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THE INTEGRATION OF MOBILE TECHNOLOGY TO LOWER THE RISK OF DEVELOPING CERVICAL CANCER IN HIV POSITIVE WOMEN

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**THE INTEGRATION OF MOBILE TECHNOLOGY TO LOWER THE RISK
OF DEVELOPING CERVICAL CANCER IN HIV POSITIVE WOMEN**

By

Tugce Kinik

A THESIS

Submitted in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

In Medical Informatics

MICHIGAN TECHNOLOGICAL UNIVERSITY

2016

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This thesis has been approved in partial fulfillment of the requirements for the Degree of
MASTER OF SCIENCE in Medical Informatics.

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Dedication

To all women so that they could be free of AIDS and Cervical Cancer.

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List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ASCUS	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical Squamous Cells Cannot Exclude HSIL
CIN	Cervical Intraepithelial Neoplasia
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HSIL	High-Grade Squamous Intraepithelial Lesion
HSV	Herpes Simplex Virus
Ig	Immunoglobulin
LSIL	Low-Grade Squamous Intraepithelial Lesion
OC	Oral Contraceptives
CC	Cervical Cancer
WHO	World Health Organization

Abstract

Cervical cancer is the most common cancer in HIV positive women in the world [1]. According to epidemiologists, HPV infection alone will not initiate cervical cancer [2]. In addition to high risk HPV types, smoking, long term hormonal contraceptive use, high parity, HIV/AIDS infection, sexual activity before 20 years of age, multiple sexual partners, exposure to sexually transmitted disease, and family history of cervical cancer are other reasons to turn an HPV infection to the cervical cancer [3]. With the increasing global population, cervical cancer cases are expected to increase 46% until 2030 [4]. Effective prevention and control efforts will be needed. In order to prevent cervical cancer in HIV infected women, it is important to notice risk factors of cervical cancer, calculate the risk percentages to be caught by cervical cancer in order to identify and lower these risks. The aim of the study is to create a mobile application which enables to reduce cervical cancer cases by showing possible cervical cancer risk percent and the ways of decreasing the risk. By using this application, women will be directed to obtain healthy habits and will help to avoid risk. First, main algorithms of cervical cancer were decided by considering WHO's procedures and three groups of risk intervals were created by accepted lab results. Second, the application was created by using Android Studio with PHP and MYSQL. Results showed that 80% of the physicians were satisfied about the application, and 60% of the physicians thought that the calculated risk percent of cervical cancer was accurate in the assessment. Also, 80% of the physicians believed the sample education section of the application helpful of very helpful to change patients habits to increase the prevention of cervical cancer. More importantly, 80% of the physicians

found the application quite useful to educate patients to understand the correlation between HIV + and cervical cancer.

Chapter 1

Introduction

1.1 Background

In 2012, more than 550,000 incidents and 270,000 deaths due to the cancer of uterine cervix were detected worldwide [5]. About 85% of these incidents and 87% of total deaths happened in developing countries chiefly due to low attainment to health care for detection and treatment of early lesions [5]. The primary reason of cervical cancer is human papillomavirus (HPV) which is one of the most common sexually transmitted infections (STIs). It has more than 200 types, which are categorized in two parts, high risk and low risk. Low risk types have the risk of causing anogenital warts, while high risk types are responsible in provoking the cancer of uterine cervix [6]. According to studies carried out in various countries by the International Association, the most prevalent high risk HPV types are HPV-16 53%, HPV-18 15%, HPV-45 9%, HPV-31 6%, and HPV-33 3% [7].

In 1981, the first HIV instance was cited in the world [8]. Since that time, HIV continues to spread. According to WHO's 2014 statement, 36.9 million people have been living with HIV [9]. There are some cancers associated with AIDS. These cancers are especially dangerous for HIV positive people. Cervical cancer is one of these cancers, since HIV infected women have much more risk of gaining HPV. Cervical cancer is the most common cancer in HIV positive women all over the world. HPV is three times frequent

in HIV positive women than with HIV negative women [10]. What is more, HIV infected women have a quite rapid progression of cervical cytology abnormalities [11]. Even if HIV positive women have negative cytology findings, they may have huge pervasiveness of one or more oncogenic HPV characters [12]. Additionally, HIV positive women are more likely to be diagnosed with cervicovaginal convections such as bakteriel vaginosis [12]. All these are because of the weak immune system in HIV positive women.

The cervix areas are covered by squamous and the grandular cells. Primary area of cervical cancer is the cervical transformation zone which is the shape of ring of these squamous epithelium tissues in the vagina. When the HPV firstly is obtained, cervix will have some atypical changes in squamous cells, which are called Atypical Squamous Cells (ASCUS). Every HPV infection does not ensure to cervical cancer. There is pre-invasive period of cervical cancer, which is called Cervical Intraepithelial Neoplasia (CIN), and it does not mean cancer. Rather, it results from cytologic cervical tissue changes after HPV infection first starts. CIN consists of three stages, CIN I, CIN II, and CIN III. These stages define the progress of dysplasia (Figure 1.1). CIN I refers to Low Grade Squamous Intraepithelial Lesion (LSIL). In this stage, HPV infection mostly would clear itself, but in case of triggers or any unhealthy habits, it could progress to CIN II and CIN III, which refer to High Grade Squamous Intraepithelial Lesion. These stages are indicators of progression to cervical cancer. If they are left untreated, it is most likely to result in cervical cancer. There are many investigations about precancerous lesions of the cervix. According to previous studies, regression of CIN I is over 60% then progression to cancer

is about 1 %. CIN II have 40% regression and 5% progression to cancer. CIN III's regression is 30% and progression to cancer is 12% [13]. The average progression time to CIN III from HPV's initial infection is anticipated to be about 10 years. There is 10 to 15 years average to develop cervical cancer after CIN III [14]. Nicholas et al. detected 5-6 years to progression to CIN I from first HPV infection, and about 7 years to progression to CIN II or CIN III from CIN I [15]. Nicholas highlighted that HPV types must be considered to define progression times [15], because every high risk HPV types affect body differently and their carcinogenic effects are different.

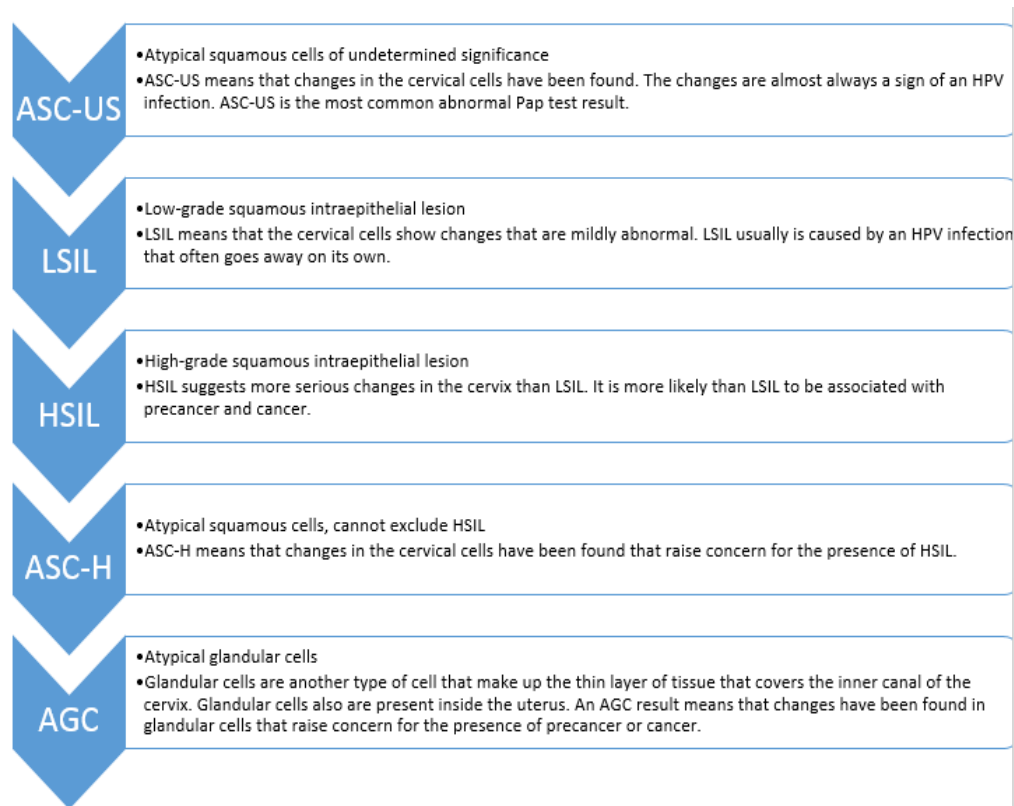


Figure 1.1: Progress of Cervical Cancer

Cervical cancer (CC) characteristically is introduced by an infection of high risk HPV type, but there may be decades to progress to cervical cancer. Women older than 40 years have the most common prevalence of CC with 70%. The most affected population by HPV is the women are 15 and 25 years old [16]. In Brazil, there are 64 million women, who are 15 years and above [17]. The HIV positive women population was 360,000 in Brazil in 2014 [18]. The risk of developing CIN and CC is quite related in this population. Cervical cancer needs to be screened, and its abnormalities should be followed up regularly. The high incidence of cervical cancer is quite related to missing of cervical cancer screening and follow up of abnormalities. Recent studies prove that the highest prevalence of cervical cancer is seen in SubSaharan Africa 24%, Eastern Europe 18%, Latin America and Caribbean 16%, unlike Western Asia 1.7% has the lowest percentage [19].

There is a study in the city of Sao Paulo among prostitutes. The risk of obtaining sexually transmitted infection include HIV and HPV is higher for these women. This is due to prostitution behaviors such as large number of partners, not using condom, and socioeconomic agents [20]. Another scientific study shows that Hispanic and black women are in greatly impressionable to gain cervical cancer [21]. They are twice the risk compared to non-hispanic women [22]. This may be because of some genetic factors or risky behaviors. By 2050 in the United States, hispanic population is expected to increase 128%, from 49 million to 111 million, while non Hispanics expected 11% [23]. As a result of this increase, the USA is expected to increase in cervical cancer diagnosis.

Cervical cancer has some stages (Figure1.2) that define the infection's enlargement and situation. The first stage is 0 which is not totally cancer, but if it is not treated, cervical cancer may develop. In stage 1, cervical cancer's area is contained to the cervix. There are two groups in stage 1; group A and B. In stage 1A, there is a minor 5-7 millimeters microscopic cancer in the cervix. In stage 1B, the cancer might spread slightly and is between 7 mm and 4 cm which is visible without a microscope. In stage 2, the upper part of the vagina is subjected to the cancer. In stage 2A, cancer spreads almost 65 percent of the vagina, but the cancer does not affect the other tissues yet. On the other hand, in stage 2B, these tissues are embedded with abnormalities. In stage 3, lower part of the vagina, pelvic walls and the surrounding lymph nodes are affected. In stage 3A, pelvic walls are not affected. In stage 3B, the tumor of cervical cancer is large enough to block ureters. There is a risk of enlargement to kidney and even lymph nodes. In stage 4 which is the most dangerous stage, cervical cancer affects bladder and rectum. In the stage 4B, liver and lungs are fatally affected [24].

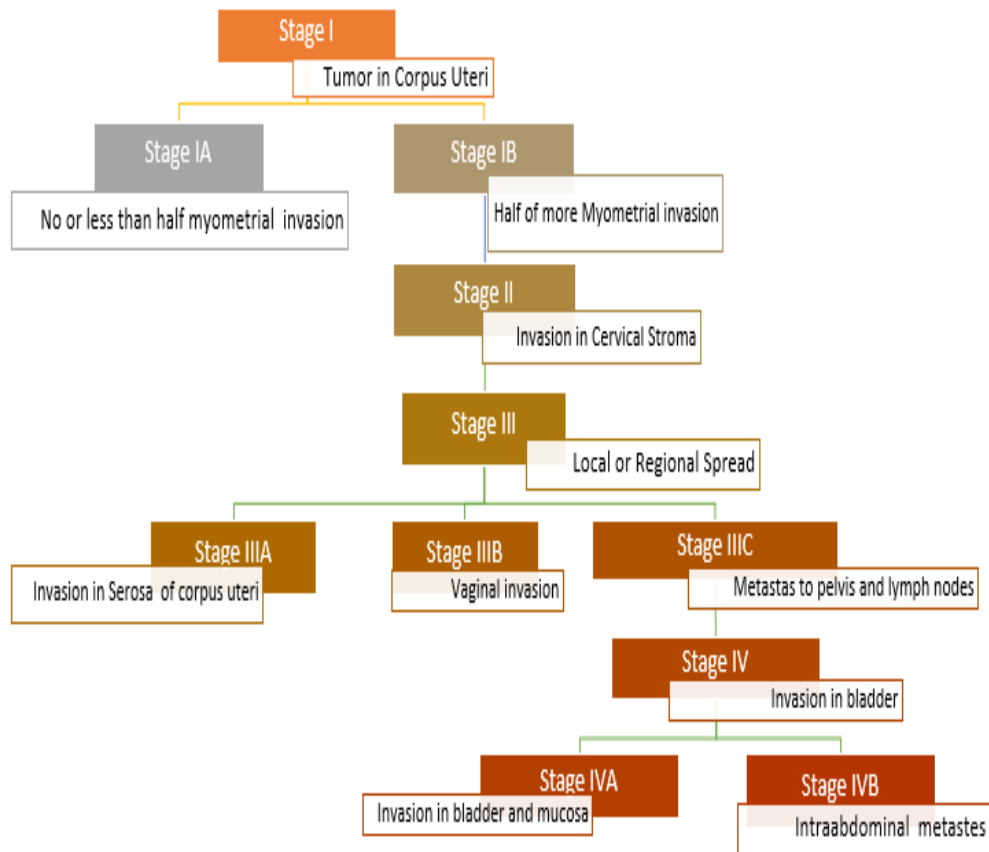


Figure 1.2: Cervical Cancer's Stages and Affected Body Parts

Women may experience cervical pain during coitus. Women older than 35 years old with post-coital bleeding are more likely to develop cervical cancer than women who are younger than 35[2]. In advanced stages, women may lose their appetite. This may cause weight loss. Other advanced problems are pelvic, back and leg pain, heavy bleeding, leakage, smelling, vaginal discharge, and even bone fractures on pelvic area [24]. Some complications of cervical cancer such as post-coital bleeding may be seen in women who have genital chlamydia, trichomonos infection, post-menopausal bleeding, postcoital,

intramenstrual and abnormal vaginal bleeding. These symptoms and complications are not related with just cervical cancer, rather they are signs of endometrial cancer's as well. That is why, women need to receive a pelvic exam to establish the right diagnosis.

It is possible to prevent cervical cancer [25]. The number of physicians suggest cytology test for cervical cancer screening [25]. Pap smear test can prevent practically most deaths caused from cervical cancer by means of regular screening and follow up [25]. Although Brazil, and other Latin America countries use cytologic screening, cervical cancer cases could not be diminished at an expected rates [26]. This may be because of the lack of education, follow ups and other social determinants.

1.2 Reasons of Cervical Cancer

There are some other factors related to operate cervical cancer in addition to high risk HPV types [3]. The risk factors of invasive cervical cancer are generally related to sexual actions and habits [27]. These reasons are smoking, long term hormonal contraceptive use, high parity, HIV/AIDS, some sexual behaviors such as early sexual activity before 20 years of age, multiple sexual partners, exposure to sexually transmitted diseases, and family history of cervical cancer [3]. Nutritional and genetic factors, herpes simplex virus, chlamydia infection, sexual activity, and low socioeconomic status are other possible factors [4].

1.2.1 Human Papillomavirus and Cervical Cancer

In a person's lifetime, women and men, who are sexually active, are exposed to HPV at least once [28]. Human Papilloma Virus have 200 known types. The number of listed high risk types are 15-20, while the others are considered low. Typically, low risk types may not show any symptoms, or may cause some cervical lesions. These lesions give symptoms such as small pink or red warts, and cause itching and burning in genital area. Prior infection with high risk HPV types is 99.7 % related to the cancer of uterine cervix [29]. The transmission methods are not only intercourse, but also can occur even through skin to skin contact to the genital areas. HPV can be also transmitted from mother to child during birth. Most sexually active women may be exposed to HPV, although this does not necessarily mean the cultivation of cervical cancer. Generally, majority of infections occur in the early years after sexual activity. Persistent infection with one or more high risk carcinogenic HPV is the strongest ordinary risk factor in the development of cervical cancer [30]. HPV 16 and 18 are the most common types, found over 70% of invasive cervical cancer prevalence in the world [31]. Women who are 20 years and younger have the highest possibility to be infected by HPV, whereas women older than 30 would have less chance [32]. That is why, young aged women need to use preventative methods.

1.2.2 HIV and Cervical Cancer

There are some evidences about the correlation between HIV and HPV. Transmission of both HIV and HPV are unprotected sex with multiple partners. A HIV infection triggers

HPV infection progression. CD4 count helps body to fight against to infections [33]. HIV infection causes a deep decrease of CD4 count. As a result of decreasing CD4 count below 200, AIDS will lead to occurrence [34] (Figure 1.3), and body will result in a state. HIV infection causes the weakness of immune system. According to a study in South Africa, HIV positive women were 2-3 times more detected with cervical cancer [35]. Another study on 500,000 female HIV patients found these individuals had an excessive increased risk of 6-10 times more endemic of obtaining cervical cancer [1]. Getting HIV in past 3-6 months raises recently diagnosed high risk HPV infection by 2.5-5 times more [12]. Normally, healthy women may clear HPV infection before progression, but HIV positive women are not be able to clear the HPV infection enough [36]. This may be another symptom of weakness of immune system.

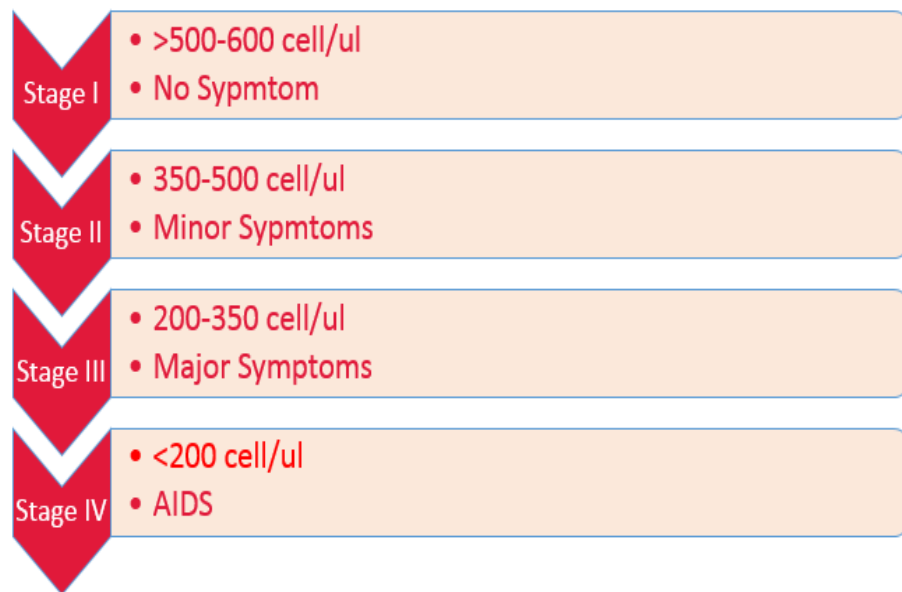


Figure 1.3: HIV Stages to AIDS

1.2.3 Sexual Behavior

Having multiple sexual partners is another huge risk for women to catch cervical cancer. Women who have 10 or more partners have three times risk than women having one partner [37]. This may be because the transmission risk of STIs and germs is high in these women. A crucial factor for women is the sexual practices of husbands or male partners. If male partners have more than one sexual partner, they can easily conduct STIs. Moreover, the high risk infections of cervical cancer such as HPV and HIV can be easily transferred by male partners. Several studies showed that women have 5 times high risk of catching cervical cancer, if their partners have more than one partner [38].

1.2.4 Age of First Sexual Intercourse

One of the risk factors of obtaining HPV infection and cervical cancer is the age of sexual debut. There is an increased sensitivity in women who started their sexual activity at 15 years or earlier [39] because of the developing body. A study showed that women, who are sexually active since the age of 18, are 5 times higher risk than women who started to sexual activity at 22 years and above [40]. Starting at an early age to sexual debut means more exposure to HPV and other carcinogenic risk factors of cervical cancer [37].

1.2.5 Contraceptive Methods

Unprotected sex causes an increased risk of receiving STIs and cervical cancer. Condom use is the only way of partial preventive HPV agent transmission. It is proven that condom use reduces HPV transmission by almost 70%, but HPV presents not only penis and vagina, but also scrotum, labia and perianal area [41]. The reason of partial prevention is that HPV can expose to other genital areas, which are not covered by condoms. A recent study in Denmark proved past genital warts are the most significant factors of developing cervical cancer [42], which is related to not utilizing a condom. Some studies shows that microbicides can block HPV's spread [43]. Additionally, there is a relationship with long term use of oral contraceptive. A study showed that women who preferred to use oral contraceptive methods for more than four years are twice risky than women who have preferred some barrier methods such as condom [44]. This could be because of synthetic hormonal changes.

1.2.6 Smoking

Smoking is an independent reason of cervical cancer [37]. Studies showed that there is a biological effect of smoking on cervical mucus. Smoking increases cervical mucus and distorts the function of mucus. Additionally, it is known that carcinogens are produced by cigarette and therefore, smoking may weaken the immune system. That is why the body may not be effective enough to fight with infectious agents such as the HPV and it will cause HPV persistence. Smokers who have smoked frequently or long term have twice the risk of cervical cancer [37].

1.2.7 Use of Alcohol

There is a relation between alcohol consumption and HPV. Women who consume excessive alcohol are a higher risk for cervical cancer. There is no significant enhancement in women who drink alcohol one to three times in a month, but women who take alcohol four or more times in a month are at twice the risk of HPV infection [38]. Additionally, increased alcohol consumption causes risky sexual behavior and may prompt carcinogenic agents either state what “others” are or remove it.

1.2.8 Viral Infections

Epidemiological studies prove that some sexually transmitted agents significantly increase the risk of cervical cancer. These agents are chlamydia, herpes simplex, bacterial vaginosis, syphilis and gonorrhea. Women who have STIs are in 1.8 times more risk [45].

1.2.9 Increased Parity

Parity is a descriptive term of the number of pregnancies [46]. There is a high risk in multi-parious women. The reason could be the enlargement of the transformation zone. In conclusion of hormonal changes during pregnancy and giving birth, the enlargement occurs. In a study, women have 7 or more parity are twice risky [39].

1.2.10 Race

A study made in the USA showed that African Americans and Hispanics in the USA are twice affected in getting HPV and gaining cervical cancer [20]. This could be as a result of unhealthy sexual behaviors, genetic factors, or socioeconomic factors.

1.2.11 Religions

There are some religions which are not typically categorized as high risk. These women are from specific religious groups such as Catholic, Muslims, the Amish and Mormons. This may be due to sexual practice and behaviors. The women who belong to these groups do not prefer to have many sexual partners and risky sexual behaviors.

1.3 Cervical Cancer Treatment and Prevention

There are two classifications of prevention of cervical cancer; primary and secondary. The target of primary prevention is to prevent exposing HPV infection and other co-factors that may be related to high risk cervical cancer. Efforts of prevention and controlling should be guided by perceiving the history and development of cervical cancer [30]. Primary prevention highlights the vaccination option for women before exposure to HPV. This vaccination prevents women to expose HPV infection. This is the most effective method of prevention of cervical cancer [30].

The primary recommendation of WHO is to vaccinate targets between the ages of 9 to 13 years old girls. Secondary target group or catch up target are 14 to 26 years old women [47]. The vaccine can be successful to prevent women who are not exposed HPV infection. That is why, young aged women should be directed to this vaccine before sexual debut. Recent researches displayed that the vaccine is only preventive for covered HPV types. If a vaccine has HPV 18, it will not be preventative against to HPV 16. That is why, women may obtain the other HPV types. The vaccination is not protective for progressive of precancerous lesions [30].

The purpose of secondary prevention is screening, detection and treatment of non-developed disease. A popular method of screening of cervical cancer is papanicolaou (Pap) test. The main purpose of cervical cancer screening is to detect and deport the precancerous lesions. This can prevent women from invasive cervical cancer. If a detected precancerous lesion is not treated, women may still get cervical cancer [48] [49]. It is proven that consistent screening can prevent the cervical cancer up to 90%, if it is done every three years [50]. Also, even one-time screening can lower cervical cancer by 25% to 36% [51]. Additionally, by frequent screening, early detection of cervical cancer can be increased, helping to lower the number of advanced stages in cervical cancer [52].

The process of development to cervical cancer from a precancerous lesion takes approximately 10 years. Physicians suggest that cervical cancer screening should be started at the age of 21 or three years later from vaginal intercourse depends on which

comes first. After first normal screening result, annual screening should be repeated for the following three years. If women have abnormal results, screening should be done annually or every six months. The limit age of screening is 65. There are some high-risk groups of women such as HIV infected women. For these at risk, screening must start earlier. HIV positive women are encouraged to have strict and intense schedule of screening and treatment [41]. There must be some qualified policies that risky women can benefit from. By good control of these diseases, women can be assisted to get good habits and regular check ups. As a result of qualified policy, it is possible for women to have a healthy life. For treatment of cervical cancer, diagnosis stage is the determinative factor. The purpose of cervical cancer treatment is to remove the cancer out and heal the body which occurs by surgery and radiotherapy or chemotherapy which is a concomitant treatment of radiotherapy[53]. The early stage of cervical cancer is usually partial, and this can be treated by conization or trachelectomy. These treatment (Figure 1.4) can be applied to fertile women in case of intended pregnancy[54, 55].

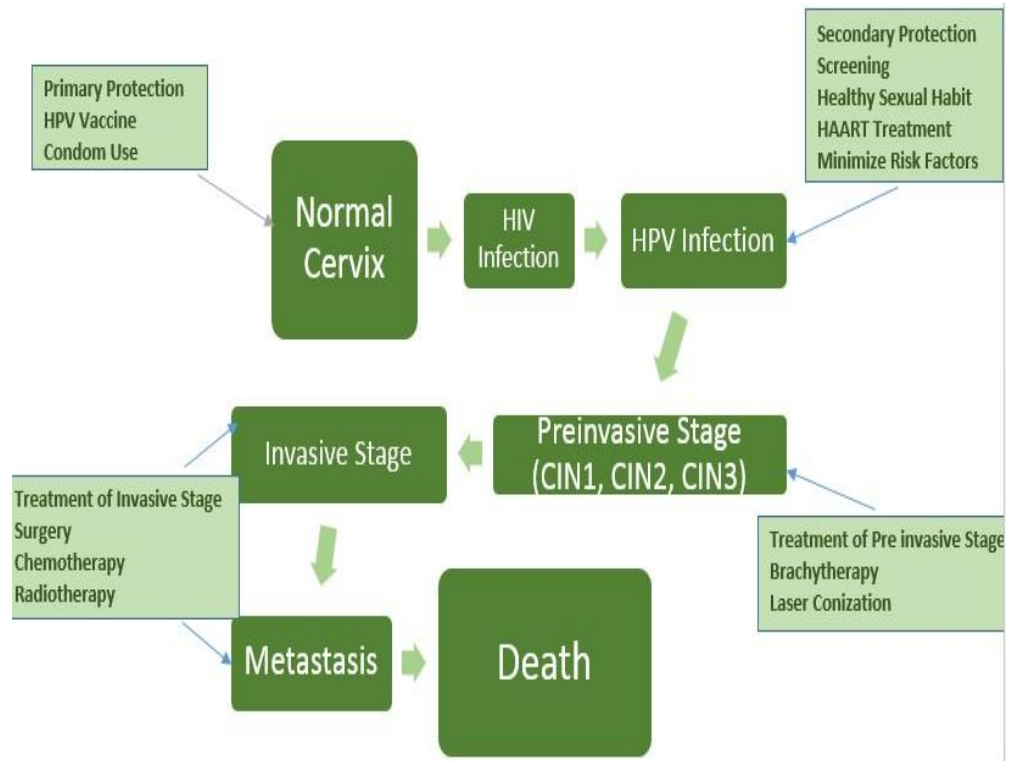


Figure 1.4: Prevention and Treatment of Cervical Cancer in Stages

Chapter 2

Methodology

2.1 Problem Statement

Over 500,000 women every year are under threat of obtaining cervical cancer. More than 270,000 women are in risk of death from this cancer type [5]. HIV is one of the biggest risk factors of cervical cancer. It can spread through oral, vaginal and anal intercourse, needle sharing, and mother to child transmission. More HIV infected women means more potential cervical cancer diagnosed women. There are numerous problematic tendencies of cervical cancer patients. First, there is a problem with follow up of patients diagnosed with cervical cancer. Patients need regular follow up which is an extremely important factor in evaluating their current condition. Second, patients and physicians do not have much time in visits that may be needed. Third, patients may forget their follow up appointments. They may need a reminder. Fourth, sexually active women need a helper tool to foresee their risk in cervical cancer and other STIs. Finally, distance and transportation are important issues that patients may not reach to health services on time and needed. These mentioned difficulties are crucial factors for patients' lives.

2.2 The Project

In our global society, mobile technology continues to evolve. As a result of the developments, there lies potential solutions for healthcare facilities to improve health outcomes. Creating a mobile application will be a helpful tool for patients, physicians,

and healthcare providers. These groups need to communicate with each other and provide accurate data, to ensure best quality of care is given. Additionally, patient problems, symptoms, tests and results need to be recorded. An application can monitor patients, remind them of their visits, collect information, and educate patients. Since cervical cancer is the second most common cancer in women, we hope to reduce and prevent cervical cancer prevalence. That is why we aimed to create an application to demonstrate the ways of reducing cancer risk, while providing HIV positive women and their respective clinician a definitive and clinically approved predictive cervical cancer risk score. We focused specifically on HIV positive women, since they have great risk to progress cervical cancer.

The utilization of this application is, to track an individual's health, provide critical preventive education about cervical cancer, develop an algorithm to show the health risks associated with poor health habits, how these risks scores can be minimized with proper care and treatment, help to eliminate risk factors, and reduce cervical cancer cases. HIV positive women will be able to see their estimated risk percentage based on the algorithms outcome regarding correlation with cervical cancer. As a result of this, women can reduce the risk of cervical cancer and improve their quality of life. This application is also a potentially significant solution for patients who typically do not receive adequate health care and education, whom are often under stress, and do not frequently attend clinical appointments due to reasons such as transportation, limited time, and insufficient funding.

Brazil had 360,000 HIV positive women in 2014[18]. Current and future HIV + women population is under threat of cervical cancer. In Brazil, some of these women do not have enough access to health care facilities. The reasons could be socioeconomic status, location or other factors. Also, some of these women do not attend clinic regularly which was the main complaint of physicians of Escola Bahaina de Medicine e Saúde Pública. This may be due to lack of education about the correlation between HIV and cervical cancer. Since Brazilian HIV + women are the one of the biggest population of cervical cancer incidences, we wanted to address this target group with our application.

2.3 Aim of The Study

The aim of our study is to analyze how HIV positive women in Brazil can benefit from the mobile applications designed to monitor health and provide education.

2.3.1 Specific Objectives

- i)** to determine the quality of our application,
- ii)** to find out the common interval of the percentage and risk factors of cervical cancer among HIV positive women,
- iii)** to reduce the prevalence of cervical cancer in HIV positive women in Escola Bahaina de Medicine e Sade Pública where we cooperated, and
- iv)** to determine physicians' satisfaction with the application.

2.3.2 Application Development

The application we created is an Android application (Figure 2.1, 2.2). We preferred Android, because 81% of all smart phones in use have Android Operating System [56]. It allows to the patient to log in and begin monitoring their health. When the log in button is clicked, the data is collected and sent to the database. By the database, we can follow the personal health data and clinical tests and results. This is very important, so that physicians can monitor patients, see the patient's situation and risk percent, easily access the data patient entered, educate patients by it, and explain how to improve their health outcomes. By the user's entries, risk percent of cervical cancer is calculated. To calculate risk percent, the algorithms of cervical cancer are implemented. We have two versions of the application one in English and the other in Portuguese, since it was created in the USA and currently applied in Brazil.

There is also education section in the application containing cervical cancer risk factors which are related to the algorithms in our application. Patients can go through this part of the application and view what the risk factors and the relationships are between the algorithms and cervical cancer. By this part, we aimed to educate patients and change their habits to improve their health outcomes. The application was also examined for clarity, ambiguity, time taken to complete risk analysis and analyzability. Completing the application takes 5 to 10 minutes, depending on user's ability.

```

private TextView errorDisplay;

@Override
protected void onCreate(Bundle savedInstanceState) {
    super.onCreate(savedInstanceState);
    setContentView(R.layout.activity_page_eighth);

    sharedPreferences = PreferenceManager.getDefaultSharedPreferences(this);

    errorDisplay = (TextView)findViewById(R.id.error_display);

    serumVDRL1 = (CheckBox) findViewById(R.id.serumVDRL);
    gonorrhea1 = (CheckBox) findViewById(R.id.gonorrhea);
    chlamydia1 = (CheckBox) findViewById(R.id.chlamydia);
    trichomoniasis1 = (CheckBox) findViewById(R.id.trichomoniasis);
    vaginosis1 = (CheckBox) findViewById(R.id.vaginosis);
    herpessimplex1 = (CheckBox) findViewById(R.id.herpessimplex);
    vaginalsmell1 = (CheckBox) findViewById(R.id.vaginalsmell);
    partnerspartner1 = (CheckBox) findViewById(R.id.partnerspartner);

    nextButton = (Button)findViewById(R.id.next);
    nextButton.setOnClickListener(new View.OnClickListener() {
        @Override
        public void onClick(View v) {

            String id = sharedPreferences.getString(Helper.USERID, "");
            String serum = String.valueOf(isCheckBoxChecked(serumVDRL1));
            String gonorrhea = String.valueOf(isCheckBoxChecked(gonorrhea1));
            String chlamydia = String.valueOf(isCheckBoxChecked(chlamydia1));
            String trichomoniasis = String.valueOf(isCheckBoxChecked(trichomoniasis1));
            String vaginosis = String.valueOf(isCheckBoxChecked(vaginosis1));
            String herpessimplex = String.valueOf(isCheckBoxChecked(herpessimplex1));
            String vaginalsmell = String.valueOf(isCheckBoxChecked(vaginalsmell1));
            String partnerspartner = String.valueOf(isCheckBoxChecked(partnerspartner1));

            double score = serumScore();

```

Figure 2.1: Java Class Codes

```

//////////////////// Page 7 //////////////////////
public function isPageSevenExist($id){
    $dbobject = new DbConnect();
    $sql = "select * from pageseven where id = '$id'";
    $result = mysqli_query($dbobject->getDb(), $sql);
    $number = mysqli_num_rows($result);
    if($number > 0){
        return 1;
    }
    return 0;
}

public function insertupdatePageseven($id, $hvpstatus, $hvp16, $hvp18, $doublehvp, $hivrna){
    $dbobject = new DbConnect();
    $sql = "";
    $id = (int)$id;

    //echo json_encode(array('isLogin' => '7'));

    if($this->isPageSevenExist($id) == 1){
        // update
        $sql = "UPDATE pageseven SET hvpstatus='$hvpstatus', hvp16='$hvp16', hvp18='$hvp18', doublehvp='$doublehvp', hivrna='$hivrna' WHERE id='$id'";
    }else{
        // insert
        $sql = "insert into pageseven (id, hvpstatus, hvp16, hvp18, doublehvp, hivrna) VALUES($id, '$hvpstatus', '$hvp16', '$hvp18', '$doublehvp', '$hivrna')";
    }

    $result = mysqli_query($dbobject->getDb(), $sql);
    if(!$result){
        echo json_encode(array('isLogin' => '0'));
    }
    echo json_encode(array('isLogin' => '1'));
}

```

Figure 2.2: One of PHP Sample Codes of Our Application

2.4 Risk Scores and Algorithms of Cervical Cancer

There are some variables which are known to lead to cervical cancer according to WHO's cervical cancer protocol [57]. The project involved the collaboration with Escola Bahaina de Medicine e Saúde Pública in Salvador, Brazil. We customized the algorithms and took 32 of them as a result of acknowledgement with Escola Bahaina de Medicine e Saúde Pública for our study. These variables are chiefly HPV and HIV infection. High parity,

having multiple sexual partners, using oral contraceptive, having unprotected sex, viral infectious, unhealthy behaviors such as smoking, drinking, drug use and some lab tests are some of the variable within our algorithms used in this study (Figure 2.3). Moreover, laboratory algorithms of cervical cancer were classified by physicians and infectiologists of Escola Bahiana de Medicina e Saúde Pública. The algorithms of cervical cancer are mainly the same for most countries since these countries take their protocols from WHO. However, small differences in algorithms might occur depending on the countries which have their own protocols under WHO. These different algorithms could be used in different countries by consulting with physicians and Health Protocols.

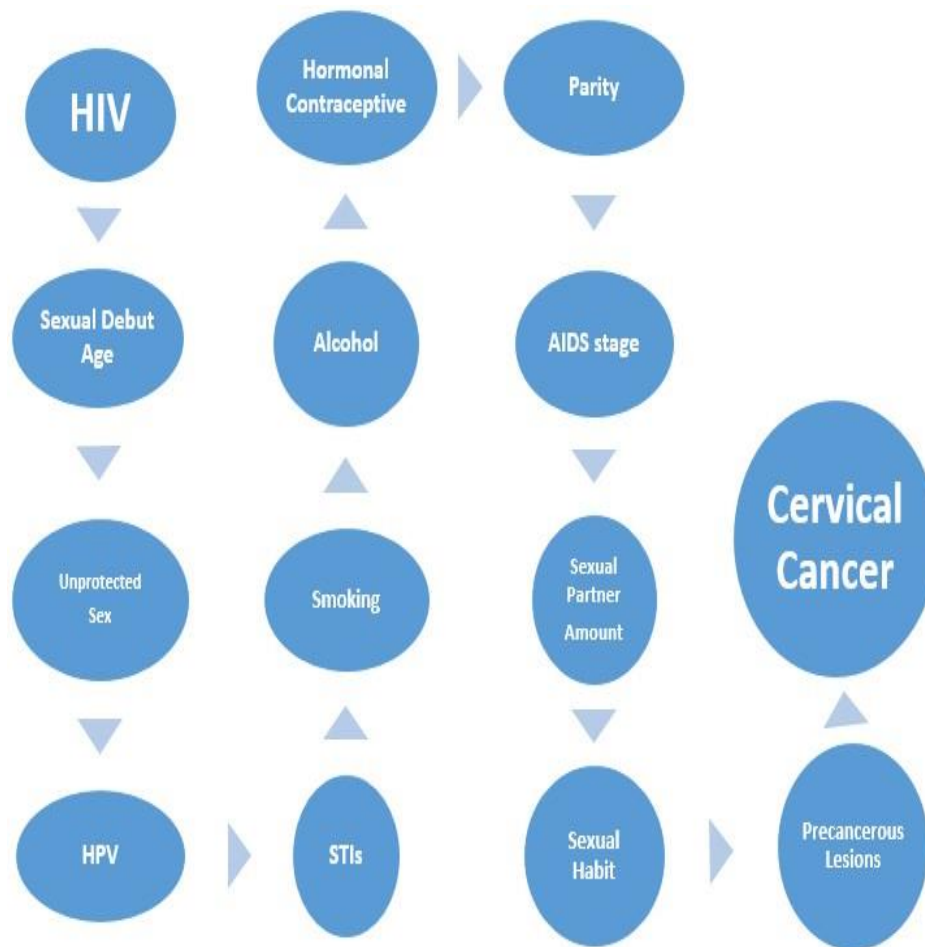


Figure 2.3: Main Algorithms of Cervical Cancer in Our Study

Even though the risk scores for algorithms might be seen quite distinct among different studies, the risk scores taken from some studies which researchers focused on a large number of women were considered to be more reliable than the risk scores found by the studies that used less number of women. Another reason of using these risk scores was due to the studies considered being concentrated on considerable number of variables and aspiring to calculate a more reasonable risk score. Some researchers gave more

dominancy to some variables without considering the rest of the critical algorithms which were also vital in this study. Lastly, time intervals for the frequency of obtaining these health variables is a concern due to different time intervals decrease or increase the cervical cancer, drastically. Time intervals are vital for our study to calculate risk percentage and determine risk scores because different time intervals will increase or decrease the risk score. That is why, we did not prefer to use the studies that ignored time intervals.

First and foremost, if women are infected by HIV infection, the risk score will be 5.4% [62], but the persistence of HIV infection also needs to be considered to identify the possibility of cervical cancer for women. For instance, if HIV persistence is more than 6 months, the risk score of catching cervical cancer will be 1.1% while having HIV infection more than 5 years will increase the risk 1.48% times more. If HIV persists on more than 10 years, the risk score will be 1.84% [58]. The progression of HIV and the weakness of immunity can be detected by the number of CD4. Decreasing number of CD4 will destroy the immunity and trigger the cervical cancer. If the number of CD4 is under 200, the risk score will be 4.26% whereas having CD4 between 201 and 350 will correspond to 2.84% risk score. On the other hand, CD4 which is between 351 and 500 will cause the risk score to be 1.42% [63].

Another main variable within our algorithm to determining the possibility of cervical cancer is HPV infection. Generally, the HPV infection will cause the risk score to be 5%

[61], but having high risk carcinogenic HPV types such as HPV 16 and HPV 18 will cause additional 4.6% and 2.4% risk scores, respectively. Another reason of increase in the risk score is having more than one HPV infection which will also add extra 5.5% risk score on the calculations [55].

Other algorithms must also be considered for the risk score calculations of cervical cancer to better identify the risk for women. The risk score of sexual debut at 18 years old women was identified 5% times higher than the risk score of sexual debut at 25 years old women in Brewer's study [13]. Also, we took the risk score of using of alcohol more than 4% times in a month between 2.0 and 3.1 from Sierra-Tores's study [58]. La Vecchia divided the risk scores of smoking into three different category, depending on the frequency of usage. According to his study, smoking less than 5 years, between 5 and 10 years, and more than 10 years resulted in the risk scores of 1.6%, 3.0%, and 5.0%, respectively [59]. On the other hand, use of oral contraceptives more than 10 years, between 5 and 10 years, and less than 5 years gave the risk scores of 2.5%, 1.9%, and 0.9% to trigger the cervical cancer, respectively [44]. The risk score for the women who had 7 or more parity was taken 2.0% from La Vecchia's study [59]. Also, Coinfection with other STI had 1.8% risk score to determine the possibility of catching the cervical cancer [60].

Based on these studies, we classified risk intervals and risk scores. Several variables of WHO which have not been studied by scholars, were also included in this study. The risk scores for these variables were estimated, considering the importance of intervals of this

health data on cervical cancer. The risk scores and intervals of the variables are shown in the tables 2.1, 2.2, 2.3, and 2.4.

Table 2.1 Risk Score Algorithms Part 1

Algorithms	Interval	Risk Arrangement	Risk Percent %
HIV Test	Positive		5.4
	Negative		0
HIV Persistence	>6 Months	1	1.1
	>= 5 Years	2	1.48
	>= 10 Years	3	1.84
CD4 Count	>= 500	0	0
	350=< CD4 <500	1	1.42
	200< CD4 <350	2	2.84
	<=200	3	4.26
CD4 Percentage	40<CD4 percentage<=50	0	0
	30<CD4 percentage<=40	1	1
	14< CD4 percentage<=30	2	2
	CD4 percentage<=14	3	3
CD4/CD8 ratio	>=1	0	0
	0.8, 0.9	1	1
	0.8>CD4/CD8>=0.5	2	2
	0.3, 0.4	3	3
	0.1, 0.2	4	4
HPV test	Positive		5
HPV 16	Positive		4.6
HPV 18	Positive		2.4
Double HPV	Positive		4.7

Table 2.2 Risk Score Algorithms Part 2

Algorithms	Interval	Risk Arrangement	Risk Percent %
Unprotected Sex	0 times in a month	0	0
	2 or 3 times in a month	1	3
	>=4 times in a month	2	5
Alcohol Use	0 times in a month	0	0
	<4 times in a month	1	1.3
	>4 times in a month	2	2
Smoking	No smoking	0	0
	<=5 years	1	1.6
	5 years <smoking<10 years	2	3
	>=10 years	3	5
Needle use	0 times in a month	0	0
	1 time in a month	1	1.3
	2 times in a month	2	2.6
	3 times in a month	3	3.9
	4 or more times in a month	4	5.2
Oral contraceptive use	0	0	0
	<=5 years	1	0.9
	5 years< Oral<10 years	2	1.3
	>=10 years	3	2.5
Parity	0	0	0
	<4	1	1
	4=<Parity<7	2	1.5
	>=7	3	2

Table 2.3 Risk Score Algorithms Part 3

Algorithms	Interval	Risk Arrangement	Risk Percent %
Quantitative HIV RNA	<50	0	0
	50=<Quantitative HIV RNA<500	1	1
	500=<Quantitative HIV RNA<5000	2	2
	5000=< Quantitative HIV RNA<10000	3	3
	<=10000	4	4
Serum VDRL	Positive		2
Gonorrhea	Positive		1.8
Chlamydia	Positive		1.8
Trichomoniasis	Positive		1.8
Vaginosis	Positive		1.8
Herpes Simplex	Positive		1.8
Vaginal Smell	Positive		0.9
Partner' Sexual Partner	>1		4.2
HTLV Test	Positive		1
Sexual Debut	<18	4	5
	22>Sexual Debut>=18	3	3
	22=<Sexual Debut<25	2	2
	25=<Sexual Debut	1	1
Sexual Partner	1	1	1
	2	2	2
	3 or 4	3	3
	>4	4	4
Vaginal Lesion	Positive		1

Table 2.4 Risk Score Algorithms Part 4

Algorithms	Interval	Risk Arrangement	Risk Percent %
Vaginal Bleeding	>1 times in a month		3
Sex During menses	0 times in a month	0	0
	1 time in a month	1	1.5
	>=2 times in a month	2	3
Sexual Devices Use	0 time in a month	0	0
	1 time in a month	1	1
	2 times in a month	2	2
	3 times in a month	3	3
	4 or more times in a month	4	4
Anal Sex	0 times in a month	0	0
	1 time in a month	1	1
	>= 2 times in a month	2	2

We classified the risk of cervical cancer into three categories in terms of calculations: low, moderate, and high risk scores which are between 0% and 25.72%, 25.73% and 55.12%, 55.13% and 100%, respectively.

2.4.1 Low Risk Calculation

Depending on the intervals and risk scores, risk percentages were calculated. We divided the risk arrangement into three categories to calculate low, medium and high risk percentages. To calculate the maximum percentage for low risk category, the lowest intervals which corresponds to the highest scores were included. Since we focused on HIV positive women in our study, the HIV score will be the same (5.4%) for low, medium

and high intervals to calculate their minimum and maximum percentages. Also, having HIV infection between 6 months and 5 years will cause maximum 1.1% risk score for low risk interval. For the maximum percentage calculation of the low risk interval, CD4 count must be at least 350 and maximum 500 and the related risk score will be 1.42%. CD4 count which is more than 500 will be regarded as healthy women in this study. The highest score of CD4 percentage (between 30% and 40%) for low risk interval will be 1%. On the other hand, if CD4/CD8 ratio is between 0.8 and 1, 1% will be added to the maximum percentage calculation.

Having HPV infection will result in 5% risk score, automatically. If Quantitative HIV RNA is between 500 and 50, it will correspond to 1% risk score which is the maximum value for low risk interval. Moreover, in case of starting coitus between 22 and 25 years old, 2% risk score will be chosen as the maximum score. Having maximum 2 partners in lifetime is also risky to have cervical cancer and will result in 2% risk score. For low risk category women, alcohol usage and unprotected sex would be assumed to be 0% in lifetime and will cause 0% in the calculation. Smoking is also a bad habit for progression to cervical cancer and using it maximum 5 years will risk the woman 1.6% more. Furthermore, needle usage once in a month will correspond to 1.3% risk score. If oral contraceptive usage is maximum 5 years, 0.9% will be taken for calculation whereas the usage of sexual devices once in a month will risk even 1% more. To consider the parity as low risk interval, women must have less than 4 children, which will result in 1% maximum. One of the most critical assumptions for low risk category women is not to

have anal sex and sex during menstruation, which means 0% risk score in this study. To understand the maximum value for low risk interval, we aggregated all percentages mentioned above and found 25.72% (Figure 2.5).

Table 2.5 Low Risk Score Intervals

Algorithms	Interval	Risk Arrangement	Risk Score in Percent
HIV Test	Positive		5.4
HIV Persistence	>6 months	1	1.1
CD4 count	>=500	0	0
	350< CD4 count <500	1	1.42
CD4 percentage	40< CD4 percentage <=50	0	0
	30<CD4 percentage <=40	1	1
CD4/CD8 Ratio	>=1	0	0
	0.8, 0.9	1	1
HPV Test	Positive		5
Quantitative HIV RNA	<=50	0	0
	500> Quantitative HIV RNA>50	1	1
Sexual Debut	28>Sexual debut >=25	1	1
	25> Sexual debut>=22	2	2
Sexual Partner	1	1	1
	2	2	2
Unprotected Sex	0 times in a month	0	0
Alcohol Use	0 times in a month	0	0
Smoking	0 times in hall life	0	0
	<=5 years	1	1.6
Needle Use	0 time in a month	0	0
	1 times in a month	1	1.3
Oral Contraceptive Use	0	0	0
	<=5 years	1	0.9
Sex During Menses	0	0	0
Sexual Devices Use	0 time in a month	0	0
	1 times in a month	1	1
Parity	0	0	0
	<4	1	1
Anal Sex	0 time in a month	0	0

2.4.2 Medium Risk Calculation

Similar to low risk interval, maximum percentage for medium risk interval was approximated, depending on health variables within the algorithm and their persistence. Obviously, the minimum percentage for medium risk interval and the maximum percentage of low risk interval will be identical. On the other hand, to find the maximum percentage for medium risk interval, the same algorithms were used and the percentages were discussed. Similar to the low risk calculation, HIV score for medium risk calculation will be 5.4% constantly for HIV positive women. If HIV infection carries on a woman between 5 and 10 years, 1.48% risk score will be added in the calculation. To have the maximum risk score for the medium risk interval which is 2.84%, CD4 count is assumed to be between 350 and 200. Significantly, having the CD4 percentage between 14 and 30 will correspond to 2% risk score. Additional 2% risk score will be added in case of the fact that CD4/CD8 ratio is between 0.8 and 0.5. Another algorithm which we took constant for each category is HPV infection. That is why, the risk score will be 5% for medium risk interval and will be the same to the low risk interval. In addition to having HPV infection, the highest carcinogenic HPV types (HPV 16 and HPV 18 [31]) will increase the risk score even more. Whereas HPV 16 will cause 4.6% risk score, HPV 18 will result in additional 2.4% risk score. To calculate the maximum percentage for the medium risk interval, the risk score of HPV 16 was only included rather than considering the risk score HPV 18, as well. Moreover, we took 2% for Quantitative HIV RNA between 500 and 5000. If a woman's male partner has another sexual partner, an additional 5.2% risk score will be added to the calculations in this study. Starting sexual activity between

22 and 18 years old will cause 3% risk score. If a woman has 3 or 4 sexual partners in lifetime, the risk score will be 3%. Not using condom twice or more times in a month for sexual activity will increase the risk for cervical cancer and the risk score for this negligence will be 3%. Additionally, for medium risk interval to calculate the maximum score, smoking between 5 and 10 years and alcohol usage between once and three times in a month will result in 3% and 1.3% risk scores, respectively. Needle usage twice in a month will correspond to 2.6% risk score while oral contraceptive usage between 5 years and 10 years will cause 1.3% risk score. Furthermore, using sexual devices twice in a month, having children between 4 and 7, having anal sex once in a month, and sex during menstruation once in a month correspond to the medium risk interval and will increase the risk 2%, 1.5%, 1.0% and 1%, respectively. Overall, we found the highest risk score as 55.12% for the medium risk interval (Figure 2.6).

Table 2.6 Medium Risk Score Intervals

Algorithm	Interval	Risk Arrangement	Risk Score in Percent
HIV Test	Positive		5.4
HIV Persistence	≥ 5 years	2	1.48
CD4 count	$200 < \text{CD4 count} < 350$	3	2.84
CD4 percentage	$14 < \text{CD4 percentage} \leq 30$	2	2
CD4/CD8 Ratio	$0.8 > \text{CD4/CD8 ratio} \geq 0.5$	2	2
HPV Test	Positive		5
HPV 16	Positive		4.6
HPV 18	Positive		2.4
Male partner's partner	> 1		5.2
Quantitative HIV RNA	$5,000 > \text{Quantitative HIV RNA} \geq 500$	2	2
Sexual Debut	$22 > \text{Sexual Debut} \geq 18$	3	3
Sexual Partner	3, 4	3	3
Unprotected Sex	≥ 2 times in a month	1	3
Alcohol Use	< 4 times in a month	1	1.3
Smoking	$5 \text{ years} < \text{Smoking} \leq 10 \text{ years}$	2	3
Needle Use	2 times in a month	2	2.6
Oral Contraceptive Use	$5 \text{ years} < \text{Oral contraceptive} < 10 \text{ years}$	2	1.3
Sex During Menses	1 times in a month	1	1.5
Sexual Devices Use	2 times in a month	2	2
Parity	$7 > \text{Parity} \geq 4$	2	1.5
Anal Sex	1 times in a month	1	1

2.4.3 High Risk Calculation

To calculate the highest risk percentage for cervical cancer which is expected to be %100, the highest risk percentages for each algorithm were considered. Similar to the low and medium risk intervals, HIV and HPV scores were taken as 5.4% and 5.0% for high risk interval, respectively. If HIV infection persists on longer than 10 years, the risk for cervical cancer will increase 1.84% more. CD4 count less than 200 and CD4 percentage less than 14 were assumed to be within the high risk interval and will result in maximum 4.26% and 3% risk scores, respectively. If the ratio of CD4/CD8 is higher than 0.1,

additional risk score will be 4% to be counted in the calculations. More interestingly, women must carry both HPV 16 and HPV 18 types to be considered in the high risk interval and on the calculation the risk scores of both HPV 16 and HPV 18 will be added, which are 4.6% and 2.14%, respectively. In addition to having HPV infection and their fatal types (HPV16 and HPV 18), having more than one HPV types will cause additional 4.7% risk score for the high risk level. Having Quantitative HIV RNA more than 10,000 will result in 4%. If serumVDRL and HTLV are positive, additional 2% and 1% risk scores will be counted. If a woman's partner has another sexual partner, 4.2% will be added in the calculations. To be considered in the high risk interval, women must have vaginosis, trichomoniasis, herpes simplex, chlamydia, and gonorrhea vaginal infections. Each of these vaginal infections will cause additional 1.8% risk scores. For high risk interval calculation, if a woman's vagina smells, a 0.9% risk score will be added. If a woman was not mature (under 18), sexual activity of this woman will be an additional 5% which is quite high in comparison to other algorithms. Having sex more than 4 partners in lifetime will result in 4% risk score for cervical cancer. For the maximum score of the high risk interval, women must consume alcohol more than four times in a month. This bad habit will cause additional 2% risk score for the estimations of possible cervical cancer. As mentioned before, another bad habit which triggers the cervical cancer is smoking. Smoking more than 10 years is considered as high risk level and will result in 5%. Moreover, if a woman does not use condom during sex more than 3 times in a month, extra 5% will be automatically added. Usages of needle more than 4 times in a month and of oral contraceptives more than 10 years are other main criteria for high risk level and correspond to 5.2% and 2.5% risk scores, respectively. More than 7 parities,

using sexual tools four times in a month, having anal sex at least twice in a month, and sex during menstruation twice or more in a month will increase the risk of cervical cancer as 4%, 2%, 2%, and 2%, respectively. Our calculations matched to 100% for the highest risk percentage of the high risk interval (Figure 2.7).

Table 2.7 High Risk Score Intervals

Algorithms	Interval	Risk Arrangement	Risk Score in Percent
HIV Test	Positive		5.4
HIV Persistence	>=10 years	3	1.84
CD4 count	<=200	3	4.26
CD4 percentage	<=14	3	3
CD4/CD8 Ratio	0.3, 0.4	3	3
	0.1, 0.2	4	4
HPV Test	Positive		5
HPV 16	Positive		4.6
HPV 18	Positive		2.4
Double HPV	Positive		4.7
Quantitative HIV RNA	10.000>Quantitative HIV RNA >=5.000	3	3
	>=10.000	4	4
Serum VDRL Test	Positive		2
Gonorrhea	Positive		1.8
Chlamydia	Positive		1.8
Trichomoniasis	Positive		1.8
Vaginitis	Positive		1.8
Herpes Simplex	Positive		1.8
Vaginal Smell	Positive		0.9
Partner's sexual partner	>1		4.2
HTLV Status	Positive		1
Sexual Debut	<18	4	5
Sexual Partner	>4	4	4
Unprotected Sex	>=4 times in a month	2	5
Alcohol Use	>=4 times in a month	2	2
Smoking	>10	3	5
Needle Use	3 times in a month	3	3.9
	4 times in a month	4	5.2
Oral Contraceptive Use	>10 years	3	2.5
Vaginal lesion	Positive		1
Vaginal bleeding	>1		3
Sex during Menses	2 times in a month	2	3
Sexual Devices Use	3 times in a month	3	3
	4 times in a month	4	4
Parity	>7	3	2
Anal Sex	2 or more times in a month	2	2

2.5 Study Site

The study was done at Escola Bahaina de Medicina e Saúde Pública as a result of a collaborative project utilizing clinical informaticist expertise. The university was founded in 1952 in Salvador, Bahia, Brazil. It is a private, non-profit organization and one of the most well-known educational institutions of Northeastern Brazil known for its achievements.

Our study was a Cross-Sectional Descriptive Study. The main aim of which was to customize the WHO cervical cancer algorithm and create an application which develop risk percentage for HIV infected women. Secondly, we aimed to measure the validity of our application and satisfactions of physicians about the application, during this initial prototype phase.

2.5.1 Data Collection and Analysis

After developing the application, we requested the clinicians in Escola Bahaina de Medicina e Saúde Pública to use the application and requested feedback by an electronic survey. The education was also provided by a tutorial sent to them before using the application. It is shown in Appendix B. Also, the survey questions we created is placed in Appendix A. Our survey and application are translated from English to Portuguese by a translator proficient in Portuguese and English.

Chapter 3

Results

Five physicians associated with the research of this study replied our survey. We asked how often they use the application on their smart phone. 60% of them use the application every day, 20% of use one time in a week, and 20% use one time in a month. 80% of have health-oriented applications on their smart phone while 20% do not. 25% of these access health-oriented apps every day, 25% three times in a week, and 50% once a week. 80% of physicians find the health-oriented application helpful. Prior to using the application, 60% of found their patients did not have adequate education regarding the correlation between HIV and cervical cancer. 80% agreed that the application will help patients understand the correlation between HIV + and cervical cancer. 60% agreed while another 40 % strongly agreed with the calculated risk correlation algorithm of contracting cervical cancer, given the input variables, was accurate in its assessment. 40% of found the sample education section helpful 40% of found it very helpful to changing patients habits in the prevention of cervical cancer. 40% of found very easy and 60% of found easy to navigate the application. 40% of strongly agreed and 40% of strongly disagreed that the application will help to improve patients' attendance in their follow up clinical appointments. This may be due to not having an appointment or calendar option. 80% of rated the application over all satisfied.

Chapter 4

Discussion

Research shows that the cancer of uterine cervix is the second most prevalent cancer of women in developing countries. Usually HIV positive women have multiple types of HPV. The explanation for it could be immune system weakness. Since developing countries are often known to have higher rates of HIV and HPV is more aggressive in HIV infected women, the highest potential for global public health impact by a HPV vaccine would be conferred by its effectiveness in the HIV infected population. It is known that cervical cancer based from HIV positivity cause high morbidity and mortality rate in developing countries. What is more, the risk of catching HPV is also associated with HIV positivity since both are sexually transmitted infections. Unification of both will cause cervical cancer. Cervical cancer has long precancerous period that may give the opportunity of diagnosis and treatment on time. Until that time, we have the chance to foresee risk and reduce the prevalence. Each society has own culture and social factors that affect health and disease. There are some processes to show the relations between behaviors and attitudes of society. These processes make prediction and explanation of health behaviors possible for us and health care. Our application is one of these methods. Our developed health application is designed to collect and analyze data about patients. It does this by combining information from patients, previously not recorded, with test results and examinations from clinicians, to develop proactive methods of health to improve the lives of patients. Our research described the analysis of our application on predicting of cervical cancer probability in HIV positive women. A HIV-cervical cancer

algorithm is used to help to shape the calculations. As it is seen in the results, physicians are quite satisfied about the application that will help both patients and physicians. The application has not been tested on patients. After applying on patients and aiming to reach more physicians, we may have more accurate data.

4.1 Future Studies

Globally, governments should take the action against prevalence of cervical cancer. It is vital that women should be educated to obtain healthy behaviors and get regular cervical cancer screening and treatment. Women should be prompted about taking a step in screening and treatment. By the education policies and government actions, it is expected to increase target group and reduce mortality and morbidity. For now, there is a great need to more research in cervical cancer, its prevention, and treatment ways. To make people educated and accessible facilities, the opportunities should be developed more. In the future work scholars may be interested on trying many classifications of algorithms and different feature of extractions and selection of algorithms may result better performance in terms of accuracy sensitivity and specific in other disease. Also, calendar, health checkup reminder, and appointment alternatives may be added to the application.

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Appendix A

A.1 Study Questionnaire

A.1.1 The Evaluation of a Mobile Application to Assist in Determining the Risk of Cervical cancer in HIV + Women

- 1) What is your name?
- 2) What is your email address? So that we may contact you with changes or improvements to this application.

3) What is your current position or title *

4) How many years have you worked in health care sector? *

Less than one year

15 years

6-10 years

10-15 years

More than 15 years

5) How often do you use applications on your smart phone? * Mark only one oval.

1 2 3 4 5

Never Every Day

6) Does your smart phone contain any health oriented applications? *

Yes

No

60

7) If yes to the above question, how often do you access these health oriented applications in a given week?

1 2 3 4 5

Never Every Day

8) Do you find health oriented applications helpful for diagnosis, treatment and prevention? *

1 2 3 4 5

Not helpful Very helpful

9) How important is the self management of your health to you? *

1 2 3 4 5

Non important Extremely

10) Prior to using the application, on average, how would you rate your patient's knowledge of the correlation between HIV+ women and cervical cancer? *

1 2 3 4 5 6 7 8 9 10

No knowledge Very Informed

11) I believe this application will help female patients who are HIV+ better understand the correlation and risks of obtaining cervical cancer? *

1 2 3 4 5

I strongly disagree I strongly agree

12) I feel the calculated risk correlation algorithm of contracting cervical cancer, given the input variables, was accurate in its assessment. *

1 2 3 4 5

Strongly disagree Strongly agree

13) If you feel the risk correlation algorithm was not accurate, please explain why.

14) Did you find the sample education section within this application as helpful to change patients' habits that increase prevention of cervical cancer? *

1 2 3 4 5

Not helpful Very helpful

15) Is the design of application easy to navigate? *

1 2 3 4 5

I found difficult to navigate within the application Very easy to navigate

16) Is the design of application easy to navigate? *

1 2 3 4 5

I found difficult to navigate within the application Very easy to navigate

17) Did you encounter any errors or bugs in the application? *

Yes

No

18) If yes to the previous question, please explain which bugs or errors you had.

19) What recommendations or alterations would you suggest to improve the application?

20) Estimated time you conducted in evaluating this application. *

21) I feel this application will help improve patients' attendance in their follow up clinical appointments. * .

1 2 3 4 5

Strongly agree Strongly disagree

22) I feel this application will help patients induce preventive measures against cervical cancer.

1 2 3 4 5

Strongly agree Strongly disagree

23) Over all, how would you rate this application? *

Very unsatisfied

Unsatisfied

Average

Satisfied

Very satisfied

Other:

A.1.2 Avaliao do aplicativo mvel para ajudar a determinar o risco de cncer cervical em mulheres com HIV+.

1) Qual o seu nome?

2) Qual o seu email? (Dessa forma ns poderemos entrar em contato com voc a respeito de mudanas e melhorias deste aplicativo.)

3) Qual a sua atual posio ou ttulo? *

4) H quanto tempo voc trabalha na rea da sade? *

Menos de 1 ano

15 anos

6-10 anos

10-15 anos

Mais de 15 anos

5) Com que frequncia voc usa aplicativos em seu smart phone? *

1 2 3 4 5

Nunca Todos os dias

6) Seu smart phone contm aplicativos voltados para a sade? *

Sim

No

7) Se sim para a pergunta acima, com que frequencia voc acessa estes aplicativos voltados para a sade em uma determinada semana?

1 2 3 4 5

Nunca Todos os dias

8) Voc considera aplicativos voltados para a sade teis para diagnsticos, tratamento e preveno? *

1 2 3 4 5

No til Muito til

9) O quo importante a autoadministrao da sua sade para voc? *

1 2 3 4 5

No importante Extremamente importante

10) Antes de usar este aplicativo, em mdia, como voc avaliaria o conhecimento do seu paciente da correlao entre mulheres com HIV+ e cancer cervical? *

1 2 3 4 5 6 7 8 9 10

Sem conhecimento Muito informado (a)

11) Acredito que este aplicativo ir ajudar pacientes femininos que so HIV+ a entender melhor a correlao e riscos de se obter cncer cervical. *

1 2 3 4 5

Discordo profundamente Concordo profundamente

12) Eu acho que o risco calculado do algortmo de correlao de contrair cncer cervical, dadas as variveis de entrada, foi preciso nesta avaliao. *

1 2 3 4 5

Discordo profundamente Concordo profundamente

13) Se voc acha que o risco de correlao do algortmo no foi preciso, por favor explique o porqu.

14) Voc acha que a mostra na sesso de educao neste aplicativo foi til para mudar os hbitos dos pacientes para aumentar a preveno de cncer cervical? *

1 2 3 4 5

No til Muito til

15) O projeto do aplicativo fcil para navegar? *

1 2 3 4 5

Eu achei difcil de navegar no aplicativo Muito fcil para navegar

16) Voc encontrou erros ou defeitos no aplicativo? *

Sim

No

17) Se sim para a questo anterior, por favor explique quais erros ou defeitos voc teve.

18) Quais recomendaes voc sugeriria para melhorar o aplicativo

19) Tempo estimado voc conduziu em avaliar este aplicativo. *

20) Eu acho que este aplicativo ir ajudar a melhorar o comparecimento dos pacientes na consultas clnicas de reviso. *

1 2 3 4 5

Concordo profundamente Discordo profundamente

21) Eu acho que este aplicativo ir ajudar os pacientes a induzir medidas preventivas contra o cncer cervical.

1 2 3 4 5

Concordo profundamente Discordo profundamente

22) No geral, como voc avaliaria este aplicativo? *

Muito insatisfeito

Insatisfeito

Mdio

Satisfeito

Muito satisfeito

Other:

Appendix B

B.1 Application Tutorial

This is the 13 pages application. The application is formed in 4 steps, Registration and Log in, Personal Information, Algorithms and Calculation. The user can click the application to launch. The first section will allow users to register and log in. In registration, users should enter name, username, e-mail and password. After completing registration, users will be allowed to log in the app by log in button. After log in, users are asked to fill personal information includes patients clinic id in step two, so that it would be easy to track patients by clinicians. In the third step, users will need to check the appropriate check boxes and radio buttons of their habits and test results for algorithms. By clicking next button, users are allowed to pass next pages. If users are not sure about what they checked, the application allows to go back and change the variables.

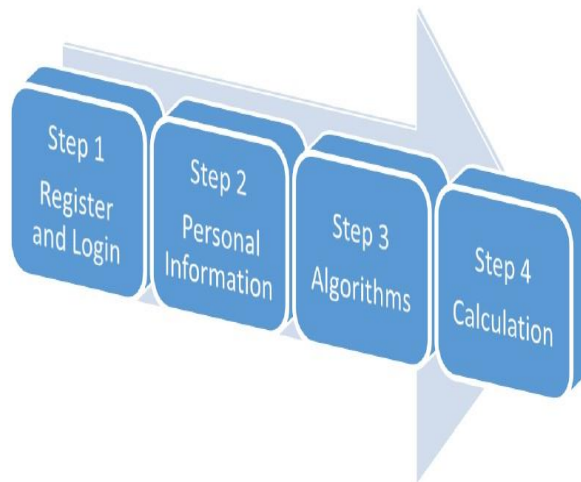
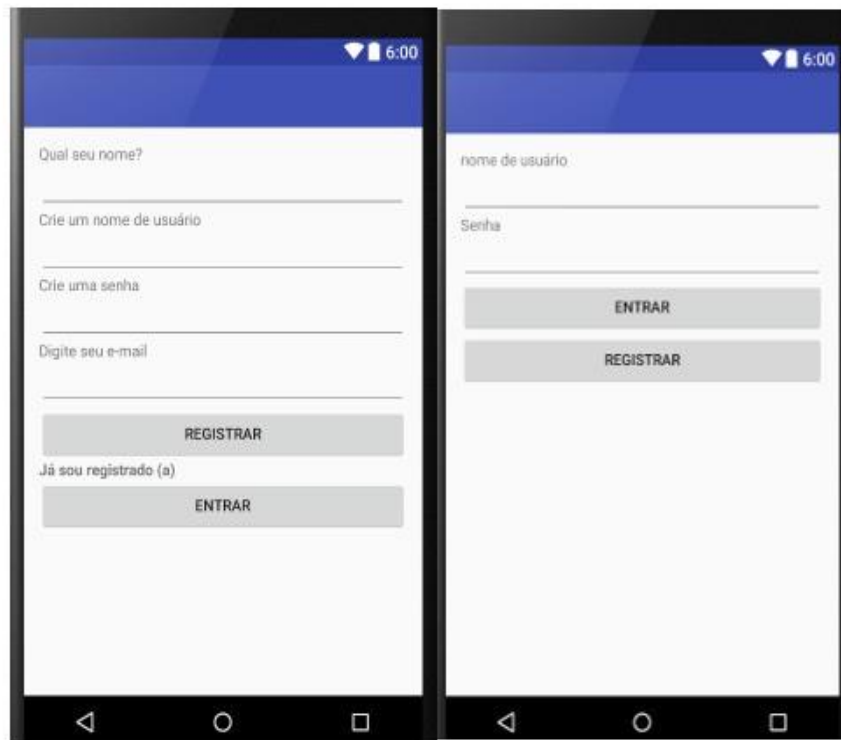


Figure B.1: Application Progress

In the last step, all variables are completed and it will allow to calculate. When the users click the calculate button, they will see the risk percent of cervical cancer. After completing and seeing result, they can log out by log out button. We arranged the risk score classification for users. Since users could be afraid of high or medium percentage, it will just be allowed to seen by clinicians.



Registration and Login

Figure B.2: Picture of The Application's Login and Registration Pages

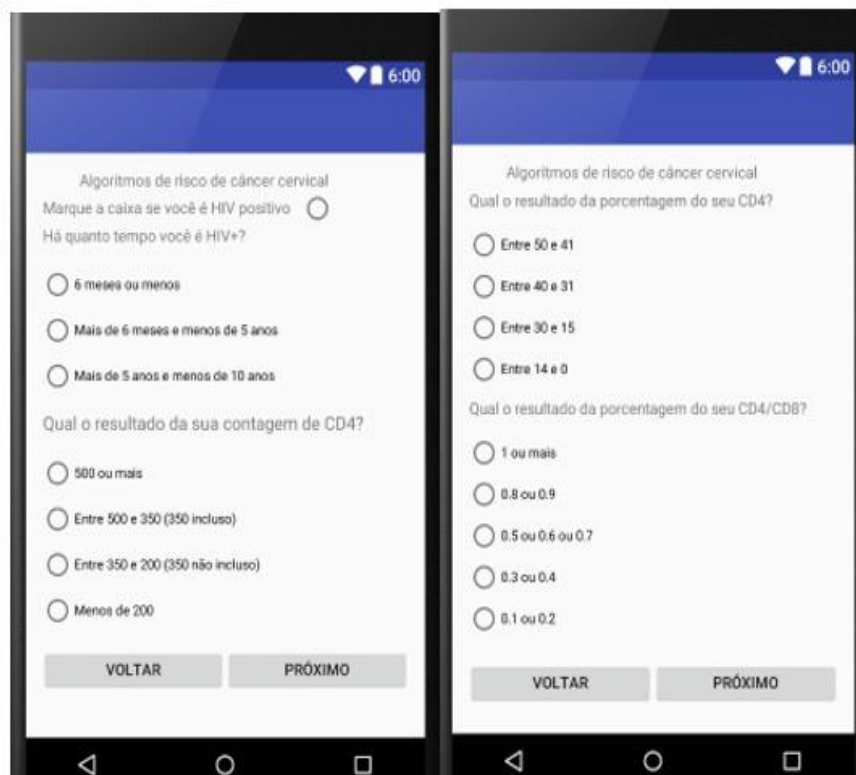
B.2 Disclaimer

This application is currently a prototype aimed at displaying accurate risk scores for HIV+ women and their potential in contracting cervical cancer. Future versions of the application will include features such as health education customized for the patients health needs, appointment scheduling, and uploading capabilities to the patients Personal Health Record (PHR).

A screenshot of a mobile application interface for entering personal information. The screen has a blue header bar with a white status bar at the top showing signal, battery, and time (6:00). The title 'Informações pessoais' is centered below the header. The form contains five input fields with labels: 'Data de nascimento', 'Qual é a sua idade?', 'Qual é o seu gênero?', 'Telefone', and 'Endereço'. At the bottom of the form are two buttons: 'VOLTAR' and 'PRÓXIMO'. The device's navigation bar is visible at the very bottom.

Personal Information

Figure B.3: Application's Personal Information Pages



Algorithms

Figure B.4: Application Algorithms Page



Calculation

Figure B.5: Application Calculation Page

Appendix C

C.1 Study Education

C.1.1 Education of Cervical Cancer Reduction

- 1) You can reduce your risk by regular HIV treatment.
- 2) You can prevent sexually transmitted diseases using condom for every sexual activity.
That way it can help reduce the risk of cervical cancer.
- 3) Multiple sexual partners increase the risk. If you do not have multiple sexual partners, the risk will reduce.
- 4) Drinking alcohol is related to cervical cancer. If you drink 4 or more times in a month, your risk of contracting cervical cancer will double. Lowering the amount, will help to reduce this risk.
- 5) Smoking triggers all kinds of cancers. Long term smokers have 5 times more risk of cervical cancer. Cutting smoking would be the most significant factor in helping to reduce the risk of cervical cancer.
- 6) Needle and drug use will cause unhealthy habits, and the transmission of HIV and other STIs with the use of injectable drugs. To protect your health, you need to avoid drugs and needle use.
- 7) Having sex before the age of 18 is found to 4 times more risky to your health. To best protect your health status, women should not start sexual activity until the age of 25.

- 8) A sexual partner's habits are related to the risk of contracting cervical cancer, since every risk can be transmitted sexually from partner to partner. This is why, partners are suggested to be in a monogamous relationship.
- 9) Long term (5 or more years) oral contraceptive use will cause undulate in hormones which will increase the risk of cervical cancer. That is why, women should use other types of contraceptive use.
- 10) Sex during menstruation can increase the risk of cervical cancer, that is why it should be avoided.
- 11) The use of sexual devices and objects could increase the risk of cervical cancer.
- 12) Having 4 or more pregnancies may increase your risk of cervical cancer, since giving birth could cause cervical zone enlargement. That is why, women are suggested to have less than 4 pregnancies.
- 13) Women having anal sex may be doubling their risk of cervical cancer. Attention to good hygiene and protection is suggested to reduce this risk.
- 14) All sexually active women are suggested to have regular screening every 6 months to prevent cervical cancer.
- 15) According to the CDC Centers for Disease Control and Prevention, all children who are 11 or 12 years old should get the three-dose series of HPV vaccine to protect against HPV. Young women can get HPV vaccine through age 26.

16) Women need to be conscious of their vaginal health. It is suggested that they receive regular screenings to ensure they have no cervical lesions.

17) Women who are not having their period regularly should consult their physician, as this could be a symptom of cervical cancer.

C.1.2 Educao para reduo de cancer cervical

1) Voc pode reduzir seu risco com o tratamento regular para HIV.

2) Voc pode prevenir doenas sexualmente transmissveis usando camisinha em todas as atividades sexuais. Dessa maneira, pode ajudar a reduzir o risco de cncer cervical.

3) Mltiplos parceiros sexuais aumentam o risco. Se voc no tem mltiplos parceiros sexuais, o risco ir diminuir.

4) O consumo de lcool est relacionado com cncer cervical. Se voc bebe 4 ou mais vezes em um ms, seu risco de contrair cncer cervical ir dobrar. Baixando a quantidade ajudar a reduzir o risco.

5) Fumar pode causar todos os tipos de cnceres. Fumantes de longo prazo tem 5 vezes mais chance de cncer cervical. Parar de fumar seria o fator mais significativo para ajudar a reduzir o risco de cncer cervical.

6) Agulha e uso de drogas causam hbitos no-saudveis, podendo transmitir HIV e outras DSTs com o uso de drogas injetveis. Para proteger a sua sade, voc precisa evitar o uso de drogas e agulha.

- 7) Ter sexo antes dos 18 anos considerado 4 vezes mais perigoso para a sua sade. Para proteger melhor a sua sade, mulheres no deveriam comear atividade sexual at os 25 anos.
- 8) Os hbitos do parceiro sexual esto relacionados ao risco de contrair cncer cervical, j que cada risco pode ser transmitido de um parceiro para outro. Por isso que parceiros so orientados a estarem em um relacionamento monogamo.
- 9) O uso de contraceptivo oral a longo prazo (5 anos ou mais) pode causar variaes nos hormnios, o que pode aumentar o risco de cncer cervical. Por isso que mulheres deveriam usar outros mtodos contraceptivos.
- 10) Sexo durante a menstruao pode aumentar o risco de cncer cervical, por isso deve ser evitado.
- 11) O uso de dispositivos e objetos sexuais podem aumentar o risco de cncer cervical.
- 12) Tendo 4 ou mais gravidezes podem aumentar seu risco de cncer cervical, j que dar luz poderia causar um alargamento da rea cervical. Por isso mulheres so aconselhadas a terem menos de 4 gravidezes.
- 13) Mulheres que praticam sexo anal estariam dobrando o seu risco de cncer cervical. Ateno boa higiene e proteo aconselhada para se reduzir este risco.
- 14) Todas as mulheres sexualmente ativas so aconselhadas a fazerem exames regulares a cada 6 meses para prevenir cncer cervical.

15) De acordo com o Centro de Controle e Prevenção de Doenças, todas as crianças de 11 ou 12 anos deveriam tomar a série de 3 doses da vacina contra o HPV para se protegerem. Mulheres novas podem tomar a vacina contra o HPV até os 26 anos.

16) Mulheres precisam estar atentas a respeito da sua saúde vaginal. aconselhado que elas passem por exames regulares para ser certificado que elas não têm lesões na região cervical.

17) Mulheres que não estão menstruando de forma regular devem consultar o (a) seu (sua) médico (a) pois este poderia ser um sintoma de câncer cervical.

Appendix D

To create application, we used Android Studio which has version 23. JSON has been used to retrieve data in our javaclass. It is known as an independent data exchange format [101]. This was the best way to progress our XML le to obtain what we wanted to do. Firstly, we identified our algorithms in the JSON data. After that, we created a class of JSONObject and string values containing specified JSON data to parse the object of JSON.

We have a webserver, and we wanted to access it from our android application to get results. We used XAMPP to create a local web server. Everything is needed to set up our web server is included in it. That is why, we decided to use MYSQL as a database at the webserver and PHP is used to help with JSON to fetch data from the database. Our application communicates with the PHP page with necessary parameters and PHP contacts MYSQL database and fetches the result and return the results to us.

```
<?php
include_once 'database.php';

$id= $_GET['id'];
$hpvstatus = $_GET['hpvstatus'];
$hpv16 = $_GET['hpv16'];
$hpv18 = $_GET['hpv18'];
$doublehpv = $_GET['doublehpv'];
$shivrna = $_GET['shivrna'];

$databaseObject = new DatabaseLayer();
$databaseObject->insertUpdatePageSeven($id, $hpvstatus, $hpv16, $hpv18, $doublehpv, $shivrna);

?>
```

Figure D.1: One of PHP Sample Codes of Our Application