenience sample of 300 women in 2 age groups was recruited from 3 ambulatory obstetrics and gynecology practices in Philadelphia. "Participants completed the Awareness of HPV and Cervical Cancer Questionnaire to determine their HPV and cervical cancer knowledge, health beliefs, and preventive practices". A total of 280 responses were received. Significant differences were found between the 2 groups in knowledge only, but not health beliefs and perceived seriousness. Significant differences in select preventive practices were also noted between these 2 groups. These included Pap smear, use of condoms, and use of oral contraception [30].

Schoenberg et al, in 2013, conducted a research entitled: "Patterns and Determinants of Breast and Cervical Cancer Non-Screening among Appalachian Women". Researchers examined patterns of non-screening among Appalachian women. "In-person interviews were conducted with 222 Appalachian women who fell outside of screening recommendations for timing of Pap tests and mammograms. These women, from six Appalachian counties, were participating in a group-randomized, multi-component trial aimed at increasing adherence to cancer screening recommendations. Results indicated that participants who were rarely or never screened for breast cancer were also likely to be rarely or never screened for cervical cancer. In addition, four key barriers were identified as independently and significantly associated with being rarely or never screened for both cervical and breast cancer" [73].

Arbyn et al, conducted a research entitled: "Attendance at Cervical Cancer Screening and Use of Diagnostic and Therapeutic Procedures on the Uterine Cervix Assessed from Individual Health Insurance Data (Belgium, 2002-2006)", in 2014 "to assess the coverage for cervical cancer screening as well as the use of cervical cytology, colposcopy and other diagnostic and therapeutic interventions on the uterine cervix in Belgium, using individual health insurance

data. The Intermutualistic Agency compiled a database containing 14 million records from reimbursement claims for Pap smears, colposcopies, cervical biopsies and surgery, performed between 2002 and 2006". Cervical cancer screening coverage was defined as the proportion of women aged 25–64 that had a Pap smear within the last 3 years. "Differences between the 3 regions were small, but varied more substantially between provinces. Coverage was 70% for 25–34 year old women, 67% for those aged 35–39 years, and decreased to 44% in the age group of 60–64 years. The median screening interval was 13 months. The screening coverage varied substantially by social category: 40% and 64%, in women categorised as beneficiary or not-beneficiary of increased reimbursement from social insurance, respectively. In the 3-year period 2004–2006, 3.2 million screen tests were done in the target group consisting of 2.8 million women. However, only 1.7 million women got one or more smears and 1.1 million women had no smears, corresponding to an average of 1.88 smears per woman in three years of time. Colposcopy was excessively used. The proportion of women with a history of conisation or hysterectomy, before the age of 65, was 7% and 19%, respectively" [74].

Low et al, in 2012 published an article entitled: "What do British women know about cervical cancer symptoms and risk factors". The aim was "to identify levels of cervical cancer risk factor and symptom awareness, as well as predictors of higher awareness in a United Kingdom (UK) female population". It was a population based study, in Participants' homes in the UK. "Sample: UK representative sample of females aged 16 years and over (n = 1392). Respondents completed the Cervical Cancer Awareness Measure which included questions on awareness of cervical cancer symptoms and risk factors. Linear regression analyses were used to identify predictors of higher symptom and risk factor recognition scores. The results showed that Sixty-five percent of respondents were unable to recall any risk factors and 75% were unable to recall any symptoms. Awareness was higher when women were prompted. Independent predictors of risk factor recognition were older age and higher education. Symptom recognition was associated with older age, White ethnicity, higher education and having a close experience of cervical cancer" [75].

Gedefaw et al published an article entitled: "The Prevalence of Precancerous Cervical Cancer Lesion among HIV-Infected Women in Southern Ethiopia: A Cross-Sectional Study" in 2013. "This study aimed to assess the prevalence of and factors associated with precancerous cervical cancer lesion among HIV- infected women in southern Ethiopia. A hospital-based

cross-sectional study was conducted from October 2012 to February 2013 among HIV-infected women in Southern Ethiopia. Four hundred forty eight HIV-infected women who had been screened and treated for precancerous cervical cancer lesion were included in the study. Data were collected by using structured and pretested questionnaire. Visual inspection with acetic acid was applied for screening and treatment. SPSS version 16.0 was used for data entry and analysis. Logistic regression analysis was fitted and odds ratios with 95% Confidence intervals and p-values were computed to identify factors associated with precancerous cervical cancer lesion. Results showed that out of 448 study participants, 99 (22.1%) were found to be positive for precancerous cervical cancer. Being currently on highly active antiretroviral treatment history of sexually transmitted disease and having only one lifetime sexual partner were factors associated with precancerous cervical cancer lesion" [6].

Ratanasiripong et al in 2013 published an article entitled:"What college women know, think, and do about human papillomavirus (HPV) and HPV vaccine". It was a cross-sectional study, "guided by Ajzen's Theory of Planned Behavior, aimed to identify factors that influence the decision to obtain an HPV vaccine among college women and to examine the relationships among these factors. An electronic self-administered survey was utilized to collect data. An email invitation was sent to 3074 college women attending a large, public university in southern California, aged between 18 and 26 years. The email directed the recipient to click on a link to a web-based survey if she wanted to participate in the study. Participants in this study were college women. They knew that a Pap test is still needed after HPV vaccination and that the HPV vaccine does not protect against other Sexually Transmitted Infections. Both non-vaccinees and vaccinees had positive attitudes about mandating HPV vaccine. Knowledge and attitudes toward the vaccine were not directly linked to the outcome predictors – intention to obtain the vaccine and vaccine uptake. Attitude about receiving HPV vaccine, subjective norms (complying with the expectations of others), and perceived behavioral control were correlated with the outcome predictors. Subjective norms consistently predicted intention to obtain HPV vaccine and vaccine uptake" [76].

Gillet et al conducted a research entitled: "Association between Bacterial Vaginosis and Cervical Intraepithelial Neoplasia: Systematic Review and Meta-Analysis" in 2012. Bacterial vaginosis has been suggested as co-factor in the development of cervical cancer. "Previous studies examining the relationship between BV and cervical intra-epithelial neoplasia (CIN)

provided inconsistent and conflicting results. The aim of this study was to clarify the association between these two conditions. A systematic review and meta-analysis were conducted to summarize published literature on the association between BV and cervical pre-cancerous lesions. An extensive search of electronic databases Medline and Web of Science was performed. The key words 'bacterial vaginosis' and 'bacterial infections and vaginitis' were used in combination with 'cervical intraepithelial neoplasia', 'squamous intraepithelial lesions', 'cervical lesions', 'cervical dysplasia', and 'cervical screening'. Eligible studies required a clear description of diagnostic methods used for detecting both BV and cervical pre-cancerous lesions. Publications were included if they either reported odds ratios and corresponding 95% confidence intervals representing the magnitude of association between these two conditions, or presented data that allowed calculation of the OR. Out of 329 articles, 17 cross-sectional and 2 incidence studies were selected. In addition, two studies conducted in The Netherlands, using the national KOPAC system, were retained. After testing for heterogeneity and publication bias, meta-analysis and meta-regression were performed, using a random effects model. Although heterogeneity among studies was high, a positive association between BV and cervical pre-cancerous lesions was found, with an overall estimated odds ratio of 1.51. Meta-regression analysis could not detect a significant difference between studies based on BV diagnosis, CIN diagnosis or study population" [77].

Raychaudhuri & Mandal in 2012 conducted a research project entitled: "Socio-Demographic and Behavioral Risk Factors for Cervical Cancer and Knowledge, Attitude and Practice in Rural and Urban Areas of North Bengal, India". "This study was conducted to: (1) determine the prevalence and (2) make a comparative analysis of the socio-demographic and behavioral risk factors of cervical cancer and knowledge, attitude and practice between rural and urban women of North Bengal, India". This is a Community-based cross-sectional study. A survey (first in North Bengal) was conducted among 133 women in a rural area and 88 women in an urban slum using predesigned semi-structured questionnaires. "The respondents were informed of the causes (including HPV), signs and symptoms, prevention of cervical cancer and treatment, and the procedure of the Pap test and HPV vaccination. The prevalence of risk factors like multiparity, early age of marriage, use of cloth during menstruation, use of condom and OCP, early age of first intercourse was 37.2%, 82%, 83.3%, 5.4%, 15.8% and 65.6% respectively. Awareness about the cause, signs and symptoms, prevention of cervical cancer, Pap test and HPV vaccination was 3.6%, 6.3%, 3.6%, 9.5% and 14.5% respectively.

Chi-square testing revealed that in the study population, significant differential at 5% exists between rural and urban residents with respect to number of children, use of cloth/sanitary napkins, family history of cancer and awareness regarding causes of cervical cancer. Regarding KAP, again using chi-square tests, surprisingly, level of education is found to be significant for each element of KAP in urban areas in contrast to complete absence of association between education and elements of KAP in rural areas" [78] .

Sicsic & Franc conducted a research project in 2014 entitled: "Obstacles to the uptake of breast, cervical, and colorectal cancer screenings: what remains to be achieved by French national programs?" The aim in this study was to analyze the obstacles to and levers for breast, cervical, and colorectal cancer screening uptake and their trends over time. "Based on representative data from the French Health Care and Health Insurance Survey (three independent, cross-sectional surveys: 2006, 2008, and 2010), multivariate logistic regressions were used to model the association between the nonuse of screening for the three cancers and various independent variables". Then, interactions with survey year dummies allowed the changes in the determinants of these cancer screenings over time to be estimated. Whereas the incentives for screening were strengthened during the period considered, cervical and breast cancer screenings decreased, and colorectal cancer screenings increased sharply in 2006 to 38.9% in 2010. Under-users of the three cancer screenings were primarily unskilled workers, individuals without complementary health insurance, or individuals with free complementary health insurance who more rarely use outpatient care. Moreover, individuals neither reporting either risky behaviors, namely heavy smokers and high-risk drinkers or very safe behaviors, namely neither smoking nor drinking underused screenings. Despite the implementation of national programmes for breast and colorectal cancer screenings, the disparities and inequalities in screening uptake did not decrease over the study period [79].

Gedefaw et al in 2013 published a research article entitled: "The Prevalence of Precancerous Cervical Cancer Lesion among HIV-Infected Women in Southern Ethiopia: A Cross-Sectional Study". "This study aimed to assess the prevalence of and factors associated with precancerous cervical cancer lesion among HIV- infected women in southern Ethiopia. A hospital-based cross-sectional study was conducted from October 2012 to February 2013 among HIV-infected women in Southern Ethiopia. Four hundred forty eight HIV-infected women who had been screened and treated for precancerous cervical cancer lesion were

included in the study. Data were collected by using structured and pretested questionnaire. Visual inspection with acetic acid was applied for screening and treatment. SPSS version 16.0 was used for data entry and analysis. Logistic regression analysis was fitted and odds ratios with 95% Confidence intervals and p-values were computed to identify factors associated with precancerous cervical cancer lesion. Out of 448 study participants, 99 (22.1%) were found to be positive for precancerous cervical cancer. Being currently on highly active antiretroviral treatment, history of sexually transmitted disease and having only one lifetime sexual partner were factors associated with precancerous cervical cancer lesion"[6] .

Menvielle et al in 2014 conducted a research project entitled: "To what extent is women's economic situation associated with cancer screening uptake when nationwide screening exists? A study of breast and cervical cancer screening in France in 2010". The aim of this study was to investigate the association between women's economic situation and breast and cervical cancer screening. Researchers used data from a large French national health survey conducted in 2010. "The economic situation was assessed using the number of adverse economic conditions respondents were facing, based on three variables (low income, lacking food, and perceived financial difficulties). Logistic regressions were adjusted for socioeconomic and sociodemographic characteristics, healthcare use and insurance, and health behaviors". Results showed that Mammography was less frequent among women experiencing two or more adverse economic conditions, whereas Pap smear was less frequent among women experiencing at least one adverse economic condition. "For both screenings, higher rates were observed among women who lived in the Paris region. Sociodemographic indicators and health behaviors were associated with Pap smear, whereas healthcare use and insurance characteristics were associated with mammography" [80].

Almeida has published a research article in 2012 entitled: "Evaluating associations between sources of information, knowledge of the human papillomavirus, and human papillomavirus vaccine uptake for adult women in California". "The purpose of this study was to determine the pattern of associations between information source and level of knowledge about HPV and vaccine receipt/intention. Researchers analyzed the 2007 California Health Interview Survey, a population-based, statewide random digit dial survey, using data on adult females ages 18–65 who had heard about HPV (n = 16,806). One-way ANOVA and multivariate logistic regression assessed the associations between source of information (advertisement only,

advertisement plus other sources, and non-advertisement sources) and knowledge of HPV (3 or greater correct on a 4-point scale). Multivariate logistic regressions were conducted on a subsample of vaccine-eligible women and parents to assess vaccine uptake or intention. Less than half of respondents (43%) correctly answered 3 or more of the HPV knowledge questions. Mean knowledge scores were significantly different when comparing women who reported advertisement only, non-advertisement, and advertisement plus other sources of information ($p < 0.001$). In multivariate analysis, women who reported non-advertisement sources and advertisements plus other sources were more likely to have knowledge scores above the 75% level than women who relied on advertisements alone. In the subsample of vaccine-eligible women and parents, those who reported advertisements plus other sources were more likely to have received or intend to receive the vaccine than those who reported advertisements as their sole information source" [81].

Mullins et al have published a research article in 2013 entitled: "Human papillomavirus vaccine communication: Perspectives of 11–12 year-old girls, mothers, and clinicians". Researchers explored communication between 11- and 12 year-old girls, mothers, and clinicians regarding HPV vaccines and concordance in reports of maternal and clinician communication. Researchers conducted individual interviews with 33 girls who had received the quadrivalent HPV vaccine in urban and suburban clinical settings, their mothers, and their clinicians. Data were analyzed using qualitative methods. From the perspectives of both girls and mothers, clinicians and parents were the preferred sources of HPV vaccine information for girls. "Vaccine efficacy and risks/benefits of vaccination were the most commonly reported desired and actual topics of discussion by mothers, girls, and clinicians". "Clinician recommendation of vaccination was reported by nearly one-fifth of girls and nearly half of mothers. The most common concordant messages were related to efficacy of the vaccine, with concordance in 70% of triads. The most common discordant messages were related to sexual health. Approximately half of clinicians (16) reported discussing sexual health, but only 5 mothers (15%) and 4 girls (12%) reported this. Triads recruited from suburban (vs. urban) practices had higher degrees of concordance in reported vaccination communication" [82].

Gerend & Magloire (2008) had an article entitled: "Awareness, Knowledge, and Beliefs about Human Papillomavirus in a Racially Diverse Sample of Young Adults". The aim was "to assess current levels and correlates of awareness, knowledge, and beliefs about human

papillomavirus (HPV) in a racially diverse sample of young adults. Correlates of interest in HPV education and the HPV vaccine were also examined. A total of 124 students 18–26 years of age from two southeastern universities (including a historically black university) completed a survey assessing demographic characteristics, sexual history, awareness and knowledge of HPV, HPV-related beliefs (perceived risk of HPV infection, perceived shame associated with HPV infection), interest in learning more about HPV, and interest in the HPV vaccine (women only). More than 75% of the sample had heard of HPV. Although some misunderstandings were observed, HPV knowledge was relatively high. Women reported greater awareness and knowledge of HPV than did men. Higher perceptions of risk were observed among sexually active participants and those with multiple sexual partners. Younger participants, men, and those with less HPV knowledge indicated they would feel more ashamed if diagnosed with HPV. Black/African-American and sexually active participants reported greater interest in HPV education. Greater interest in the HPV vaccine was observed among women who were sexually active, had multiple sexual partners, and felt vulnerable to HPV infection" [83].

Bowyer et al published an article in 2014 entitled: "Association between human papillomavirus vaccine status and other cervical cancer risk factors". "This study aimed to measure the association between vaccine status and cervical cancer risk factors in adolescent girls. Methods: Girls (15–16 years) from the first two cohorts to be offered routine HPV vaccination in the NHS immunization programme completed a survey 3 years post-vaccination. Recruitment took place at 13 schools in London. Results: Of 2768 girls registered in Year 11, 1912 (69%) took part and provided analyzable data. Questions assessed vaccine status, demographic characteristics, smoking status, sexual behavior and intention to attend cervical screening. Overall, 78% had completed the three-dose vaccine course. There was no association between vaccine status and smoking behavior or sexual experience. In adjusted analyses, girls from black or 'other' ethnic backgrounds were less likely to be fully-vaccinated than those from white backgrounds. Those with low intentions to attend cervical screening were less likely to be fully vaccinated than those with high intentions" [45].

Parish et al published an article in 2013 entitled: "Determinants of cervical cancer screening among women with intellectual disabilities: evidence from medical records". The objective was "to examine receipt of cervical cancer screening and determinants of screening for women with intellectual disabilities in one Southeastern state. Methods: Using medical records data

from 2006 through 2010 for community-dwelling women with intellectual disabilities who were 18–65 years of age (n=163), we employed descriptive and bivariate statistics and a multivariate regression model to examine receipt of cervical cancer screening and the determinants of cervical cancer screening across women's sociodemographic and health-care provider characteristics. Results: Of women 18–65 years of age with intellectual disabilities, 55% received a Papanicolaou (Pap) test during 2008–2010, markedly below the Healthy People 2020 targets or rates of Pap test receipt of women without intellectual disabilities. Women with intellectual disabilities who lived in residential facilities, those who lived in rural communities, and those who had an obstetrician/gynecologist had higher rates of receipt of care than other women with intellectual disabilities" [84].

Chen et al published an article in 2013 entitled: "Human papillomavirus 33 worldwide genetic variation and associated risk of cervical cancer". "The current study aimed to characterize the genetic diversity of HPV33 and to explore the association of HPV33 variants with the risk for cervical cancer. Methods: Taking advantage of the International Agency for Research on Cancer biobank, the researchers sequenced the entire E6 and E7 open reading frames of 213 HPV33-positive cervical samples from 30 countries. Results: We identified 28 HPV33 variants that formed 5 phylogenetic groups: the previously identified A1, A2, and B (sub) lineages and the novel A3 and C (sub) lineages. The A1 sublineage was strongly over-represented in cervical cases compared to controls in both Africa and Europe" [85].

Hopkins & Wood published an article in 2013 entitled: "Female human papillomavirus (HPV) vaccination: Global uptake and the impact of attitudes". In this review, the researchers summarized the current trends in female HPV vaccination coverage throughout the world, and place it in the context of available research on attitudes towards vaccination amongst the public and health professionals. Results: "Where countries have the resources for mass vaccination programmes, uptake has varied. School-based opt-out programmes consistently achieve highest coverage, whilst countries and regions without systematic vaccination schemes have low coverage. In all countries, the success of vaccination programmes is dependent on the support of the public and healthcare professionals. Whilst public acceptance is dependent on multiple factors, it has repeatedly been shown that recommendation by a health professional, particularly clinicians, is the key to vaccine uptake. Worryingly, it appears that a proportion of clinicians still have significant reservations about promoting vaccination,

particularly for younger age groups. A commitment now, to fully educating both the public and clinicians, has the potential to make a dramatic future impact" [13].

Sossaue et al conducted a research entitled: "Impact of an Educational Intervention on Women's Knowledge and Acceptability of Human Papillomavirus Self-Sampling: A Randomized Controlled Trial in Cameroon". "Human papillomavirus (HPV) self-sampling (Self-HPV) may be used as a primary cervical cancer screening method in a low resource setting. The aim in this study was to evaluate whether an educational intervention would improve women's knowledge and confidence in the Self-HPV method. Methods: Women aged between 25 and 65 years old, eligible for cervical cancer screening, were randomly chosen to receive standard information (control group) or standard information followed by educational intervention (interventional group). Standard information included explanations about what the test detects (HPV), the link between HPV and cervical cancer and how to perform HPV self-sampling. The educational intervention consisted of a culturally tailored video about HPV, cervical cancer, Self-HPV and its relevancy as a screening test. All participants completed a questionnaire that assessed sociodemographic data, women's knowledge about cervical cancer and acceptability of Self-HPV. Results: A total of 302 women were enrolled in 4 health care centers in Yaoundé and the surrounding countryside. 301 women (149 in the "control group" and 152 in the "intervention group") completed the full process and were included into the analysis. Participants who received the educational intervention had a significantly higher knowledge about HPV and cervical cancer than the control group ($p<0.05$), but no significant difference on Self-HPV acceptability and confidence in the method was noticed between the two groups" [86].

Castell et al (2014) conducted a research entitled: "Feasibility and acceptance of cervicovaginal self-sampling within the German National Cohort (Pretest 2)". "In a pilot project the feasibility of female study participants of the GNC collecting a cervicovaginal lavage at home without having to involve a gynecologist or other medical personnel was thus investigated. The ability of the procedure to detect vaginal microbes and conditions including human papillomavirus (HPV), Chlamydia trachomatis and bacterial vaginosis (BV) were also explored. This cross-sectional study was conducted in two study centers (Hamburg and Hanover) of the GNC during Pretest 2 in 2012 as an add-on module to the main program of the National Cohort. Participants were randomly selected through the population registration

office. After providing written informed consent at the study center, participants self-collected a cervicovaginal lavage (Delphi Screener™) at home following written instructions. Participants mailed samples and acceptability questionnaires to the laboratory and the study center, respectively. Acceptability of self-sampling was categorized as consent, partial consent and rejection. The samples were analyzed by multiplex HPV genotyping for the presence of 27 mucosal HPV subtypes. To detect other pathogens "Sexually Transmitted Infection Profiling" (STIP) was used, a novel multiplex polymerase chain reaction (PCR) for various vaginally occurring pathogens/conditions coupled with subsequent bead-based Luminex® hybridization. Human beta-globin and DNA polymerase alpha (PolA) sequences were used as positive controls for the detection of human DNA during HPV detection and STIP, respectively. Results: The participation based on the proportion of all women in Pretest 2 who could take part in the add-on Pretest 2 was 67.3 %. The age of participants ranged from 20 to 69 years. The self-reported median duration of the collection of the lavage was 5 min. Analysis of the questionnaires revealed that the self-sampling of a cervicovaginal lavage was acceptable to 98 % of women, and considered to be easy by 89 % as well as user-friendly by 96 % of the women. Human beta-globin and PolA as markers for human DNA and sample quality were detected in all samples analyzed while HPV as a marker for pathogen detectability was identified in 18 out of 109 samples. Of the 107 samples tested with STIP as a second marker for pathogen detectability, 5 samples were excluded from statistical analyses on bacterial colonization because of signs in the laboratory results of the use of antibiotics. For the computation of the possible occurrence of bacterial vaginosis and candidiasis 7 and 8 samples, respectively, were excluded because of low signal intensities resulting in an evaluation of 95 or 94 samples, respectively.Ureaplasma parvum was detected in 22 out of 102 samples, BV in 14 out of 95 samples and candidiasis in 13 out of 94 samples. Chlamydia trachomatis was not detected in any sample" [87].

Fletcher et al published an article in 2014 entitled: "Cervical Cancer Screening Adherence among HIV-Positive Female Smokers from a Comprehensive HIV Clinic". The objective was "to assess Pap smear screening prevalence and the associated characteristics among the HIV-positive female participants (n=138)". Methods: by using baseline data from a smoking cessation trial and electronic medical records. Results: Forty-six percent of the women had at least 1 Pap test in the year following study enrollment. "Multiple logistic regression analysis indicated that younger age, African American race, hazardous drinking, increased number of

cigarettes smoked per day, and smoking risk perception were associated with non-adherence to Pap smear screening. Cervical cancer screening was severely underutilized by women in this study. Findings underscore the importance of identifying predictors of non-adherence and addressing multiple risk factors and behavioral patterns among HIV-positive women who smoke" [88].

Lim et al (2014) in their research entitled: "Delays in diagnosis of young females with symptomatic cervical cancer in England: an interview-based study", which was conducted to "examine the extent and determinants of delays in diagnosis of young females with symptomatic cervical cancer, interviewed with 128 patients <30 years with a recent diagnosis of cervical cancer. "Patient delay was defined as ≥3 months from symptom onset to first presentation and provider delay as ≥ 3 months from first presentation to diagnosis". Results showed that "Forty (31%) patients had presented symptomatically: 11 (28%) delayed presentation. Patient delay was more common in patients <25 than patients aged 25–29 (40% versus 15%, P = 0.16). Vaginal discharge was more common among patients who delayed presentation than those who did not; many reported not recognising this as a possible cancer symptom. Provider delay was reported by 24/40 (60%); in some no report was found in primary care records of a visual inspection of the cervix and some did not re-attend after the first presentation for several months. Gynaecological symptoms were common (84%) among patients who presented via screening" [89].

William et al published the results of their research entitled: "Assessment of psychological barriers to cervical cancer screening among women in Kumasi, Ghana using a mixed methods approach". "This exploratory study was to identify psychological barriers to cervical cancer screening among Ghanaian women with and without cancer using a mixed methods approach. Methods: Semi-structured interviews were conducted with 49 Ghanaian women with cancer and 171 Ghanaian women who did not have cancer. Results: Analysis of the qualitative data revealed several psychological barriers to cervical cancer screening including, common myths about cervical cancer, misconceptions about cervical cancer screening, the lack of spousal support for screening, cultural taboos regarding the gender of healthcare providers, and the stigmatization of women with cervical cancer" [90].

Issaha et al (2011) have an article entitled: “Expressions of cervical cancer-related signs and symptoms”. “The purpose of the study was to explore how women treated for cervical cancer at an academic hospital in Tshwane, South Africa, expressed their cervical cancer-related signs and symptoms during the initial consultation with health care professionals”. To achieve the aim, a qualitative, exploratory and contextual research design was used. “The sampling method was purposive and convenience”. “Self-reported data were gathered using semi-structured interviews. Diekelmann’s hermeneutical analysis approach was used to analyze the data. The sample size totaled 12”. Results showed that all participants lacked knowledge and awareness of the signs and symptoms of cervical cancer. “The majority failed to communicate the real nature of their signs and symptoms and was only diagnosed after several visits to the primary health clinic” [91].

Begum published an article in 2014 entitled: “Mobilizing Women from a Low Income Community to Attend Cervical Cancer Screening Camps: Insights from a Study in an Urban Slum of Mumbai”. This study used mixed interventional approach aiming to create awareness among couples about cervical cancer and Pap smear and to increase the rate of Pap smear screening. The study was carried out in Mumbai and followed a quasi-experimental design. “Women aged between 18 to 49 years and their husbands were randomly selected for the survey. Pre and post intervention survey was conducted to see the impact of intervention on creating awareness and utilization of Pap smear services. Multilevel intervention program was adopted to achieve the objectives. In the results, significant increase in awareness about cervical cancer among couples was observed from pre (5.5%) to post (97.7%) intervention survey. About 32.2% women were found to be infected with HPV” [92].

Verma et al (2014) conducted a research project entitled: “Application of Bethesda System for Cervical Cytology in Unhealthy Cervix”. The objective was “to detect epithelial cell abnormalities in unhealthy cervix using the 2001Bethesda system of reporting for cervical cytology and to confirm histopathologicaly the findings of Pap smear. In this study, 125 women with clinical diagnosis of unhealthy cervix underwent conventional cytology. Cervical biopsies were taken from abnormal areas seen on colposcopy and sent for histopathology. Results showed that Out of 17 (13.60%) cases with epithelial cell abnormality, ASC-US was seen in 6 (4.80%), LSIL in 7 (5.60%), HSIL in 1 (0.80%), squamous cell carcinoma in 1 (0.80%), AGC endocervical in 1 (0.80%) and adenocarcinoma in 1 (0.80%) patients. Cervical

biopsy was taken in 67 women. Diagnostic accuracy of Pap smear for preinvasive and invasive disease was 81.15% with overall sensitivity and specificity 78.57% and 88.67% respectively and predictive value of 64.71% " [58].

Farshbaf-Khalili has an article (2015) entitled: "Cervical cancer screening in women referred to healthcare centers in Tabriz, Iran". The aim of this study was "to assess the status of cervical cancer screening in women referred to health care centers in Tabriz, northwest Iran. This descriptive-analytical study was done on 441 women referred to health care centers of Tabriz, northwest Iran. The centres were selected using the multi-stage cluster sampling method. The participants were selected from the active records of those centers. A questionnaire regarding the socio-demographic characteristics and cervical cancer screening and reasons for referring or not referring for screening was completed by the participants A $P < 0.05$ was considered as significant. Results showed that Out of the participants 49.4% of women had done the Pap smear test while 50.6% had never done this test. The main reason why women had not performed cervical cancer screening was being unaware of the importance of it (46.1%). Logistic regression analysis with adjustment showed a significant relationship between screening and awareness scores (OR = 1.17, CI = 95%:1.12-1.23), when the effect of other confounding factors [total awareness scores, risk factors (marriage or having sexual intercourse at a young age, history of obvious cervical infection, cautery, cryotherapy or repeated curettage), age and type of family planning] in screening was controlled" [20].

Chapter 3

Methodology

In this chapter the study design, research process, study population, sampling method and sample size, inclusion and exclusion criteria, the research environment, data collection instruments, scientific validity and reliability of data collection tools, data collection methods, analysis of the data, methodology and study limitations will be stated.

STUDY DESIGN

The present study has performed in 2 phases.

1- Developing the research tool entitled: " Risk factors and clinical manifestations assessment tool for the cytological changes towards cervical cancer in Pap test"

2- Conducting a case-control study to compare the risk factors and clinical manifestations in women with and without atypical cytological findings in Pap test and developing the Regression Model of its determinants in Iran.

FIRST PHASE OF THE RESEARCH

DEVELOPING THE RESEARCH TOOL

This is a methodological study. Methodological research is the development and evaluation of data collection instruments, scales or techniques [93]. This phase concluded two stages as follow.

FIRST STAGE:

To identify full content domain and items generation an extensive article study was conducted. Some keywords including risk factors, Pap smear, HPV, facilitators and inhibitors and cervical cancer were used to obtain the relevant articles in Pub Med and Google Scholar Databases.

THE INITIAL DRAFT

According to the articles mentioned in the chapter 2, the initial draft of the research tool with 68 items was developed as follows:

1. Age [30, 73-75]
2. Age of menarche [6]
3. Ever having sex[76]
4. Number of sexual Partners [30, 76, 77]
5. Sex of partners[76]
6. Residency [73, 75, 94]
7. Type of housing [75]
8. Race/ Ethnicity [30, 75]
9. Marital Status [30, 73, 76]
10. Education[30, 73, 75]
11. Class Major[11, 76]
12. Religion [6, 30]
13. Occupational status [73, 75, 80]
14. Income Level per year (Euro) [30, 73]
15. Perceived financial status [73]
16. Health Insurance [30, 73, 81]
17. History of genital warts [30, 82]
18. Age of the first sex [30, 76, 94]
19. Age at the first birth [6]
20. Taking illegal drugs[30]
21. Lifetime history of STDs [30, 76]
22. Smoking status[11, 80]
23. If smoking [30, 94]: How many per day and How long
24. Status of diet or nutrition [20, 30, 95]
25. Using tampons[30]
26. Use of oral contraceptives [30, 94]
27. Sexual experience [30]
28. Use of protection (condom) [30, 76, 83, 94]

29. Ever have Pap screening test [30, 73, 74]

30. Pap test has been done[45, 81]

31. Frequency of Pap test [84]

32. Date of the last Pap test [96]

33. The last Pap test status[76]

34. History of HPV infection [83, 85, 94]

35. Family member diagnosed with HPV [30, 85]

36. History of HPV Vaccination [13, 81, 82, 85]

37. Education about cancer of cervix/ Pap Smear [82]

38. Number of deliveries [6, 86, 94]

39. Presence of white discharge [94]

40. Family history of cancer [6, 75, 94]

41. Use of cloths/ sanitary napkins [94]

42. History of abortion [94]

43. Unprotected sex [75]

44. Infection with Chlamydia [75]

45. Having a sexual partner with many previous partner [75]

46. Having a weakened immune system [75]

47. History of Bacterial Vaginosis [77, 87]

48. Ever history of pelvic infection [6]

49. History of abnormal Pap test[81]

50. Age at the first sexual intercourse[86]

51. When was the last Pap screening test[86]

52. Alcohol drinking status[11, 80]

53. BMI Status [25, 80, 88]

54. Had ever heard of HPV[83]

55. Reason for the current Pap screening test[26]

56. Existence of Symptoms [89-91]: Vaginal bleeding with clots, Bleeding between periods, Bleeding after sex, Bleeding during pregnancy, Any changes in menstrual period, Persistent Vaginal discharge, unexplained weight loss, Foul-smelling vaginal discharge, Post-menopausal, bleeding, purulent vaginal discharge, yellowish vaginal discharge,

57. Existence of Signs [4, 89, 91, 92]: Painful sex, Abdominal pain, Pelvic pain, Unusual fatigue, Severe headache, Low back pain, sensation of hardness or enlargement in the uterus, Loss of appetite,

58. Contraceptive method [89]: Hormonal contraceptive, IUD, Condom, Pregnant at first attendance, Other: …….

59. Status of the cervix [58]: Healthy Cervix, Unhealthy cervix,

60. If unhealthy Cervix [58]: Chronic cervicitis, Erosion, Erosion, bleeds on touch, Hypertrophied, Hypertrophied, bleeds on touch, Congestion, bleeds on touch, Healed laceration, Cervical Polyp, Congestion, Suspicious, Flushed with Vagina, Irregular Contour, White Plaque on Anterior lip

61. History of HIV-Positive [88]

62. Knowledge of Pap test [28, 84]

63. exposure to diethylstilbestrol (DES) in uterus [20]

64. History of repeated curettages [20]

65. Having partner with penile cancer [20]

66. partner's other wife having cervical cancer [20]

67. Low personal hygiene [20]

68. History of trauma to the cervix [20]

An expert panel including three professors (Gynecologist and midwives), confirmed the assimilation of the items into usable form [97]. So the items were classified in three parts: demographic characteristics, health history and clinical manifestations.

SECOND STAGE

In this stage, the research tool which was developed in the previous stage was assessed for the validity and reliability.

VALIDITY

"Validity refers to whether a measurement instrument accurately measures what it is supposed to measure. Content validity represents the universe of content, or the domain of a given construct. A subtype of content validity is face validity, which is a rudimentary type of validity that basically verifies that the instrument gives the appearance of measuring the concept. It is an intuitive type of validity in which colleagues or subjects are asked to read the instrument and evaluate the content in terms of whether it appears to reflect the concept the researcher intends to measure" [98].

To assess the Research Tool for the face validity, 10 faculty members of various specialties related to the fields of Gynecology and Midwifery were asked to leave a comment about reasonableness, appropriateness, and logical sequence of items.

Content validity was determined by content validity rate (CVR) and the content validity index (CVI).

"The CVR is an item statistic that is usual in the rejection or retention of specific items" [99]. To examine the CVR, the Research Tool was given to 10 experts in the specialties related to the field of Gynecology; the answers were designed based on a three-point Likert scale consisting of: "It is necessary", "It is useful but not necessary", and "It is not necessary". Then the Research Tool 's CVR was assessed; according to the Lawshe table if the item score was over 0.62, the item was considered as an appropriate and necessary one [99].

In the stage of assessing the CVR, 10 items were removed or merged together and 50 items entered the second stage for the measurement of the CVI. The mean of the total CVRs was 94.39.

After the items have been identified for inclusion in the final form, the content validity index (CVI) is computed for the whole test. To distinguish between CVI of the means and Waltz and Bausell's CVI, the views of 10 faculty members of related fields were used. The indexes of "Relevance", "Clarity", and "Fluency" examined the questions of the questionnaire based on four-point scale [100, 101].

CRITERIA TO MEASURE THE CONTENT VALIDITY INDEX (CVI)

❖ RELEVANCE:

1) The item is not relevant (is irrelevant).
2) The item is relevant but needs to be reformed.
3) The term is relevant but needs to be reviewed.
4) The term is very relevant

❖ CLARITY:

1) The item is not clear (is unclear).
2) The item is clear but needs to be reformed.
3) The item is clear but needs a little revision.
4) The item is very clear.

❖ FLUENCY:

1) The item is not fluent (is influent).
2) The item is fluent but needs to be reformed.
3) The item is fluent but needs a little revision.
4) The item is very fluent.

The item-level CVIs (I-CVIs) were calculated for each item. Items with the score of over 0.78 were retained as appropriate ones. The Criteria of CVI were also calculated and the results were as follow, Relevance= 94.96, Clarify=96.67 and Fluency=96.39. The Scale's CVI (S-CVI) was 96.01 while the excellent content validity is equal or higher than 0.90 [101]. There was not any eliminated question in the CVI assessment, and all the questions had a score above 0.78. Although the experts were asked to suggest for the items that should be added into the questionnaire, no more items were recommended.

RELIABILITY

For reliability, intra-rater reliability was determined and the internal consistency of the tool was examined by Cronbach Alpha.

The reliability of a measure denotes the consistency of measures obtained in the use of a particular instrument and is an indication of the extent of the random error in the measurement method. The comparison of the two observers when they measure the same event is referred to as inter-rater reliability [102, 103].

Homogeneity testing examines the extent to which all the items in the instrument consistently measure construct. It is a test of internal consistency. The statistical procedure used for this process is Cronbach alpha coefficient. Usually alpha should be equal to or greater than 0.8 [102].

Therefore, the researcher and one of the colleagues, after training, gathered the data of 10 subjects simultaneously. According to the results of chi-square test no significant differences were found ($P>0.05$).

The Cronbach's alpha coefficient value for assessment of the research tool's reliability was 0.96 (the total means); for the demographic part was 0.97; for the health history was 0.95; and for clinical manifestations (Sign & Symptom) was 0.97.

SECOND PHASE OF THE RESEARCH

This phase is including a case-control study to compare the risk factors and clinical manifestations in women with and without atypical cytological findings in Pap test and develop the regression Model of its determinants in Iran.

DESIGN

This is a case-control study. "A case-control study is designed to help determine if an exposure is associated with an outcome. First, identify the cases (a group known to have the outcome) and the controls (a group known to be free of the outcome). Then, look back in time to learn which subjects in each group had the exposure(s), comparing the frequency of the exposure in the case group to the control group. By definition, a case-control study is always retrospective because it starts with an outcome then traces back to investigate exposures" [104].

RESEARCH ENVIRONMENT

Research environment were clinics of gynecology and oncology affiliated with the Hamadan University of Medical Sciences in province of Hamadan. Fatemieh Women Hospital in Hamadan, where the most of data in this research was obtained, is a well equipped center for therapeutic, educational and research purposes with a lot of referred patients from west region of the country. So it was enough crowded during the day week and made it possible to access the required data.

RESEARCH POPULATION

"In statistics, a population is an entire group about which some information is required to be ascertained" [105].

Research population included all women attended in the clinics affiliated with the Hamadan University of Medical Sciences in city of Hamadan between 15/Sep/2015 to 30/Nov/2015.

THE RESEARCH SUBJECTS

The research subjects included the people among the research population who were eligible according to the inclusion and exclusion criteria.

INCLUSION CRITERIA

Inclusion criteria included the following:

1. Women who are referred to the research field with a result of Pap smear
2. Being in reproductive age
3. Have begun sex activity already
4. Not being pregnant
5. Have a pap test over the past three months
6. Being able to answer the relevant questions accurately

EXCLUSION CRITERIA

Exclusion criteria were included the lack of informed consent or unwillingness to participate in the study.

SAMPLING METHOD

"Research studies are usually carried out on sample of subjects rather than whole populations"[105]. In this research, we chose our subjects by convenience sampling. In convenience sampling, as the name implies subjects are selected on the basis of accessibility [106].

SAMPLE SIZE

To determine the sample size, according to the local reports the exposure probability in the control group is considered about 10% [107], and the control to case proportion is 3 units. So with 95% confidence and test's power 90%, we need to at least 27 subjects in case and 81 in control group. But because of the large number of variables, the unification was not possible so we increased the sample size to 51 and 150 in case and control groups respectively to

control covariate effects. The Logistic Regression model was used as well, to adjust these effects.

$$n=\frac{\left[Z_{1-\frac{\alpha}{2}}\sqrt{(1+\frac{1}{c})\overline{P}(1-\overline{P})}+Z_{1-\beta}\sqrt{P_1(1-P_1)+\frac{P_0(1-P_0)}{c}}\right]^2}{(P_1-P_0)^2}$$

$Z_{1-\frac{\alpha}{2}}=1.96,$ $P_0=10\%^2$

$Z_{1-\beta}=1.28$ $P_1=\frac{0.2\times 3}{1+0.2(3-1)}=0.42$ $\overline{P}=\frac{P_1+cP_0}{1+c}=0.42$

$OR=3$ $P_1=\frac{P_0\times OR}{1+P_0(OR-1)}=0.42$

DATA COLLECTION METHOD

After obtaining the necessary permits and coordinating with the relevant authorities, the researcher attended in the research environments. To find the research subjects, the patients referred to the clinic of gynecology were interviewed in the waiting room, while waiting for their appointment.

If they were eligible for inclusion criteria and were willing to cooperate, they were guided to a room which was assigned for this purpose. Then the research objectives and methods were explained completely and the written informed consent (Index 1) was obtained one by one. Then the researcher examined the results of their Pap test. If the result represented benign/reactive changes, the subject was allocated to **control group**. If the result represented epithelial cell abnormalities such as: ASC-US, ASC-H, LSIL, HSIL, AGC, AIS, the subject was allocated to **Case group.**

After that those questions about "demographic characteristics" and "health history" were completed according to the subjects' answers and investigating of medical records (if there was any).

Now it was the time to go with the patients to the examination room where the doctor or the midwife was attended to visit them one by one. In this room, the data for those items in physical exam category were collected based on clinical examination and direct observations while the examiner was examining. Thus, we prevent of frequent examinations and lying down in gynecological position which is undesirable to everyone. The necessary treatment or medical care would offer to the patients as well.

During the sampling, the researcher was attending in the clinics both in the morning and in the afternoon. Sampling took for around 10 weeks from 15/Sep/2015 until 30/Nov/2015. In order to speed up the sampling, researcher detected the crowded days in each clinic at first and then attended on the same day in the clinic so in each work day the data of 8 - 10 subjects were collected in different clinics.

STATISTICAL METHODS

Mean, Standard Deviation and Ratios were used to describe the gathered data and the odds ratio and Logistic Regression Models were used to determine the effects of independent variables on the dichotomous outcomes. All Odds ratios were determine age adjusted. To compare some variables between two groups we used Chi-Square Test.

It should also be mentioned that the significance level was considered "<0.05" and SPSS software package (version 16; SPSS Inc., Chicago, IL, USA) was used for data analyses.

ETHICAL CONSIDERATIONS

Firstly, the research project was approved in the University of Ferrara. Secondly, the Ethics Committee of the Hamadan University of Medical Sciences approved this project

(IR.Umsha.rec.1394.121) on 23/May/2015. After getting permission to begin the sampling from the recent university (1394/6/3235،24/1/35/16/پ), the researcher with a written introduction and coordination with the in charges started to collect the data. In this study in order to maintain the integrity, the names of the subjects are not mentioned.

At any stage of the data collection, entry and preparation of the final report, information of participants were not disclosed and will not be available to any natural or legal person as well.

LIMITATION OF THE PROJECT

Although all the smears were prepared by registered midwives, and read by the expert pathologist, having no control on equality of their operation may be the limitation of this project.

There were some limitations also in data collection due to costums, cultural and religious conditions.

Chapter 4

Results

Results in line with the research objectives are as follow:

FIRST PHASE OF THE STUDY

Result for the first Phase of the research led to create a tool entitled: "Risk factors and clinical manifestations assessment tool for the cytological changes towards cervical cancer in the Pap test". It is a questionnaire with 50 questions which can be used for other researchers in their related projects and also for the midwives, health care givers and physicians. Using this tool will enable them to be more careful about their patients' health and make an on time action in relation with treatment or preventive proceedings.

The tool has two subscales including risk factors and clinical manifestations.

- The first subscale consists of demographic characteristics and health history that form the "risk factors". Based on the studies, these risk factors can lead to the atypical cytologic changes in the Pap test.
- The second subscale consists of clinical manifestations (signs and symptoms) which may be along with the atypical changes in Pap test.

RISK FACTORS AND CLINICAL MANIFESTATIONS ASSESSMENT TOOL FOR THE CYTOLOGICAL CHANGES TOWARDS CERVICAL CANCER IN PAP TEST

DEMOGRAPHIC CHARACTERISTICS/ HEALTH HISTORY					
1-	Age (Year): ……				
2-	Age of menarche (Year): ……				
3-	Residency:	❒Rural	❒Urban	❒Other	
4-	Type of housing:	❒Tenant	❒Owner	❒Other	
5-	Education:	❒Illiterate ❒Undergraduate	❒Primary school ❒Postgraduate	❒Secondary school	
6-	Class Major	❒Health- related	❒Non health-related		
7-	Race	❒White	❒Black	❒Caucasian	
8-	Ethnicity	❒Fars ❒Kord	❒Tork ❒Lor	❒Other	Please name: …
9-	Religion	❒Muslim ❒Christian	❒Catholic	❒Jewish	❒Other
10-	Occupational status	❒Employed	❒Unemployed	❒Retired	
11-	Income Level per year (Rials): …….				
12-	Health Insurance:	❒None	❒Private	❒ Publicly funded	
13-	BMI Status:	❒Underweight	❒Normal	❒Overweight	❒ Obese
14-	Smoking status: If smoking	❒Smoker	❒Ex-smoker	❒Non smoker	❒ Expose to How many per day (Number): …….. How long (Year): ……
15-	Taking illegal drugs:	❒No	❒Yes		
16-	Alcohol drinking status	❒Non drinker	❒User	❒Alcohol dependent	
17-	Marital Status:	❒Single ❒Divorced	❒Married ❒Dating	❒Widowed ❒Living with significant other	
18-	Number of vaginal Delivery: ……				
19-	Age at the first birth (Year): …….				
20-	History of abortion:	❒No	❒Yes	If “yes”, How many times?	

21-	History of Using Hormonal contraceptive	❒Never	❒ < 5 Years	❒ > 5 Years	
22-	History of Using IUD	❒Never	❒ < 5 Years	❒ > 5 Years	
23-	History of Using protection (condom):	❒Never	❒Rarely	❒Usually	❒Always
24-	Age of the first sex (Year): ……				
25-	Using tampons:	❒No	❒Yes		
26-	Status of doing Pap test up to now	❒Never	❒Irregularly	❒Regularly	
27-	If irregularly or never, Why?	❒Never heard of it	❒It is not important	❒It is expensive	❒It is hard to access
28-	The current Pap test status	❒Benign/Reactive	❒ASCUS	❒LSIL	
		❒HSIL	❒Squamous Cell Carcinoma		
29-	Having a sexual partner with many previous partner:		❒No	❒Yes	
30-	Sex of partners:	❒Men	❒Women	❒Both	
31-	Number of sexual Partners: …..				
32-	Sexual experience:	❒Currently involved	❒Not currently involved	❒Never had sexual intercourse	
33-	History of HPV infection:	❒No	❒Yes	❒Not known	
	Did you get any treatment?	❒No	❒Yes	If "Yes" how many weeks ago? …	
34-	History of Bacterial Vaginosis:	❒No	❒Yes	❒Unknown	
	Did you get any treatment?	❒No	❒Yes	If "Yes" how many weeks ago? …	
35-	History of Chlamydia Infection	❒No	❒Yes	❒Unknown	
	Did you get any treatment?	❒No	❒Yes	If "Yes" how many weeks ago? …	
36-	History of pelvic infection	❒No	❒Yes	❒Unknown	
	Did you get any treatment?	❒No	❒Yes	If "Yes" how many weeks ago? …	
37-	History of HPV Vaccination	❒No	❒Yes	❒Unknown	
38-	Lifetime history of STDs	❒No	❒Yes	❒Unknown	
39-	Family member diagnosed with HPV	❒No	❒Yes	❒Unknown	
40-	Family history of cancer:	❒No	❒Yes	If "Yes" Kind of cancer: ……	
				Kind of relative: ……..	
41-	Having a weakened immune system (e.g. because of HIV/AIDS, immunosuppressant drugs or having a transplant)			❒No	❒Yes ❒Unknown

42-	Had ever heard of HPV:	❒No	❒Yes		
43-	Reason for the current Pap screening test:	❒Visit a doctor	❒Check up		
44-	Chief complain for visiting a doctor/ midwife	❒Pain (low Abdominal, Low back, Pelvic) Disparonia	❒ Vaginal discharge	❒ Post coital spotting	❒ AUB
45-	History of trauma to cervix (Cotter /Cryo)	❒No	❒Yes		
46-	History of Curettage	❒No	❒Yes	❒Recurrent	

Clinical Manifestations

47-	Status of the Cervix:	❒Healthy Cervix	❒Unhealthy cervix

48- If unhealthy Cervix:

- ❒Chronic cervicitis
- ❒Erosion/ Laceration
- ❒Cervical Polyp
- ❒Hypertrophied
- ❒Congestion
- ❒Bleeds on touch
- ❒Irregular Contour
- ❒White Plaque on Anterior lip

49- Existence of Signs

- ❒Bleeding after sex
- ❒Any changes in menstrual period
- ❒Persistent vaginal discharge
- ❒Unexplained weight loss
- ❒ Genital warts

50- Existence of Symptoms

- ❒Painful sex
- ❒Abdominal pain
- ❒Pelvic pain
- ❒Unusual fatigue
- ❒Severe headache
- ❒Low back pain
- ❒Sensation of hardness or enlargement in the uterus

SECOND PHASE OF THE STUDY

Results for The second phase of this research, which was conducted with the aim of "Compare the risk factors and clinical manifestations between women with (Case group) and without (Control group) atypical cytological findings in Pap test and develop the regression model of its determinants in Iran", were provided in 14 tables as follow:

Table 1 Absolute and relative frequency of the case and control groups according to the result of the current Pap test

Pap test status \ Groups		Case group	Control group	Total
Benign or Reactive changes	N (%)	0 (0.0%)	150 (100%)	150 (74.6%)
ASCUS	N (%)	20 (39.2%)	0 (0.0%)	20 (10.0%)
ASC_H	N (%)	5 (9.8%)	0 (0.0%)	5 (2.5%)
LSIL	N (%)	21 (41.2%)	0 (0.0%)	21 (10.4%)
HSIL	N (%)	4 (7.8%)	0 (0.0%)	4 (2.0%)
Carcinoma In Situ	N (%)	1 (2.0%)	0 (0.0%)	1 (0.5%)
Total	N (%)	51 (100%)	150 (100%)	201 (100%)

This table shows that in case group, the result of Pap test cytological findings in most of the subjects were LSIL (41.2%) and ASCUS (39.2%). Just one person affected with Carcinoma in Situ. All the subjects in control group were in Benign/ Reactive changes category.

Table 2 Comparison of the case and control groups according to the reason for conducting the current Pap test

Reason		Case group	Control group	Total	Chi-Square Test
Visit a doctor/ Midwife	N (%)	43 (84.3%)	81 (54.0%)	124 (61.7%)	X^2= 14.799 df=1 p< .001
Checkup	N (%)	8 (15.7%)	69 (46.0%)	77 (38.3%)	
Total	N (%)	51 (100%)	150 (100%)	201 (100%)	

According to this table, despite the fact that the reason for conducting the current Pap test in the most of the subjects in case (84.3%) and control group (54.0%) has been "Visit a doctor or midwife" but Chi-Square test showed that there is a significant difference between two groups related to this variable (p< .001). It means that the majority of the subjects in case group have done the current Pap test due to a medical prescription while in control group it was performed as a routine check up in about half of the subjects.

Table 3 Comparison of the case and control groups according to the chief complain (CC) for visiting a doctor or midwife

C.C. \ Groups		Case group	Control group	Total	Chi-Square Test
Pain (low Abdominal, Low back, Pelvic) & **Dyspareunia**	N (%)	13 (30.2%)	17 (21.0%)	30 (24.2%)	X^2=30.371 df=3 P< 0 .001
Vaginal discharge	N (%)	10 (23.3%)	41 (50.6%)	51 (41.1%)	
Post coital spotting	N (%)	15 (34.9%)	2 (2.5%)	17 (13.7%)	
AUB	N (%)	5 (11.6%)	21 (25.9%)	26 (21.0%)	
Total	N (%)	43 (100%)	81 (100%)	124 (100%)	

The above table shows that the most frequent CC in case group was pain (30.2%) and in control group was vaginal discharge (50.6%).

Chi-Square Test showed that there is a significant difference between two groups related to the chief complains when visiting a doctor or midwife ($p < .001$).

Table 4 Comparison of the case and control groups according to the status of doing Pap test up to now

Status of doing Pap test	Case group (n=51)	Control group (n=150)	Total (n=201)	Chi-Square Test
	N (%)	N (%)	N (%)	
Never	5 (9.8%)	17 (11.3%)	22 (10.9%)	X^2= .238
Irregularly	43 (84.3%)	122 (81.3%)	165 (82.1%)	df=2
Regularly	3 (5.9%)	11 (7.3%)	14 (7.0%)	P= .888

This table shows that the most frequent of the subjects in both the case group (84.3%) and control group (81.3%) have conducted the Pap test irregularly and according to the Chi-Square test there is no significant difference between two groups in this regard (P> 0.05).

Table 5 Comparison of the case and control groups based on the reason for not doing Pap test regularly

Reasons	Case group (n=51)	Control group (n=150)	Total (n=201)	Chi-Square Test
	N (%)	N (%)	N (%)	
Never heard of it	0 (0.0%)	2 (1.3%)	2 (1.0%)	X^2=.865 df=3 P= .834
It is not important	15 (29.4%)	47 (31.3%)	62 (30.8%)	
It is expensive	35 (68.6%)	99 (66.0%)	134 (66.7%)	
It is hard to access	1 (2.0%)	2 (1.3%)	3 (1.5%)	

This table shows that being expensive is the most frequent reason for not doing the Pap test regularly in the case (68.6%) and control (66.0%) groups. Chi-Square Test showed that there was no significant difference between two groups related to the reason for not doing Pap test regularly ($p > .05$)

Table 6 Comparison of the case and control groups according to the studied risk factors (demographic characteristics; quantitative variables)

Variables	Case group (n=51)		Control group (n=150)		OR	P-value
	Mean	SD	Mean	SD		
Age (Year)	40.82	5.41	36.69	7.79	1.08	0.001
Age at menarche (Year)	13.06	1.10	13.47	1.30	0.75	0.045
Age at the first birth (Year)	18.57	1.97	19.06	1.59	1.08	0.817
Number of delivery	3.27	1.415	2.45	1.298	1.44	0.048
Age of the first sex (Year)	17.43	3.90	18.14	1.83	0.65	0.182
Family income (Euro)	275.88	67.53	270.90	91.15	1.00	0.705

According to the the Logestic Regression in the above table:

- Age is a determinant for abnormal cytological findings in Pap test. The risk of detecting abnormal cytological findings in Pap test will increase about 8% with increasing each year to the age ($p>0.05$, OR= 1.08).
- Age at the menarche is a determinant for abnormal cytological findings in Pap test. The risk of detecting abnormal cytological findings in the Pap test will increase about 75% along with decreasing 0ne year of the age at the menarche ($p>0.05$, OR=0.75).
- Number of delivery is a determinant for abnormal cytological findings in the Pap test. The risk of detecting abnormal cytological findings in Pap test will increase about 44% with increasing each number to the deliveries ($p>0.05$, OR=1.44).

Table 7 Comparison of case and control groups according to the studied risk factors including residency, type of housing, education level, major, and ethnicity (demographic characteristics; qualitative variables)

Variables	Case group (n=51)	Control group (n=150)	Total (n=201)	OR	P-value
	F (%)	F (%)	F (%)		
Residency					
Rural	7 (13.7%)	9 (6.0%)	16 (8.0%)	-	-
Urban	44 (86.3%)	141(94.0%)	185 (92.0%)	0.507	0.215
Type of housing					
Tenant	15 (29.4%)	47 (31.3%)	62 (30.8%)	-	-
Owner	36 (70.6%)	103 (68.7%)	139 (69.2%)	0.53	0.130
Education level					
Illiterate	3 (5.9%)	7 (4.7%)	10 (5.0%)	-	-
Primary school	8 (15.7%)	21 (14.0%)	29 (14.4%)	1.175	0.844
Secondary school	27 (52.9%)	87 (58.0%)	114 (56.7%)	0.922	0.912
Undergraduate	11 (21.6%)	30 (20.0%)	41 (20.4%)	1.336	0.714
Postgraduate	2 (3.9%)	5 (3.3%)	7 (3.5%)	1.148	0.901
Major					
Health-related	3 (5.9%)	9 (6.0%)	12 (6.0%)	-	-
Non health-related	48 (94.1%)	141 (94.0%)	189 (94.0%)	0.869	0.844
Ethnicity					
Fars	24 (47.1%)	79 (52.7%)	103 (51.2%)	-	-
Kord	11 (21.6%)	19 (12.7%)	30 (14.9%)	1.806	0.201
Tork	16 (31.4%)	52 (34.7%)	68 (33.8%)	1.013	0.973

This table shows that in our study the residency, type of housing, education, major, and ethnicity are not determinants for abnormal cytological findings in the Pap test ($p > 0.05$). In other words:

- Being Urban, compared with being Rural, is not a determinant for abnormal cytological findings in Pap test.
- Being educated, compared with being illiterate, is not a determinant for abnormal cytological findings in Pap test.
- Having Non health-related education, compared with health-related education, is not a determinant for abnormal cytological findings in Pap test.
- Regarding to ethnicity, being Kord or Tork, compared with Fars, is not a determinant for abnormal cytological findings in Pap test.

Table 8 Comparison of case and control groups according to the studied risk factors including occupational status, BMI and marital status (demographic characteristics/ nominal variables)

Variables	Case group (n=51)	Control group (n=150)	Total (n=201)	OR	P-value
	N (%)	N (%)	N (%)		
Occupational status					
Unemployed	44 (86.3%)	112 (74.7%)	156 (77.6%)	2.13	.091
Employed	7 (13.7%)	38 (25.3%)	45 (22.4%)	-	-
BMI					
Normal	23(45.1%)	97 (64.7%)	120 (59.7%)	-	-
Overweight/ Obese	28(54.9%)	53 (35.4%)	81(40.3%)	2.598	.004
Marital status					
Married	51 (100%)	143 (95.3%)	194 (96.5%)	-	-
Widow/divorce	0 (0.0%)	7 (4.7%)	7 (3.5%)	1.000	1.347

This table shows that in our study:

- Occupational status and marital status are not determinants for abnormal cytological findings in the Pap test.
- But BMI is a determinant for abnormal cytological findings in Pap test. To be more precise, being overweight/ obese, compared with being normal, will increase the risk of detecting abnormal cytological findings in Pap test about 2.6 times ($p>0.05$, OR=2.598).

Table 9 Comparison of case and control groups according to the studied risk factors including history of using hormonal contraceptive, IUD, and protection

Variables	Case group (n=51)	Control group (n=150)	Total (n=201)	OR	P-value
	N (%)	N (%)	N (%)		
Using hormonal contraceptive					
Never	14 (27.5%)	44 (29.3%)	58 (28.9%)	-	-
< 5 Years	25 (49.0%)	71 (47.3%)	96 (47.8%)	0.491	0.208
> 5 Year	12 (23.5%)	35 (23.3%)	47 (23.4%)	0.981	0.967
History of using IUD					
Never	29 (56.9%)	91 (60.7%)	120 (59.7%)	-	-
< 5 Years	10 (19.6%)	29 (19.3%)	39 (19.4%)	1.004	0.992
> 5 Year	12 (23.5%)	30 (20.0%)	42 (20.9%)	1.050	0.933
Status of using protection (condom)					
No	41(80.4%)	108 (72.0%)	149 (74.1%)	-	-
Yes	10 (19.6%)	42 (28.0%)	52 (25.9%)	0.123	<.001

This table shows that in our study:

- History of using hormonal contraceptive and using IUD are not determinants for abnormal cytological findings in Pap test.
- Use of hormonal contraceptive (≥5 or <5 years), compared with never use of it, is not a determinant for abnormal cytological findings in Pap test.
- History of using IUD (≥5 or <5 years), compared with never use of it, is not a risk factor for abnormal cytological findings in Pap test.
- But lack of using protection (condom) is a determinant for abnormal cytological findings in Pap test. To be more precise, use of protection, compared with never use of it, will decrease the risk of detecting abnormal cytological findings in Pap test about 88 % ($p>0.05$, OR=0.123).

Table 10 Comparison of case and control groups according to the studied risk factors including the sexual experience and family history of cancer (Health history)

Variables	Case group (n=51)	Control group (n=150)	Total (n=201)	OR	P-value
	N (%)	N (%)	N (%)		
Status of sexual experience					
Currently not involved	2 (3.9%)	9 (6.0%)	11 (5.5%)	-	-
Currently involved	49 (96.1%)	141 (94.0%)	190 (94.5%)	1.546	0.773
Family history of cancer					
No	32 (62.7%)	110 (73.3%)	142 (70.6%)	-	-
Yes	19 (37.3%)	40 (26.7%)	59 (29.4%)	2.001	0.213

This table shows that in our study:

- Being currently involved with sexual activity, compared with not being currently involved with sexual activity, was not a determinant for abnormal cytological findings in Pap test.
- Having a family history of cancer, compared with not to have a family history of cancer, was not a determinant for abnormal cytological findings in Pap test.

Table 11 Comparison of case and control groups according to the health status of the cervix

Health Status of the Cervix		Case group	Control group	Total	Chi-Square test
Healthy	N (%)	2 (3.9%)	89 (59.3%)	91 (45.3%)	X^2= 47.166 df=1 P< .001
Unhealthy	N (%)	49 (96.1%)	61 (40.7%)	110 (54.7%)	
Total	N (%)	51 (100%)	150 (100%)	201 (100%)	

The table above demonstrates that 96.1% of subjects in the case group were suffering of unhealthy cervix while this figure in the control group was only 40.7%.

Chi-square test showed that there is a significant difference between two groups according to the health status of cervix (p< .001).

Table 12 Frequency of the case and control groups according to the kinds of unhealthy cervix

Variables		CASE 51 (100%)	CONTROL 150 (100%)	Total 201 (100%)	
Chronic cervicitis	No	7 (13.7%)	133 (88.7%)	61 (30.3%)	X^2= 101.12 df=1 P< .001
	Yes	44 (86.3%)	17 (11.3%)	61 (30.3%)	
Erosion/ laceration	No	20 (39.2%)	119 (79.3%)	139 (69.2%)	X^2= 28.72 df=1 P< .001
	Yes	31 (60.8%)	31 (20.7%)	62 (30.8%)	
Cervical Polyp	No	49 (96.1%)	147 (98.0%)	196 (97.5%)	.447
	Yes	2 (3.9%)	3 (2.0%)	5 (2.5%)	
Hypertrophied cervix	No	25 (49.0%)	144 (96.0%)	169 (84.1%)	X^2= 62.76 df=1 P< .001
	Yes	26 (51.0%)	6 (4.0%)	32 (15.9%)	

This table shows that:

- The variety of unhealthy cervix in our study was including: Chronic cervicitis, Erosion/ Laceration, Cervical Polyp and Hypertrophied cervix.
- In the case group, 86.3% of the subjects were suffering of the chronic cervicitis while this amount was only 11.3% in the control group. Chi-Square Test showed that there is a significant difference between two groups related to this variable (P< .001).
- In the case group, 60.8% of the subjects were suffering from erosion/ laceration while this amount was only 20.7% in the control group. Chi-Square Test showed that there is a significant difference between two groups related to this variable (P< .001).
- There was not cervical polyp in 96.1% of the subjects in the case group and 98.0% of the subjects in the control group. Chi-Square Test showed that there is no significant difference between two groups related to this variable.
- In the case group, 51% of the subjects were suffering from the Hypertrophied cervix while this amount was only 4% in the control group. Chi-Square Test showed that there is a significant difference between two groups related to this variable (P< .001).

Table 13 Comparison of the case and control groups according to the studied clinical manifestations (symptoms)

VARIABLES		CASE 51 (100%)	CONTROL 150 (100%)	TOTAL 201 (100%)	CHI-SQUARE TEST
Painful sex	No	13 (25.5%)	137 (91.3%)	150 (74.6%)	X^2= 87.140, df=1, P< .001
	Yes	38 (74.5%)	13 (8.7%)	51 (25.4%)	
Low abdominal pain	No	35 (68.6%)	135 (90.0%)	170 (84.6%)	X^2= 13.328, df=1, P< .001
	Yes	16 (31.4%)	15 (10.0%)	31 (15.4%)	
Pelvic pain	No	18 (35.3%)	147 (98.0%)	165 (82.1%)	X^2= 101.786, df=1, P< .001
	Yes	33 (64.7%)	3 (2.0%)	36 (17.9%)	
Sensation of hardness/ enlargement in the uterus	No	44 (86.3%)	135 (90.0%)	179 (89.1%)	X^2= 47.676, df=1, P= .061
	Yes	7 (13.7%)	15 (10.0%)	22 (10.9%)	
Unusual fatigue	No	41 (80.4%)	124 (82.7%)	165 (82.1%)	X^2= 52.174, df=1, P= .064
	Yes	10 (19.6%)	26 (17.3%)	36 (17.9%)	
Severe headache	No	44 (86.3%)	134 (89.3%)	178 (88.6%)	X^2=.351, df=1, P= .553
	Yes	7 (13.7%)	16 (10.7%)	23 (11.4%)	
Low back pain	No	6 (12.0%)	128 (85.3%)	134 (67.0%)	X^2= 91.211, df=1, P< .001
	Yes	44 (88.0%)	22 (14.7%)	66 (33.0%)	

- The above table shows that the varieties of symptoms in our study were including: Painful sex; Low abdominal pain; Pelvic pain; Sensation of hardness/ enlargement in the uterus; unusual fatigue; severe headache and Low back pain.

- In the case group, 74.5% of the subjects were suffering of the Painful sex while this amount was only 8.7% in the control group. Chi-Square Test showed that there is a significant difference between two groups related to this variable ($p < .05$)
- In the case group, 31.4% of the subjects were suffering from the Low abdominal pain while this amount was only 10.0% in the control group. Chi-Square Test showed that there is a significant difference between two groups related to this variable ($p < .05$)
- In the case group, 64.7% of the subjects were suffering of the Pelvic pain while this amount was only 2.0% in the control group. Chi-Square Test showed that there is a significant difference between two groups related to this variable ($p < .05$)
- In the case group, 13.7% of the subjects were suffering of the Sensation of hardness/ enlargement in the uterus while this amount was only 10% in the control group. Chi-Square Test showed that there is no significant difference between two groups related to this variable ($p > .05$)
- In the case group, 19.6% of the subjects were suffering of the unusual fatigue while this amount was 17.3% in the control group. Chi-Square Test showed that there is no significant difference between two groups related to this variable ($p > .05$)
- In the case group, 13.7% of the subjects were suffering of the severe headache while this amount was only 10.7% in the control group. Chi-Square Test showed that there is no significant difference between two groups related to this variable ($p > .05$)
- In the case group, 88% of the subjects were suffering of the Low back pain while this amount was only 14.7% in the control group. Chi-Square Test showed that there is a significant difference between two groups related to this variable ($p< .05$)

Table 14 Frequency of the subjects in the case and control groups based on some studied variables

VARIABLES		CASE N (%)	CONTROL N (%)	Total N (%)
Race	White	51 (100%)	150 (100%)	201(100%)
	Other	0 (00.0%)	0 (00.0%)	0 (00.0%)
drinking alcohol	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Smoking	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Having Health Insurance	Yes	51 (100%)	150 (100%)	201(100%)
	No	0 (00.0%)	0 (00.0%)	0 (00.0%)
Taking illegal drugs	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Using tampons	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Sex of the partner	Man	51 (100%)	150 (100%)	201(100%)
	Other	0 (00.0%)	0 (00.0%)	0 (00.0%)
Having a sexual partner with many previous partner	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
History of HPV infection	Unknown	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
History of Bacterial	Yes	51 (100%)	150 (100%)	201(100%)

Vaginosis	No	0 (00.0%)	0 (00.0%)	0 (00.0%)
History of Chlamydia Infection	Unknown	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
History of pelvic infection	Unknown	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
History of HPV vaccination	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
History of STDs	Unknown	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Family member diagnosed with HPV	Unknown	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Knowledge of HPV	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Having a weakened immune system [HIV/AIDS, Drugs]	No	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)
Having History of trauma to cervix	N o	51 (100%)	150 (100%)	201(100%)
	Yes	0 (00.0%)	0 (00.0%)	0 (00.0%)

The above table shows that the both case and control groups were exactly similar based on the mentioned variables. These variables are related to demographic characteristics and health history in our subjects.

The frequency of the above mentioned variables in all the subjects in the both groups were reported as zero and that is why no statistical test was done.

Chapter 5

Discuss
&
Conclusion

In this chapter, the findings of the first and the second phase of the study are discussed in details. Then the conclusion is rendered and finally, topic for the future researches is suggested.

THE FIRST PHASE OF THE STUDY

The first phase of our research which has been conducted in the line of the first objective, led to develop a reserch tool with 50 items. The tool is containing of 46 items about risk factors for Pap test cytological findings and cervical cancer in the field of Demographic Characteristics and Health History, and 4 items with 21 subcategories in the field of Clinical Manifestations. Our study is unique in this part, because we gathered the risk factors for cytological changes towards cervical cancer in Pap test along with the Clinical Manifestations which is specialized and standardized in this field. So it can be used easily not only in Iran and the other developing countries but also in areas where access to medical facilities is limited. And this is the importance of having such a tool.

Based on the studies, there are some scientific tools for cervical cancer assessment and one of them is The Pittsburgh Cervical Cancer Screening Model (PCCSM). According to Austin et al (2010) the "PCCSM is a dynamic Bayesian network consisting of 19 variables available in the laboratory information system, including patient history data, Papanicolaou test results, high-risk HPV results, procedure data, and histopathologic results" [108]. Despite being more detailed and precised, PCCSM is totally different from our tool. It is more useful in societies with well documented medical records and higher health care systems. But in the most of the developing countries, lack of medical documentation for the patients makes it useless. Moreover, vaccination against HPV and HPV test in developing countries like Iran is not pervasive now and it means that we do need to use of a local standardized tool. Such a tool provided in our study.

Lee and colleagues (2014) also rendered a model of risk factors for cervical cancer in the Eastern Asia, Taiwan. Although being similar to the present study by the aim, it is a cohort study and is focused on HPV infection and cervical cancer and there is not any assessment tool presented as well [109]. That is while according to Castle et al (2007) "evaluation of women

with abnormal screening results, decisions on treatment and proper post treatment follow-up require increasing degrees of individualization and clinical judgment as the risk becomes more clearly defined. A risk assessment model for cervical cancer can result in better allocation of resources and increase safety for women at greatest risk and increase well-being for women at lowest risk" [110]. So using of the assessment tool is emphasized.

A Hospital based group matched case-control study (2005) was conducted in India to devise a risk scoring system for the prediction of cervical cancer at the Gynecology Clinics considering that the risk scoring system can be used for reducing the cost of universal screening by including only high-risk subjects to laboratory screening procedure (Pap test) in population setting [111]. The recent study confirms that having a risk assessment tool has been in view of the scientists for many years to enhance the ability of prediction for cervical cancer even before doing screening tests. It is necessary to update the risk assessment tools along with the cultural and socioeconomic changes in different communities and also along with the passage of the time. What that we did in our research.

So, considering the scientific development of the rendered tool in this research and observing all stages such as the use of relevant literature and expert opinion, the CVI (96.01), the CVR (94.39) and the reliability (0.96), it is a standardized tool which can be used for predicting the occurrence of the cytological changes in Pap test.

STRENGHS OF THIS STANDARDIZED TOOL:

- Given that we utilized the studies conducted in different populations to develop this tool, it is a perfect tool which can be used in all communities.
- Being free of charge is the importance of using this tool. So the examiner can estimate how much the patient is at risk of cytological changes toward cervical cancer according to the information obtained from her health history, clinical manifestations and laboratory results.
- This tool is useable not only by midwives and physicians but also by the healthcare givers and even in the remote areas where the access to specialists and equipped clinics is limited. Attention to the raised issues in this tool, while dealing with women referred to the health centers, helps the examiner to estimate the situation of the cervical health more precisely. So

there will be more motivation to perform diagnostic and treatment procedures provided to the women.

- In this tool the clinical manifestations are taken into the consideration along with the risk factors. So the assessment of the women's health status will be more accurately.
- Application: This tool can be used to evaluate risk factors for cervical cancer electronically in a wide range of community without having to attend there. There is already some online screening tools for cancers [112] but ours is a special tool just for cervical cancer with the more details.

The remarkable point is that this tool must be adapted in every society when using according to the culture and customs, religion, race, ethnicity, and habits of the people before use. In this regard, we had exactly similar data in some variables for both the case and control groups thus no statistical test was done about these variables (table 14). It is more discussed in following.

SECOND PHASE OF THE STYDY

This phase was performed based on the second objective of our study.

- In the present study, it was not possible to completely access to our subjects' information about HIV because: a) HPV testing and vaccination against HIV is not routinely done in Iran. Vaccination against HIV is done just by the physician's prescription in special cases. b) There is not a systematic documentation about it in the community. Therefore, this section of the tool was not applicable in the second phase of our study.

However, there are many studies that confirm the role of HPV infection as the main cause of cervical cancer. Vesco et al (2011), Sushma et al (2014), Schiffman and Wentzensen (2013) and Katki et al (2011) emphasizeed that the persistent infection with high-risk human papillomavirus (HPV) types is a necessary cause of almost all cases of the cervical cancer [113-116] .

In confirmation of the positive impact of vaccination in different populations against HPV infection Khatun et al (2012) and Center for Disease Control and prevention (2012) reported

that the HPV vaccine was well tolerated and highly effective in young adolescent females and could be helpful for the prevention and control of cervical cancer [117, 118].

However, there is a controversy about HPV vaccination. For example, Melancon reported autoimmune diseases like Guillian Barre syndrome, lupus, nervous system disorders and many others, including death as the sever side effects of HPV vaccination. She emphasized that every medical intervention may follow by a kind of side effects but the important point is that its benefits for the human health should be much more than its harms. Gardasil as a HPV vaccine reduce only 17-44% of HPV infection risk in clinical trial and this is not enough in face with its serious side effects [119].

Based on findings by Zhang et al (2013) the rate of HPV infection among the women was 12.6% and HPV 52, 16, 58, 18 and 33 were the most frequent types in order. "Moreover, HPV-positive rates were higher in women with older age, lower educational level, younger age of the first sexual intercourse, multiple sexual partners, no usage of condom for contraception, multiple deliveries, vaginal delivery, menopause, vaginal inflammation, cervical erosion and no regular cervical cytological examination" [120].

- The situation for alcohol consumption was as like as HIV in our study. Since all the subjects were Muslims and alcohol consuming is forbidden based on believes, they either do not consume alcohol or do not report it. To observe ethical principles, we did not do any additional search in this matter as well. So there was not a chance to examine the effects of alcohol on the cytological changes towards cervical cancer in the second phase of our study.

But the impact of alcohol on some types of cancer such as breast and cervical cancer have already been proven [11, 80, 121, 122]. Hemminki, Dong and Frisch (2000) showed that "the tonsillar cancers were increased among women with cervical cancer in-situ aged 50 years or more. It ascribed to the effects of HPV, smoking, alcohol or their interaction. They also reported that husbands of patients with cervical cancer developed an excess of both tonsillar cancer" as well [123].

Although alcohol consumption is belong to a category of individual characteristics that are theorized, or previously demonstrated, to be associated with the uptake of preventative health screening services [124], we could not find a recent study focused just on alcohol and cervical

cancer. So the researcher recommends conducting a study on impact of alcohol on cytological changes in Pap test and cervical cancer in a society with easily access to the relevant subjects.

- In the present study, all the subjects were Asian white. So it was not possible to assess the effect of race on cytological changes towards cervical cancer in the second phase of this study. In this line, Rauh-Hain et al (2013) studied the differences in cervical cancer patients' survival between African-American and white women. They found that "there was a significant difference in cervical cancer specific mortality between 1985 to 1989 and 1990 to 1994 but not after 1995" [125]. Before that, Simard et al (2012) had reported that although cervical cancer incidence rates have decreased in both black and white women in the U.S. since the mid 1950s due to widespread screening, rates continue to be higher among blacks aged 50 years and older than among whites in the same ages [126].

  Watson et al (2008) discussed about the role of the race and ethnicity in cervical cancer. They showed that Asian and Pacific Islander women had lower rates of HPV-associated cancers than white women, and also, Black and Hispanic women had higher rates of HPV-associated cancer than white women [127, 128]. To sum up all the above findings about race/ethnicity and cervical cancer, it seems that preventive behaviors and the quality of conducting screening programs in different races have the essential role in the rate of these cancers.

- All the subjects in our study reported themselves as non-smokers and non-drug consumers. Considering that in terms of cultural, Smoking and drug consumption is not accepted for a woman in Iran this situation can be justified. In the other hand, to observe moral principles we did not try to seek more about this matter. Therefore, it was not possible to assess the effect of smoking on cytological changes in Pap test towards cervical cancer in the second phase of the present study. But Jemal et al (2011) have reported smoking as a behavior that can cause the cancer particularly in the developing countries [129].

  Schabath et al (2012) also showed that current smoking is linked with an increased risk of HPV infection including especially oncogenic ones. According to previous findings the cigarette smoking in women is attached with HPV load, prevalence, incidence, and persistence. Smoking can stimulate cellular proliferation and metaplasia in different tissues and cells. So it leads to enhance in replication or production of HPVs. On the other hand, the cellular immune response can be weakened by smoking and subsequently viral load will be

increased. The latter is due to deleterious effects of smoking on immune cells function. In nutshell, we can conclude that the current smokers are gravely connected with an increased risk of oncogenic HPV infection [130].

Roura et al (2014) also found a statistically significant linear increases in the risk of cervical cancer with rising years of smoking, smoking intensity, and pack-years of smoking. To quit smoking and increase the years since the habit has stopped compared to current smoking can reduce the risk of cervical cancer. In this way, the risk of the cervical cancer in those who has quitted smoking for more than 20 years is similar to that of non-smokers. Moreover, the number of the years living with the smoking habit is more strongly linked with the risk of the disease than the number of cigarettes smoked [131].

- Lack of the health insurance as one of the important components of socioeconomic status in some communities considered as a risk factor for cervical cancer [11]. Levy et al (2012) wrote that "screening and earlier treatment of breast and cervical cancer can reduce death rates, but being uninsured reduces the likelihood of screening by about half. A randomized experiment in Oregon demonstrated that an increase in Medicaid coverage increased the percentage of subjects who received Pap tests in the previous year from 41% to 58%" [132].

  According to the low in Iran, all the people from all walks of the life should have public health insurance. Although they are responsible to pay a part of the cost of screening which maybe expensive for some of them, all the subjects in the both case and control groups were quite similar hereof in our study. Therefore, no statistical analyzing was done about this variable.

- There has been a controversy since many years ago about using tampons as an effective factor on cytological changes in Pap test [30, 133]. None of our subjects reported using tampons during their menstrual bleeding so no statistical test was done in this regard.

  Maybe a good reason for not using tampons among our subjects is being more expensive than sanitary napkins which make tampons inaccessible especially for low income women in Iran. The necessity of having knowledge about the reproductive system in those who use tampons can be the second reason while our subjects were mostly low income and non-educated in health related major (94%).

There is a suggestion to study this variable in those communities where the access to subjects who use tampons is possible.

- It is approved that HPV infection can be reduced through limiting the number of sexual partners due to lower exposure to HPV [134, 135]. We also know that different pattern of sexual partnerships can affect the long-term impact of vaccination [136].

  In Iran having multiple sexual partners or a partner of the same sex is forbidden for women because of religion, culture and customs conditions. So even if a woman either has multiple sexual partners or a female partner, she never reports it. All of our subjects reported having one male partner therefore no statistical test was done in the second phase of our study about this variable.

- In the present study due to lack of referral system and family doctor in the research environment leading to the lack of access to medical records and complete medical history of the subjects, there was no entrance to information about history of bacterial vaginosis, chlamydia infection, pelvic infection and history of STDs. Therefore no statistical test regarding these variables was done.

  Based on the studies there is a huge controversy about the association between Bacterial Vaginosis and cervical precancerous lesion. As the results of the relevant studies varied from none to very strong association between these two situation [77].

  Regarding to Chlymdia and cervical cancer, Lehtinen et al suggest that "if infection with Chlymidia trachomatis plays an independent co-factor role in the development of cervical neoplasia the effect is likely to take place at an early stage of cervical carcinogenesis and/or restricted to some cases only. The questions of which of the two infections, HPV or Chlymidia trachomatis, has to occur first, and whether the latter increases the risk of acquiring HPV could not be fully answered yet" [137]. These findings correspond with those of Bhatla et al in 2013. They emphasized that longitudinal studies with carefully selected study sample would be able to answer these unanswered questions [138].

- Based on the results in the present study, there is a statistically significant difference between the case and control group in terms of the reason for doing current Pap test. The subjects in the case group were referred mainly due to a disease in genital system whiles the subjects in the control group were referred mostly in order to do a routine checkup. The logical interpretation of this finding is that if a woman sees a doctor because of a clinical manifestation in genital system, it would be more likely to have abnormal cytological changes in Pap test and it is highly recommended to be examined from this aspect as well (Table 2).

In this regard according to our findings in table 3, Post coital bleeding and Pain (low Abdominal pain, Low back pain, Pelvic pain & Dyspareunia), are the most common chief complaints in the case group whilst in control group vaginal discharge and AUB are the most common chief complaints for visiting the gynecological clinics and doing a Pap test and this difference was statistically significant. It means that a patient with Post coital bleeding and Pain is more likely to have an abnormal result in her Pap test than the others.

In confirmation of our findings there is a research conducted by Bal et al (2012) in which they studied smears from 300 patients with complaints like post-coital bleeding, inter-menstrual bleeding, dyspareunia, vaginal discharge and low abdominal pain. Epithelial cell abnormalities were found in 5% smears which was considerable [8].

Kulkarni et al (2013) reported that vaginal discharge was the common complaint in women with dysplasia. They also mentioned irregular menstrual cycles and post menopausal bleeding as the other chief complaints in patients with abnormal cytological results of cervix [139].

Based on our findings, health care providers must be more sensitive and careful about a woman who attends in the clinic and her chief complaint is post coital bleeding or pain related to genital system. A Pap test is absolutely necessary in this case (table 3). Paying attention to this part of our findings can prevent of missing high risk patients.

According to Gyenwali et al (2014) “delay in diagnosis is a major issue in cancer prevention, treatment and control. Longer delays observed all over the diagnostic pathway is of serious concern as this result in high prevalence of advanced stage at diagnosis and high mortality. Therefore, education of both the patient and health care providers is essential for early diagnosis. There is a need of comprehensive approach to address two major delays: patient

delay and health care provider delay by increasing the patient's awareness, enhancing the health care provider's capacity for early recognition of cervical cancer symptoms" [140].

In this regards, Singh and Badaya (2012) have reported a large amount of lack in awareness and perception in Indian women. They found that just less than 10% of the women had heard about cervical cancer and its symptoms [141]. So it is very important to enhance the level of knowledge and awareness not only in health care providers but also in women as the clients.

- The majority of subjects in the both case and control groups had a health history in which Pap test was not conducted on a regular basis (Table 4). The most common reasons have been announced by the subjects for that included: 1) the high cost; 2) not being important (Table 5). These could be due to a variety of problems in the Health Care System.

  Findings by Gesouli-Voltyraki et al (2010) that introduced the negligence as a main cause for not conducting the Pap test, confirms these part of our findings [142].

  Mo et al (2013) found that anxiety, embarrassment, and pain are the main barriers to regular Pap tests in Korean women [143].

  In Estonia, the main reasons for non-participation in the national screening programme were fear to give a Pap test, long appointment queues and unsuitable reception hours [144].

  Some researches have been conducted to change this situation to have a community with women who consider Pap test as a necessity. In this regard the positive efficacy of a health advisor intervention for improving Pap testing rates has been shown by Paskett et al in 2011. They showed that a health advisor can improve screening behaviors and push the barriers away [145].

  Kivistik et al (2011) also confirmed that women's knowledge should be enhunced about cervical cancer, the risk factors and the screening programme by personally sharing information [144].

  According to Clay et al (2015) even among a highly educated population of women, participants had limited knowledge of cervical cancer and current screening guidelines. Many participants reported discomfort with less frequent screening intervals. This study supports the

need for improvement in cervical cancer prevention education especially with regards to the new screening guidelines [146].

Regarding to the above findings it seems that to have an efficient referral system is a necessity which has not been yet starting up in Iran. The lack of family doctor and strong referral system in this country, leading the absence of following-up the screening programs, can be considered as the main problems. So the researcher draws health authorities' attention to this significant topic and it is strongly recommended to take an appropriate action in order to address that.

On the other hand, it should be considered that the screening costs are not completely payable by the public health insurance in Iran. This is also a serious finding in the present research. To have a high quality screening performance the expenses should be covered by public insurance completely.

In support of this topic, Finkelstein et al (2008) conducted a study on a group of uninsured low-income adults in Oregon. Their subjects were selected by lottery to be given the chance to apply for Medicaid. It was a randomized controlled design study providing a unique opportunity to gauge the effects of expanding access to public health insurance on the health care use, financial strain, and health of low-income adults. Then they found that in the first year, the treatment group had substantively and statistically significantly higher health care utilization, lower out-of-pocket medical expenditures and medical debt and better self-reported physical and mental health than the control group [147].

REGRESSION MODEL OF THE DETERMINANTS

A long-term unresolved infection by specific oncogenic types of HPV has been confirmed as the necessary cause of most premalignant and malignant cervical lesions. However, HPV-infection alone is not sufficient to lead to cervical carcinoma because infected women are likely to regress. Cervical carcinoma not only has a biomedical spectrum, but also has a wide cultural and socio-economic background. Prospective studies have reported that approximately 91-93% of HPV-infected women with normal or abnormal cytology, or with high-risk subtypes (HPV 16 and 18), were clear of infection in 2-3 years. Thus, in addition to HPV, other exogenous and endogenous factors may modulate the risk of progression from HPV-infection to cervical highgrade lesions and carcinoma [6, 109, 148].

In this study, according to the logestic regression, the age, age at the menarche, number of deliveries (parities), BMI and the use of protection during the intercourse (candom) are determinants for abnormal cytological findings in Pap test (Tables 6, 8, 9).

These parts of findings are expanded as follow:

- The first determinant for abnormal cytological findings in Pap test in this study is age. Along with increasing each year to the one's age the risk of detecting abnormal cytological findings in Pap test will be added as much as 8%.

Findings by Benard et al (2012) support our result. They reported that "cervical cancer is very rare in young women. Widespread implementation of Pap testing over the past four decades has detected very few cases of cervical cancer in women younger than 25 years old" [149].

Vesco et al (2011) also confirm our findings by reporting that cervical cancer is rare among women younger than 20 years. They wrote that "screening for cervical cancer in this age group is complicated by lower rates of detection and higher rates of false-positive results than in older women" [113].

Our finding about age as a determinant for cervical cancer is approved by Rositch et al (2014) and Fonn et al (2015) as well. They even described cervical cancer as a disease of older women [150, 151].

- Age at the menarche is another determinant we found for abnormal cytological findings in Pap test. Along with decreasing each year of the age at the menarche the risk of detecting abnormal cytological findings in Pap test will be added as much as 75%.

  This is a uniqe finding. In our study age at the menarche is a determinant for abnormal cytological changes but age at the first sexual intercourse is not. It can be due to the imprecise information following the shame and pudency in our subjects when talking about sex. So, maybe they announced a later time for starting to have intercource. So the age at the first intercource has been ignored. Or maybe there are other reasons which should be considered. Anyway, the further research is needed to make it clear.

  Plummer et al (2012) analyzed the effect of the delay between age at menarche and age at the first intercource, testing the hypothesis that the increased risk of cervical cancer in women with early age at frst intercource may be due to an increased vulnerability of the immature cervix to HPV infection. They used women with a delay of 5 years or over as the reference category. The findings showed a small excess risk among women with a delay of 4 years or less [152].

  Natphopsuk et al (2012) also reported age at first sexual intercourse (≤16 years) as a risk factor for cervical cancer. They suggested that a delay of 6 or more years after menarche before sexual intercourse would be safer and afford some protection from sexually-transmitted diseases (including HPV infection) and susceptibility to cervical cancer [153].

- In the present study, the third determinant for abnormal cytological findings in Pap test is the number of deliveries. Along with increasing each number of deliveries the risk of detecting abnormal cytological findings in Pap test will be added as much as 44%. This is a very important finding in our study which can be due to hormonal factors and/ or cervical trauma during each delivery.

  Jensen et al (2013) confirmed our findings. They reported that multiparous women with persistent HPV infection had a significantly increased risk for cervical cancer [154]. Muñoz et al (2002) also found a direct association between the number of full-term pregnancies and the

risk of squamous-cell cancer. They reported that "a general decline in parity might therefore partly explain the reduction in cervical cancer recently seen in most countries" [155].

Findings by Natphopsuk et al (2012) confirm this part of our results too. They found that multiple pregnancies (≥3), multiple parities (≥3) and also , age at first delivery (≤18 years) are among the risk factors for cervical cancer [153]. About the impact of the number of deliveries on the other gynecological cancers in women, Högnäs et al (2014) found that in women with 10 or more deliveries the incidence of uterine sarcoma was markedly increased [156]. Sogukpınar et al (2013) found that among the cervical cancer related risks vaginal delivery and having three or more pregnancies had the highest rates that supports our findings [157].

- BMI is the other determinant for abnormal cytological findings in our study. Along with increasing BMI to getting overweight/ obese compared with having normal BMI, the risk of detecting abnormal cytological findings in Pap test will increase as much as 2.6 times.

Findings by Bhaskaran et al (2014) support ours. They reported that "BMI was associated with 17 of 22 cancers, but effects varied substantially by site. Each 5 kg/m2 increase in BMI was roughly linearly associated with cancers of the uterus, cervix, gallbladder, kidney, thyroid, and leukaemia. But these effects varied by underlying BMI or individual-level characteristics" [158].

Frumovitz et al (2014) reported that morbid obesity is an independent risk factor for death due to cervical cancer. They also mentioned that overweight and obese women have the same prognosis as normal-weight women [159]. So it seems that BMI has negative impact not only on creat the disease but also on prognosis in the patients.

Acording to Arnold et al (2015) obesity is a cause for many kinds of cancers in human. They reported: "Worldwide, we estimate that 481000 or 3·6% of all new cancer cases in adults in 2012 were attributable to high BMI. A quarter (about 118 000) of the cancer cases related to high BMI in 2012 could be attributed to the increase in BMI since 1982. These findings emphasise the need for a global effort to abate the increasing numbers of people with high BMI. Assuming that the association between high BMI and cancer is causal, the continuation of current patterns of population weight gain will lead to continuing increases in the future burden of cancer" [160].

Lee et al (2013) found that elevated BMI (overweight and mild obesity) is a risk factor for cervical cancer while physical activity, regardless of total calorie which has taken, is an inhibitor for cervical cancer [161].

There is another research in this line which has conducted by Meyer et al (2015). They found that obesity was associated with the higher risk of dying from cancer of the cervix, uterine, ovary and the liver.They added that more than 20% of all cancer deaths can be ascribed to ever smoking and overweight (BMI ≥ 25 kg/m2) [162].

But there are some conflicting results in the studies about this case. For example, Song et al (2014) reported that there is not any significant association between BMI and cervical cancer and obesity is associated with an increased of incidence of ovarian cancer. [163].

- Using protection (condom) compared with never use of it, will decrease the risk of detecting abnormal cytological findings in Pap test about 88 %.

Although it is known that transmission of HPV can be reduced through using condom and limiting the number of sexual partners [118], there is an ongoing debate and conflicting findings on whether use of condom protect against HPV infection and subsequent development of HPV-related illnesses in females [164]. To justify this topic we should consider that HPV can be transmitted by skin contact and is found in male genital areas not covered by a condom and also the errors and problems such as breakage, slippage, or late application are common [165].

However in the line of our results, Lam et al (2014) found that "there is a statistically significant protective effect of condoms in prevention of HPV infections and cervical neoplasia". They also reported that "consistent users had: a significantly lower risk of becoming infected with HPV, a higher chance to clear the existing infections, or a higher chance of high-grade CIN regression without surgical intervention". We should also consider that "the risk of acquiring HPV is strongly related to the number of sexual partners. Condom use appears to be higher among casual and new sexual partners than among regular ones". Hence, "exposure to infections is often imbalanced between condom users and non-users, and would need to be accounted for in the analyses". Another important point should be considered

is that condoms using is socially desirable so it might be reported more frequently than justified by the reality lead to diluting the observed protective effect of condoms [165, 166].

Consistent with the observations , there is low rates of condom use among Asian female and the barriers to condom use have been reported, such as embarrassment, cost, moral values, ethnic and religious factors, gender inequality, and the lack of a dialogue between partners [143].

In a study conducted by Frazier et al (2015) in US it was found that among HIV-Infected sexually active women 20% reported sex without condoms [167]. This is a disaster. Overall, using of protection in a correct way can reduce the risk of detecting abnormal cytological findings in Pap test about 88 % and subsequently cervical cancer. It is the responsibility of health authorities to take steps to increase the use of condom by raising the level of information and removal of the other obstacles.

OTHER RESULTS

In the present study, age at the first birth, age at the first sex and family income (Table 6), type of the residency, type of the housing, the educational level, major of education and ethnicity (Table 7), and occupational status and marital status (Table 8) as well as history of using hormonal contraceptive and using IUD (Table 9) are not the determinants of cytological findings in Pap test. This is the same situation for status of sexual experience and having a family history of cancer (Table 10).

In line with our results, Jensen et al (2013) reported that there was no association between use of IUD, sexual behaviour and using hormonal contraceptives with persistent HPV infection [154].

But according to Gedefaw et al (2013) there is a statistically significant association during bivariate logestic regression analysis between educational status, occupation, being currently on highly active antiretroviral treatment, age at the first marriage, age at the first sexual intercourse, life time number of sexual partners and precancerous cervical cancer lesion [6].

In another study conducted by Natphopsuk et al (2012) a significant accociation between prolonged use of injective contraception (>2 years), prolonged use oral contraceptive pills (>2 years), multiple sexual partners (>1) and cervical cancer were found [153].

Different findings in this regards indicate that different societies should investigate separately due to some Specified and unspecified reasons which surely differ from community to community.

In our study, although nearly all the subjects in the case group were suffering of unhealthy cervix, about less than half of the subjects in the control group had the same situation. This difference was statistically significant.

The unhealthy cervix in the present study was including: chronic cervicitis, erosion and laceration in the cervix and hypertrophied cervix. (Tables 11, 12). In this regard, Banik et al (2011) in a cross-sectional descriptive study found that overall two-third of the patients with an abnormal Pap smear result showed unhealthy cervix in the vaginal examination [168] which is a confirmation to our findings.

According to Bhalerao et al (2012) cervical erosion can be seen in 78% of women with unhealthy cervix. In these patients vaginal discharge is the most common presenting symptom followed by pelvic pain. While the most common biopsy result in women with inflamation found in their Pap test is choronic cervicities [169].

Shekhar et al (2014) also found that among patients with abnormal Pap test cervical erosion, cervicitis, vaginitis and cervical hypertrophy were the most common pathological conditions [170].

Regarding these findings we realize that more attention should be absorbed to women with unhealthy cervix but there are reports including our results suggesting that even the healthy looking cervix can have cytological abnormality as well.

Among them we can cite to Pradhan et al (2015). According their results cytological changes are difficult to prognosticate just by looking at the cervix and it is necessary for all sexually active women to undergo cytological evaluation whether the cervix looks healthy or not [171].

In the present study painful sex, low abdominal pain, pelvic pain and low back pain in case group were significantly higher than that of the control group (Table 13).

Shekhar et al (2014) also found that in the patients with abnormal Pap test vaginal discharge was the most common presentation and low abdominal pain and low back pain were 2nd and 3rd common presentations [170].

In a similar study Bal et al (2012) found that vaginal discharge was the most common presenting complaint and a history of pain in the lower abdomen, inter menstrual bleeding, dyspareunia and Postcoital bleeding were the other common symptoms in the patients reffered to gynecological clinics respectively [172].

In another study having symptoms like post coital bleeding, vaginal discharge, dyspareunia, pelvic or lower abdominal pain were considered as the main symptoms for abnormal pap test and cervical cancer [173].

In this regard, Low et al (2015) wrote that "attributions of symptoms potentially indicative of a gynaecological cancer were varied, but most often involved women fitting symptoms into their expectations of what was 'normal'. Normalising acted as a barrier to seeking help from a healthcare professional, alongside competing time demands and negative attitudes towards help-seeking. These barriers may lead to later diagnosis and poorer cancer survival" [174].

Our findings in this research can also be used to enhaunce the sensation of ontime help-seeking by the women and resonable action by health care givers.

CONCLUSION

In this study, a risk factor assessment tool for the cytological changes towards cervical cancer in Pap test was methodologically developed. We strongly recommend it to be considered and applied in facing with patients in all clinics that are open to women about gynecological problems. It can help the physicians and the other health care providers to predict their patients' health situation in order to have a suitable and quick action especially in those ereas with limited access to the specialists.

To protect women against abnormal cytologivcal changes and subsequently cervical cancer it is neccessary to include HPV vaccination and HPV screening in Public health program along with promotion regular pap test screening in all over the country. Surely, prevention and early detection would be much cheaper than treatment in terms of both financial and spiritual. To save most lives, both prevention and early detection should also be covered totally by public health insurance especially in low income people. On the other hand, available facilities should be used entirely to enhaunce women's knowledge and awareness about cervical cancer, its risk factors, and also about its main cause (HPV). Women's health care professionals, media and press or any printed matters can have an operational and effective role about it. The regression model obtained from this study could be a good guide to determine the priority for pathological checks and will be effective in reducing the medical expenses as well.

THE APPLICATION OF THIS RESEARCH

- In clinic: The developed assessment tool in the first phase and all the findings in the second phase of this research can be used by family physicians, midwives and health care providers in all the public and private clinics. Using this tool will enable them to be more careful about their patients' health and make an on time action in relation with the treatment or preventive proceedings.
- In the society: The tool developed in this study can be used as an online free screening program for cervical cancer in all the societies. In this regard, the tool should be scoring in particular for each society individually.

- In education: The tool can be included in the curriculum of midwifery, nursing and health-care provider students. So it can enable them to care of their clients more carefully.
- In research: It can be used as a risk factor assessment tool for the cytological changes in cervix and also for clinical manifestation of the cervical cancer and its pre cancerous changes in the related studies.

SUGGESTION FOR THE FUTURE STUDIES

It is suggested to use of this assessment tool in the other societies with the different characteristics, customs and cultures so it will be possible to compare the risk factors in different communities and make our knowleges more accurate.

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Written consent

I, … hereby agree to be one of the subjects in the research project related to PhD thesis belonged to Ms. Gita Sangestani, PhD candidate. It has explained to me that all the information about me will remain confidential and the results, without mention any name and addresses, will be published as general. The researcher answered all my questions and my participation is voluntarily. I can stop my contribution any time and it will not affect on the diagnosis and treatment process of my status. This written consent does not prevent legal actions if any improper or inhumane operation performs.

Signature

Date