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Evaluation of Pap smear test role in the detection of cervical lesions among West Bank females and the risk factors associated with them

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Dedication

To my father soul

To my great mother for her prayers

To my sisters and brother

To all my friends

Declaration

I certify that this thesis submitted for the degree of Master in Public Health is the result of my own research, except where otherwise acknowledged, and this (or any part of the same) has not been submitted for a higher degree to any other university or institution.

Signature: …….
Nancy Fawzi Abdallah Falah
Date: 5/5/2019

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First of all, I am grateful to God (Allah) who enlightened my way in choosing this particular issue for my thesis. Without God‘s guidance and will, I would not be able to do this work and endure all the obstacles and difficulties I encountered throughout my work. Thank you God.

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Abstract

Background: Globally cervical cancer is the fourth most common cancer in women, and is considered a highly preventable disease if precancerous lesions are detected and diagnosed before they progress to malignancy.

Palestine lack accurate or rare epidemiological statistical data on cervical lesion but it is estimated that the annual incidence of cervical cancer is 2.4 per 100,000.(Feraly et al,2014) Cervical lesion researches in Palestine have been neglected and the Palestinian health system has not been committed to the cervical screening program, despite the fact that it is a highly preventable disease and multiple modifiable risk factors play a role in increasing its incidence, but unfortunately, few studies about cervical lesion factors were done before in Palestine

This study could be a baseline for decisions makers to develop a national strategy that can help in preventing precancerous and cancerous cervical lesions

Aim & Objectives: This study aims to determine the role of Pap smear screening in the detection of various cervical lesions among Palestinian women. The objective of the study is to determine the associations between the various socio-demographic, reproductive health , participant health status, family history of malignancy, and life style behavior factors as smoking, with the risk of developing different cervical lesions seen as different positive findings in Pap smear test, and by that determine the effectiveness of Pap smear test in detecting cervical lesion.

Study methodology: A cross sectional study design was used. And by using a non-probability convenience sampling method, a 100 female participants from Ramallah governorate were interviewed by the researcher and cervical Pap smears were collected by a Gynecologist and then was tested by specialized pathologist, so three data collection tools were constructed; a face to face questionnaire , a medical form for the use of the physician and laboratory form.

Statistical Analysis: IBM SPSS 23.0 was used for data entry and analysis. Frequencies were calculated for all study variables . Cross tabulation and the significance of Pearson chi-square test or fisher's exact test was used to examine the binary association between dependent and independent variables. Forward logistic regression models comparing odds ratio with confidence interval of 95%. *P-value* < 0.05 was used in the multivariate analysis.

Results: Analysis of the data revealed that Pap smear test was able to detect 82% cervical lesions; 76% were infection, 66% were inflammation, 43% were Candida, 7% were precancerous, 3% were Atypical Sqaumous cell and 2% were Atypical glandular cells.

In multivariate analysis, age at marriage , age at first baby , high parity, oral contraceptives having vaginal infection, cigarette smoking and water-pipe smoking were the risk factors for cervical lesions with an adjusted odds ratio, 7.6 (CI 95%: 2.5-23), 1.9 (CI 95%: 1.1-3.4), 0.28 (CI 95%: 0.11-0.7) , 4.3(CI 95% 1.3-14.2), 30(CI 95% 9.2-50.7), 1.9(CI 95% 1.8-4.1) and 5.6(CI 95% 1.2-26.2) respectively.

Conclusion: The study revealed that Pap smear test is effective in screening and detecting multiple cervical lesions and factors such as age at marriage, age at first baby, high parity, using oral contraceptives use, having vaginal infection and smoking are all associated with increased risk of cervical lesions. Therefore, the study recommendation for policy makers is to adapt a national strategy and screening program for cervical lesion in Palestine.

تقييم دور اختبار مسحة عنق الرحم في الكشف عن مختلف إصابات عنق الرحم من آفات او سرطان، بين إناث الضفة الغربية وعوامل الخطورة المسببة له

اعداد: نانسي فوزي عبد الله فلاح
اشراف: د. غسان بعلوشة

ملخص

خلفية الدراسة: سرطان عنق الرحم عالمياً هو السرطان الأكثر شيوعاً لدى النساء، ويعتبر مرضاً يمكن الوقاية منه بشكل كبير إذا تم اكتشاف وتشخيص وعلاج اللآفات الحميدة التي تسبق المرض الخبيث.

تفتقر فلسطين إلى بيانات إحصائية دقيقة أو حتى لا توجد بيانات إحصائية عن آفة عنق الرحم، لكن يقدر أن معدل الإصابة بسرطان عنق الرحم السنوي هو 2.4 لكل 100،000 شخص. (Feraly et., 2014)

نادرة هي أبحاث سرطان عنق الرحم في فلسطين، ولا يلتزم نظام الصحة الفلسطيني ببرنامج فحص عنق الرحم ، على الرغم من أنه مرض يمكن الوقاية منه بشكل كبير، كما أن عوامل الخطورة المتعددة له القابلة للتحويل تؤدي دورًا في زيادة حدوثه، ولكن للأسف يوجد القليل من الدراسات عن عوامل الخطورة المؤدية لأمراض عنق الرحم في فلسطين.

لذلك تعد هذه الدراسة بمثابة نقطة الإنطلاق الأولى لصانعي القرارات لوضع خطة استراتيجية وطنية يمكن أن تساعد في الوقاية من آفات عنق الرحم المسببة لسرطان عنق الرحم

أهداف الدراسة: تهدف هذه الدراسة إلى تحديد دور فحص مسحة عنق الرحم في الكشف عن آفات عنق الرحم المختلفة بين النساء الفلسطينيات. وكذلك تحديد الارتباط بين مختلف العوامل الاجتماعية – الديموغرافية، والصحة الإنجابية، والحالة الصحية للمشاركين، والتاريخ العائلي للأورام الخبيثة، وعوامل السلوك مثل التدخين، مع خطر الإصابة بآفات عنق الرحم المختلفة التي تظهر على شكل نتائج إيجابية في اختبار مسحة عنق الرحم، والتي تحدد فعالية اختبار مسحة عنق الرحم في الكشف عن آفة عنق الرحم.

منهجية الدراسة: اعتمدت الدراسة تصميم دراسة مقطعية. وباستخدام الطريقة الغير احتمالية لأخذ العينات ، حيث تمت مقابلة 100 امرأة من محافظة رام الله وتم جمع عينة مسحة عنق الرحم لهم من قبل أطباء متخصصين، وتمت قراءة النتائج من قبل أخصائي علم الأنسجة، حيث تم بناء ثلاث

أدوات لجمع البيانات. الأداة الأولى كانت عبارة عن استبيان يعبئ من قبل الباحث، والثانية كانت تقرير طبي يعبئ من قبل الطبيب، والثالثه عبارة عن تقرير مخبري يعبئ من قبل اخصائي الأنسجة.

التحليل الإحصائي : تم إدخال جميع البيانات وتحليلها باستخدام برنامج SPSS-IBM 23. تم احتساب النسب لجميع المتغيرات في الدراسة. من تم تم استخدام اختبار Pearson chi-square لفحص الارتباط الثنائي بين المتغيرات المستقلة والغير مستقلة. ومن ثم تم استخدام نماذج الانحدار اللوجستي لمقارنة نسبة الأرجحية حيث استخدمت قيمة p <0.05 في التحليل متعدد المتغيرات.

النتائج الرئيسية: كشف تحليل البيانات أن اختبار مسحة عنق الرحم تمكن من الكشف عن 82٪ من آفات عنق الرحم. كان 76٪ منهم مصابين بالإلتهابات المعدية ، 66٪ منهم كانوا مصابين بالإحتقان، و43٪ كانوا مصابين بنوع من الفطريات (المبيضة)، 7% خلايا ما قبل السرطانية
في التحليل متعدد المتغيرات، كان العمر عند الزواج، والعمر عند الطفل الأول، وتعدد الولادات، وموانع الحمل، ألإلتهابات المهبلية، وتدخين السجائر وتدخين الأرجيلة عوامل خطورة لآفات عنق الرحم مع نسبة الأرجحية المعدلة، 7.6 ((CI 95٪: 2.5-23)، 1.9 (CI 95٪: 1.1-3.4)، 0.28 (CI 95٪: 0.11-0.7)،
4.3 (CI 95٪:1.3-14.2) ، 30 (CI 95% 9.2-50.7) ، 1.9(CI 95%: 1.88-4.1) و 5.6 (CI 95٪ 1.2-26.2) على التوالي.

الخاتمة: كشفت الدراسة أن اختبار مسحة عنق الرحم فعال في فحص وكشف آفات عنق الرحم المتعددة وأن العمر عند الزواج ، والعمر عند الطفل الأول، وتعدد الولادات ، واستخدام موانع الحمل، الإلتهابات المهبلية كلها مرتبطة بزيادة خطر آفات عنق الرحم لذا، فإن هذه الدراسة توصي صانعي القرار بالعمل على ايجاد استراتيجية وطنية وبرنامج ممنهج للإستصقاءعن آفات عنق الرحم باستخدام مسحة عنق الرحم في فلسطين.

List of abbreviations

ACOG	**American Congress of Obstetricians and Gynecologists**
ACS	**American Chemical Society**
AGCUS/AGC-NOS	**Atypical Glandular cells of undetermined significance**
AOR	**Adjusted Odds Ratio**
ASCP	**American Society for Clinical Pathology**
ASC-US	**Atypical squamous cell of undetermined significance**
ASR	**Age Standardized Rate**
CDC	**Centre of Disease Control and Prevention**
CI	**Confidence Interval**
CIN	**Cervical Intraepithelial Neoplasia**
COR	**Crude Odds Ratio**
CVD	**Cardiovascular Disease**
DALYs	**Disability Adjusted life years**
DHIS2	**District Health Information System 2**
DM	**Diabetes Mellitus**
DNA	**Deoxyribonucleic acid**
EA	**Ethyl-alcohol**
ECA	**Epithelial Cell Abnormalities**
GBD	**Global Burden of Disease**
HCL	**Hydrochloric acid**
HPV	**Human Papilomavirus**
H2O	**Water**
HR	**Hazard Rate**
HSIL / HGSIL	**High- Grade Squamous Intraepithelial Lesion**
HTN	**Hypertension**
IACR	**International Agency for research on Cancer**
IUD	**Intrauterine Device**
Krt	**Keratin**
LSIL / LGSIL	**Low Grade Squamous Intraepithelial lesion**
MOH	**Ministry of Health**
NGOs	**Non-governmental organization**
NIH	**National Institute of Health**
NILM	**Negative for Intraepithelial Lesions or Malignancy**
OCP/OC	**Oral contraceptive pills**
OR	**Odds Ratio**
OS	**Ostuim**
Pap	**Papanicolaou**
PAS staining	**Periodic acid–Schiff staining**
Ph	**Potential hydrogen**
PHC	**Primary Health Directorate**
PV	**Vaginal Examination**
RNA	**Ribonucleic acid**
RR	**Relative Risk**

SCC	**Squamous cell carcinoma**
SC junction	**Squamocoluminar junction**
SIL	**Squamous Intraepithelial Lesion**
SPSS	**Statistic Package for Social Sciences**
STIs	**Sexual Transmitted Infections**
UAE	**United Arab Emirates**
UK	**United Kingdom**
UNRWA	**United Nation Relief and Work Agency**
USPSTF	**United States Preventive Services Task Force**
US/USA	**United State of America**
WHO	**World Health Organization**

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Thesis chapters

This thesis is presented in 6 chapters as follows:

Chapter one: Contains the background of the study, cervical anatomy and metaplesia. Pap smear, Bethesda system, problem statement and study justification, and study aim and objectives.

Chapter two: Includes related data (literature review) of a conducted international, regional and in country studies and researches

Chapter three: Includes the study conceptual framework.

Chapter four: Includes the study area, study methods, population, sampling, and sample size, ethical consideration will also include data collection, processing and analyzing.

Chapter five: Presents the results.

Chapter six: Includes discussion and recommendations.

Chapter One: Introduction

1-1 Background

Globally Cervical malignancy is considered the 4th most common cancer in women, the 2nd most common cancer in female between the age 15-44 years old , and the seventh overall (Burni et al., 2014), it contributes nearly to 8% of all cancers and 12% of all women cancers. However, in developing countries after breast cancer, cervical cancer in women is considered to be the second most prevalent where 85% of the global burden occurs. (Ferlay et al., 2014). However, in 2012 WHO has had estimated the cervical cancer deaths to be 266,000, which was 7.5% of all women cancer deaths (WHO, 2012). In developed countries, cancer in general is considered the leading cause of death among males and females , while in developing countries, is considered the second leading cause of death(WHO, 2008; WHO, 2013; WHO,2018).

While cervical cancer is one of the cancers that can be treated if diagnosed early, it has been noted that in most of the developing countries, cervical cancer presents at its late stages thus making its management difficult(Akinlaja et al., 2014).
As a result, cancer of the cervix in developing countries, has been associated with high mortality and morbidity in women.(Sasco,2000), and according to WHO, in 2015, low and middle income regions have had almost 90% of all 270,000 deaths occurred from cervical cancer (WHO,2015); WHO,2018).

However, developed countries have had decreased the cervical cancer incidence by 70-90% and this decline has been attributed to well established cancer cervix screening programs (Akama et al., 2008). On the other hand, due to limited access to screening services or because these services don't exist at all, developing countries suffer from higher incidence of cervical cancer morbidity and mortality compared to developed countries (Juneja et al.,2007).

Fortunately, Cervical cancer has a 10-20 year lag between cervical precancerous phase and cancerous phase and by that and it is considered to be a highly preventable disease in women and is easily identified by its clinical features in an easily accessible organ (Utoo et al., 2016), therefore, adapting a comprehensive approach of prevention, screening diagnosis, and effective management may reduce the high morbidity and mortality rate of cervical cancer globally (WHO,2014).

Several risk factors determine the occurrence of precancerous and cancerous cervical cancer, but the most common cause is chronic infection with Sexually transmitted infections , especially with one of the oncogenic high risk types of the most common sexually acquired infection , human papillomavirus (HPV) that are acquired early in life for those sexually active (Makuza et al., 2015). However, other contributory factors

include early age at marriage or first sexual intercourse, high parity, multiple sexual partners, contraceptives and tobacco use (Das CR et al., 2014).

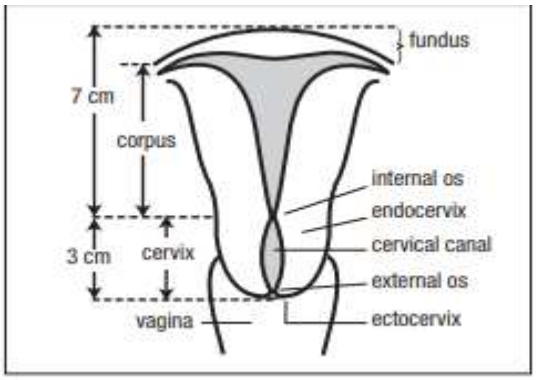
1-2 Cervix

1-2-1 Cervix anatomy :(Figure 1-1)

One part of women reproductive system is the female cervix, which is almost 2.5-3 centimeter long and 2-2.5 centimeter in diameter (Kurman, 1999). It is considered to be the continuous lower narrower (1/2 to 1/3 the uterus length) of the uterus (Gray et al., 1995). It is cylindrical in shape and it connects corpus uteri which is the uterus body, to the vagina through endocervical canal with no junction between the epithelium lining junction the body of the uterus and endocervical canal. The cervix is composed from ectocervix which is the component of bulging of cervix through the anterior vaginal wall and has two lips; one anteriorly and the other posteriorly, it is completely encircled by the vaginal fornix and from cervix supravaginal part that is situated above the cervix (Gray et al., 1995).

However, the vaginal lumen is connected to the uterus body by a central cervical canal, which has two orifices; the internal os and external os (Gray et al., 1995)(Gray et al., 1995). The canal is lined by a 7 to 8 mm fusiform mucosa 3 mm in thick , called endocervix with Pilca palmatae longitudinal ridge anteriarly and arbor vitae oblique ridge posteriorly (Drake at al., 2005), while the ectocervix is covered by the exocervix mucosa (Ovall et al., 2013). The inner mucosal cervical layer consists of; smooth thick muscular layer and at the posterior supravaginal part consist of serosal layer of connective tissue and peritoneum (Gray et al., 1995).

Figure 1.1: Cervix anatomy of a woman of reproductive age



1-2-2 Cervix histology: (Figure 1-2)

However, huge portion of the cervix consist of fibromuscular canal garmented by either columnar epithelium cells or squamous epithelial cells. The mucosa of the endocervical portion is garmented with one layer of columnar epithelial mucosal cells, and the underlying lamina propria has many mucosal tubular glands that are responsible for the

shedding alkaline viscous mucus into the cervical lumen. However, in a cross sectional view, the epithelium has multiple ring like shapes that look like clefts or glands and the mucosa is leaned on an ill defined layers of cells (Gray et al., 1995).

In contrast, nonkeratinized sqaumous stratified epithelium cells covers the ectocervix, that could be indigenous or metaplasti (Gray et al., 1995), and resembles the squamous epithelium lining the vagina (Beckman et al., 2013).

Moreover, the SC junction is the area were columnar epithelial cells and sqaumous epithelial cells assembled and is lined by cytokeratin 7 + non-stratified cuboidal cells that due to the increase effect of the hormone estrogen and the bacterial vaginal flora growth can cause metaplastic replacement of columnar epithelial cells to sqaumous epithelial cells, producing new squamo-columnar junction. Moreover, multiple studies concluded that this site of SC junction is the origin of the population of the embryonic cells that are responsible for cervical changes (microglandular hyperplasia and metaplasia), and are the cell origin for precancerous and cancerous cervical lesions (Beckman et al., 2013)(Herfs et al.,2013). (Figure 1-3). Underlying both types of epithelium is a connective tissue lamina propria with tough layer of collagen (Deakin et al., 2006). During menstrual cycle, the endocervix mucosa is not poured out (Gray et al., 1995). The cervix contains huge number of collagen and elastin fibrous tissue more than the other parts of the uterus (Gray et al., 1995).

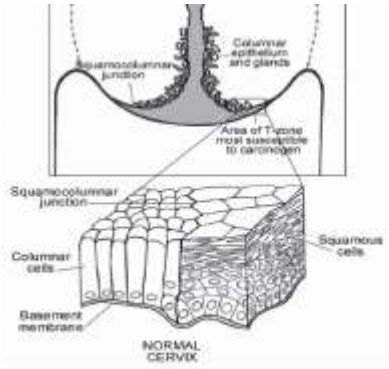
Ectropion or the transformation zone is the production of metaplastic regenerative changes between the native and new SC junction, where more than 90% of dysplasia and squamous cell carcinomas occurs.

The cellularity of the cervix includes, reserved basal cuboidal to low columnar cells obtained from SC junction cells with few oval nuclei and cytoplasm, mature eisonophilic cytoplasm, low weight molecular keratin and estrogen hormone receptors, no high weight molecular keratin (Herfs et al.,2013).

Furthermore, the cervix has different quantities of glycogen in its supra-basal cells that can be detected by iodine in Lugol-Schiller's exam or by PAS stain (Herfs et al., 2013).

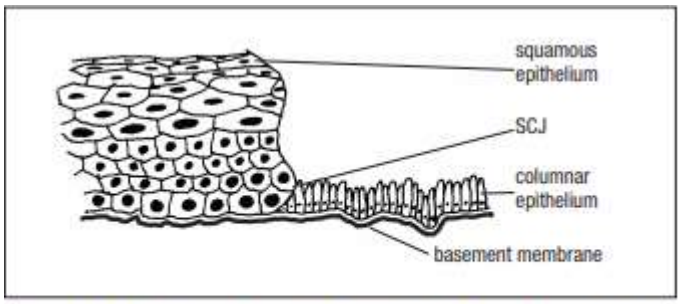
Estrogen is produced by the ovaries during menarche this causes vaginal and cervical mucosa to regenerate glycogen, which promotes endogenous microorganism growth in the vagina , causing lowering in vaginal pH by increasing the production of acids; causing the proliferation of reserved Basel cells, leading to metaplasial changes and overgrowth of squamous epithelial cells in relation to columnar cells and by that forbidding the opening of crypt causing Nabothian cysts.

Figure 1.2: Cervix histology



Source: Blumenthal PD, McIntosh N. Cervical cancer prevention guidelines for low-resource settings. Baltimore (MD): Jhpiego; 2005.

Figure 1.3: The squamocolumnar junction (SCJ) cervical epithelial cells

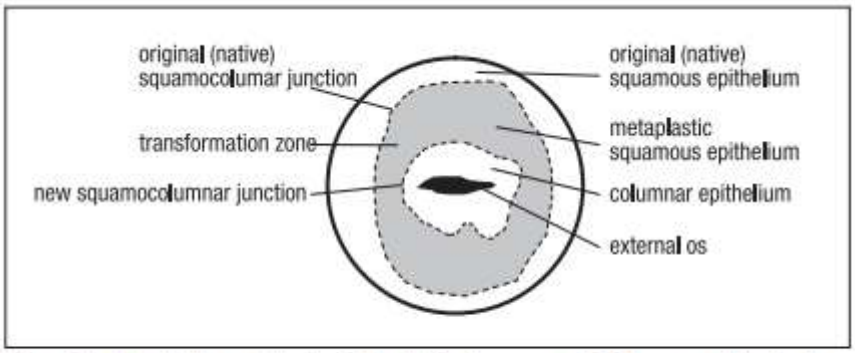


Source: Adapted with permission from Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: International Agency for Research on Cancer; 2003.

1.3 Cervical metaplasia (Figure 1-4)

A non-neoplastic change of one kind of mature cell to a completely another kind of mature cell that is not present at that site in normal situation is called metaplasia. The most common metaplastic changes of endocervical epithelium are squamous metaplasia. . Cervical metaplasia is considered a physiological change; however, it could be pathological as non-malignant transformation of respiratory epithelium into squamous one due to dust or smoke severe exposure.

Figure 1.4: Cervical transformation zone of a female at her reproductive age



Source: Reproduced with permission from Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners' manual. Lyon: International Agency for Research on Cancer; 2003.

1.3.1Site

Sites of metaplasia mostly at the squamocolumnar junction, as well as, prolapsed decubitus ulcer, etc.

1.3.2 Patho-physiology

The endocervical reserve sub-columnar epithelial cells differentiate, proliferate and change into squamous epithelial cells, and at the squamo-columnar junction they become the progeny of embryonic cells, that has "top-down" pattern of differentiation and become more susceptible to sexually transmitted infections, mainly with high-risk HPV that may cause neoplastic changes on the future

1.3.3 Etiology

Cervical infection with STIs, cervical trauma or explored to chronic irritation can stimulate metaplastic changes or it could be the effect of the iatrogenic cause, for example; cryosurgery.

1.4 Papanicolaou (Pap) smear test:

The Papanicolaou smear test (Pap or cervical smear test) is a histological multichromatic staining technique established by George Papanikolaou, a Greek medical doctor , it is a screening procedure to detect precancerous and cancerous lesions of cervix. Followed by more specific and sensitive diagnostic tools and procedures for those with abnormal findings, so as to start early interventions to precancerous lesions to stop progression to cervical cancer (Pathology, 2011).

However, in Pap smear test, a fixed alcohol preparation is used, rather than air fixed preparation, because it has the ability to provide more effective nuclear information. Its classical form involves; five dyes in three solutions that cause blue to green staining to the ribosomes, especially mesothelial, para-basal and squamous metaplastic cells, as well as, staining inactive metabolic cells, for example; superficial cells, also it cause orange staining to thick keratinized cells either benign or malignant. But in order to prepare a successful staining, the technicians must perform a quick staining because of the inadequacy of dried air smears (Pathology,2011).

Furthermore, to collect the Pap smear sample from the cervix, a device called speculum must be inserted into the vagina, so as to open it, then cells from the transformation zone, at the outer cervical opening, where the inner endocervical glandular cells fuse with the outer cervical squamous cells are collected. Then these sample cells are placed and examined, for any abnormalities, using an electronic microscope.

The Pap smear staining test goal is to find any precancerous and cancerous cervical cell changes, for example; cervical dysplasia or CIN (cervical intraepithelial neoplasia) and SIL(sqaumous intraepithelial lesions), caused by HPV sexually transmitted DNA virus infection .Furthermore, the test is considered a widely used, effective procedure for precancerous and cancerous cervical cancer early detection, as well as, good method to detect any inflammation, infection, endometruim and endocervical abnormalities (Pathology,2011).

In the USA, cervical Pap smear screening protocols recommends that sexually active and non-sexually active females around the age of 21 years must start screening until 65 years of age , where as non-sexually active female is not recommended to perform Pap smear test in many other countries (Moyer, 2012). Frequency guidelines for performing cervical Pap smear test vary from 3-5 years (Moyer, 2012) (Saslow et al., 2012) (ACS, 2010). Abnormal results must be repeated in 6-12 months according to the type of abnormality (ACOG, 2009). However, the female patient must be referred to do more detailed colposcopy investigation for the cervix, if the abnormality require more investigations, or referred to do HPV DNA testing which can be routinely done as an adjunct to cervical Pap smear testing, or other evolving biomarker tests available for cervical cancer detection (Shidam et al., 2011).

1.4.1 Pap screening:

Guidelines for cervical Pap smear screening differ from country to country. In general, cervical Pap smear screening must begin at the age 20-25 years old and may be repeated in a frequency of 3-5 years interval, as long as there is no abnormal findings in the test, until the age 50-60 years old (Arbyn et al., 2010, Strander 2009).
The Pap smear screening test should be performed a few years after the female has had her

first sexual intercourse and shouldn't start screening for those less than 20 years old (some countries don't perform Pap smear screening test till the age of 25 or later)

HPV positive women mostly acquire the viral infection after becoming sexually active. And it requires an average of one to four years to overcome the infection by the women immune system (ACS, 2010). Moreover, during this period, a cervical Pap smear test may detect the repair done by the immune reaction as a mild abnormality , which is normally not associated with precancerous or cancerous cervical lesions , but may increase women stress and drive them to do further tests and try different kind of treatments. Cervical cancer usually takes time to develop, so delaying the start of screening a few years causes little risk of missing a potentially precancerous lesion (Sasiani et al., 2009). On the other side, minor benefits would occur from screening females who have never had sexual contact. For instant, the USPSTF guidelines recommendation is not to start Pap cervical smear screening until at least 3 years after first sexual intercourse.

Frequency of cervical Pap smear screening vary; from 3-5 years for females with no abnormal Pap smear results (Arbyn et al., 2010). Previous recommendations suggested every 1-2 years but there has been no evidence base benefits from such frequent Pap cervical smear screening. Instead of that, frequent screening procedures, had been reported to be costly and are followed by multiple, unwanted procedures and managements (Saslow et al., 2012). Therefore, it has been concluded that decrease frequency of screening has been a better choice for public health (Smith et al., 2002). Other guidelines depend on female age to determine frequency of cervical Pap smear frequency. For example; in Great Britain, screening for those less than 50 years of age is performed every 3 years, while those 50 years old and above every 5 years.

Guidelines recommended that Pap cervical smear screening procedures must stop around the age of 65 years, unless there have been an abnormal findings or diseases in previous screening tests. Also that, there is no benefits from screening females at 60 years of age or above, with no documented previous positive Pap smear test.(Sasiani et al 2003). According to the guidelines from USPSTF, ACOG, ACS and ASCP any female with negative three Pap smear test should stop screening at the age of 65 years old (Saslow et al., 2012). Moreover, after total hysterectomy for benign lesions or diseases, there is no benefits from continue cervical Pap smear screening.

Furthermore , for those that have been vaccinated for HPV infection, cervical Pap smear screening is still a recommendation (Arbyn et al., 2010), since not all cervical cancer causing strains of HPV are been covered by the vaccination, and previously exposed females to HPV are not covered by the vaccination.

Endometrial cancer female patients should stop routine cervical Pap smear screening tests (ACOG, 2009). Recurrence of cancer are unlikely to be detected by screening but may cause increase risk of false positive results ,that urge people to seek more unnecessary investigations (Salani et al., 2011).

However, if Pap cervical smears screening results showed abnormal findings, or after positive biopsy results or after cancer treatments, more frequent cervical Pap smear screening tests must be performed. (see table 1.1)

Table 1.1: Indication for Pap smear screening

Evidences for screening indications		
Futures and characteristic	**Recommendation**	**Reasons**
Female who has never had sexual intercourse	No need to do Pap smear screening test	HPV infection is transmitted by sexual intercourse (Strander, 2009)
Female age <20, no irrespective to her sexual history	No need to do Pap smear screening test	Pap smear testing causes harm effects more than benefits (Apgar et al., 2003)
Female from 20–25 years of age till 50–60 years of age	If Pap smear test results are normal repeat test every 3–5years	General recommendation(Arbyn et al., 2010)
Female above 65 years of age and with no abnormal previous findings	No need to do further Pap smear screening test	USPSTF, ACOG, ACS and ASCP recommendations (Strander 2009)
Female who have had had total hysterectomy with cervical removing for disease other than cancer	No need to do further Pap smear screening test	Post hysterectomy screening have more harms than benefits (Arbyn et al., 2010)
Female who have had partial hysterectomy with no cervical removing	Testing should be continued as normal females	
Female has been vaccinated with HPV vaccine	Testing should be continued as normal females	Not all strains of HPV are covered by vaccination (Arbyn et al., 2010)
Female with positive history for endometrial cancer	Stop routine testing	Ineffective screening test with more chance of false positive(Salani et al., 20011)

1.4.2 Effectiveness

An effective combined program of cervical Pap smear testing, referral and follow up can reduce 80% of deaths from cervical cancer (Arbyn et al., 2010).

However, many reasons can cause the failure in preventing cervical cancer by Pap smear screening test, for example; irregular screening, no follow-up for abnormal findings, and errors in sampling and analysis (Deny 2007). More than 50% of invasive cervical cancer in the USA occurs in women whom in their life have never performed a cervical Pap smear screening test, and those whom never have had a cervical Pap smear screening in previous five years accounts for 10 to 20% of invasive cervical cancer cases. Approximately, 25% of invasive cervical cancers in the USA occurred in females who were not appropriately followed up (no referral, no return for follow up or the right care and management were given to them).

Pap cervical smear screening test was not reported to stop cervical adenocarcinoma occurring. For example, cervical adenocarcinoma accounts for 15% of all cases of cervical cancer in the UK, despite the effective cervical Pap screening program (Deny 2007). However, the effective screening program in the UK can prevent approximately 700 deaths from invasive cervical cancer deaths. One death from cervical cancer can be prevented each 38 years from 200 cervical screening test done by medical physician and despite the effective screening, one female during the 38 years at least might die from invasive cervical cancer (Raffle et al., 2003). Furthermore, around 15-20 million of the 61 million UK population might receive Pap smear screening, allowing the saving of one female out of approximately 20,000 tested, if yearly 15,000,000 women have been investigated, but if yearly 10,000,000 women have had a cervical Pap smear screening test one life would be saved if about 15,000 women investigated.

1.4.3 Results

Generally, Pap cervical smear screenings are negative in populations with low risk of cervical cancer. For example, 2-3 million abnormal results of cervical Pap smear are found in the USA annually. (Salani R et al., 2011), most of these abnormal Pap smear results (2-5%) have mild abnormality; ASC-US or (2% of results) low-grade squamous intraepithelial lesion (LSIL).

Although, spontaneously resolved HPV infection is the cause of almost all cervical low grade dysplasia; dysplasia must be considered a warning sign that has to be additionally investigated and followed up .

Approximately , 0.5% of positive cervical Pap smear screening results are high-grade SIL (HSIL), about < 0.5% of them are cancerous lesions , and almost 0.2 -0.8% of Pap smear screening positive results are AGC-NOS (Eversole et al 2010).

1.5 Bethesda classification system:

Bethesda system has been used to report abnormal cytological cervical or vaginal diseases in Pap cervical smear screening tests (Nayer et al., 2009, Apgar et al., 2003) . Bethesda system was initiates in 1988, where it contained the following:

SIL (Squamous Cell Lesions)

ASC-US (Atypical Squamous Cells of Undetermined Significance)

ASC-H (Atypical Squamous Cells – cannot exclude HSIL)

LGSIL OR LSIL (Low-Grade Squamous Iintraepithelial Lesion)

HGSIL or HSIL (High-Grade Squamous Intraepithelial Lesion)

Squamous Cell Carcinoma

Glandular Epithelial Cell Abnormalities

AGC or AGC-NOS (Atypical Glandular Cells not otherwise specified) ((Apgar et al., 2003)

Number of other abnormalities such as Yeast, Trichomoniasis, Herpes and other Sexually transmitted infections, endocervical and endometrial lesions can also be detected, and classified according to the Bethesda system. However, this system is not so sensitive for detecting multiple infectious lesions, so negative results for infection in Pap smear does not exclude infection (Nayer et al., 2009).

1.6 Study problem

Cancer is becoming a main public health problem because of its high incidence, and mortality, and has a high burden on the health system especially in developing countries such as Palestine. Cervical cancer etiology is complex, and multi-factorial, with precancerous phase of 10 to 20 year apart between precancerous and cancerous cervical cancer. Unfortunately, few local studies (at least four studies between the years 1990-2000) have been concerned with studying the effect of Pap smear screening in decreasing mortality and morbidity from cervical lesions; especially cancer as well as studying the determinants of cervical lesions, which makes it a rich area for research in Palestine. Therefore, studying Pap cervical smear screening benefits is very important in improving Palestinian women health, which may be used in developing, polices and determining priorities in public health programs in the future.

1.7 Justification of the study:

Globally, invasive cervical carcinoma is considered to be the fourth most common cancer in female; it contributes nearly to 8% of all cancers. However, developing countries cervical cancer rates accounts for approximately 85% of all worldwide cervical cancer, with a 15.7 Age-Standardized Rate per 100,000. The Caribbean, Latin America and Africa have the highest cervical cancer incidence in the world. Due the expanded use of the Pap cervical smear screening programs in developed countries, cervical cancer rates have been extremely reduced , 9.9 Age-Standardized Rate per 100,000, by that Northern America and Oceania has had the lowest cervical cancer incidence (Ferlay et al., 2014).

In Palestine, the annual mortality rate per 100,000 people from cervical cancer has decreased by 28.3% since 1990, an average of 1.2% a year (Global Health Data Exchange, 2016).

More than 500,000 new cases are diagnosed annually (Utoo et al., 2016).More than 93% of all cervical cancers cases are preventable. Fortunately, precancerous cervical lesions that are detected by the inexpensive cervical Pap smear screening test, which has been used for a long time, can be treated as early as possible to stop progression to cancer. The continuous efforts of Pap cervical pap smear screening caused the significant decrease in death incidence caused by cervical cancer in USA between the year 2008-2010 (National Institutes of Health, 2015).

In 2017, the Palestinian female population were 2.3 million , 28.3% were between 15-64 years of age (PCBS,2017) where as the total number of Pap smear obtained from primary health clinics in Palestinian MOH that covers 58.5% of the Palestinian population, were 484 sample , 7 were positive for Cervical cancer (MOH,2017).

Precancerous and cancerous cervical cancer is believed not to run in families (not hereditary). However, persistent infection with high risk HPV, which is commonly transmitted from person to another through genital skin contact, has been responsible for approximately 99.7% of cases. Approximately 80% (4 out of 5) of adults, who are sexually active, will acquire at least one strain of HPV once in their lives. But fortunately, most of HPV infected females will not progress to precancerous or cancerous cervical cancer, because precancerous and cancerous cervical lesions are rare despite the fact that HPV infection is common (Dilman, 2009).

Early age of marriage or having sexual intercourse, early age at first childbirth, multi-para, weak immune system, consuming oral contraceptive, smoking habits and having multiple sexual partners are considered much less important risk factors for cervical cancer than HPV infection. Typically, it takes 10-20 years for a cervical lesion to progress to cervical cancer, where Sqaumous cell carcinoma accounts for 90% of them, Adenocarcinomas accounts for 10 % of them (National Institutes of Health, 2015).

Cervical cancer usually develop slowly because it is one of the rare cancers that have a precancerous phase, which lasts 10-20 years before progressing to invasive cervical cancer, giving a wide opportunity for early diagnosis and managements. Unfortunately, even it is preventable, most of the cervical cancer cases are diagnosed late; leading to poor outcomes because they do not have a well-established screening system , prevention and management programs , as well as the widespread of gender and cultural barriers (CDC,2014). The understanding of the risk factors for cancerous and pre-malignant lesions of cervical cancer can help establishing an organized screening program for controlling and prevention of cervical cancer among women (Makuza et al., 2015).

Treatment of non-cancerous cervical lesions after early diagnosis of cervical lesion changes using cervical smear screening, can prevent the development of invasive cervical cancer. Cervical cancer screening has been part of a woman's health checkup in many countries worldwide including Palestine.

Since, to date, there have been no published study to exactly identify cervical Pap smear effectiveness in early detection of precancerous cervical diseases in Palestinian female, nor the determinates of precancerous and cancerous cervical cancer. Data on precancerous and cancerous cervical cancer prevalence and associated risk factors between healthy females are extremely helpful to convince policy makers on how to distribute their priorities and to urge them to establish an organized cervical cancer screening programs strategies that aims at female health improvements . However, in Palestine, no study has had documented, the associated risk factors and prevalence, for precancerous and cancerous cervical lesion among healthy females cervical. So, this study will be the baseline for future researches in this field and may help in developing polices and determining priorities in public health programs in future specially in primary level of prevention and control to prevent cervical cancer mortality and morbidity.

1.8 Aim of the study :

To study the role of Pap smear screening in the detection of various precancerous and cancerous cervical lesions among Palestinian women and to asses the risk factors associated with cervical abnormalities.

1.9 Study Objectives:

1. To determine the Pap cervical smear screening test effectiveness in the early detection of pre-cancerous cervical lesions in Palestinian female.

2. To determine the role of cervical Pap smear screening test in detecting clinically significant precancerous lesions and cancer

3. To determine the association between various factors and the risk for developing different cervical lesions .

4. To evaluate the cervical cytological non cancerous lesions that are supposed to be found

1.10 Expected outcomes

Our study is expected to show the efficiency of early cervical lesions detecting screening policies in decreasing incidence of invasive cervical cancer and how this will help in saving many lives with low costs. In addition, it will identify the most common cervical lesions among Palestinian woman.

Also, it will help determine the most important risk factors for cervical lesions among Palestinian females.

Moreover, we hope that these results will be of great values for health policy and decision makers, and could be used in Palestinian health planning and national strategies for controlling cervical cancer.

1.11 Study limitations

Every study, no matter how well it is conducted, has some limitations. Various limitations and obstacles may affect the study. In our study the main limitation was the small number of the studied population and this was caused mainly by the fact that Pap smear screening has not been a part of primary prevention and control strategies in MOH, UNRWA and even NGOs and also caused by the limited awareness of Palestinian females about the importance of early detection of cervical lesions. However, more samples would have been better for the study.

As any cross sectional studies, it was considered inadequate to assess cause and effect relationship, besides that we were not able to measure the risk, instead we studied the outcomes and looked backward to find out the risk or protective factors. Moreover, there may have been some biases which might have affected the results like information bias, recall bias, selection bias, and reporting bias because of the stigma that surrounds some of the risk factors for Cervical lesions. Female compliance was also an important limitation due the stigma associated with this subject

Also we were limited for recourses and time, and since the study included personal experience in detecting physical signs, taking the specimen, doing slide fixation and reading the results, human errors and experience was an important issue.

Chapter Two: Literature review

2-1 Introduction

In this chapter, literature related to the epidemiology of cervical lesion worldwide, in the Arab world and in Palestine will be presented, in addition to literature related to risk factor associated with cervical lesions.

Cervical lesions, including cancer, trends have been depending on the availability of effective screening programs and in the of risk factor profile time changes (Freedman et al., 2007, Vaccarella et al.,2013). Cervical lesion incidence including invasive cervical cancer has decreased in a steady manner over the last few decades in developed countries.

However, the cause of geographic differences in precancerous and cancerous cervical rates among countries , are due to the variation in the availability of cervical lesions screening, which can prevent the development of precancerous and cancerous cervical cancer through early diagnosis and managements of precancerous lesions, and to the variation in the prevalence of human papillomavirus (HPV) infection (Sherris et al., 2001, Formana et al.,2012).

2.2 Cervical cancer epidemiology worldwide:

Cervical carcinoma is considered worldwide as the 4th most common female cancer, and the 7th cancer from all types of cancer, despite the improvements made by using cervical Pap smear screening, in preventing precancerous and cancerous cervical lesions, cervical cancer globally is still considered a critical cause of women death and is a major problem for public health. Worldwide, in 45 countries , cervical cancer is considered the most common female cancer and in 55 countries, it has been causing death more than any other type of cancers among females. This include 22.5% of all female cancers in sub-Saharan Africa, also many cases in Asia (including India), and some countries in South and Central American (Ferlay et al., 2014).

Precancerous and cancerous cervical cancer mortality and incidence rates have declined in many countries in the last 35 years, especially in developed countries (Aryn et al., 2011) including USA (Adegoke et al., 2012) and Canada.(Dickinson et al.,2012, Mosavi et al.,2013) in which they have experienced a huge improvement in socioeconomic status. This is attributed to the adaptation of effective primary and secondary prevention programs , with effective cervical smear screening tools, early detection and early and effective managements for precancerous lesions (WHO,2012). On the other hand, the precancerous and cancerous cervical lesion incidence has

had minor changes in developing countries, except those that have had demographic and epidemiologic transition (WHO, 2009), as 85% of the global burden(9 out of ten) occurs in the low socioeconomic developing regions, where 12% of female cancers is the results of cervical cancer (Tebeu et al., 2013). High-risk regions in the world, with an ASRs estimation of more than 30 cases per 100,000 of the population ,including 42.7% in Eastern Africa, which has been considered the most heavily affected areas , 30.6% in middle and 31.5% in southern Africa and 33.3% in Melanesia. On the other hand, rates have been 5.5% in Australia and New Zealand , where it is considered the lowest and 4.4% in Western Asia and North Africa, Middle East and North Africa (GBD, 2015) . Precancerous and cancerous cervical lesions are still the most common female cancer in Middle and Eastern Africa (WHO,2012).(figure 1-5)

However, mortality rates varies between world regions by 18-fold , ranging from 2 case per 100,00 population of Australia, Western Europe and Western Asia to > 20 cases per 100,000 population of Eastern (27.6) and Middle (22.2) Africa and Melanesia (20.6) (WHO,2012) . (figure 1-6)

However, 485,000 female with precancerous and cancerous cervical lesions were diagnosed worldwide in 2013, causing the death of 236,000 female (approximately 7.5% of all women deaths worldwide) compared to about 528,000 diagnosed in 2012 and 266,000 died, from them, developing countries have 87% of cases and developed countries have 13% of cases. However, 6.9 million DALYs have been caused by invasive cervical carcinoma, 15% of them in developing countries and 85% in developed countries. One female from 70 develops cancerous cervical lesions between birth and 79 years of age and in year 2012 the cumulative risk factor for female <75 years of age was 1.42% worldwide (GBD, 2013, Feraly, 2014).

Furthermore, in 2013, at the following countries; Central African Republic, Zimbabwe, Uganda, Cameroon, Guatemala, Liberia, Nigeria, Somalia Afghanistan, Benin, , Eritrea, Ghana, Sierra Leone, Guinea, Gambia, Guinea-Bissau, Lesotho, Mali, Mauritania, Malawi, Niger, Nicaragua, Senegal, , El Salvador, Chad, Togo and Zambia, cancerous cervical lesions was the most commonly diagnosed female cancer. Also in the same year, at Democratic Republic of the Congo, Senegal, Equatorial Guinea, Togo, Nigeria, Angola, Burundi, Benin, Burkina Faso, Central African Republic, Côte d'Ivoire, Cameroon, El Salvador , Congo, Comoros, Djibouti, Eritrea, Ethiopia, Ghana, Guinea, Guinea-Bissau, , Indonesia, Kenya, Liberia, Lesotho, , Mali, Mozambique, Mauritania, Malawi, Niger, Nicaragua, Papua New Guinea, Paraguay, Rwanda, Sierra Leone, El Salvador, Somalia, South Sudan, Sao Tome and Principe, Swaziland, Madagascar, Chad, Tanzania, Uganda, Zambia, and Zimbabwe cervical cancer was the most common cause of female deaths from cancer (GBD,2013).

The main reason for the difference between countries, is the lack of active, effective organized programs for cervical screening, prevention, early diagnosis, management and program inequity access, within the same population. However, precancerous and cancerous lesions are diagnosed at late stages -where mortality rate is high- if there were no effective screening intervention programs and the treatment is introduced late in the process. However, these results reflect the obvious neglect of this issue by policy makers in low, middle socioeconomic countries, where policy makers are advised to revise their priorities (Ferlay et al., 2014).

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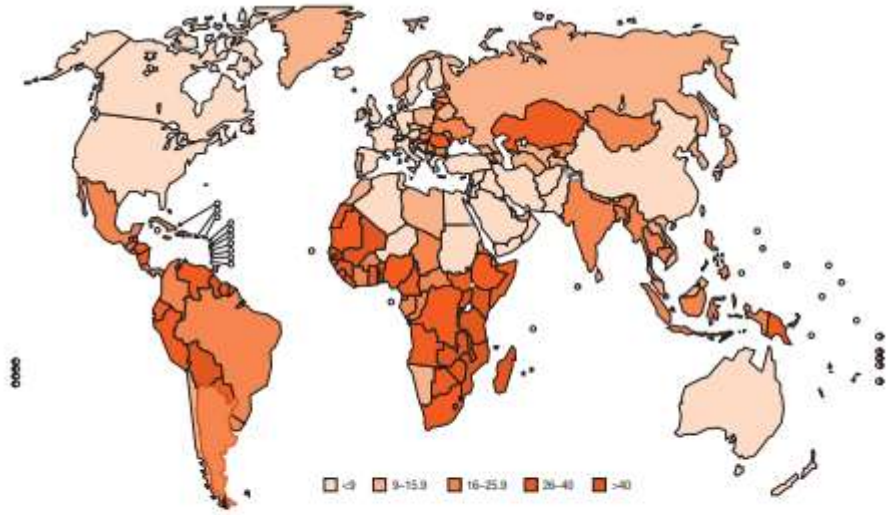
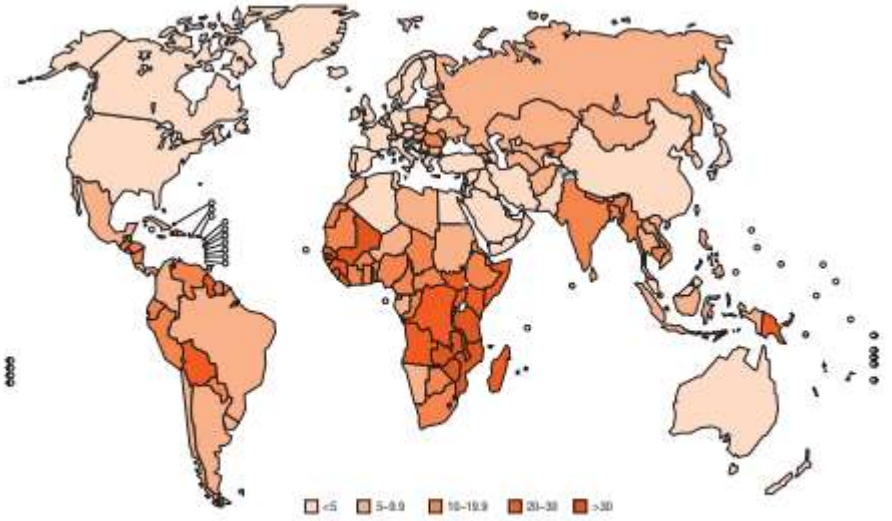


Source: International Agency for Research on Cancer (IARC), World Health Organization (WHO). GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012: cancer fact sheets: cervical cancer. Lyon: IARC; 2014.

Figure 2.1: Year 2012: estimated incidence of cervical carcinoma worldwide.



Source: International Agency for Research on Cancer (IARC), World Health Organization (WHO). GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012: cancer fact sheets: cervical cancer. Lyon: IARC; 2014.

Figure 2.2: Year 2012, estimated mortality rate of cervical cancer worldwide.

2.3 Cervical cancer epidemiology in the Arab world.

Despite the well known cervical cancer epidemiology in many countries in the world, there are few available data in the Middle east including the Arab world.(Mosavi A et al., 2013). Moreover, the incidence of cancerous cervical lesions in the Middle East, is lower than that in developed countries with most cases detected at a late stage (Sancho et al., 2013).

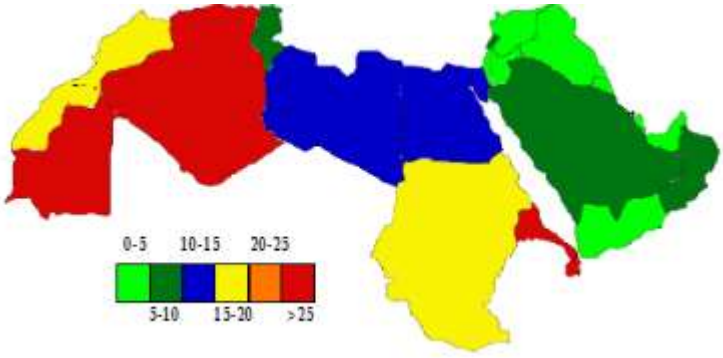
However, the Arab world , stretching from Lebanon and Syria in the north, through to Morocco in the west, Yemen in the south and Iraq in the east, is the home of more than 300 million people, and is considered to be part of developing countries, with a well ongoing effort to develop effective screening and control program for all types of cancer;-including cervical cancer- which in general is considered a major problem with increasing burden on public health due to multiple factors including aging, population growth and changing life style (Salem et al., 2011).

Furthermore, in general, cancerous cervical lesions rates are low in Arab words and do not seem to incline but in frequency is still in second position in Algeria, Tunisia and Oman (Elsayed et al., 2007). Underreporting is a huge issue in the Arab world, for example in Saudi Arabia the reported abnormal cervical Pap smear was 1.6%, which is lower than the results reported in one prospective cohort study that reported a percentage of 4.7% abnormal cervical Pap smears (Altaf, 2006). Adencarcinomas account for about 10% of the lesions (Curdo et al., 2007).

The highest age standardized rates (ASR) among Arab females for cervical cancer was in Algeria with incidence of 11.6 per 100,000 followed by UAE with incidence of 9.8 per 100,000 Tunisia with incidence of 7.1 per 100,000, Bahrain 5.9 per 100,000, Oman 5.3 per 100,000, Qatar 5.1 per 100,000, Lebanon 4.6 per 100,000, Kuwait 4 per 100,000, Yemen 3.1 cases per 100,000 population , while the lowest rate incidence were in Iraq, Saudi Arabia, Jordan, Syria and Egypt , which equal to 2.8, 2.7, 2.6, 2.6, 2.1 per 100,000, respectively (Bazarbashi et al., 2001, Curado et al., 2007,Freedman et al., 2007, Bener et al., 2008) (Feraly et al., 2014). (Figure 2-1)

Unfortunately, Arab health systems have not been committed to precancerous and cancerous cervical Pap smear screening programs, mostly due to the attitudes of the health workers and the stigma that surrounds the risk factors. In a study that was performed in the UAE, of the 98 participants, who were all physicians, only 40% had referred a woman to do pap smear (Badrinath et al., 2004).Moreover, in a survey that was done in Jordan, approximately three-quarters of women didn't know the causes of cervical cancer and 25% of them were unaware of the important effect of positive cervical Pap smear (Maaita and Barakat,2002).

Figure 2-3: Cervical cancer incidence/100,000 in the Arab world



2.4 Cervical cancer epidemiology in Palestine

Accurate or even no epidemiological data on cervical cancer in Palestine is available since the national population-based cancer registry is lacking detailed and important data. However, there is no official statistics from the Palestinian Ministry Of Health concerning cervical cancer, but the Journal of Asian Pacific of prevention and cancer reported in 2009 that the age standardized rates (ASR) in Palestine (including West bank, Gaza Strip and Israeli-Palestinian women) was 2.4 per 100,000, which is considered among the low incidence in Arab world and worldwide, while in 2012 was 2 per 100,000 (Feraly et al., 20014).(table 2-1)

Table 2-1: ASR Cervical cancer incidence\100,000 over time in Palestine

Year	1982	1987	1992	1997	2002	2007	2009	2012
Incidence	2.1	3	2.6	3	2.5	4.5	2.4	2

Muir et al., 1987; Feraly et al., 2014; Parkin et al., 1992; 1997;2002; Waterhouse et al., 1982; Curado et al., 2007, Asian Pacific Journal, 2009,

In Palestine, the annual mortality rate per 100,000 people from cervical cancer has decreased by 28.3% since 1990, an average of 1.2% a year (Global Health Data Exchange, 2016).

The Palestinian health system is not committed to the cervical screening program neither on MOH who covers 58.5% of the population, nor in UNRWA clinics that covers about 41.2% of the population and considers pap smear test an invasive procedures and according to the International UNRWA regulation, invasive procedures are not part of screening programs. Unfortunately, in Palestine there is no established national screening program for cervical cancer. Nevertheless there are scattered efforts of screening in Ministry of Health, and private sector. In 2017, the total No of Pap smear performed in primary health clinics in Palestinian MOH, were 484 sample ,7 were positive for Cervical cancer (MOH,2017).

2.5 Risk Factors for cervical lesions

Most women are unaware of cervical lesions including cancer, its risk factor and the importance of precancerous screening. Multiple associated risk factors for precancerous cervical lesions including cancer have been investigated and some of them have greater importance than others, some factors have had been concluded to be either as cause for or associated with precancerous and cancerous cervical lesion. Such as, socio-demographic, ethnic , age at marriage or age at first sexual contact , number of sexual partners, age at first child birth , contraception, and sexually transmitted infectious agents such as persistent HPV infection , Chlamydia trachomatis and type II herpes simplex , and others (Shields et al., 2004)

HPV infection is known as the most common precancerous and cancerous cervical lesion risk factor and in general the trends of cervical precancerous lesions including cancer follow the trends of HPV infection. Unfortunately, almost all cancerous and precancerous cervical lesions are the effect of high risk HPV infection (CDC,2018).

Exogenous or endogenous factors had been identified to, in conjunction with HPV infection, influence the risk for precancerous and cancerous cervical lesions, HPV infection cofactors may be classified into two categories : (1) exogenous or environmental cofactors, such as lifestyle factor (tobacco smoking habits including waterpipe, consuming of OCPs, dietary factors , multiple sexual partners, high parity) cervical trauma, socioeconomic status and sexually transmitted infections ; for example, infection with HIV, (2) endogenous factors or host cofactors –demographic factors; including endogenous hormones, age, family history , human leukocyte antigen genetic factors, and other host immune factors (Castellsague et al., 2003).

2.5.1 Exogenous factors

2.5.1.1 Sexually Transmitted Infections and risk of cervical lesions

Precancerous and cancerous lesions are not by themselves sexually transmitted disease, but are the consequence of damage from a sexually transmitted diseases. Worldwide, epidemiological and molecular studies have unequivocally shown that the vast majority- almost 99.7% -of precancerous and cancerous cervical lesion cases are caused by persistent infections with some high-risk types of the most common viral STIs of the reproductive tract HPV infection (Dilman, 2009).Most of sexually active adults will acquire HPV infection at least once in their lives- the lifetime risk of contracting the virus is estimated to be 75%-90% (Like et al., 2003) – and many sexual active adults will be infected multiple times and the estimated time of acquiring HPV infection is a short time after first sexual contact. However, most of HPV infections automatically will be cured without causing any symptoms or persistent disease. However, precancerous and cancerous cervical lesions occur from persistent infection with certain strains of HPV agents; mostly with 16 and 18 strains of HPV, and if those lesion were not treated , they may become cancer (WHO,2013).

Moreover, women with sexually transmitted infections other than HPV, such as Chlamydia, gonorrhea, Syphyllis, or herpes, also have high risk of acquiring precancerous and cancerous cervical cancer.

Various studies have had pointed out the significance of sexually transmitted disease in increasing risk for cervical lesions. A retrospective institutional based cohort case control study, that was made in Ethiopia in 2017, showed an association between risk of precancerous and cancerous cervical lesions and STIs (AOR = 2.5; P < 0.015; COR = 2.2; 95% CI 1.18,-4.4) (Kassa,2018).

Another cross-sectional institution based study ,made in Ethiopia in 2016, assessed the association between risk factors and prevalence of precancerous and cancerous cervical lesion between Ethiopian female , concluded that females who have acquired STIs were more exposed to precancerous and cancerous cervical lesion than those free of STIs infection. Moreover, in this cervical lesion screening study campaign, females who were infected with STIs have had fifty folds more likely to acquire precancerous and cancerous cervical lesion than those with no STIs .(AOR=49.9 ; 95% CI: 16.6- 149.9) (Misgina et al., 2017).

Another study done in Southern Ethiopia gave similar results (Gedefaw et al., 2013), in this study, female infected with STIs had higher risk to have precancerous and cancerous cervical lesions as well. Occupation, income level, level of education, age at first sexual contact or age at marriage , multi-parity, lifetime pelvic infection, STI, and multiple of sexual partners were in bivariate logistic regression analysis statistically significant at this study with a P- value =0.2. However, in multivariate analysis, only multiple sexual partners and persistent STIs have had significant statistical association with cancerous and precancerous cervical lesion with P-value<0.05. Additionally, STIs infected females have 2.3 fold increase in risk of having precancerous and cancerous cervical lesions than females with negative history of STIs (AOR=2.3, 95%; CI: 1.2- 4.3) (Gedefaw et al.,2013).

Another unmatched hospital case control based were done study in Addis Ababa in 2018, found significant statistical association between female with STIs and risk of precancerous cervical lesion, with 3 folds increase in risk compared to those with no history of STIs (Adjusted Odds Ratio = 3.20, 95% CI: 1.26–8.10) (Team et al., 2018).

A positive association between genital STIs and precancerous and cancerous cervical lesions was found in a hospital-based control study that made on Turkish women in 2011. This study concluded that women with history of STIs such as Chlamidia, Trachomatis, gonorrhoeae …etc, have had more risk to develop cervical lesion with an OR=5.2 (95% CI: 3.5-7.6) compared with females with no STIs (Nesrin et al.,2011).

However, globally, the most common sexually transmitted infection is HPV , affecting millions of women each year, but only a small subgroup of them progress to precancerous or cancerous cervical lesions (WHO, 2013). However, persistent HPV cervical infection is

necessary for the occurrence of precancerous and cancerous cervical lesion. The reason why some females acquire cervical cancers and many do not, even though they share the status of being infected by HPV, is related to multiple co-factors . However, many co factors for HPV may play a role in getting cervical cancer through two or more possible pathways. The first pathway is through causing cervical intraepithelial injury promoting HPV infection , such as high parity, early age of marriage or early age at first sexual contact and early age at first child birth , and number of sexual partners (Louie et al., 2009, Matos et al., 2005, Kahn et al., 2002). The second pathway is through promoting HPV persistent cervical tissue infection ,for example; prolonged OCPs use (Delvenne et al., 2007), which can increase the risk of acquiring precancerous and cancerous cervical lesions in long use OCP females . On the other hand, multiple sexual activities may force the females to use OCPs for a long time and by that increase the risk of being infected with many types of STIs especially HPV.

Increase risk of HPV infection for cervical lesions was noted in multiple studies worldwide, for example in a case control study, made by Sitakan et al., in Thailand 2012, found that the case group HPV prevalence with cervical cancer was 85.9% and was 14.1% in control group. And the increase risk for cervical cancer was the same for HPV infected females and active smoking habits even after adjusting with multiple logistic regression, with AOR = 38.1 (P-value =0.001). This study, highly confirm that being infected with HPV infection stays an important cervical lesion risk and cause (AOR = 38.07 (P-value < 0.001), and that other co- factors such as active and passive smoking, sexual habits , active or passive smoking habits as well as genetic predisposition play a role alongside HPV in increasing risk of acquiring precancerous and cancerous cervical lesions (Settheetham-Ishida et al., 2005, Settheetham-Ishida et al., 2004, Almonte et al., 2008, Au et al., 2007). However STIs mainly persistent HPV infection, sexual behavior and smoking behavior were found to be major risk factors for precancerous and cancerous cervical lesions among women (Sitakana et al.,2012).

In 2013, another case control study made in Thailand found that the high risk HPV prevalence was 10.1% (21) in the control sample and 152 (76.8%) in the cases with precancerous and cancerous cervical lesions. Moreover, a significant increase in risk for precancerous and cancerous cervical lesions was found with those infected with HPV (OR = 42.4; 95%CI: 22.4-81.4, p<0.001, AOR =40.7; 95%CI: 21.5-76.8; p <0.001). Also this study showed that the most prevalent HPV strain was HPV16. And by that concluded that HPV infection is still a dangerous risk factor for cervical precancerous and cancerous lesions.(Natphopsuk et al., 2013)

A meta analysis study conducted in India, 2008 and used multiple studies that used HPV detecting polymerase chain reaction for stains 6, 11,16,18 and other types of HPV. HPV infection prevalence was 94.6% for abnormal cytological findings of precancerous and cancerous cervical lesions and 12.0% in females with normal cytology/histology, respectively. However, in precancerous and cancerous cervical lesions the most common HPV strain was HPV 16 with about 64.8% . An estimation of 78.9% 16;18 HPV positive strain fraction was found in those with precancerous and cancerous cervical lesions, in South India it was about 77.2%

and in North of India it was 87.7% and these with normal cytological finding were approximately 3.9% (Bhatala et al, 2008).

A case control study in china 2016, studied multiple HPV strains effects on number of cervical lesions revealed strong association between different HPV strains and cancerous and precancerous cervical lesions. However, the most frequently detected genotypes were HPV16, and 18. A triple combined HVP infection from HPV 16,31,58 strains was the most common (accounts for about 4.2%) and those females at the ages < 24 years are the most affected from all kinds of precancerous and cancerous cervical (Meizhu et al.,2016).

Moreover, a cross sectional study done in 2018, at Zimbabwe was done to specify different HPV strains distribution and prevalence in females suffering from precancerous and cancerous cervical lesions and were referred to perform cytology smear testing at 4 urban hospitals. The rates for the most prevalent strains were as follow for HPV strains 16,18,33, 35, 45 and 56; 81.5%, 24%,13%, 11%, 7.4% and 9% respectively. HPV strains 16 and 18 accounted for about 83% of all cases (Washington et al., 2018).

A cross section study on women having stage II invasive cervical cancer or higher in South Africa ,where 50 sample from invasive cervical positive females were taken for a DNA molecular HPV testing . HPV test was positive in 47 cases(94%), indicating a powerful association between cervical invasive cancer and HPV infection (Nomonde al., 2016) .

Moreover, a population based survey in China was conducted to determine the distribution and prevalence of HPV strains among female with positive cervical cancer and showed 14.71% of tested females have been infected with HPV, 85% were having high risk HPV strains while 14.8% were having low risk HPV strains. While stains HPV 16,18, 58 and 66 were the most prevalent (Xiujie et al., 2015).

Furthermore, a cohort population based study to evaluate the cumulative incidence of precancerous and cancerous cervical lesions after short term persistent of HPV infection, done on Costa Rica in 2009; showed a 17 % precancerous and cancerous cervical lesion cumulative incidence for 3 years with 95% CI=12-22; P=0.002) concluding that persistent infection with HPV can predict future precancerous and cancerous cervical lesions, due to the strong association between them (Castle et al., 2009).

2.5.1.2 Tobacco smoking and risk for cervical lesions

It is well known that HPV infection is the main cause of precancerous and cancerous cervical lesions (Bosch et al., 2002) However, a small number of case infected with HPV progress to precancerous and cancerous cervical lesions, while most infections resolves spontaneously in 2 years time (Jensen et al., 2012). Smoking habits (either active or passive) have also been reported in many epidemiological studies to increase risk of cancerous and precancerous transformation from positively HPV infected lesions. Additionally, IARC has categorized tobacco smoking habits as causative agent for precancerous and cancerous cervical lesions from reviewing existing evidence (IARC,2004) . However, the causal association evidence between the occurrence of precancerous and cancerous cervical lesions and smoking different types of tobacco,

without the present of HPV infection, is yet not clear, and there is no prove on the cofactor effect of smoking or whether it causes increasing in the risk of persistent effect of HPV or the risk of acquiring HPV (Appleby et al., 2006).

An association between acquiring cervical lesions and the effect of tobacco smoking habits has been found in most of epidemiological published surveys and studies. For example, in Europe in 2014 a large prospective multicentre cohort study confirmed the association between increasing risk of precancerous and cancerous cervical lesions and female smoking habits, even after taking into consideration history of HPV infection, and found a strong positive associations duration of smoking , and inversely with stopping smoking, even after adjustment for STIs and HPV strains (Esther et al., 2014).

Furthermore, in 2012 a published meta analysis study by Zeng and collogues 2012 based on published case-control studies, showed a 20.8 fold increase in cervical lesion risk with female who were passive smoker compared with non passive smoker, (OR = 2.8, 95% CI: 1.97–4.25) (Zeng et al., 2012).

Another Norwegian nested case control study in 2009 found a strong significant statistical association between heavy smokers infected with HPV virus and the risk of developing cervical precancerous and cancerous lesions(OR= 2.71; 95%; CI:1.73-4.34), and after HPV infection adjustment similar risk of cervical lesions risk was high in females with a habit history of heavy smoking (OR=3.25; 95%; CI: 2.62-4.22), by that confirming the independent association between smoking habits and cervical lesions in those infected with HPV (Aline et al., 2009).

It has been difficult to justify smoking behavior independent role in precancerous and cancerous cervical lesions due to the strong correlation between smoking behavior and being infected with HPV,in nested case control study found that cigarettes agents and chemicals, for example nicotine or metabolite co-tinine that are consumed while smoking can lead to squamous epithelial cells DNA damage , in mucosal tissues of smoker cervix, confirming the independent effect of smoking behavior in increasing risk for precancerous and cancerous cervical lesions in HPV infected females (Kapeu et al., 2009).

In a case control population based study conducted in the US/ Sweden found a significant increase risks of cervical precancerous and cancerous lesions in positively HPV infected smoker women, compared with negative HPV non smokers (OR=5.23 - 7.22 for precancerous cervical lesions and 15.3 for cancerous cervical lesions) (Gunnel et al.,2006, Kjelleberg , 2000).

In a review of literature done by Gadduci and collogues, it concluded that the most significant exogenous, environmental risk agent for cervical precancerous and cancerous cervical lesions was female smoking behavior, and that the risk significantly increases with smoking duration and intensity of smoking habit (Gadduci et al.,2011).

2.5.1.3 Socioeconomic factors and risk for cervical lesion

Socioeconomic Factors as income level, social class and level of education have had significant effect on individual's general health. However, socioeconomic status and level of education may play a significant role in causing precancerous cervical lesions including cancer.

However, in USA, precancerous and cancerous cervical lesion is one of many complicated abnormalities that are socioeconomically, ethnically/racially and geographically strongly linked, as annual rates of precancerous and cancerous cervical lesion incidence and cervical cancer mortality are similar to some low income countries rates and much more higher than the general population rates (Freeman et al., 2005;Spenceet al., 2007).

Various studies have pointed out the relationship between cervical lesions and socioeconomic factors. Latha and colleagues conducted a cross section study to find out the prevalence of risk factors for precancerous and cancerous cervical lesions including socioeconomic status among women in the provincial areas of Karanataka, India 2017, and found that the precancerous cervical lesions prevalence was 10% , concluding that it was high due to multiple factors including low socioeconomic status, low level of education and reproductive health factors . These study results were similar to the results concluded from the study conducted by Mhaske M et al at Pune, in India 2011, where precancerous cervical lesion prevalence was 12.7% and of cervical cancer lesion was 4.4%, in addition to the study that was made by Makuza JD et al in Rwanda 2015 where precancerous cervical lesion prevalence was 5.9% and of cervical cancer was 1.7%.

The association between precancerous and cancerous cervical lesions and low level of education and low level of income was reported in year 2017 through a cohort retrospective study that was made in Lithuania, targeting 2513 women (Vincerzevskiene et al., 2017).

Multiple cross section studies that were made in India reveled the relationship between low socioeconomic factors such as low level of education and low income with increasing risk factor for cervical precancerous and cancerous lesions.(Aswathy et al., 2012, Chankapa et al., 2011) . Retrospective cross-sectional study done by Hailemarian and colleagues(2017) in Southern Ethiopia revealed that the risk factors that showed significant association with precancerous and cancerous cervical lesions were place of residency , occupation, education level, having multiple sexual partners, early age of marriage or early age of sexual intercourse being HIV positive, and exposure to STI with a prevalence of 16.5%.

A hospital based cars control study that were made on Turkish women and showed a positive relationship between low educational level and risk for cervical lesions (Nesrin et al., 2011). Another prospective cohort study made on women at India in 2012, gave a

very strong evidence that education in low socioeconomic countries is considered an important risk factor for precancerous and cancerous cervical lesions among other socio-demographic and reproductive factors . There was a decrease in precancerous and cancerous cervical lesions risk in educated females (HR=0.5 ; 95% ; CI 0.243,-0.8) compared to illiterate females with a dose response relationship significant increase with level of education (P=0.018) (Jissa et al., 2012).

In 2015, a case control based study in Himachal Pradesh found that there was a significant association on multiple logistic regression between low level of education (OR=1.6; 95%; CI 1.1-2.2), low socio-economic status (OR= 1.4 ; 95% ; CI 1.3-2.6) and increase risk for precancerous and cancerous cervical lesions (Anita et al., 2015).

Kalawole and colleagues reported a high amount of HPV –positive cases among married females (62.5%) compared with (5%) in divorced and widowed females (Kalawole et al., 2015).

Vaccarella et al. reported that marital status played a significant role in increasing HPV risk, and by that increase the risk for cervical precancerous and cancerous lesions (Vaccrella et al., 2010).

In an opposing results from a cross sectional study, 21.1% divorced females and 30.5% widowed females compared to 9.1% married females, have had a higher risk acquiring cervical lesion. The researcher attributed the difference to the possibility of multiple sexual contact for widowed and divorced females compared to married females (Getinet et al.,2015).

2.5.1.4 Reproductive health and risk for cervical lesions

Risk factors studies for precancerous and cancerous cervical lesions have found female sexual behavior to be highly associated with cervical lesion. For example, multiple sexual partner females who have had the first sexual contact at early age have higher risk for precancerous and cancerous cervical lesions. Also, sexual acquired causes lead to the progression of precancerous and cancerous cervical lesions from low to high grade diseases. Primary prevention of cervical lesions is mostly achieved by monogamy, not using OCPs, individual hygiene and late commencement of sexual activity (Murthy et al., 2000).

A strong association between early age of sexual contact or early age of marriage and increase risk being infected with HPV, which in vulnerable female has been the cause of major cases of precancerous and cancerous cervical lesion (Bosch et al., 2002). Moreover, early age of sexual contact or marriage, multiple sexual contacts, unprotected sexual behavior and polygamy determine the increase exposure to HPV. Also, readiness of the adult immature cervical tissue, to changes done by multiple biological agents increase the

risk of acquiring persistent HPV and therefore for higher risk of precancerous and cancerous cervical lesion development ((Kjaer et al, 1998).

In UK, where teenage pregnancies rates are high, female having sex at early age ⩽17 years old had a 2–3 times higher risk for precancerous and cancerous cervical lesions compared with females their first sexual intercourse ⩾20 years (Green et al., 2003).

Multiple studies have had identified increased risk for cervical precancerous and cancerous lesions in females having sex or married at early age (IARC,2007).

A large pooled case control study, from eight developing countries, with high rate of precancerous and cancerous cervical lesions incidence reported that females married or have had sex at early age have a 2.4 times higher risk for cervical cancer than those married or had sex at older age (OR =1.9 ; 95% CI; 1.5–2.4) and those who had their first born child at early age< 16 years have a 2.3 fold higher risk (OR= 2.31 95% CI: 1.85–2.87; P<0.001) compared to those who had their first child at age ⩾21 years. Moreover, the study showed that if pregnancy follows marring or having sex at early age an additional increase in risk of precancerous and cancerous cervical lesions is yield (Louie et al.,2009).

Two studies that were made in Ethiopia in 2013 and 2017 concluded that marriage or having sex at early age are independent predictors of precancerous and cancerous cervical lesions. The first one was a cross section study made by Deksissa and colleagues , it showed that women who got married or started intercourse at early age <16 years have more risk to develop precancerous and cancerous cervical lesion by 2.2 folds (OR= 2.23, 95% CI 1.1-4.3). The other one was case control study made by Kassar R, to assess the association between marriage or having sex at early age and risk for precancerous and cancerous cervical lesions, showed that females married or have had sex at early age <15 years has increase risk of 5.6 folds to acquire precancerous and cancerous cervical lesion (Kassar, 2017).

Another two cross sectional study showed the high prevalence of precancerous and cancerous cervical lesions among female who were early at age of marriage or early at age of first sexual intercourse; in Nigeria 2018, Utoo and colleagues reported that 77% of the tested positive female for precancerous and cancerous cervical lesions were early at age of marriage or early at age of first sexual intercourse.(Utoo BT et al., 2018). In 2013, in Pakistan, Chandra and colleagues reported 59.4% of patients with precancerous and cancerous cervical lesions have early age marriage < 15 years (Chandra et al., 2013).

An opposing conclusions by Latha K and collogue and Chankapa and collogues were shown in tow cross sectional study that were made in Karnataka in 2017 and India 2011, and found that there is no association between marriage or having sex at early age and risk for precancerous and cancerous cervical lesions(Latha et al., 2017; Chankapa et al., 2011).

High parity has been reported in multiple studies, to be significantly associated with precancerous and cancerous cervical lesions risk , such as the cross sectional study that

was made by Andrew and collogues in Uganda in 2017 and found a significant association between high parity and precancerous and cancerous cervical lesion, and the cross sectional study that was made by Kalawole and collogues in Nigeria in 2015 and found a strong association between high parity as a co-factor risk and precancerous and cancerous cervical lesions (Andrew et al.,2017; Kalawole et al.,2015).

Another case control study that was done in Ethiopia, 2015 concluded that there is a strong independent association between high parity (female having >4 children) and precancerous and cancerous cervical lesions .(OR =10.3, 95% CI= 3.6–29.0). However, those having > 4 children were 8 folds more susceptible to precancerous and cancerous cervical lesions than females having one or two children. However, parity (No of child birth) is considered an excellent indicator for multiple traumas to the cervix and for circulating estrogen throughout female fertile life for females with multi-parity (Bezabih et al.,2015).

Moreover, a cross sectional study by Getinet M and colleagues in 2015 concluded that high parity > 3 children has been a significant predictor of prevalence of precancerous and cancerous cervical lesions , high parity women > 3 children were 11 folds more susceptible to precancerous and cancerous cervical lesions than with<3 children (OR= 11; 95 % ; CI: 4.2 − 16.8, p < 0.001) (Getinet et al.,2015).

Marriage at small age, means engagement in sexual intercourse with high possibility of having first baby at small age . Also, having sex at early age , or having fist child at small age can cause trauma to the cervical tissues and by that increase risk for precancerous and cancerous cervical lesions (IARC, 2007).

However, early age at first pregnancy, has been studied less than other possible risk factors for its contribution to precancerous and cancerous cervical lesions. For example, in case control pooled study analysis taken from 8 developing countries in 2009, concluded that precancerous and cancerous cervical lesions risk increases by 2.4-fold in females who reported early age at fist baby birth ≤16 years (with OR= 2.31,95% CI: 1.85 – 2.87) compared with those with early age at fist baby birth ≥ 21 years. So by that, confirming that early age at fist childbirth has been risk factor for precancerous and cancerous cervical lesions in eight developing countries, but as a cofactor with no independent effect (Louis et al., 2009).

In an opposing conclusion made by Bezabih and colleagues in 2016, they had reported having first child at small age ≥25 years, a significant risk factor that contributes to having cancerous and precancerous cervical lesions as well as the advancement of cervical carcinoma, so they considered it to be an independent risk factors for acquiring precancerous cervical lesion and invasive cervical cancers in their study, and suggested that intervals among deliveries also contribute to the disposition of precancerous and cancerous cervical lesions, not only the small age at fist child birth (Bezabih et al.,2016).

Also Chankapa and colleagues in their cross sectional study in India 2011 found no significant association between early age at first full term delivery and risk for precancerous and cancerous cervical lesions but found an increase incidence of precancerous and cancerous cervical lesions with increasing age, prolonged sexual intercourse and high parity (Chankapa et al., 2011)

In a cross sectional study by Mhaske and colleagues in India 201, they highlighted the significant associations between risk of cervical precancerous and cancerous lesions and early age of marriage<17 years of age (prevalence was 19.04% compared to 7.94% for those married >17 years of age 7.94%), female with first child birth before 20 years of age (26.31%) and those with high parity (Mhaske et al., 2011).

The risk of precancerous and cancerous cervical lesions is affected to a great extend by female's partner sexual habits, such as polygamy, multiple sexual partners and having intercourse with prostitutes by the husband or partner, and by that increase the risk of acquiring HPV infection , which will increase the risk of precancerous and cancerous cervical lesions.. Polygamy is not a rare practice, especially among Muslims and is considered among positive HPV females a cofactors that could lead to precancerous and cancerous cervical lesions among HPV infected female .(Bayo et al., 2002). However, a cross sectional study in 2009 by Domfeh and colleagues found a high HPV prevalence in polygamies Ghanaian females were incidence of precancerous and cancerous cervical lesions has been high (Domfeh et al., 2009).

In a case control study done by Bezabih and colleagues in 2015 found that polygamist husbands was significantly statistically associated with high risk of precancerous and cancerous cervical lesions, and that husband sexual habits may play an important role in acquiring precancerous and cancerous cervical lesions (Bezabih et al., 2015).

Owki and colleagues in their cross sectional study in 2017 found a strong association between cancerous and precancerous cervical lesions and multiple endogenous and exogenous risk factors, such as STIs, polygamy and marriage or having sex at early age and that these factors were highly linked to one another (Owki et al., 2017).

2.5.1.5 Contraceptive hormones, devices and the risk of cervical lesions

Many studies have had illustrated that OCPs consuming females for ≥5 years have a higher risk of precancerous and cancerous cervical lesions than female who have had never used oral contraceptives, also the longer a female uses oral contraceptives, the greater the increase risk of precancerous and cancerous cervical lesion (National Cancer institute, 2018).

Because, hormone replacement therapy has no obvious correlation with precancerous and cancerous cervical lesions. So, by weighing risks and benefits, no changes have been done in OCPs protocols and recommendation by the World Health Organization (WHO, 2011).

In 2016, Roura E and collogues in their large cohort prospective study, that was done in 10 European countries showed the relationship between certain exogenous and endogenous hormonal factors and precancerous cervical lesions and cervical carcinogenesis, it highlighted the strong positive associations between OCPs and risk of precancerous and cancerous cervical lesions((HR = 1.6 and HR = 1.8 respectively for ≥15 years versus never use); specifically, the risk increased with increase number and duration of oral contraceptive use and decreased with cessation of use and increase years since last oral contraceptive have been used. However, the study found a significant association between using menopausal hormone therapy and reduce risk of precancerous and cancerous cervical lesions (HR = 0.5, 95%; confidential interval: 0.4–0.8), and a non-significant reduce risk of cancerous and precancerous cervical lesions with the use of intrauterine devices (IUD) as a contraceptive method (OR = 0.6). However, oral contraceptive risk factor mostly induces precancerous and cancerous lesions not independently but as HPV cofactors (Roura et al.,2016).

Another case control study results has shown the increase risk for precancerous and cancerous cervical lesion for those using OCPs and the increase risk with OCPs time duration consumption (relative risk = 1.91 with 95% ; CI: 1.7-2, for those using ≥5 years compared with females who have never use) . The cervical lesions risk have decrease after stopping OCPs consumption and have return to the same risk for those never used by 10 or more years Moreover, estimated cumulative incidence increase by age 50 years for precancerous and cancerous cervical lesions for those who have started OCPs use between the age of 20-30 years and kept on using it for 10 years by age 50 from 3.8 per 1000 to 4.5 per 1000 in developed countries and from 7.3 per 1000 to 8.3 per 1000 in developing countries (Appleby et al.,2007).

In a systematic review by Gadduci A and colleagues showed an increase in RR for precancerous and cancerous cervical lesions with increasing OCPs consumption duration compared to those who had never used oral contraceptive pills. Similar results were seen for Adenocarcinoma and Sqaumous cell carcinoma, with RRs been declined after stopping OPCs (Gadduci et al. 2011).

Another case control study done in Ethiopia by Kassa R, in 2017 , showed that risk for precancerous and cancerous cervical lesions increase 2 times more with OCPs consumption (OR = 2.1; 95% ; CI 1.- 4.2; AOR = 2.3; P < 0.03) (Kassa, 2017). On the other hand Herrero and collogues in their large study in 2006, showed that injecting females for 5 years or more will increase risk for precancerous and cancerous lesions by 430% (Herrero et al., 2006).

An opposing conclusion was made by Syrjanen K on a prospective cohort study that was made in Russia in 2006 found that the use of OC is not an independent risk factor for precancerous and cancerous cervical lesions .In their multivariate regression model, they

found that all mode of contraception were of no value for either cancerous and precancerous cervical lesions, and concluded that main risk factor was sexual behavior, which was different among oral contraceptive users and nonusers and it was the main factor predisposing women to precancerous and cancerous cervical lesions, and it determined the outcome of their cervical lesion (Syrjanen et al.,2006).

A two case control pooled study analysis made by the Institute Català d'Oncologia and International Agency for Research on Cancer an concluded that there was a strong(OR= 0·6, 95%; CI: 0·4–0·71; P<0·0001) inverse association between using intrauterine contraceptive device (IUDs) and precancerous and cancerous cervical lesion and a protective association was noted for Adenosquamous carcinoma and Adenocarcinoma (OR= 0·5, 95% CI:0·2–0·94; P=0·04) and Squamous cell carcinoma, (OR=0·6; 95%;CI:0·4–0·7; P<0.0001) but no association was found between HPV infected cervix with no lesions and using IUD. Furthermore, the triggered cellular immunity by the IUD device makes it a protective factor against cervical precancerous and cancerous lesions (Castellsague et al.,2011)

Moreover, a cross sectional study by Getinet M and colleagues in 2015 concluded that the using OCPs for a long time was a significantly increase the prevalence of precancerous and cancerous cervical lesions (OR= 11.9, 95 % CI: 2.1 − 16.7, p = 0.02) (Getinet et al., 2015)

2.5.2 Endogenous factors

2.5.2.1 Demographic factors and risk of cervical lesions

Studies concluded that 47 years old was the peak age of developing precancerous and cancerous cervical lesion. Approximately 47% of women with precancerous and cancerous cervical lesions are diagnosed at the age <35 years old. However, those >65 years females are about 10% of patients with precancerous and cancerous cervical lesions. Although only 10% of cases are presented at older age, they are more likely to die of cervical cancer, because diagnosis occurs at late stages (Gattoc et al., 2015).

Furthermore, the age difference among females with precancerous and cancerous cervical lesions could be the result of the long time needed for precancerous cervical lesions to progress after persistent infection with HPV (Shiferaw et al., 2016)

In 2018, Team H and colleagues in their case control study reported that women between the age of 40 and 49 years, had 2.4 time more risk for precancerous and cancerous cervical lesions compared to women between the age 30–39 years old (AOR = 2, 95% CI: 1.3–4.5). A retrospective cohort study results done in Addis Ababa, and reported similar results; in which the age group between 40 and 49 years had the peak

incidence for precancerous and cancerous cervical lesion.(Abate,2016). Moreover, similar findings were reported in 2015 at Ethiopia, in a case control study, where greater risk for precancerous and cancerous cervical lesion in female with age group between 40-59 years old compared to female < 40 years (Bezabih et al.,2015).

Getinet and colleagues reported in their cross sectional study in 2015 that female aged ≥ 30 years were at greater risk of acquiring precancerous and cancerous cervical lesions, so the older the women the greater the risk (Getinet et al., 2015).

Moreover, the prevalence of precancerous and cancerous cervical lesions was equally found to vary according to age, was the results obtained from cross sectional study by Okwi and colleagues in 2017, where they documented that the prevalence of precancerous and cancerous cervical lesions (1 (0.6%)) seen among females < 30 years, was lower than the prevalence seen among women between 31-40 years(3 (2.5%)) , 6 (11.5%) between 41-50 and 4 (26.7%) above 50 years. The lower prevalence among women <30 years old could be attributed to the established and effective programs for screening and early diagnosis for precancerous and cancerous cervical lesions among young reproductive women (Okwi et al.,2017).

However, there are also some documented studies, which reported contradicting findings. For example, Gessesse et al. in his case control study that took place in Northern Ethiopia in 2015 documented that there was no significant statistically association between precancerous and cancerous cervical lesion and age of the females . Also, Makuza JD and colleagues in their cross sectional analytical study in 2015 documented older age (OR= 0.52; 95% CI= (0.28, 0.97) as a protective factor (Gessesse et al.,2015; Makuza et al.,2015).

Another opposing results were seen in Embolo and colleagues cross sectional study in Cameroon and found that around 20.52% of Cameroonian females have precancerous and cancerous cervical lesions at early stages of their life, extended from 20 to 30 years old (Emblo et al., 2016)

2.5.2.2 Genetic susceptibility and risk for cervical lesions

Epidemiological studies supported the genetic link for precancerous and cancerous cervical lesion development. A hereditary component of cervical lesions was detected in twins comparisons and studying mother-daughter family (Galloway , 2003). By observing the biological first degree relatives of females who have developed a cervical lesions , the possibility of host genetic predisposition has been strengthened because biological first degree relatives of females suffering from cervical lesions , experience a two-fold risk of developing precancerous and cancerous lesions compared to non-biological relatives of females with cervical lesions (Magnusson et al., 1999) The heritability of precancerous and cancerous cervical lesion has been determined as 27% (Hemminki et al., 1999).

Being infected with persistent high risk HPV strains are considered to be the most common cause of precancerous and cancerous cervical lesions, despite the fact that huge numbers of sexually active young females acquire different types of HPV infection, only few of them develop precancerous and cancerous cervical lesions, this might be attributed to host genetic variation and body responses to different HPV genotypes and the ability to acquire precancerous and cancerous cervical lesions, Furthermore, the complex multifactorial cervical diseases outcomes are highly affected by the host genetic factors that are also known to regulate precancerous and cancerous cervical lesion rate progression (Chattopadhyay , 2011) .

Moreover, genome-wide and preclinical association studies have had reported the associations of genetic variations in several susceptible female for acquiring precancerous and cancerous cervical lesions (Bahrami et al.,2018).

Furthermore, the host immune system genetic variability has an extremely important role in the defense against HPV infection and therefore to the probability of developing precancerous and cancerous cervical lesion.

Worldwide, several international studies have reported that some genetic variations in host immune system, are associated with susceptibility to precancerous and cancerous cervical lesions , but there have been no conclusive studies about how genetic susceptibility is mechanically related to precancerous and cancerous cervical lesions and the HPV infection (Mora et al., 2016).

2.5.2.3 Family history and risk for cervical lesion

Unfortunately, cervical cancer runs in some families. The familial tendency is suspected by many researchers to the cause of an inherited factors making female more susceptible to HPV infection than others, or that , females may share other risk factors that are not genetic in origin. (ACS,2017)

The theory of familial aggregation of precancerous and cancerous cervical lesions has been supported by many published studies, which have had suggested, that the etiology of precancerous and cancerous cervical lesions might be affected by genetic variation, also suggesting a 2 time risk increase for precancerous and cancerous cervical lesions associated with positive history of cervical lesions .Regardless of the relationship or the first degree affected female relative, a significant association was observed for both precancerous and cancerous cervical lesions (Paltrik et al., 2000).

However , full-blooded relatives showed a stronger risk as compared to adapted to half-blooded relatives. The full siblings familial risk was 1.84, compared with 1.40 for half-

siblings maternal and 1.27 for paternal. Familial risk for cancerous and precancerous and cervical lesions in full siblings of the total risk accounts for 36% for the environmental component and 64% for the heritable component (Hemminki et al.,2006).

Also, strong familial aggregation was suggested by multiple studies for precancerous and cancerous cervical lesions among dizigoteic -monozygotic twins when evaluating precancerous and cancerous cervical lesions (Ahlbon et al.,1997).

However, in order to determine if the familial aggregation of cervical lesions that was observed was the cause of shared environmental exposures among family members or the cause of mutual genetic susceptibility. Patrik and collogues reported that shared genes (heritability) explain 27% of the total precancerous and cancerous cervical lesion risk (95% ; CI: 0.26–0.29) are attributed to hereditary factors (shared genes) with no significant effect of shared environmental familial factors between mother and daughters but a significant effect of shared environmental familial factors between sisters. However, specific sister shared environment was about 2% (95% CI 0.01–0.04). Their study results indicated that development of precancerous and cancerous cervical lesions depends on factors that were inherited, which affect cervical tissue sensitivity to persistence HPV, as well as , precancerous and cancerous cervical lesions development rate (Patrik et al.,2000).

2.6 Pap smear screening test and role in detecting cervical lesions:

Carcinoma of the cervix is considered one of the most preventable cancers, where precancerous lesions can easily be detected through cytology screening before they become cancerous. When detecting precancerous lesions by screening , treatment can start as early as possible, so as to avoid cervical cancer development. Also, cancerous lesions can be detected by cervical Pap smear screening at early stages so as to be treated early leading to high potential of cure(WHO, 2015).

Cervical cancer in developing countries is considered one of the leading cause deaths related to cancer among female. 75% of females are screened for precancerous and cancerous cervical lesions in developed countries , mostly by cervical Pap smears screening test, which is a method for cervical screening and has been used to find precancerous and cancerous lesions in the cervix, on the other hand, in developing countries 55 of females are screened (Denny et al., 2006). The Pap smear cytology based cervical screening has the ability to detect the incidence of cancerous and precancerous cervical lesions for decades despite the argument that has had been surrounding the ability of medical and public community to use Pap smear test for screening (Gedefaw et al.,2013).

Preventing cervical cancer morbidity and mortality is the goal for precancerous and cancerous cervical lesion screening. However, screening strategies should be maximizing the benefits of screening by identifying those precancerous cervical lesions , which might to progress to carcinoma and to decrease the harmful effect associated with screening, by avoiding undesired treatment for HPV infection and for benign lesions that may not progress to cancer. In countries with good effective screening programs, a decrease in mortality and incidence from precancerous and cancerous cervical lesion was seen as the results of using cervical Pap smears screening test. Despite the fact that false positive abnormal cytology results are common and precancerous and cancerous lesions doesn't develop in most cervical tissue with abnormal results on Pap smear, cervical cancer is of a concern (Castle et al., 2010).

WHO reported in 2013 that repeated Pap smear cytology screening test organized programs in developed countries has helped a lot in decreasing incidence and mortality rates from cervical cancer. In contrast, in developing countries and due to the absence of effective screening organized programs cervical lesions and cancer remain largely prevalent.

Sqaumous cell cancer of the cervix accounts for 80%-90% of all cervical carcinomas, and has been decreased globally due to the effective screening with Pap smear cytology test (Debbie et al., 2012). In the middle of the 20th century, USA introduced Pap smear cytology screening test , which obviously lead to decrease in precancerous and cancerous cervical lesions and instead of being the most common cause of cancer deaths in female to the 14th rank as the cause of female cancer deaths (Siegel et al., 2012). Invasive cervical cancer early detection, by cervical Pap smear test , has reduced mortality, and made the survival 5 years rate almost 92% , also by using the detection screening methods precancerous cervical lesions were caught treatment earlier, and by that decreasing cervical carcinoma incidence (Debbie et al., 2012). In USA , almost about 50% , of precancerous and cancerous cervical lesions were diagnosed in females who never had Cervical screening , and another 10% were females who didn't had any cervical screening in the past 5 years (Freeman et al., 2005;Spence et al., 2007).

Various studies have pointed , cervical Pap smear screening test role in catching precancerous and cancerous cervical lesions including invasive cancer, Sachan and colleagues (2018) in their prospective study, evaluated the effectiveness of the cervical Pap smear cytology test screening procedure to detect precancerous and cancerous cervical lesions in Indian female , concluded that Pap smear testing is a very economical, useful, simple, and safe tool for detecting cancerous and precancerous cervical epithelial lesions. However, 48.84% were negative for malignancy and 43% were diagnosed with infection and/or inflammation . High-grade squamous intraepithelial lesion (HSIL) atypical squamous cells of undetermined significance (ASCUS), and were

detected in 0.5%, 3% and 5.%, respectively. ECA was detected in 8.48% (Sachap et al., 2018).

Two Indian retrospective studies have recommended that cervical Pap smear test should start at 30 years old age for all females , because Pap smear is inexpensive, simple, practical and safe diagnostic procedure, for precancerous and cancerous cervical lesions early detection in high risk population, and must be adapted as an organized routine screening procedure. The study also, concentrated on Pap smear test role in diagnosing inflammatory lesions and causative agents, radiation therapy changes, rare tumors and atrophic changes. In the first study Patel et al., 2011 found that out of the 995 patients who were screened 95% were inflammatory and benign and 6% were precancerous and cancerous lesion, out of the precancerous lesions 84% were ASCUS and AGUS. While in the second study Veghela et al., 2014 found that from all the cases ; LSIL was the most common (12.4%) of cases, followed by HSIL (5%), then ASCUS(2.8%), Squamous cell carcinoma (2.4%) and AGCUS (1.2%)

In another retrospective study that were made in UAE to estimate abnormal epithelial cell frequency in female undergoing Pap smear examinations; 0.4% was screening rate with Pap smear was, 3% were abnormal epithelial cells , with atypical ASCUS found in 2%, LSILs found in 1%, HSILs found in 0.3% and there was no abnormal squamous cell carcinoma. And found an ECA detection rate, of 9.% (Eyad et al.,2012).

Another cross sectional study made in 2012 by Sarma and colleagues to differentiate cervical precancerous and cancerous lesion using cervical Pap smear test and Bethesda system, found that cervical Pap smear test has an important role precancerous and cancerous cervical lesions early detection , after obtaining the study results that showed the detection of precancerous and cancerous cervical lesions in 4 % of all cases, while 88% were negative for cancer and ECA with 12 % out of which 30 % smears were equally having invasive squamous cell carcinoma, HSIL , LSIL and ECA detection rates of 12%

Verma and colleagues in their cross sectional study that were made in 2017, to determine the specificity and sensitivity of Pap smear test to detect precancerous and cancerous cervical lesions, concluded that cervical Pap smear screening method was specific and sensitive in finding precancerous and cancerous cervical lesions. In this study, NILM were 56% , 33% were inflammatory, nonspecific findings were 2% . ASCUS was in 1%, LSIL in 6% and HSIL in 3 % women. LSIL detecting sensitivity and specificity were 77%, 96% and for HSIL were 67% and 98 %.

In a retrospective cohort study Cervical Pap smear test showed abnormal epithelial high prevalence among the population at the East part of Saudi Arabia . About 624 abnormal cases were found (53%), 58 cases had SIL , accounting for 5% of total smear samples, most of the SIL were ASCUS, representing 60%. The prevalence was 0.3% for abnormal squamous cervical cells (Magdi et al.,2011).

However the prevalence of cervical Pap cytological smear abnormalities done on Turkish population in 2012 was 2.8%, epithelial abnormalities were ASCUS: 2% , Atypical squamous cell suspicious for high-grade squamous intraepithelial lesion, LSIL= 0.2%, HSIL= 0.5% , AGUS=0.1%, and squamous cell carcinoma (SCC)= 0% (Atilgan at., 2012).

Furthermore, the was a strong significant and independent association between abnormal results of Pap and age, lack of awareness about cervical Pap smear screening tests and HPV infection, in the cross sectional study that were made by Maleki A and colleagues in Iran in 2015, mild inflammatory changes were found (37%) , 4% abnormal epithelial cells and ASCUS were the highest abnormal percentage of changes with 2% .

Chapter Three: Conceptual Framework

In this chapter major definitions, dependent and independent variables, variables operational definitions and the study conceptual framework will be presented.

3.1 Cervical lesions definition

A precancerous cervical lesion, or intraepithelial lesion, is considered changes or abnormalities in the cervical cells that if not early treated can progress into cervical cancer. Precancerous conditions are not cancer, but these abnormal changes have higher chance than normal cells to become cancerous if not properly treated.
Moreover, if these precancerous changes or lesions are left untreated, it may take them 10 years or more to be transformed into cancerous cervical lesions, but sometimes these cancerous lesions occur in less time. Squamous and glandular cells are the two main types of cervical cells that line the ecto and endo cervix respectively and where abnormalities can occur (Canadian Cancer Society, 2018) .

3.2 Cervical cancer definition:

Abnormal cervical cell growth into the lining of cervix is referred to as cervical cancer, where the transformation zone is the first to be affected most of the time , and may spread to nearby tissues, for example , the vagina, or may cause metastases to other body organs , such as the liver as well as the lungs . The most frequent types of cervical cancerous lesions are: 1)Squamous cell carcinoma (SCC), accounts for 70% of case (7 of every 10 cases), and is considered the most common type. 2) adenocarcinoma that starts in the glandular cells , accounts for 25% of cases and is considered less common type of cervical cancerous lesions . However, the abnormal glandular cells are harder to recognize and occurs higher up in the cervix that is why adenocarcinoma is more difficult to diagnose than SCC.
Moreover, cervical cancer may contain tow types of cell growth called adenosqaumous or mixed carcinoma that consists of squamous cells and glandular cells. Cervical sarcoma and small cell carcinoma are rare types of cervical cancer (Hammond , 2017).

3.3 Cervical lesions determinants risk factors model:

Figure 3.1 Presents the conceptual framework model for the exogenous and endogenous risk factors for precancerous and cancerous cervical lesions used in this study

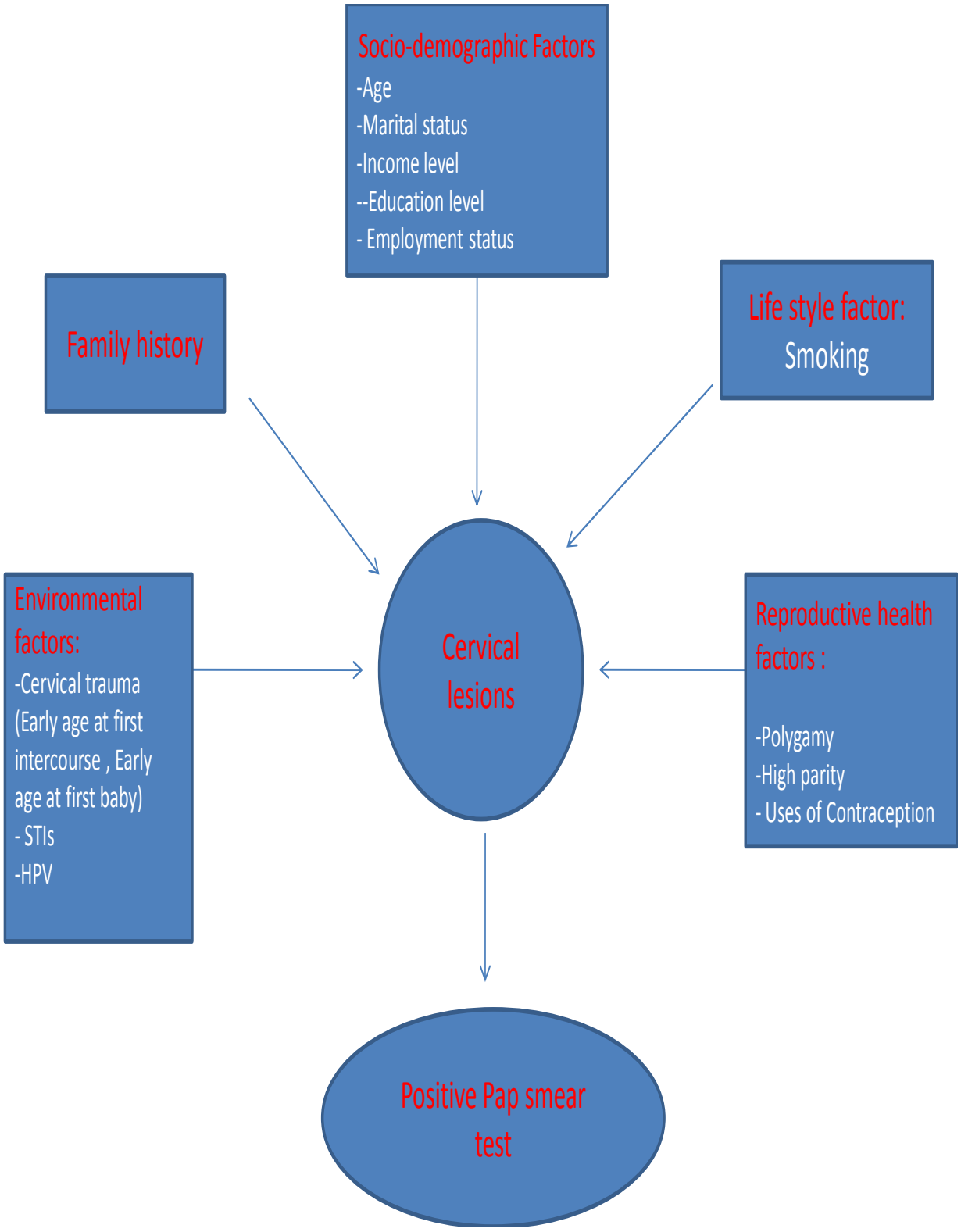


Figure 3.1: The Study conceptual framework

Endogenous factors such as family history, genetic predisposition and age may play a major role in developing precancerous cervical lesion that at the long term may evolve to cervical cancer.(Medscape,2014)

Exogenous factors that are found to be associated with cervical lesions; such as lifestyle factors, including smoking, multiple sex partners, polygamy, high parity. In addition to environmental risk factor, such as cervical trauma and STIs.

Cervical lesion determinants and risk factors causing positive Pap smear results:

1. Lifestyle factors: Smoking different types of tobacco
2. Reproductive health factors: polygamy, multi-para and using OCPs
3. Environmental and exogenous factors: cervical trauma if sexual contact starts at small age or having children at small age and STIs especially the most common cause of cervical lesions HPV infection
4. Socio-demographic factors; age , income level, education level and employment status
5. Family history and genetic predisposition that make females more susceptible to persistent HPV infection

3.4 Independent variables

3.4.1 Socio-demographic variables (annex 1)

1. **Age**: represented in intervals in the constructed questionnaire
2. **Marital status**: Cervical lesions incidence is much more higher in married women and formerly married women due to multiple sexual partners (Leck et al,1978).
    a. This variable was categorized into three groups, constructed as follow: married, divorced, widowed, no single group was used because culturally no Pap smear test can be performed on single female.
3. **Income level**: Low socioeconomic status increase females vulnerability to acquire cervical lesions, for example, most of those living in low social-economic circumstances are unable to provide enough income to seek medical care and treatment for STI's including HPV infection (Tadesse,2015).
   This variable was categorized into five categories, constructed as follow: low income , middle income, high income, no income and do not know
4. **Level of education**: Females with low level of education tend to suffer more from STIs including HPV and the don't seek medical treatment as these with high level of education (Nejo et al,2018). Level of education for the participants was categorized into four groups constructed as follow: primary school or less, high school, Bachelor degree and postgraduate
5. **Employment status**: categorized in five groups constructed as follow: house wife, self employee, wage worker, field officer and office employee

3.4.2 Environmental variables (annex 1)

a- Cervical trauma which is measured by assessing the following**:**

1- Early Age at first intercourse, which was categorized in six age intervals: <15, 15-24. 25-34, 35-44 and ≥45 years old and I don't know

2- Early Age at first baby which was categorized in 9 age intervals : ≤15 year , 16-20 year , 21-25 year , 26-30year , 31-35year , 36-40year ,41-45year , >45 years old and I don't know

In developing countries, starting sexual contact or marriage and getting pregnant at early age are considered important risk factors for precancerous and cancerous cervical lesions (Louie et al, 2009)

The hormonal effect on HPV and host immune response to it during the period of pre-adolescence and adolescence can explain how early marriage or sexual contact and early pregnancy play a role in increasing the risk of precancerous and cancerous cervical lesion. The cervical epithelium site, which is mostly liable to cancerous lesions by HPV infection, is the transformation zone area, in which high susceptibility might be related to stratified epithelium excoriation , and by that facilitates basal layer exposure to HPV infection with scant trauma. Another additional susceptibility factor is biological immaturity during adolescence (Singer et al., 2000, Elson et al., 2000, Moscicki et al., 1989;).
Moreover, during adolescence and pregnancy , changes to the cervical tissue are induced by high level of hormones .(Singer et al., 2000), where the acidification of vaginal activity is stimulated by estrogen, causing squamous cell meta-plasia when the endo-cervical epithelial changes (Elson et al., 2000).
Furthermore, he presence of HPV infection during the metaplastic transformation induced by estrogen increases the probability of transforming the cervical cells into neoplastic cells (Shai et al., 2008; Elson et al., 2000; Hwang et al., 2009). The neoplastic transformation changes are primarily the effect of multi-parity, especially during the first pregnancy (Singer et al., 2000). Although metastatic changes is suspected to be affected by the mechanism of trauma and repair during deliveries, but there has been no clear evidence that those trauma can increase risk for precancerous and cancerous cervical. (Munoz et al., 2002).

Moreover, another postulated explanation could the effect of estrogens on the host immune response (Arbei et al.,1996; Mitrani et al., 1989), specially during pregnancy and during the ovarian follicular phase cycle, when there is a 3-8 fold increase in the normal level of the estrogens hormone (Marzi et al., 1996; Duncan et al., 1994; Jabbour et al., 2008). The effect of HPV oncoproteins in addition to the presence of high level of estrogen and high density of estrogen receptors in the transformation zone, decrease the level of cytotoxic cytokines and the mediated immune response by the cervical cells - that usually cause the clearance of infection- casing the persistent of HPV infection. (Giannini et al., 2002; Marzi et al., 1996; Jacobs et al., 2003).

b- Sexually transmitted infections including HPV: Cervical cancer risk increases in women havening persistent STIs, almost all precancerous and cancerous cervical lesions are caused by certain high risk types of HPV, which are extremely common. For example, in USA 20 million of the population is already infected with certain types of HPV, six million acquire it each year, and more than half of all sexually active adults will acquire the HPV infection once in their life (CDC,2014).

This variable was assessed in the questionnaire by asking directly about being diagnosed or infected with STIs previously and whether have ever had abnormal discharge or still having any STIs symptoms

3.4.3 Life style factors: (Annex 1)

- Smoking: HPV infection prevalence and incidence that is associated with cervical lesions is highly affected by smoking behavior, the carcinogenic effect of tobacco is related to multiple factors including local immune-suppression effect or direct local carcinogenic effect (Moutinho,2011).
  Participants were asked if they are currently smokers or whether previously had been smoking (Cigarettes or waterpipes) and the amount smoked per day

3.4.4 Reproductive health factors: (Annex 1)

1- Polygamy: Polygamies marriages or random sex done by husbands make their female partner more prone to precancerous and cancerous cervical lesion , especially with low personal hygiene husbands, polygamy has been a main co-factor for precancerous and cancerous cervical lesions in populations were HPV infection is common (Bayo et al., 2002).
   Participants were asked whether they were married more than one time or whether their partners have multiple wives

2- High parity: is considered a main cofactor for precancerous and cancerous cervical lesions among females suffering from persistent infection with HPV(Jensen et al.,2013).
   Participants were asked about No of deliveries, which was categorized into four groups as follow: No deliveries, 1-4 times, 5-10 times and > 10 times

3- Use of contraceptives: Risk of precancerous and cancerous cervical lesion increases in women who have had used or still using oral contraceptive pills for ≥ 5 years. The longer the use of oral contraceptive the higher the risk of acquiring cervical lesions, and after stopping the use of them the risk decreases over time (NIH,2018).
   Participants were asked about current or past using of oral contraceptives.

3.4.5 Family history and genetic factors: (annex 1)

Persistent HPV infection is considered the most common etiological cause of most precancerous and cancerous cervical lesions, rather than genetic susceptibility or family history, so little information and knowledge is available about the role of family history and genetic predisposition for cervical lesion, but still they are considered as co-factor with persistent HPV infection to cause precancerous and cancerous cervical lesions. (Bellingeret al., 2013)**.**
Participants were asked whether they have family history of cervical, ovarian and uterine cancer or not.

3.5 Dependent Variable

3.5.1 Precancerous and cancerous lesions with positive Pap smear findings

1- Cervical lesions were assessed clinically so as to compare the clinical findings with the test results (annex 2)

The most common symptoms for cervical lesions are vaginal bleeding which is usually postcoital bleeding, abnormal vaginal discharge especially with bad odor, dysuria, vaginal discomfort or pelvic pain.

These symptoms were assessed by asking the participant whether they have any vaginal bleeding or discharge, menorrhagia, postcoital or contact bleeding, spotting between periods, postmenopausal bleeding , dysuria, lower abdominal or pelvic pain and vaginal mass

-However, in early stages of precancerous and cancerous cervical lesions, physical examination done by Gynecologist could be normal but with the progression of the disease abnormal appearance of the cervix become obvious for the physician, including gross erosion, ulcer and even mass.

These signs were assessed by the Gynecologist, who reported whether he/she could see vaginal bleeding or discharge, erosions, ulcers, external polyps, ecto-cervical polyps, masses, warts, pelvic or parametrial metaplasia, leukoplakia and ectopy.

2- Pap smear results (annex 3)

Pap smear test can detect precancerous cervical cell lesions that may progress to cancerous cells if not treated properly and it can detect cancerous cells ,as well, in early stages giving the chance for early treatment and good prognosis. It also can detect noncancerous condition such as inflammation as well as infection.

However, for every female, cervical lesion screening must be part of her routine health care. Routine precancerous cervical lesion screening has shown a great reduction in both invasive cervical cancer incidence and death from cervical cancer, it is rare for Pap smear test to miss cervical abnormalities in females $\geq$ 30years old if the procedures of obtaining the biopsy and reading the biopsy were with no fouls.

Unfortunately, Pap smear test alone is not effective in detecting adenocarcinoma and glandular cell abnormalities which are less common than sqaumous cell abnormalities and sqaumous cell carcinoma that are more likely to be detected by Pap smear test, so it would more beneficial to add the HPV contesting screening to Pap smear screening in almost all cases (NIH,2014).

The cervical lesions were assessed by Pap smear test screening and this procedure was performed by Gynecologists using the same kits for all the participants and using the same procedure for obtaining the smear by following the written instructions on the kits, also it has been fixed and read by the same professional histo-pathologist with the same universal routine procedure for performing Pap smear test.

Moreover, the test assessed the presence of inflammation and degree of inflammation(mild, moderate and severe), fresh or old blood , atypical glandular cells, atypical sqaumaous cells, CIN 1,2,3 cervical cancer, Candida and inadequate sample

Chapter four: Methodology

4.1 Introduction

In this chapter, study setting, study designs, sampling method and sample size, selection of the study population with its inclusion and exclusion criteria, study tools (questionnaire, medical form and Lab results form), field work and data collection are presented. In addition, study statistical analysis methods, as well as study ethical considerations are presented.

4.2 Study settings

The study was done in Ministry of Health -primary health care Obstetrics and Gynecology clinic- and in Al-Zakat committees Gynecology clinics in addition to private clinics all in Ramallah district.

Primary Health Care (PHC) directorate is one important division of Palestinian Ministry of Health . It's considered the main first line of defence because it provides screening and preventive measurements in addition to primary care services.
PHC through its 466 centres in West Bank provides Palestinian citizens with primary health services, these services differ from one center to another according to the level of the primary health care center. These centers are divided into: comprehensive health centers, second, third, and fourth, depending on the size of the medical staff in each health center, and the level of medical services provided. PHC centres provide services to approximately 2,881,687 inhabitants in West Bank including; women and maternal health, child health, mental health, dental health , non-communicable , preventive medicine, environmental, educational and school health services through general, family medicine and specialized clinics. PHC centres in MOH offer a range of health services to Palestinian females through its 313 Gynaecological centres, and this specialized clinic is considered one of the main clinics in PHC that provides STIs treatments, Pap smear screening, family planning and other gynaecological counselling and treatments.

Ramallah and Al-Bireh directorate is one of the 14 directorates of PHC centres in West Bank that provides services to approximately 328,861 inhabitants with its 56 centres, including gynaecological health services, Pap smear screening and follow up . All female medical records are computerized under the DHIS2 system. In these centres with the help of nurses and gynaecologist the Pap smear biopsies were taken and send to a specialized histopathology centre in Ramallah for the fixation and microscopic reading of the results

Al-Zaka Committees is a nongovernmental nonprofit organization that provides health services in addition to welfare activities in West Bank and Gaza Strip. Zakat committees have two major best rank hospitals and 14 medical service clinics and centers in West Bank.

Basic health services with small drug costs are provided by the Zakat clinics and centers so as to decrease health care financial burden on patients. These clinics cover the main cities with limited services in rural areas

Zakat committee in Ramallah, is situated in the city center where it is available for all types of people, offering many health services including general health practices and specialized health practices such as gynecological health services including Pap smear screening in addition to a pharmacy services , dental services, basic cardiological orthopedic and lab test services . In addition, private doctors attend the clinics on a regular base to offer free checkups on fixed schedules during the month, and by that providing an additional option of healthcare system for poor and marginalized people beside governmental public health services. From this centre Pap smear biopsies were taken by a gynaecologist and send to a specialized histopathology centre in Ramallah for the fixation and microscopic reading of the results

Private sector Obstetric and Gynecologic clinics are clinics managed by gynecologist, and offers many specialized services for females attending the clinics especially Pap smear screening service, which are then send to special labs for the final results. From these clinics multiple Pap smear biopsies were taken by the specialists and then send to a specialized histopathology centre in Ramallah for the fixation and microscopic reading of the results

Pathocare histopathology lab is a private laboratory that was established on 2015. It is a specialized Tissue Center for all Tissue Biopsy and Early Diagnosis of Cancer, situated in Ramallah district in Israel Street in the center of Ramallah city. It receives biopsies from all districts of West Bank and it is managed by professional certified pathologist Dr Ghassan Balosha who diagnoses the cases. All technical work including fixation and staining is accomplished by lab technicians. The researcher had performed the technical process of her cases under the supervision of the technicians and followed up the process of diagnosis on the microscope screen with her supervisor.

4.3 Study Design

A cross-sectional quantitative design was employed to achieve study objectives and had aimed to recruit Palestinian females, in their productive age.

4.4 Study population

All Palestinian female, in their productive age attending Gynecological clinics (MOH, NGOs and private clinics) in Ramallah, West Bank. A sample of 100 female were interviewed and tested, after giving their approval to be part of the research, during the time of the study data collection period, i.e. December 2017 to July 2018.

From the 100 sample, 60 were from PHC centers in MOH, 20 from Al-Zaka Committee clinics and 20 from private clinics.

4.4.1 Inclusion criteria:

- Palestinian female at her productive age(20-55 years old)
- Those with no history of uterine or cervical lesions, diseases or cancer
- Those who were in the past or are still sexually active.
- All Palestinian females visiting the gynecology clinics and seeking counseling or treatment for gynecological problem other than cervical disease.
- Participants' consent to participate in the study was required.

4.4.2 Exclusion criteria

- Female with positive cervical cancer or disease history.
- Those not in their productive age.
- Those how have never been married(never had sex before)
- Those not Palestinian
- Those not living in West Bank.

4.5 Study period

The study collection data was carried out in the period December 2017 until July 2018. The questionnaire, the medical form, the lab form, the consent form, Ministry of Health Al-Zaka committee and private sector approval and permission, and the logistic preparation were ready by the end of November 2017. Data collection and study population interviews started in December 2017. After eight months, the number of eligible participants that were included in the study was 100 female participants and Pap smear sample were collected.
Laboratory microscopic testing started in December 2017 and finished in September 2018.

4.6 Sampling and sample size

4.6.1 Sampling method

A non-probability convenience sampling methods was used, including the accessible female population by the researcher. From Ramallah district; a random selection from MOH, NGOs and private sector gynecological clinics, so one clinic from each will be selected. The sample was convenient and the sample size was dependent on the number of patients attending the gynecological clinic (500 female ; 300 attended MOH clinics , 100 attended Al-Zakat and 100 attended private clinic) evenly- proportion to size, all female patients attending the gynecological clinic during the study period have been invited to participate , after they have signed the concept form, they were asked to perform the Pap smear test and were interviewed to fill a questionnaire designed by the researcher, and the medical forms for the participants were filled by the gynecologist.

4.6.2 Sampling size

Using the sample size calculation software available online on EpiTools epidemiological calculators (epitools ,2016), the sample size was estimated to be about 100, according to a specific formula:

$$N = \frac{t^2 * p\,(1-p)}{d^2}$$

N= appointed sample size.
t= CI 95% (1.96)
P= estimated prevalence
D= margin error at 5% (.05)

The estimated prevalence in Palestine was 2.4% (Asian Pacific journal, 2009)

4.7. Data source and study tools

4.7.1 Structured interview questionnaire

A face-to-face structural interview questionnaire was developed by the researcher after reviewing similar studies and previously validated questionnaires. The questionnaire was divided into sections to cover the study objectives. The full questionnaire, in Arabic is presented in Annex 1 . The following sections cover the questionnaire and source of questionnaire parts.

- Section one: The socio-demographic and economic characteristic, it included questions about participant's age, marital status, physical characteristics , profession, education, residence type, residence area, history of polygamy and level of income.
- Section Two: Reproductive health, it included questions about participant's age at menarche, history of menstrual cycle and menopause , age of marriage, hormonal history and oral contraceptive use, history of parity and gravidity , abortions, age at first child birth, history of ectopic pregnancy and history of Pap smear screening test.
- Section three: Present and past medical history, it included questions about health status of the participants vaginal discharge and bleeding, pelvic and low abdominal pain, history of STIs, history of hormonal dysfunction, past medical and surgical history ,history of malignancies, inherited disease and chronic diseases.
- Section four: Family history: it contained questions regarding family history of malignancy, chronic diseases and STIs
- Section five: The lifestyle section included questions about smoking habits, alcohol drinking and physical activity.

4.7.2 Medical form

A structural medical form was constructed after reviewing gynecological medical files form gynecological departments in hospitals and outpatient clinics and previously valid medical forms used by professionals, Annex 2. The form was divided into two sections:

- First section : covers the participants symptoms and complains that are connected to STIs and cervical lesions , it included questions about vaginal bleeding and discharge, menorrhagia, contact and postcoital bleeding, spotting , menopausal bleeding , pelvic and lower abdominal pain and vaginal masses.
- Second section: covers the physical findings by the Gynecologist. It included the observation of vaginal bleeding and discharge, the presence of erosions, ulcers, polyps, masses warts leukoplakia, parametrial or pelvic metastases and ectopy.

4.7.3 Laboratory Form

A structural laboratory result form was constructed by the expert pathologist containing the required information to cover the study objectives, Annex 3. It contained the observed results from reading the fixed Pap smear , whether the results showed inflammation , infection , precancerous lesions, cancerous lesions or inadequate cell.

4.7.4 Validation for the instruments

The questionnaire and the medical form were structurally built by the researcher, based on literature review of previous studies (Elamurugan et al., 2016; Sabrina et al., 2010; Harsha et al.,2014), and the two instruments as a whole were reviewed by experts in the research field, Gynecologist and Pathologist. The Lab result form was structurally built by a Pathologist who is an expert in his field.

4.8 Field work

The field work has been done in three steps; step one was the interview by the researcher, step two was obtaining the Pap smear biopsy and filling the medical form(Annex 2) by the gynaecologist at the gynaecology clinics and step three was reading the results by the pathologist at the histopathology lab

4.8.1 Interviews

The researcher face to face interviewed the study participants during their waiting time for clinic visit in Primary health care clinics in MOH, Al-Zaka and private Gynecological clinics

Before filling the study questionnaire, study aim and objectives were clarified for the participants. After the participant accepts to participate, she signed the consent form (Annex 8).

4.8.2 Pap smear

To obtain the Pap smear biopsy a uniform tool was distributed by the researcher to all the clinics that were part of the study, with the same instructions on how to take the biopsy and from where and how to use the fixing stain gel

A PAP-PAK kit was used containing one microscope slide, one cervical-vaginal scraper, one CytoSoft cytology brush one cytology fixative pouch, and instruction how to use the kit.

Before starting the procedures the researcher explained to the physicians how to use the kit and from where to obtain the sample and how to apply the fixation solution

All procedures were observed by the researcher who is a medical physician.

After visual inspection of the cervix and looking for any abnormalities or specific signs, a Pap smear biopsy was taken by the physician.

The Pap smear biopsy has involved collecting cell sample from the cervical tissue of participants, then placing the cell tissue on a slide made up of glass, then using Papanicolau stain substance to stain the tissues.

So, as to complete the procedure the gynecologist use the following instruments light for examination, foot support table examination , examination light, metal speculum, sterile gloves, cyto-brush, cervical spatula and cytology base liquid glass slide and fixative.

Procedure took about 15 min: while the woman positioned on her back, the gynecologist examined the outside area of female rectal and genital areas as well as, the urethra to make sure that they have no abnormalities then

1. A metal speculum was inserted by the gynecologist into the vagina
2. A small brush or swab (cervical spatula and cytobrush) was inserted into the cervix opening and turned around to collect enough cell samples.
3. As part of Pap smear sampling, a second sample has been collected from cervical tissue surface
4. The samples were in a glass slide and a fixating solution was added to it to isolate cells in the slides for laboratory evaluation

4.8.3 Laboratory test

After obtaining the Pap smear biopsy the sample was send to Pathocare histopathology lab were the sample was placed in a Coplin jar with 99% ethyl or reagent alcohol for 15 minutes. Then it was placed in Alcohol 70% for 2 min, then in H2O for 2 min, then in Hematoxylene for 4 min, then in HCL 0.05% for another 1.5 min, then in H2O for 5 min, then in Orange G for 3 min, then in alcohol 95% for 2min then EA for 4 min then another 2 min in alcohol 95% then at last for 2 min in alcohol 100%, then it was ready to be examine by the pathologist under microscope. Annex 3

4.9 Statistical analysis

Data collected was entered, cleaned and analyzed by using Statistical Package for Social Sciences (SPSS® version 23.0)

For descriptive analysis, frequencies were calculated for all study variables and were presented in tables and figures
To examine the binary associations, univariate analysis was done using the cross tabulation and the significance of Pearson and Fisher exact chi square-as needed- at *P*-value 0.05 was calculated, to study the association between dependent and independent variables.

Multivariate analysis was done after the univariate analysis, all the variables that showed significant association were introduced in the multivariate analysis. Logistic regression model was used. The logistic regression was used to compare odds ratio with confidence interval of 95%. P-value < 0.05 was used.

4.10 Ethical approval

Before starting the study, we got the approval from Al Quds University-Local Helsinki of research committee. In addition, we obtained the approval to conduct the study at Ramallah and Al-Bireh primary health directorate from PHC directorate in MOH (Annex 4.7), from Al-Zakat Committee in Ramallah and Al-Bireh Governorate (Annex 5) and from the Private sector (Annex 6). Also all female participants were informed about the study aim, objectives and signed a consent form before participating (Annex 8).

Chapter Five: The Results

5.1 Introduction

In this chapter, study results will be presented in three parts. In part one; descriptive analysis will be presented for all the data from the three questionnaires, the participant interview questionnaire, the medical form data and the laboratory result data. In part two, univariate statistical analysis for the association between dependent and independent variables will be presented. In part three, the multivariate statistical analysis results will be presented.

5.2 Part 1: Descriptive analysis

5.2.1 Socio-demographic characteristics of the participants:

The response rate of study was 100% ; 100 participants were included in study. 34% of them were between the ages of 35-44 years, while 86% of them were married, 68% of them were housewives , More than three quarter of them (84%) came from intermediate income families. More than half of them lives in the city (55%), around (40%) the of participants finished their high school education.(table 5.1)

5.2.2 Reproductive health related characteristics

More than three quarter of the participants (79%) got married between the age of 15-24 years old. 45% of them had 5-10 childbirth, 61% had their 1st baby between the ages of 16-20 years old . Around three quarter of the participants (70%) have had used oral contraceptives; of these 63% have had used oral contraceptive. Almost less than half of the participants (49%) have had a Pap smear test in their life. (Table 5.2).

5.2.3 Past medical history

Among the 100 participant, 67% reported having a history of vaginal infection after being previously examined and tested by physicians , 66% still having symptoms of infection , 3 reported having cervical lesions before and 5% reported having other types of cancer.(Table 5.3)

5.2.4 Family and genetic history :

Among the 100 participants, 31 reported that their husband have had suffered from infection , 34% have a family history of different kind of malignancies including cervical cancer, breast , uterine and ovarian cancer, 14% of them reported having some form of genetic diseases in their families.(Table5.4)

Table (5.1): Socio-demographic distribution of participants

Variable		Frequency n=100	Percentage
Age(in years)	<15	2	2%
	15-24	7	7%
	25-34	18	18%
	35-44	34	34%
	45-54	23	23%
	≥55	16	16%
Marital status	Married	86	86%
	Divorced	8	8%
	Widow	6	6%
Residency	City	55	55%
	Village	38	38%
	Camp	7	7%
Education level	Elementary or no education	21	21%
	High school	40	40%
	Bachelor degree	31	31%
	Post graduate	8	8%
Income status	Low	8	8%
	Intermediate	84	84%
	High	4	4%
	Don't know	4	4%
Occupation	Housewife	68	68%
	Field work Employee	5	5%
	Hand paid workers	2	2%
	Office clerk	23	23%
	Free business(self employee)	2	2%

Table 5.2 Reproductive health characteristic distribution

Variables		Frequency(n=100)	percentage
Age at Marriage(in years)	<15	3	3%
	15-24	79	79%
	25-34	17	17%
	35-44	1	1%
	≥45	0	0
Parity(No of childbirth)	None	3	3%
	1-4	44	44%
	5-10	45	45%
	>10	8	8%
Age at first baby(in years)	≤15	5	5%
	16-20	61	61%
	21-25	23	23%
	26-30	9	9%
	31-35	1	1%
	41-45	1	1%
Use of contraceptives;	Yes	70	70%
	Oral	63	90%
	Metallic IUD	4	5.7%
	Plastic IUD	3	4.3%
	Others	0	0%
Pap smear done before	Yes	49	49%
	Once	33	67.3%
	Twice	9	18.4%
	3 times	6	12.2%
	>3	1	2%

Table 5-3: Medical history of the Participants

Variables	Frequency n=100	Percentage %
Past History of infection	67	67%
Treated for past hx of infection	67	100%
Present symptoms of infection	66	98.5%
Cervical lesions	3	3%
Other type of cancer *	5	5%

*Breast cancer, ovarian and uterine cancer

Table 5-4: Family and genetic history among participants

Variable	Frequency n=100	Percentage %
Husband with infection	31	31%
Family history of cancer*	34	34%
Genetic diseases in family	14	14%
Chronic diseases**	23	23%

*Breast, ovarian, uterine and cervical cancer. ** DM, HTN, CVD and Respiratory diseases

5.2.5 Smoking behavior among participants .

Almost half of the participants (49%) smoke cigarettes , 36% smoke water-pipe.(Table 5.5)

Table5-5: Smoking behavior among Participants

Risk factor		Count	percentage
Smoking cigarettes	Nonsmoker	42	42%
	Smoker	49	49%
	Ex-smoker	9	9%
Cigarettes per day	<10	8	16.3%
	10-20	41	83.7%
	>20	0	0%
Period of cigarette smoking	<one year	2	4.1%
	1-5 years	8	16.3%
	6-10years	23	46.9%
	>10years	16	32.7%
Smoking water-pipe	Nonsmoker	64	64%
	Smoker	36	36%
Water-pipe per frequency	Daily	9	25%
	4-6times/wk	7	19.4%
	2-3times/wk	16	44.4%
	1-3times/month	4	11.1%
Period of water-pipe smoking	<one year	6	16.7%
	1-5 years	24	66.7%
	6-10years	6	16.7%

5.2.6 Medical symptoms and signs

Table 5.6 shows that the main complains for participants at presentation were vaginal discharge (74%) , vaginal bleeding(58%) and 22% presented with lower abdominal pain. While the main physical findings by the physician were ; vaginal discharge (68%) , 51% vaginal bleeding and 21% were presented with erosions.(Table 5.6)

Table 5-6: Symptoms and signs distribution among participants

Variable		Frequency	Percentage
Symptoms	**No symptoms**	19	19%
	Vaginal bleeding	58	58%
	Vaginal discharge	74	74%
	Menorrahagia	6	6%
	Contact bleeding	8	8%
	Blood spots	13	13%
	Dysuria	9	9%
	Post menopausal bleeding	3	3%
	Post coital bleeding	16	16%
	Pelvic pain	10	10%
	Lower abdominal pain	22	22%
	Pain during sexual intercourse	17	17%
	Vaginal mass	2	2%
Sings	**No significant clinical observation**	18	18%
	Vaginal bleeding	51	51%
	Vaginal discharge	68	68%
	Erosion	21	21%
	Ulcers	12	12%
	External polyps	1	1%
	Ecto-cervical polyps	2	2%
	Endo-cervical polyps	3	3%
	Well defined mass	4	4%
	Warts	1	1%
	Vaginal bleeding after PV	2	2%
	Ectopy	3	3%

5.2.7 Histopathology findings

Table 5.7, shows that 82% of the participants have positive Pap smear; (presence of cervical lesions) . Infection was the most common histological findings among the participants with 76%, followed by non-infectious inflammation that accounted for 66 % and 7% have precancerous lesions; from them 3% atypical sqaumous cells, 2% atypical Glandular cells. 1% CIN I&II and 1% CIN III (Table 5.7)

Table 5-7: Histopathological findings among participants

Variables *		Frequency (n=100)	Percentage
Pap Smear positive	Yes	82(n=100)	82%
Inflammation	Yes	66	66%
Infection	Yes	76	76%
	Candida	43	43%
Precancerous	Yes	7	7%
	Atypical sqaumous cells	3	3%
	Atypical Glandular cells	2	2%
	CIN I,II	1	1%
	CIN III	1	1%
Cervical cancer	Yes	0	0%
Inadequate	Yes	7	7%
Within normal limits	Yes	11	11%

*some participants may have more than one histopathological finding

5.3 Part 2 : Association between dependent and independent variables

Chi-square test was applied to check associations between different independent variables and dependent variables, which is cervical lesions that are measured by Pap smear test.

5.3.1 Risk factors association with positive Pap smear

5.3.1.1 Association between socio-demographic (independent) variables and the dependent variable.

Participants were classified according to their Pap smear results (positive and negative), which was used as an indication for the presence of cervical lesion.

Results showed that there no significant association between socio-demographic variables, including age, level of income, level of education, occupation and marital status with the dependent variable which was Pap smear results. (Table 5-8)

Table 5.8: Associations between socio-demographic (independent) variables and dependent variable(positive Pap smear)

Variable		Positive Pap smear frequency N=82	Negative Pap smear Frequency N=18	*P value*
		N(%)	N(%)	
Age(in years)	<15	1(50%)	1(50%)	0.367
	15-24	5(71.4%)	2(28.6%	
	25-34	14(77.8%)	4(22.2%)	
	35-44	31(91.2%)	3(8.8%)	
	45-54	17(73.9%)	6(26.1%)	
	≥55	14(87.5%)	2(12.5%)	
Marital status	Married	71(82.6%)	15(17.4%)	0.865
	Divorced	6(75%)	2(25%)	
	Widow	5(83.3%)	1(16.7%)	
Residency	City	44(80%)	11(20%)	0.104
	Village	34(89.5%)	4(10.5%)	
	Camp	4(57.1%)	3(42.9%)	
Education level	Elementary or no education	18(85.7%)	3(14.3%)	0.766
	High school	34(85%)	6(15%)	
	Bachelor degree	24(77.4%)	7(22.6%)	
	Post graduate	6(75%)	2(25%)	
Income status	Low	5(62.5%)	3(15.5%)	0.108
	Intermediate	71(85.5%)	13(15.5%)	
	High	2(50%)	2(50%)	
Occupation	housewife	56(82.4%)	12(17.6%)	0.892
	Field work Employee	4(80%)	1(20%)	
	Hand paid workers	2(100%)	0(0%)	
	Office clerk	18(78.3%)	5(21.7%)	
	Free business(self employee)	2(100%)	0(0%)	

5.3.1.2 Association between reproductive health (independent) variables and Pap smear results

Results showed that age at marriage was significantly associated with Pap smear results (P<0.001) , Parity or Number of child birth indicated significant association with Pap smear results (P=0.03), in addition age at first baby was significantly associated with Pap smear results (P<0.001) and contraceptive use including oral contraceptive was significantly associated with Pap smear results (P<0.001 for contraceptive use and P=0.002 for oral contraceptive use). (Table 5.9)

Table 5.9: Reproductive health variables and association with Pap smear results

Variables		Positive Pap smear frequency N=82	Negative Pap smear Frequency N=18	*P value*
		N(%)	N(%)	
Age at Marriage(in years)	<15	3(100%)	0(0%)	0.001
	15-24	71(89.4%)	8(10.1%)	
	25-34	7(41.2%)	10(58.8%)	
	35-44	1(100%)	0(0%)	
	≥45	0	0	
Parity(No of childbirth)	none	2(66.7%)	1(33.3%)	0.03
	1-4	31(70.5%)	13(29.5%)	
	5-10	41(91.1%)	4(8.9%)	
	>10	8(100%)	0(0%)	
Age at first baby(in years)	≤15	3(60%)	2(40%)	0.001
	16-20	58(95.1%)	3(4.9%)	
	21-25	16(69.6%)	7(30.4%)	
	26-30	3(33.3%)	6(66.6%)	
	31-35	1(100%)	0(0%)	
	41-45	1(100%)	0(0%)	
Use of contraceptives;	Yes	64(91.4%)	6(8.6%)	0.001
	Oral	60(95.2%)	3(4.88%)	0.002

5.3.1.3 Association between Participant medical history and Family history (independent variables) with Pap smear results

Results showed that history of having vaginal infection was significantly associated with Pap smear results (P<0.001) , family history of cancer indicated significant association with Pap smear results (P=0.03), in addition husband having infection was significantly associated with Pap smear results (P=0.01) .While history of cervical cancer, and other types of cancer was not significantly associated with Pap smear results. (Table 5.10)

Table 5-10: Association between Medical and family history and Pap smear results

Variable	Positive Pap smear frequency N=82	Negative Pap smear Frequency N=18	*P value*
	N(%)	N(%)	
History of vaginal infection	66(98.5%)	1(1.5%)	0.001
Family history of cancer *	24(70.6%)	10(29.4%)	0.03
Husband with history of infection	30(96.8%)	1(3.2%)	0.01

***Breast, ovarian and uterine cancer**

5.3.1.4 Smoking behavior and association with Pap smear results

Results showed a significant association between smoking behavior whether it was cigarette smoking (P=0.01) and water-pipe smoking (P=0.01) and Pap smear results. (Table 5.11).

Table 5.11: Association between smoking behavior and Pap smear results

Variables		Positive Pap smear frequency N=82	Negative Pap smear Frequency N=18	*P value*
		N(%)	N(%)	
Smoking cigarettes	Smoker	45(91.8%)	4(8.2%)	0.01
	Nonsmoker	29(69%)	13(31%)	
	Ex-smoker	8(88.9%)	1(11.1%)	
Smoking water-pipe	Nonsmoker	48(75%)	16(25%)	0.01
	Smoker	34(94.4%)	2(5.6%)	

5.3.1.5 Association between Symptoms and physical findings and Pap smear results

Table 5.12 shows that the only significant association between symptoms and Pap smear results were with vaginal bleeding($p<0.001$), vaginal discharge($P=0.003$), while other symptoms were not significantly associated with Pap smear results. However, concerning the physical findings there have been significant association between vaginal bleeding($p<0.001$), vaginal discharge($p=0.01$) and erosion($p=0.05$) with Pap smear results, while other findings have had no significant association.(Table 5.12)

Table 5-12: Association between medical findings and Pap smear results

Variable		**Positive Pap smear frequency N=82**	**Negative Pap smear Frequency N=18**	***P value***
		N(%)	**N(%)**	
Symptoms	**Vaginal bleeding**	56(96.6%)	2(3.4%)	0.001
	Vaginal discharge	66(89.2%)	8(10.8%)	0.003
	Menorrahagia	5(83.3%)	1(16.7%)	0.706
	Contact bleeding	7(87.5%)	1(12.5%)	0.559
	Blood spots	12(92.3%)	1(7.7%)	0.272
	Dysuria	7(77.8%)	2(22.2%)	0.509
	Post menopausal bleeding	2(66.7%)	1(33.3%)	0.452
	Post coital bleeding	15(93.8%)	1(6.3%)	0.164
	Pelvic pain	9(90%)	1(10%)	0.428
	Lower abdominal pain	20(90.9%)	2(9.1%)	0.181
	Pain during sexual intercourse	14(82.4%)	3(17.6%)	0.636
Sings	**Vaginal bleeding**	50(98%)	1(2%)	0.001
	Vaginal discharge	61(89.7%)	7(10.3%)	0.01
	Erosion	20(95.2%)	1(4.8%)	0.05
	Ulcers	11(91.7%)	1(8.3%)	0.319

5.3.2 Risk factor association with different Pap smear findings

When comparing each finding from the Pap smear test with those variables that showed significant association with Pap smear results the results were as follow;

5.3.2.1 Inflammation findings:

a) Association with Reproductive health effect

There was a significant association between age at marriage (p=0.001), age at first baby (p<0.001) and use of oral contraceptives (p=0.01) with inflammation findings in Pap smear test. In the contrary there was no significant association between inflammation findings and Parity (No of child birth)(p=0.06) (Table 5.13)

Table 5.13 Association between Reproductive health effect and inflammation

Variables		Positive Inflammation frequency N=66	Negative inflammation N=34	*P value*
		N(%)	N(%)	
Age at Marriage(in years)	<15	3(100%)	0(0%)	0.001
	15-24	58(73.4%)	21(26.6%)	
	25-34	4(23.5%)	13(76.5%)	
	35-44	1(100%)	0(0%)	
	≥45	0	0	
Parity(No of childbirth)	none	2(66.7%)	1(33.3%)	0.06
	1-4	23(52.3%)	21(29.5%)	
	5-10	41(91.1%)	4(47.7%)	
	>10	7(87.5%)	1(12.5%)	
Age at first baby(in years)	≤15	3(60%)	2(40%)	0.001
	16-20	51(83.6%)	10(16.4%)	
	21-25	9(39.1%)	14(60.9%)	
	26-30	2(22.2%)	1(77.8%)	
	31-35	0(0%)	1(100%)	
	41-45	1(100%)	0(0%)	
Use of contraceptives;	Yes	52(74.3%)	18(25.7%)	0.01
	Oral	50(79.4%)	13(20.6%)	0.01

b) Medical and family history

The results showed a significant association between having vaginal infection (p<0.001) and husband having infection (p=0.03) and inflammation findings on Pap smear test, but there was no significant association with positive family history of cancer (p=0.193)(Table 5.14)

Table 5-14 Association between Medical and family history and inflammation

Variable	Positive Inflammation frequency N=66	Negative inflammation N=34	*P value*
	N(%)	N(%)	
History of vaginal infection	55(82.1%)	12(17.9%)	0.001
Family history of cancer *	20(58.8%)	14(41.2%)	0.193
Husband with history of infection	25(80.6%)	6(19.4%)	0.03

*** Breast, cervical. Ovarian and uterine cancer**

c) Smoking behavior

The results showed a significant association between smoking cigarettes (p=0.01) and water-pipe (p=0.01) with inflammation findings with Pap smear test. (Table 5.15)

Table 5-15 Association between smoking behavior and inflammation findings

Variables		Positive Inflammation frequency N=66	Negative inflammation N=34	*P value*
		N(%)	N(%)	
Smoking cigarettes	Smoker	40(81.6%)	9(18.4%)	0.01
	Nonsmoker	20(47.6%)	22(52.4%)	
	Ex-smoker	6(66.7%)	3(33.3%)	
Smoking water-pipe	Nonsmoker	36(56.3%)	28(43.8%)	0.01
	Smoker	30(83.3%)	6(16.7%)	

d) Symptoms and physical findings

The results showed symptoms of vaginal bleeding and discharge as well as physical findings of both were significantly associated with inflammation findings in Pap smear test (P value respectively; <0.001,0.01,<0.001 and 0.01). However, erosion physical findings was not associated with inflammation findings.(Table 5.16)

Table 5-16: Association between medical findings and inflammation findings

Variable		Positive Inflammation frequency N=66	Negative inflammation N=34	*P value*
		N(%)	N(%)	
Symptoms	**Vaginal bleeding**	51(87.9%)	7(12.1%)	0.001
	Vaginal discharge	55(74.3%)	19(25.7%)	0.01
Sings	**Vaginal bleeding**	46(90.2%)	5(9.8%)	0.000
	Vaginal discharge	51(75%)	17(25%)	0.01
	Erosion	16(76.2%)	5(23.8%)	0.199

5.3.2.2 Infection findings:

a) Association with Reproductive health effect

There was a significant association between age at marriage (p=0.003), parity (No of child birth) (p=0.01), age at first baby (p=0.002) and use of contraceptives (p=0.01) with infection findings in Pap smear test. In the contrary there was no significant association between infection findings with oral contraceptives(p=0.138) (Table 5.17)

Table 5.17 Association between Reproductive health effect and infection

Variables		Positive Infection frequency N=76	Negative infection N=24	*P value*
		N(%)	N(%)	
Age at Marriage(in years)	<15	3(100%)	0(0%)	0.003
	15-24	65(82.2%)	14(17.7%)	
	25-34	7(41.4%)	10(58.8%)	
	35-44	1(100%)	0(0%)	
	≥45	0	0	
Parity(No of childbirth)	none	2(66.7%)	1(33.3%)	0.01
	1-4	27(61.3%)	17(39.6%)	
	5-10	39(86.7%)	6(13.3%)	
	>10	8(100%)	0(0%)	
Age at first baby(in years)	≤15	3(60%)	2(40%)	0.002
	16-20	54(88.5%)	7(11.4%)	
	21-25	14(60.8%)	9(39.1%)	
	26-30	3(33.3%)	6(66.6%)	
	31-35	1(100%)	0(0%)	
	41-45	1(100%)	0(0%)	
Use of contraceptives;	Yes	58(82.8%)	12(17.1%)	0.01
	Oral	54(85.7%)	9(14.2%)	0.138

b) Medical and family history

The results showed a significant association between having history of vaginal infection ($p<0.001$) and husband having infection ($p=0.01$) and infection findings on Pap smear test, but there was no significant association with positive family history of cancer ($p=0.252$)(Table 5.18)

Table 5-18 Association between Medical and family history and infection

Variable	Positive Infection frequency N=76	Negative infection N=24	*P value*
	N(%)	N(%)	
History of vaginal infection	64(95.5%)	3(4.5%)	0.001
Family history of cancer *	24(70.6%)	10(29.4%)	0.252
Husband with history of infection	29(93.5%)	2(6.5%)	0.01

*** Breast, cervical. Ovarian and uterine cancer**

c) Smoking behavior

The results showed a significant association between smoking cigarettes (p=0.04) and water-pipe (p=0.004) with infection findings with Pap smear test(Table 5.19)

Table 5-19 Association between smoking behavior and infection findings

Variables		Positive Infection frequency N=76	Negative infection N=24	*P value*
		N(%)	N(%)	
Smoking cigarettes	Smoker	43(87.7%)	6(12.2%)	0.04
	Nonsmoker	26(61.9%)	16(38.1%)	
	Ex-smoker	7(77.8%)	2(22.2%)	
Smoking water-pipe	Nonsmoker	43(67.2%)	21(32.8%)	0.004
	Smoker	33(91.7%)	3(8.3%)	

d) Symptoms and physical findings

The results showed symptoms of vaginal bleeding and discharge as well as physical findings of both were significantly associated with infection findings in Pap smear test (p value respectively; <0.001,0.001,<0.001 and 0.002). However, erosion physical findings was not associated with infection findings.(Table 5.20)

Table 5-20: Association between medical findings and infection findings

Variable		Positive Infection frequency N=76	Negative infection N=24	*P value*
		N(%)	N(%)	
Symptoms	**Vaginal bleeding**	53(91.4%)	5(8.6%)	0.001
	Vaginal discharge	63(85.1%)	11(14.9%)	0.001
Sings	**Vaginal bleeding**	47(92.2%)	4(7.8%)	0.001
	Vaginal discharge	58(85.3%)	10(14.7%)	0.002
	Erosion	18(85.7%)	3(14.3%)	0.190

5.3.2.3 Candida findings:

a) Association with Reproductive health effect

There was a significant association between age at marriage (p=0.02), age at first baby (p=0.04) and use of contraceptives (p=0.002) with Candida findings in Pap smear test. In the contrary there was no significant association between Candida findings and Parity (No of child birth)(p=0.0825) nor with oral contraceptives(p=0.062) (Table 5.21)

Table 5.21 Association between Reproductive health effect and Candida

Variables		Positive Candida frequency N=43	Negative Candida N=57	*P value*
		N(%)	N(%)	
Age at Marriage(in years)	<15	1(33.3%)	2(66.7%)	0.02
	15-24	39(49.4%)	40(50.6%)	
	25-34	2(11.8%)	15(88.2%)	
	35-44	1(100%)	0(0%)	
	≥45	0	0	
Parity(No of childbirth)	none	0(0%)	3(100%)	0.101
	1-4	22(50%)	22(50%)	
	5-10	20(44.4%)	25(55.6%)	
	>10	1(12.5%)	7(87.5%)	

Age at first baby(in years)	≤15	0(0%)	5(100%)	0.04
	16-20	32(52.5%)	29(47.5%)	
	21-25	9(39.1%)	14(60.9%)	
	26-30	1(11.1%)	8(88.9%)	
	31-35	0(0%)	1(100%)	
	41-45	1(100%)	0(0%)	
Use of contraceptives;	Yes	38(54.3%)	32(45.7%)	0.002
	Oral	35(55.6%)	28(44.4%)	0.825

b) Medical and family history

The results showed a significant association between having history of vaginal infection (p=0.002) and Candida findings on Pap smear test, but there was no significant association with positive family history of cancer (p=0.091) and husband having infection (p=0.360) (Table 5.22)

Table 5-22 Association between Medical and family history and Candida

Variable	**Positive Candida frequency N=43**	**Negative Candida N=57**	***P value***
	N(%)	**N(%)**	
History of vaginal infection	36(53.7%)	31(46.3%)	0.002
Family history of cancer *	11(32.4%)	23(67.6%)	0.091
Husband with infection	12(38.7%)	19(61.3%)	0.360

*** Breast, cervical. Ovarian and uterine cancer**

c) Smoking behavior

The results showed no significant association between smoking cigarettes (p=0.910) and water-pipe (p=0.198) with Candida findings with Pap smear test(Table 5.23)

Table 5-23 Association between smoking behavior and Candida findings

Variables		Positive Candida frequency N=43	Negative Candida N=57	*P value*
		N(%)	N(%)	
Smoking cigarettes	Smoker	20(40.8%)	29(59.2%)	0.910
	Nonsmoker	19(45.2%)	23(54.8%)	
	Ex-smoker	4(44.4%)	5(55.6%)	
Smoking water-pipe	Nonsmoker	25(39.1%)	39(60.9%)	0.198
	Smoker	18(50%)	18(50%)	

d) Symptoms and physical findings

The results showed symptoms of vaginal bleeding and discharge as well as physical findings of both and erosion were not significantly associated with Candida findings in Pap smear test (P value respectively; 0.410,0.108, 0.268, 0.298 and 0.111).(Table 5.24)

Table 5-24: Association between medical findings and Candida findings

Variable		Positive Candida frequency N=43	Negative Candida N=57	*P value*
		N(%)	N(%)	
Symptoms	**Vaginal bleeding**	26(44.8%)	32(55.2%)	0.410
	Vaginal discharge	35(47.3%)	39(52.7%)	0.108
Sings	**Vaginal bleeding**	24(47.1%)	27(52.9%)	0.268
	Vaginal discharge	31(45.6%)	37(54.4%)	0.298
	Erosion	12(57.1%)	9(42.9%)	0.111

5.3.2.4 Precancerous cells findings:

a) Association with Reproductive health effect

There has been no significant association between age at marriage (p=0.945), parity (No of child birth) (p=0.770) , use of contraceptives (p=0.232), oral contraceptives(p=0.840) and age at first baby (p=0.783) with Precancerous cells findings in Pap smear test. (Table 5.25)

Table 5.25 Association between Reproductive health effect and Precancerous cells

Variables		**Positive Precancerous cells frequency N=7**	**Negative Precancerous cells N=93**	***P value***
		N(%)	**N(%)**	
Age at Marriage(in years)	<15	0(0%)	3(100%)	0.945
	15-24	6(7.6%)	73(92%)	
	25-34	1(5.8%)	16(94.1%)	
	35-44	0(0%)	1(100%)	
	≥45	0	0	
Parity(No of childbirth)	none	0(0%)	3(100%)	0.770
	1-4	4(9%)	40(90.9%)	
	5-10	3(6.7%)	42(93.3%)	
	>10	0(0%)	8(100%)	
Age at first baby(in years)	≤15	0(0%)	5(100%)	0.783
	16-20	3(4.9%)	58(95%)	
	21-25	3(13%)	20(86.9%)	
	26-30	1(11.1%)	8(88.9%)	
	31-35	1(100%)	0(0%)	
	41-45	0(0%)	1(100%)	
Use of contraceptives;	Yes	3(4.2%)	67(95.7%)	0.232
	Oral	3(4.7%)	60(95.2%)	0.840

b) Medical and family history

The results showed no significant association between having history of vaginal infection (p=0.595), husband having infection (p=0.626) and positive family history of cancer (p=0.555) with Precancerous cells findings on Pap smear test (Table 5.26)

Table 5-26 Association between Medical and family history and Precancerous cells

Variable	Positive Precancerous cells frequency N=7	Negative Precancerous cells N=93	P value
	N(%)	N(%)	
History of vaginal infection	5(7.4%)	62(92.5%)	0.595
Family history of cancer *	2(5.8%)	32(94.1%)	0.555
Husband with infection	2(6.4%)	29(93.5%)	0.626

*** Breast, cervical. Ovarian and uterine cancer**

c) Smoking behavior

The results showed a significant association between smoking cigarettes (p=0.001) with Precancerous cells findings with Pap smear test, but there was no association and water-pipe (p=0.493) (Table 5.27)

Table 5-27 Association between smoking behavior and Precancerous cells findings

Variables		Positive Precancerous cells frequency N=7	Negative Precancerous cells N=93	*P value*
		N(%)	N(%)	
Smoking cigarettes	Smoker	0(0%)	49(100%)	0.001
	Nonsmoker	4(9.5%)	38(90.5%)	
	Ex-smoker	3(33.3%)	6(66.6%)	
Smoking water-pipe	Nonsmoker	3(8.3%)	33(91.7%)	0.493
	Smoker	4(6.2%)	60(93.7%)	

d) Symptoms and physical findings

The results showed signs of vaginal bleeding were significantly associated with Precancerous cells findings in Pap smear test (p value=0.05) . However, vaginal bleeding and discharge symptoms as well as physical findings of vaginal discharge and erosion were not associated with Precancerous cells findings. (P value respectively; 0.324, 0.587, 0.145 and 0.159) (Table 5.28)

Table 5-28: Association between medical findings and Precancerous cells findings

Variable		Positive Precancerous cells frequency N=7	Negative Precancerous cells N=93	*P value*
		N(%)	N(%)	
Symptoms	**Vaginal bleeding**	3(5.1%)	55(94.8%)	0.324
	Vaginal discharge	5(6.7%)	69(93.2%)	0.587
Sings	**Vaginal bleeding**	1(1.9%)	50(98%)	0.05
	Vaginal discharge	3(4.4%)	65(95.5%)	0.145
	Erosion	3(14%)	18(85.7%)	0.159

5.4 Multivariate analysis

All variables that were significant ($p<0.05$) in univariate analysis were included in a multivariate model, adjusted Odds ratio was calculated using forward logistic regression model.

5.4.1 Positive Pap smear

Table 5.29 shows that being married at young age increase risk (adjusted odds ratio) for cervical lesions (positive Pap smear test) by 7 folds, while increase No of child birth increase it by 0.2 folds, and the younger the age of having first baby increases the risk by 1.9 fold.(Table 5.29)

Table 5-29 Multivariate logistic regression models for the association between independent variables and Positive Pap smear test

Variable	AOR*	95% CI*	P-value
Age at marriage	7.612	2.512-23.064	0.001
Parity	0.283	0.113-0.710	0.01
Age at 1st baby	1.962	1.122-3.429	0.02
Contraceptives	7.100	2.418-20.847	0.001
Oral contraceptives	4.313	1.302-14.282	0.02
History of vaginal infection	30.800	9.222-50.725	0.001
Husband with infection	9.808	1.242-77.433	0.03
Smoking	1.908	1.888-4.100	0.04
Smoking water-pipe	5.667	1.222-26.280	0.03
Vaginal bleeding (symptom)	17.231	3.687-80.520	0.001
Vaginal discharge (symptom)	5.156	1.754-15.157	0.003
Vaginal bleeding (sign)	26.562	3.369-50.457	0.002
Vaginal discharge (sign)	4.565	1.566-13.301	0.01

* **AOR: Adjusted Odds Ratio, 95%CI: 95% confidence interval.** Variables included in the model: age at marriage and 1st baby, parity, contraceptive and oral contraceptive , history of vaginal infection and husband with infection , family history of malignancy, smoking cigarettes and water pipe, vaginal bleeding and discharge as a symptom and sign and erosions

5.4.2 Inflammation in Pap smear

Table 5.30 shows that being married at young age increase risk (adjusted odds ratio) for inflammation (positive Pap smear test) by 5 folds and the younger the age of having first baby increases the risk by 2.4 fold.(Table 5.30)

Table 5-30 Multivariate logistic regression models for the association between independent variables and inflammation

Variable	AOR*	95% CI*	P-value
Age at marriage	5.384	1.902-15.238	0.002
Age at 1st baby	2.434	1.367-4.333	0.003
Contraceptives	3.331	1.401-7.920	0.01
Oral contraceptives	6.577	1.452-29.785	0.02
History of vaginal infection	10.083	3.807-26.707	0.001
Husband with infection	2.846	1.034-7.831	0.04
Smoking water-pipe	3.889	1.422-10.636	0.01

Vaginal bleeding (symptom)	13.114	4.771-36.049	0.001
Vaginal discharge (symptom)	3.947	1.547-10.072	0.004
Vaginal bleeding (sign)	13.340	4.509-39.463	0.001
Vaginal discharge (sign)	3.400	10.403-8.239	0.01

* **AOR: Adjusted Odds Ratio, 95%CI: 95% confidence interval.** Variables included in the model: age at marriage and 1st baby, contraceptive and oral contraceptive , history of vaginal infection and husband with infection , smoking cigarettes and water pipe, vaginal bleeding and discharge as a symptom and sign

5.4.3 Infection in Pap smear

Table 5.31 shows that being married at young age increase risk (adjusted odds ratio) for infection (positive Pap smear test) by 4 folds and the younger the age of having first baby increases the risk by 1.7 fold.(Table 5.31)

Table 5-31 Multivariate logistic regression models for the association between independent variables and infection

Variable	AOR*	95% CI*	P-value
Age at marriage	4.449	1.628-12.162	0.004
Parity	0.295	0.130-.0673	0.004
Age at 1st baby	1.717	1.027-2.870	0.04
Contraceptives	3.334	1.336-8.325	0.01
History of vaginal infection	13.071	4.389-38.930	0.001
Husband with infection	4.083	1.117-4.929	0.03
Smoking water-pipe	5.372	1.476-19.554	0.01
Vaginal bleeding (symptom)	8.757	2.915-20.306	0.001
Vaginal discharge (symptom)	5.727	2.106-15.578	0.001
Vaginal bleeding (sign)	8.103	2.517-26.084	0.001
Vaginal discharge (sign)	4.511	1.712-11.883	0.002

* **AOR: Adjusted Odds Ratio, 95%CI: 95% confidence interval.** Variables included in the model: age at marriage and 1st baby, parity, contraceptive , history of vaginal infection and husband with infection , smoking cigarettes and water pipe, Vaginal bleeding and discharge as a symptom and sign

5.4.4 Candida in Pap smear

Table 5.32 shows that using oral contraceptive increase risk (adjusted odds ratio) by 5.8 folds for Candida (positive Pap smear test) while having vaginal infection increase the risk by 4 folds. (Table 5.32)

Table 5-32 Multivariate logistic regression models for the association between independent variables and Candida

Variable	AOR*	95% CI*	P-value
Oral Contraceptives	5.807	2.012-16.757	0.001
History of vaginal infection	4.147	1.579-10.897	0.004

* **AOR: Adjusted Odds Ratio, 95%CI: 95% confidence interval.** Variables included in the model: age at marriage and 1st baby, oral contraceptive , history of vaginal infection

5.4.5 Precancerous cell

Table 5.33 shows that smoking cigarettes increase risk (adjusted odds ratio) for Precancerous cell (positive Pap smear test) by 0.12 folds. (Table 5.33)

Table 5-33 Multivariate logistic regression models for the association between independent variables and Precancerous cell

Variable	AOR*	95% CI*	P-value
Smoking cigarettes	0125	0.032-0.483	0.003
Vaginal bleeding (sign)	0.143	0.017-1.238	0.07

* **AOR: Adjusted Odds Ratio, 95%CI: 95% confidence interval.** Variables included in the model: smoking cigarettes and vaginal bleeding (sign)

Chapter 6: Discussion

6.1 Introduction

Multiple associations were revealed by the study between multiple risk factors and cervical lesions among the Palestinian female population. The study aim was to assess the role of Pap smear screening in detection of various cervical lesions among Palestinian women and to study the risk factors for them . This chapter will be discussing the major finding of the study and compare it to the present literature.

6.2 Socio-demographic study factors:

6.2.1 Age factor

The risk of developing precancerous and cancerous cervical lesions is shown in this study to have no change or association with age of the participants.. This result is almost similar to previously published case control study in 2015 by Gessesse and colleagues that showed no significant association between precancerous and cancerous cervical lesions and the age of the women.(Gessesse et al.,2015)

Other opposing studies results, like a case control study by Team and colleagues (2018) showed that women aged 40-49 years old have had an increase risk (AOR=2.4,CI:1.27-4.54) of developing precancerous and cancerous lesions by 2.4 folds than those in other age groups, as well as, in another case control study done by Bezabih and colleagues in 2015 found that the peak incidence for precancerous cervical lesions was between the age of 40-59 years old (Bezabih et al., 2015)

Makuza and colleagues in a cross sectional study found that older age is a protective factor from cervical lesions (AOR=0.52; 95%CI=.028-0.97) (Makuza et al., 2015).

However, Embolo in his cross sectional study in 2016, documented that 20.52% of Cameroonian women develop precancerous cervical lesion at early age of life (20-30years old) (Emblo al., 2016).

6.2.2 Socioeconomic factors

In this study 68% of participants were housewives, 84% have intermediate level of income, 40% of them have had only high school education.

Despite that socio-economic factors such as education level and income level and social class have a significant effect on an individual's general health, in this study no significant association was found between education level, income level, occupation and positive Pap smear results for cervical lesions .These results contradicts other studies which showed a relationship between the various socioeconomic indicators and precancerous and cancerous

cervical lesions, and found a significant inverse association between the indicators of socioeconomic status and cervical lesions (Latha et al.,2017, Mhaske et al., 2011, Makuza et al., 2015, Vincerzevskiene et al.,2017). Aswathy et al.,2012, Chankapa et al., 2011)

These results may be explained by the small number of sample or due to small differences in educational level and income among the study participants. Moreover, Latha and colleagues ,2017 concluded that low socioeconomic status force women to have multiple sex partners which make them more susceptible to STDs and starting sexual intercourse at early age, these kind of behavior is restricted in Palestinian society by our religion and culture.

Moreover, in this study 86% of the participants were married, but there was no significant association between marital status and risk of cervical lesion. These results contradicted other results, which documented that marital status plays a significant role in increasing the risk for acquiring HPV and by that increasing the risk of developing precancerous cervical lesions. For example, Vaccrella and Kalawole in their studies had showed that married females have higher risk of acquiring cervical lesions (Vaccrella et al.,2010, Kalawole et al.,2015), but other opposing studies showed that being widow or divorced significantly increase the risk of developing precancerous and cancerous lesions compared to married women, attributing the results to having multiple sex partners (Getinet et al.,2015).

6.3 Reproductive health factors and cervical lesions:

6.3.1 Age at marriage factor

In this study, 79% of the participants were married between the ages 15-24 years old.
The results in this study showed significant inverse association between the age of marriage and having cervical lesions (AOR =7.612; 95%CI= 2.512-23.064; $p<0.001$). Women have 7.6-fold increase risk of developing cervical lesion if they have got married at age $\leq$24 years old . This is attributed to the fact that the earlier the sexual intercourse , the earlier the immature cervix is exposed trauma that make it more vulnerable to acquire persistent HPV, which is the main cause of almost all of the cervical lesions.

Louie and colleagues in 2009, in their case control study concluded that cervical lesion risk has increased by 2.4 folds among females that had married at early age $\leq$16 years old (AOR=1.8; 95%CI: 1.50-2.39) compared to those married at age $\geq$21 years old, and that the risk increased more when pregnancy occurred immediately after being married at early age (Louie et al.,2009).

Same results were concluded by Deksissa and colleagues in 2013, their study had documented a 2.2 fold risk increase (AOR 2.2; 95%CI; 1.1-4.3) for precancerous cervical lesion in those women married at age <16 years old (Deksissa et al.,2013). Another study made in 2017 by Kassar showed that women married at age <15 years old have 5.6 times more risk to develop precancerous and cancerous lesions (Kassar,2017).

An opposing conclusion was documented by Latha and Ranganath in 2017 and Chankapa and collogues in 2011, and showed that there was no significant association between marriage at early age and risk for precancerous and cancerous cervical lesion (Latha and Ranganath ,2017: Chnkapa et al., 2011).

This study showed a significant association between early age of marriage and acquiring cervical inflammatory lesions(AOR=5.3; 95%CI: 1.902-15.238; p<0.001) infection (AOR=4.449; 95%CI:1.628-12.162; p=0.004), so that those married at age ≤24 years old have 5.3 folds risk increase for having inflammatory cervical lesion, 4.4 folds risk increase for infection than those married at age >24 years old.

6.3.2 Age at first childbirth factor

If marriage occurs at early age this means engaging in early sexual intercourse, by that increasing the probability of getting pregnant at early age(early childbirth) and increase risk of cervical trauma which may lead to cervical carcinogenesis.

In this study, 61% of the participants had their first child between the ages 16-20 years old The results in this study showed significant inverse association between the age of having the first baby and cervical lesions (AOR =1.962; 95%CI= 1.122-3.429; p=0.018). Women have 1.9 folds increase risk of developing cervical lesion if they have had their first child at an age ≤20 years old, because the early the age of having children the early the immature cervix is exposed to trauma, that makes it more vulnerable to acquiring HPV infection that is considered the main reason for cervical lesions.

Other studies showed that the risk of cervical lesions tended to inversely increase with the age at first baby, for example in 2009 a large pooled case control study reported that females who have their first child at age ≤16 years old have an increase risk (AOR =2.31; 95%CI:1.85-2.87) of 2.3-folds to have precancerous and cancerous lesions more than those having their first baby at age ≥21 years old (Louie et al.,2009). Mhaske and Jawadekar in 2011 documented a significant association between risk of precancerous and cancerous cervical lesion and having first baby at age <20 years old.(Mhaske and Jawadekar , 2011)

In an opposing conclusion made by Bezabih and collogues in 2016, reported that having first baby at age >25 years is a significant risk factor for cervical lesions especially invasive cervical carcinoma, and suggested that intervals between deliveries play an important role for the disposition to cervical carcinoma (Bezabih et al.,2016). Also Chankapa and collogues in their study reported no significant association between early age at first baby and risk for precancerous and cancerous lesions, but found higher incidence with high parity, increasing age and prolonged sexual intercourse (Chankapa et al.,2011).

This study showed a significant association between early age of having first baby and acquiring cervical inflammatory lesions(AOR=2.434; 95%CI:1.367-4.333; p=0.003) and infection (AOR=1.717; 95%CI:1.027-2.870; p=0.039), so that those having their first child at age ≤20 years old have 2.4 folds risk increase for having inflammatory cervical lesion and 1.7 folds risk increase for infection than those married at age >20 years old

6.3.3 Parity (Number of childbirth) factor

Parity , throughout women fertile years of life, is considered a good probable marker of normal female hormone, which is estrogen, , as well as, a good marker among multiparas for repeated trauma to the female genitalia especially the cervix. More deliveries causes more trauma to the cervix, and by that make the cervix more susceptible to acquire HPV persistent infection - the most common cause of cervical lesions. In this present study, 45% of the participants have had 5-10 childbirth.

High parity have been reported in many studies as a risk factor for cervical lesions, in this study as well parity was found to have a significant direct association with cervical lesions (AOR= 0.283; 95%CI; 0.113-0.710; P=0.007), compared to two cross sectional studies that were made in 2017, 2015 and showed significant association between high parity as a co-factor and risk of precancerous and cancerous cervical lesion (Andrew et al.,2017;Kalawole et al., 2015).

Bezadih and colleagues reported in 2015 a strong independent association between women with >4 children and precancerous and cancerous cervical lesions (AOR=10.3;95%CI; 3.6-29.0), so they have 10 times higher risk to develop cervical lesions (Bezadih et al.,2015). Also, Getinet and colleagues concluded that women with high parity >3 were 10.9 folds more likely to acquire precancerous and cancerous cervical lesions than female with <3 children (AOR =11 ;95%CI;4-17 ; P<0.001) and that high parity is a significant predictor of precancerous and cancerous cervical lesion prevalence (Getinet et al.,2015).

In this study , the results showed a significant association between high parity and cervical infectious lesions(AOR=0.295; 95%CI:0.130-0.673; p=0.004) so that those having >5 children have 0.29 folds increase in risk of having cervical infection compared to those with <5 children . In the contrary, this study showed no association between high parity and precancerous and cancerous lesions. However, these results may be explained by the small number of sample.

6.3.4 Contraceptive factors

In this cross sectional study, 70% of the participants have had used contraceptives, 90% of them used oral contraceptive pills.

Additionally, it was found in the study that there was a significant association between contraceptive consuming in general and risk for cervical lesions (AOR= 7.100; 95%CI; 2.418-20.847; P<0.001), and oral contraceptive consuming in particular (AOR= 4.313;95%CI;1.302-14.282; P=0.017).

Many studies documented that women who used oral contraceptive drugs for more than 5 years have greater risk of having cervical lesions than those who have never consumed oral contraceptive pills , and that the longer the use of OCPs the higher the risk.(National Cancer Institute, 2018)

Roura and colleagues showed a strong positive association between taking oral contraceptive drugs and risk of having cervical lesions (HR= 1.6 for ≥ 15 years use and HR=1.8 for ≥15 year never use). However, they documented that increasing the number of oral contraceptives consumed and duration of using, increase cervical lesions risk , and decrease the risk with stopping the oral pills and increase years of since last pill was consumed. They also documented that oral contraceptives act as a cofactor that interact with HPV infection to cause the cervical lesions, and that they do not work independently as a risk factor (Roura et al.,2016).

In another case control study, association between using oral contraceptive and increasing risk of precancerous and cancerous lesions, and the association between increasing duration of using oral contraceptives and increasing risk of precancerous and cancerous lesions was shown by Appleby and colleagues. (RR =1.9;95%CI; 1.7 -2 for >5 years use versus never use), they also showed the decline in risk after stopping the use of oral contraceptive pills and by ≥10 years passed with no use of the pills (Appleby et al.,2007).

Another case control study done in 2017 by Kassa , showed an increase in risk for precancerous and cancerous cervical lesions by 2 folds(COR 2 ;95%CI;1-4.2; AOR=2.3;P<0.03) for those using oral contraceptives compared with those who do not use it (Kassa ,2017).

An opposing conclusion that oral contraceptive pills are not an independent risk factor for precancerous and cancerous cervical lesion was made by Syrjanen and colleagues. They found in the multivariate regression model study that all types of contraceptives mode have no significant predictive value for precancerous nor cancerous cervical lesions, and concluded that the different sexual behavior between those consuming oral contraceptives and those who not consuming is the main risk factor for precancerous and cancerous cervical lesions (Syrjanen et al.,2006)

In this study , the results showed a significant association between using contraceptives and acquiring cervical inflammatory lesions(AOR=3.331; 95%CI:1.401-7.920; p=0.006) and infection (AOR=3.334; 95%CI:1.336-8.325; p=0.01) so that those using contraceptives

have 3.3 folds increase in risk of having inflammatory cervical lesion, 3.3 folds increase in risk of infection than those not using contraceptives.
Also it showed that there is a significant association between using oral contraceptives and acquiring cervical inflammatory lesions(AOR=6.577; 95%CI:1.452-29.785; p=0.015) Candida (AOR=5.807; 95%CI:2.012-16.757; p=0.001) so that those using contraceptives have 6.5 folds increase in risk of having inflammatory cervical lesion, 5.8 folds increase in risk of Candida than those not using contraceptives

6.4 Medical history

Studies from all over the globe showed that persistent HPV infection causes 99.7% of precancerous and cancerous cervical lesions (Dilman,2009)

In this study, 67% of the participants have had acquired infection in their life, 67% of them claimed that they have treated their infection , 98.5% of them have claimed that they still have infection symptoms.
The multivariate analysis in this study showed a significant association between having infection and having cervical lesions,(AOR=30.800;95%CI; 9.222-50.725;P<0.001), so that those having infection have 30 fold increase risk of having cervical lesions than those not having infection.

Various previous studies pointed out the significant association between history of infection and the increase risk of cervical lesions. For example, a strong association between having infection and risk for cervical lesion was concluded by Kassa,(COR=2.187;95%CI; 1.078-4.440;AOR=2.485). (Kassa,2018)

This finding was consistent with the results form a cross sectional study in 2016, that showed that infection had been the only significant associated factor with the outcome variable, the study concluded that those with STDs have 50 fold more risk to have cervical lesions compared to those with no infection (AOR=49.88; 95%CI;16.59-149.91) (Misgina et al.,2017).

Another study in Southern Ethiopia made by Gedefaw and colleagues, concluded that women with infection have 2.3 fold more likely to have precancerous and cancerous cervical lesions than those with no infection .(AOR=2.3; 95% CI; 1.23-4.29) (Gedefaw et al.,2013).

Another positive significant association was found by Nesrin and colleagues in 2011,(AOR=5.17; 95%CI; 3.51-7.6) and Team and colleagues in 2018,(AOR= 3 ;95%CI;1.3-8) between women having infection and increase risk of cervical lesion.

Unfortunately, this study did not test the samples for the presence of HPV infection, which is considered the most common STIs globally and the most common cause of cervical lesion, Moreover, most of the risk factors for cervical lesions works as a cofactor for persistent HPV infection in causing cervical lesion (Matos et al., 2005; Kahn et al., 2002; Louie et al.,2009).

Sitakana and colleagues in their study and after adjusting with multiple logistic regression, showed the persistent risk increase with HPV infection for precancerous and cancerous cervical lesions with AOR =38.07(P<0.001) (Sitakana et al.,2012).

In another case control study in 2013, showed that HPV infection is significantly associated with increased risk for precancerous and cancerous cervical lesions with AOR=42.4(95%CI;22.4-81.4;P<0.001) (Natphopsuk et al., 2013).

Another case control study with the same results was conducted by Nomonde and collogues in 2016, and showed a strong association between Persistent HPV infection and precancerous and cancerous lesions especially stage II cervical cancer (Nomonde et al.,2016).

In this study , the results showed a significant association between STDs and acquiring cervical inflammatory lesions(AOR=10.083; 95%CI:3.807-26.707; p<0.001) infection (AOR=13.071 ; 95%CI:4.389-38.930; P<0.001) Candida (AOR=10.1; 95%CI:3.807-26.707; P=0.004) so that those having infection have 10 folds increase in risk of having inflammatory cervical lesion, 13 folds increase in risk of infection and 10 folds increase in risk of Candida than those not suffering from infection .
Moreover, there was no association between having infection and acquiring Precancerous cervical lesion; including Atypical squamous cells, Atypical glandular cells, CIN I,II and III.

6.5 Family history and genetic factors

Precancerous and cancerous cervical lesions may run in families, due to inherited conditions that do not allow females to fight STIs especially persistent HPV infection. Alternatively, women may share non-genetic risk factors like STIs with their partner (American Cancer Society,2017).

In this study and after adjusting with multiple logistic regressions, there was no significant association between having family history with any type of cancer and risk of precancerous and cancerous cervical lesions. Our results may be explained by the small number of sample.

In contrast to multiple published studies that supported the genetic familial aggregation of precancerous and cancerous cervical cancer, as Paltrik K and collogues concluded in 2000 that there has been a 2-fold increase in risk for cervical lesions in those with positive family history of cervical lesions (Paltrik et al.,2000).

Hemminik and colleagues concluded that there is a strong association among full-blooded relatives (RR= 1.84) with cervical lesion than those with half blooded (RR=1.4 for maternal, 1.27 for paternal half siblings) (Hemminiki et al., 2006).

Pattrik and colleagues concluded in their study that precancerous and cancerous cervical lesions depend on inherited genetic factors that may influence the sensitivity of the cervix for HPV infection (Patrik et al., 2000).

However, the sexual behavior of the husbands may have a great effect on their wives, making them more susceptible to cervical lesions. Therefore, increasing number of husband's sexual partners, for example, in polygamy, may increase their susceptibility to acquire STIs that will be transmitted to the wives.

In this study , the results showed a significant association between husband suffering from infection and increase risk of cervical lesions (AOR= 9.808m 95% CI; 1.242-77.433; P=0.03) , so females has 9.8 folds increase in risk of cervical lesions with husband having infection compared to those husbands with no infection.

Bezabih and colleagues showed in their study that husbands with multiple wives or with multiple sexual partners has a significant association with increase risk of their wives having cervical lesions (Bezabih et al.,2015). In addition, the same significant association was reported by Owki and colleagues in 2017 (Owki et al., 2017).

In this study, the results showed a significant association between husband having STDs and acquiring cervical inflammatory lesions(AOR=2.846; 95%CI: 1.034-7.831; p=0.04) infection (AOR=4.083; 95%CI:1.117-14.929; p=0.03), so that those married to a husband with infection have 2.8 folds increase in risk of having inflammatory cervical lesion and 4 folds increase in risk of infection than those married to husband with no infection.

6.6 Smoking Life style factor.

Multiple evidence based studies showed that exposure to tobacco products may have an influence in turning HPV infection from precancerous state to malignancy, but the direct causal association apart from being co-factor for HPV infection has not been clear yet (Appleby et al.,2006). Also, biological evidence showed that cigarette components is a well known carcinogenic chemicals that causes changes in cellular bases and may cause the growth of different kind of tumors (IACR,2004)

Cigarette and water pipe smoking were investigated in this study, which results reported cigarette smoking and water-pipe smoking as a significant risk factors for developing cervical lesions among Palestinian women. Women who smoke cigarettes have 1.9 folds higher risk(AOR=1.908;95% CI; 10888-4.100; P=0.04) to develop cervical lesion compared to those who never smoked tobacco and those who smoke water-pipe have 5.6 folds higher risk(AOR =5.667;95%CI;1.222-26.280;P=0.03) to suffer from cervical lesions than those who don't smoke water-pipe. Water pipe smoking is prevalent nowadays in Palestine. This habit was and is still very popular among women in Ramallah Governorate. However, additional future studies are necessary to clear up this relationship.

In this study, the results showed a significant association between water-pipe smoking and acquiring cervical inflammatory lesions(AOR=3.889; 95%CI: 1.422-10.636; p=0.01) and infection (AOR=5.372; 95%CI:1.476-19.554; p=0.01), so that those smoking water-pipe have 3.8 folds increase in risk of having inflammatory cervical lesion and 5.3 folds increase in risk of infection than those not smoking water-pipe. Moreover, this study showed a significant association between smoking cigarettes and developing precancerous lesions(AOR=0.125;95%;CI;0.032-1.238;P= 0.003).

Multiple previous studies in many countries have had reported a significant association between tobacco smoking behavior and risk of having cervical lesions . For example, in a large prospective cohort study made by Esther and colleagues, a strong positive association between tobacco smoking and risk for precancerous and cancerous cervical lesions was reported, taking into account HPV infection exposure and they also found that the strongest association was with smoking duration and inversely associated with quitting (Esther et al.,2014).

On the other hand , Aline and colleagues documented in their study a significant association between heavy smoking, HPV infested and risk of precancerous and cancerous cervical lesion (OR= 3.2;95%CI;1.7-4.3) , high risk was found even after adjusting for HPV infection.(OR=3.2;95%CI;2.6-4) (Aline et al.,2009).

However, passive smoking is a public health problem worldwide and nonsmoker women who are exposed to secondhand smoke are inhaling many of the same carcinogens substances and poisons as smokers, and that increase their risk of developing cervical lesions. Moreover, exposure to second hand smoking occurs in everyday life, at home, work, in public transport, restaurants, especially in absence of any regulations that forbid smoking in public place, but this study showed no association between second hand smoking and precancerous and cancerous cervical lesion risk was found.

Our results showed no association between smoking waterpipe and precancerous cervical lesions despite the fact that water-pipe smoking is more popular than cigarette smoking among female population in Palestine, especially in Ramallah district, and this may be explained by the small number of sample.

6.7 Pap smear test

Pap smear test in this study, was able to detect 82 abnormal cervical lesion out of the 100 participant sample, despite the fact that most of the abnormal findings were not pre-cancer or cancer cells, Pap smear test was able to detect inflammatory changes (80.4% of the positive Pap smears samples had inflammatory changes) and infection (92.7% of the positive pap smears samples had infection) that if not treated may progress to precancerous cell and eventually to malignancy.

Infections was the most common histological finding in the study results , and as we have previously discussed that globally 99.7% of cervical cancer lesions cases have been caused by the most common persistent HPV infection in the human reproductive tract. Fortunately, the majority of the STIs caused by HPV infection resolve spontaneously, but some specific kinds of persistent HVP infection may lead to precancerous and cancerous cervical lesions in approximately ten years, so detecting infection as early as possible gives the chance for treating STIs and forbid them to progress to precancerous and malignant lesions in the future

Pap smear cytology cervical screening method has been able to detect incidence of cervical lesions for many years despite the argument that has been surrounding the ability of medical and public community to use Pap smear test for screening (Gedefaw et al.,2013).

Various studies have had pointed out the important role of Pap smear in detecting precancerous and cancerous cervical lesions. Sachan and colleagues concluded -in their study to evaluate Pap smear screening ability to detect cervical lesions- that Pap smear cervical screening test is a simple, useful, cheap and safe tool for detecting precancerous and cancerous cervical lesions, 48.84% of the sample had no malignancies and 42.66% had infection and inflammation, 2.9% had ASCUS, 5.09% had LSIL and 0.48% had HSIL (Sachan et al.,2018).

Patel and collogues in their 2011 study found that 94.5% of the screened population with Pap smear had infection and inflammation and 5.5% had premalignant and malignant cervical lesions (Patel et al.,2011).

On another study made in 2012, the researchers concluded that Pap screening test has a definite role in detecting precancerous and cancerous cervical lesion , after they used Bethesda system to differentiate cervical lesions obtained by Pap smear test, and found that 88% of the samples were infection and inflammation with no premalignant nor malignant changes and 3.53% had cervical dysplasia (Sarma et al., 2012).

Additionally, it was found in Verma and collogues study that Pap smear screening test is highly specific and sensitive procedure to detect precancerous and cancerous lesions of the cervix, they reported 32.5% with inflammatory changes, 1% ASCUS, 5.5% LSIL, and 2.5% HSIL (Verma et al.,2017).

Unfortunately, this study found 7% inadequate sample results that may be due to lack of experience in obtaining Pap smear tissue sample, by the physicians who performed the procedure, and instead of taking the tissue from the appropriate site in the SC junction - the endocervical tissues as instructed by the researcher, they obtained it from the ectocervical tissues or they may have taken few inadequate cell for testing.

Finally, this study showed a significant association between some medical complains of the participants and physical findings by the medical doctors (vaginal bleeding and discharge) and the presence of positive Pap smear findings ; infection, inflammation and precancerous cells and this is attributed to the fact that these symptoms and signs almost always occur with infection .

6.8 Conclusion:

This study might be considered the first one in Palestine that aimed to evaluate the effectiveness of Pap smear screening tool, in detecting precancerous and cancerous cervical lesions and to explore the possible risk factors for cervical lesions. Most results of this study were expected and comparable to other international studies results, while some others were unexpectedly contradicted with the literature. From this study, we can conclude that Pap smear screening tool is highly sensitive and useful method to detect precancerous (including inflammation and infection) cervical lesions before they progress to malignancies, as well as, detecting malignant changes. On the other hand, the study results showed that age at marriage , age at first pregnancy, high parity, oral contraceptives, having vaginal infection or married to a husband having infection, smoking tobacco and water-pipe are all major risk factors for developing cervical lesions . However, additional studies are necessary to confirm these results.

6.9 Recommendations

6.9.1 Recommendations for policy makers and health care team:

- Activating the national screening program for the early detection of cervical lesions, by Pap smear.
- Evaluate cost-effectiveness of expanding the Cervical lesion screening programs
- Carrying out more awareness campaigns to remind people of the harm caused by tobacco and water-pipe smoking for human health. As well as, adapting the anti-tobacco law legislation so as to control smoking specially in public places
- Train more health worker on Pap test procedures so as to avoid the inadequate sampling
- More awareness campaigns should be carried out to increase community awareness especially females about the harmful effect of untreated persistent vaginal infection, harmful effect of early marriage and early childbirth, as well as high parity on the cervix
- Improve the quality of already exciting vaginal infection management procedures
- Evaluate safety versus risk in using oral contraceptives
- Develop ongoing evaluation program to all screening programs especially Pap smear screening programs
- Train more medical staff on Bethesda procedures and how to read the Pap smear slides
- Produce uniform protocols and guidelines for cervical lesion screening, and designate the exact age, when to start the screening.

6.9.2. Recommendations for the Palestinian female :

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- Living a healthy life: by stop smoking, and never start smoking . Water pipe is a bad smoking habit.
- Do regular Gynecology checkups

- Do Pap smear screening test according to the national guidelines
- Visit your physician whenever you complain of vaginal bleeding or discharge
- Follow the family planning program

6.9.3. Recommendations for the future research:

- Conducting more detailed researches with larger sample size and including more health care facilities over a more extended period of time.
- Considering the most common type of cervical lesion (histopathology) and relating it to the risk factors.
- Focusing on female with no STIs to exclude confounding by HPV infection and to explore other risk factors in more details.
- Perform more comprehensive longitudinal studies, to study the cause-effect relationship between precancerous and cancerous cervical lesion and its predictors. This could be useful for decision makers to plan properly for cervical lesion managements.

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Annex 1: The Questionnaire

استبيان رقم: .....

(كيف يتم تعبئة الإستبيان ؟ يتم وضع اشارة √ بالمربع التابع للاجابة الصحيحة)

الجزء الاول : المعلومات الشخصية

1) الفئة العمرية :

□ أقل من 15 سنة □ 15 – 24 سنة □ 25 – 34 سنة □ 35 – 44 سنة

□ 45-54 سنة □ 55 سنة وأكثر

2) الحالة الاجتماعية : □ متزوجة □ - مطلقة □ أرملة

3) هل تزوجت اكثر من مرة واحدة □ نعم □ لا

4) هل زوجك متزوج حاليا اكثر من زوجة : □ نعم □ لا

5) - الوزن (كغم) : -------- - الطول (سم) : ---------

6) المهنة : □ موظفة مكتبية □ موظفة ميدانية □ عاملة بالأجرة □أعمال حرة □ربة منزل

7) مستوى الدخل : -□ متدني □ متوسط □ عالي □ لا يوجد □ لا أدري

8) مستوى التحصيل العلمي : □ ابتدائي و أقل □ ثانوي □ بكالوريوس □ دراسات عليا

9) مكان السكن : □ مدينة □ قرية □ مخيم □ مضارب بادية □غيره(حددي) :.....

الجزء الثاني : المعلومات الانجابية

10) العمر عند أول دورة شهرية : □ 8 سنوات أو أقل □ 9-11 سنة □ 12-14 سنة

□ 15 سنة أو أكثر □ لا أدري

11) العمر عند الزواج : □- أقل من 15 سنة □ 15-24 سنة □ 25-34 سنة □ 35-44 سنة

□ 45 سنة و أكثر □ لا أدري

12) هل الدورة الشهرية مستمرة : □ -نعم □ - لا □ لا أدري

13)اذا كانت الإجابة نعم : □ منتظمة □ غير منتظمة □ لا أدري

14) اذا كانت الإجابة لا ؛ العمر عند توقف الدورة ؛ □ - أقل من 40 سنة □ -40 – 44 سنة
□ -45 – 49 سنة □ - 50 – 54 سنة □ - 55 سنة أو اكثر □ لا أدري

15) هل تلقيتِ علاجات هرمونية لانقطاع الدورة الشهرية ؟ □ - نعم □ - لا □ لا أدري

16) عدد الولادات : □ - لا يوجد □ -1 -4 مرات □ - 5-10 مرات □ - أكثر من عشرة

17) العمر عند الولادة الاولى :□ 15 سنة أو أقل □ 16 – 20 سنة □ 21 – 25 سنة □ 26-30سنة
□ 31-35سنة □ 36-40سنة □ 41-45 سنة □ - أكثر من 45 سنة □ لا أدري

18) هل تستخدمتي وسائل تنظيم الأسرة ؟ □ - نعم □ -لا □ لا أدري

19) اذا الإجابة نعم ؛ □ حبوب منع الحمل □ لولب معدني □ لولب بلاستيكي □ الواقي الذكري □ طرق أخرى

20) عدد مرات الاجهاض (ان وجد) ؟ □ - لا يوجد □ 1-3 مرات □ من 4- 5 مرات □ - أكثر من 5 □ لا أدري

21) حل حصل لديك حمل خارج الرحم ؟□ نعم □ لا □ لا أدري

22) هل قمت بعمل فحص مسحة عنق الرحم من قبل ؟□ نعم □ لا □ لا أدري

23) اذا كانت الإجابة نعم ؛ كم مرة قمتي بعمله ؟ □ مرة □ مرتان □ 3 مرات □ أكثر من 3 مرات □ لا أدري

<u>الجزء الثالث: التاريخ المرضي</u>

24) هل تعانين من افرازات مهبلية؟ □ نعم □ لا □ لا أدري

25) اذا كانت الإجابة نعم ؛ حددي لونه----------

26) هل تعانين من نزيف مهبلي ؟□ نعم □ لا □ لا أدري

27) اذا كانت الإجابة نعم حددي متى؛□ بين الدورات □ بعد الجماع □ غير ذلك ، حددي ----------

28) هل تعانين من ألآم بعد الجماع ؟□ نعم □ لا □ لا أدري □ لا يوجد جماع

29) إذا كانت الإجابة نعم حددي متى : □ دائما □ أحيانا □ نادرا

30) هل تعانين من صعوبة أو ألآم أو كثرة في إدرار البول ؟ □ نعم □ لا □ لا أدري

31) إذا كانت الإجابة نعم حددي_____

32) هل تعانين من الآم في اسفل البطن أو الحوض ؟□ نعم □ لا □ لا أدري

33) إذا كانت الإجابة نعم حددي اين؟ ----------ومتى؟ ----------

34) هل تعاني من امراض وراثية ؟ □ - نعم □ - لا □ لا أدري

35) اذا كان الجواب نعم حددي: .....

36) هل تعاني من أمراض مزمنة ؟□ - نعم □ - لا □ لا أدري

37) - اذا كان الجواب نعم حددي المرض : ..... اي عام تم اكتشافه ؟.....

38) هل تم تشخيصك من قبل بالإصابة بالإلتهابات المهبلية ؟□ نعم □ لا □ لا أدري

39) اذا كانت الإجابة نعم ، هل قمت بعالجه ؟ □ نعم □ لا □ لا أدري

40) ها ما زلت تعانين من أعراضه ؟ □ نعم □ لا □ لا أدري

41) هل عانيت أو تعانين من عدم التوازن الهرموني (هرمون الاستروجين العالي او البروجيستيرون المنخفض)؟

□ نعم □ لا □ لا أدري

42) اذا كانت الإجابة نعم ؛ هل تمت معالجة هذا الخلل في الهرمونات؟ □ نعم □ لا □ لا أدري

43) هل قمت بإجراء أي عمليات جراحية؟ □ نعم □ لا □ لا أدري

44) اذا كانت الإجابة نعم ، حددي نوع العملية ----------

45) هل سبق وأصبت بسرطان عنق الرحم ؟ □ - نعم □ -لا □ لا أدري

46) اذا كانت الإجابة نعم ؛ حددي العام : .....

47) - ما هو العمر عند تشخيص المرض ؟ □15سنة أو أقل □ - 16 – 25 سنة □ 26 – 35 سنة

□ 36- 45سنة □ - أكثر من 45 سنة □ لا أدري

48) نوع العلاج؛□ جراحي □ كيماوي □ أشعة □ جميع ما ذكر □ غير ذلك حددي_____ □ لا أدري

49) قبل تشخيصك هل قمتي بعمل فحص عنق الرحم ؟ □ - نعم □ - لا □ لا أدري

50) -اذا كانت الاجابة نعم . كم مرة قمت بذلك ؟: .....

51) هل تعانين من أي نوع من أنواع مرض السرطان ؟ □ نعم □ لا □ لا أدري

52) إذا كان الجواب نعم ، حددي ما هو : ----------

<u>الجزء الرابع : تاريخ العائلة</u>

53) هل يعاني أي من أفراد العائلة من امراض مزمنة ؟ □ نعم □ لا □ لا أدري

54) اذا كان نعم , حددي: .....

55) هل أصيب أي من أفراد العائلة بالسرطان؟ □ نعم □ لا □ لا أدري

56) اذا كانت الإجابة نعم ؛ حددي صلة القرابة ----------، نوع السرطان ----------

57) هل أصيب الزوج بالأمراض المنقولة جنسيا ؟ □ نعم □ لا □ لا أدري

58) هل يعاني أي أحد من أفراد الأسرة من ألأمراض التناسلية أو البولية؟□ نعم □ لا □ لا أدري

<u>الجزء الخامس : جودة الحياة و البيئة</u>

59) - مكان السكن: □ - بيت مستقل □ - شقة في بناية □ - مضارب و خيام

60) - هل يوجد بالقرب من منزلك: □ - منطقة صناعية □ - مكبات نفايات □ - كسارات و محاجر □ - مستوطنة □ - ثكنات عسكرية □- خطوط كهرباء ضغط عالي □ - أبراج اتصالات خليوية □ لا أدري

61) هل أنتي مدخنة ؟ □- نعم □ لا □ مدخنة سابقة □ معرضة لتدخين من قبل شخص اخر

62) اذا كان الجواب نعم , ما هو عدد السجائر في 24 ساعة؟□ اقل من 10 □ 10 – 20 سيجارة

□ أكثر من 20 سيجارة □ لا أدري

63) مدة التدخين : □ أقل من سنة □ 1-5 سنوات □ 6-10 سنوات □ أكثر من 10 سنوات □ لا أدري

64) هل تدخني الأرجيلة؟ □ - نعم □ - لا □ لا أدري

65) اذا كان الجواب نعم ،أدخن الأرجيلة□ -يوميا □ 4-6 مرات اسبوعيا □2-3 مرات اسبوعيا

□ مرة بالأسبوع □ 1-3 مرات بالشهر □ لا أدري .

66) مدة تدخين ألأرجيلة : □ أقل من سنة □ 1-5 سنوات □ 6-10 سنوات □ أكثر من 10 سنوات □ لا أدري

67) هل تشربين الكحول ؟ □ - نعم □ - لا □ لا أدري

68) هل تمارسين الرياضة ؟ □ - نعم □ - لا

69) مدة الرياضة التي تمارسينها بالأيام :

□ -يوميا □ 4-6 مرات اسبوعيا □2-3 مرات اسبوعيا □ مرة بالأسبوع □ 1-3 مرات بالشهر

ANNEX 2: Medical form to be filled by the Gynecologist

Questionnaire No: ---------- Date: _____

(Please fill the box of the corrected answer with √)

A) SYMPTOMS	B) SIGNS
1- No symptoms □	1. No significant clinical abnormalities □
2- Vaginal bleeding □	2. Vaginal bleeding □
3- Vaginal discharge □	3. Vaginal discharge □
4- Menorrhagia □	4. Erosions □
5- Contact bleeding □	5. Ulcers □
6- Blood spots or light bleeding between periods □	6. External polyps □
7- Dysuria □	7. Ecto-cervical polyps □
8- Bleeding after menopause □	8. Endo-cervical polyps □
9- Post coital bleeding □	9. Well defined mass □
10- Pelvic pain □	10. Warts (external genitalia) □
11- Lower abdominal pain □	11. Vaginal bleeding after PV □
12- Pain during sexual intercourse □	12. Metaplasia □
13- Vaginal mass □	13. Leukoplakia □
14- For follow up □	14. Parametrial or pelvic metastasis □
	15. Bleeding from mass erosion □
	16. Ectopy □

Gynecologist Signature :

Annex 3: Lab result form

Patient Name:		**Refereeing center:**	
D.O.B \ Age:	Years	**Receiving date:**	\201800\00
Case No.		**Reporting date:**	00\00\2018

History:L.M.P:

Cell Descriptions:

Superficial cells:		**Intermediate cells:**		**Para basal &metaplasia cells:**	
Basal cells:		**Endocervical cells:**		**Endometrial cells:**	
Granulocytes:					

Diagnosis:

Mild inflammation		**CIN I, II**		**Fresh blood**	
Moderate inflammation		**CIN III**		**Old blood**	
Severe inflammation		**Cervical cancer**		**Within normal limits**	
Atrophic smear		**Candida**			
Atypical squamous cells		**Unsatisfactory**			
Atypical Glandular cells		**Inadequate**			

Annex 4 :The letter from Al-Quds University to MOH.

Al-Quds University
Faculty of Medicine
Abu-Dies, Jerusalem

جامعة القدس
كلية الطب
أبوديس – القدس

2017\07\27

حضرة الدكتور: كمـال الشخرة المحترم

مدير عام الرعـــاية الأولية

وزارة الصحة الفلسطينية

تحية طيبة و بعد:

الموضوع \ مساعدة طالبة الماجستير د. نانسي فلاح

الرجاء التكرم بتسهيل مهمة الباحثة الدكتورة نانسي فلاح طالبة ماجستير بكلية الصحة العامة في جامعة القدس حيث ستقوم بجمع عينات لمسحة عنق الرحم من المرضى المراجعين لمراكز الأمومة في محافظة رام الله و البيرة و تعبئة استبيان موضوع البحث مع مراعاة خصوصية المرضى و الأخلاق الطبية في ذلك . علما بأن البحث موافق عليه من لجنة هلسنكي المحلية لأخلاق البحث العلمي بجامعة القدس و أن الوزارة لن تتحمل أي من النفقات المالية لهذا البحث.

و تفضلوا بقبول فائق الاحترام

المشرف الأكاديمي:
د. غسان موسى بطوشة
أستاذ مساعد - علم الأمراض
كلية الطب - جامعة القدس

P.O Box 20002 ص.ب 20002

Annex 5 : The letter from Al-Quds University to Al-Zakat Committee:

Al-Quds University
Faculty of Medicine
Abu-Dies, Jerusalem

جامعة القدس
كلية الطب
أبوديس – القدس

ل

حضرة مدير مؤسسة لجان الزكاة الفلسطينية الدكتور نبيل السليمان المحترم ...
2017\07\27

لجان الزكاة فرع محافظة رام الله والبيرة

تحية طيبة و بعد:

الموضوع \ مساعدة طالبة الماجستير د. تالسي فلاح

الرجاء التكرم بتسهيل مهمة الباحثة الدكتورة تالسي فلاح طالبة ماجستير بكلية الصحة العامة في جامعة القدس حيث ستقوم بجمع عينات لمسحة عنق الرحم من المرضى المراجعين لعيادات التمنانية بمركز لجنة الزكاة فرع محافظة رام الله و البيرة و تعبئة استبيان موضوع البحث مع مراعاة خصوصية المرضى و الأخلاق الطبية في ذلك . علما بأن البحث موافق عليه من لجنة هلسنكي المحلية لأخلاق البحث العلمي بجامعة القدس و أن المؤسسة لن تتحمل أي من النفقات المالية لهذا البحث.

و تفضلوا بقبول فائق الاحترام

المشرف الأكاديمي:
د. غسان موسى بطوشة
استاذ مساعد - عظم الأمراض
كلية الطب - جامعة القدس

P.O Box 20002
Tel 02-2799203, Fax 02-2796110

ص. ب 20002

Annex 6: The letter from Al-Quds University to the Gynecologist:

Al-Quds University
Faculty of Medicine
Abu-Dies, Jerusalem

جامعة القدس
كلية الطب
أبوديس – القدس

2017\07\27

حضرة الدكتور/ة ..... المحترم/ة
أخصائي/ة النساء والولادة

تحية طيبة و بعد:

الموضوع \ مساعدة طالبة الماجستير د. ناتسي فلاح

الرجاء التكرم بتسهيل مهمة الباحثة الدكتورة ناتسي فلاح طالبة ماجستير بكلية الصحة العامة في جامعة القدس حيث ستقوم بجمع عينات لمسحة عنق الرحم من المرضى المراجعين لعيادة النسائية الخاصة بكم والتي تقع بمحافظة رام الله و البيرة و تعبئة استبيان موضوع البحث مع مراعاة خصوصية المرضى و الأخلاق الطبية في ذلك . علما بأن البحث موافق عليه من لجنة هلسنكي المحلية لأخلاق البحث العلمي بجامعة القدس و أن المريضة لن تتحمل أي من النفقات المالية لهذا البحث.

و تفضلوا بقبول فائق الاحترام

المشرف الأكاديمي:
د. غسان موسى بطوشة
أستاذ مساعد - علم الأمراض
كلية الطب - جامعة القدس

P.O Box 20002
Tel 02-2799203, Fax 02-2796110

ص.ب 20002

Annex 7: Letter of approval from PHC in MOH

State of Palestine
Ministry of Health
General Directorate of PHC
Non Communicable Diseases Dept.

دولة فلسطين
وزارة الصحة
الإدارة العامة للرعاية الصحية الاولية
دائرة الامراض المزمنة غير السارية

التاريخ: 2017\10\26 الرقم:

حضرة الأخ الدكتور غسان بعلوشة المحترم،،،

تحية وبعد،

الموضوع: مساعدة طالبة الماجستير د. نانسي فلاح

إشارة إلى الموضوع أعلاه، لا مانع لدينا من بتسهيل مهمة الباحثة الدكتورة نانسي فلاح طالبة ماجستير بكلية الصحة العامة في جامعة القدس لتقوم بجمع عينات لمسحة عنق الرحم من المرضى المراجعين لعيادات النسائية بمراكز الأمومة بمحافظة رام الله و البيرة

وتقبلوا فائق الإحترام

مدير عام الإدارة العامة للرعاية الصحية الأولية
د. كمال الشوخرة

دولة فلسطين
وزارة الصحة
الادارة العامة للرعاية الاولية والصحة العامة
مدير عام الرعاية الصحية الاولية

Ramalla,
Public Health Lab. Building
Tel: 022988034
Fax: 022988033
Email: phc.moh.ps@gmail.com

رام الله
مبنى مختبرات الصحة العامة
تلفون: 022988034
فاكس: 022988033
بريد الكتروني: phc.moh.ps@gmail.com

Annex 8 : Consent form

بسم الله الرحمن الرحيم

جامعة القدس – كلية الصحة العامة

نموذج موافقة في دراسة \ بحث علمي

عنوان الدراسة: " تقييم دور اختبار مسحة عنق الرحم وعوامل الخطورة في الكشف عن إصابات عنق الرحم بين إناث الضفة الغربية "

الباحثة الرئيسية:د. نانسي فلاح , طالبة ماجستير صحة عامة

البريد الالكتروني:dr.n25f78@gmail.com جوال : 0597565421

أهداف الدراسة: تحديد فعالية فحص مسحة عنق الرحم في الكشف المبكر عن أمراض السرطان والأمراض الأخرى التي تصيب عنق الرحم ولتحديد عوامل الخطر المحتملة المرتبطة بأمراض عنق الرحم في الإناث الفلسطينيات.

الفئة المستهدفة: جميع النساء الفلسطينيات (15-55 سنة) الذين يراجعون عيادات أمراض النساء

لماذا تم اختياري:إن مشاركتك طوعية تماما دون التزام، وتم اختيارك كأحد مراجعات العيادة فقط .

ألية المشاركة: بعد اقرار المشاركة الطوعية ستقومين بتعبئة استبيان متعلق بموضوع الدراسة و من ثم اعادته للباحثة , و في حالة وجود صعوبات في فهم أو تعبئة جزء منه يرجى الرجوع للباحثة للمساعدة.

المخاطر و الفوائد الناتجة عن المشاركة: لا توجد أي مخاطر في المشاركة و بمشاركتكن تساهمن في فائدة عظيمة و هي تحديد فعالية فحص مسحة عنق الرحم في الكشف المبكرعن آفات عنق الرحم في مناطقنا الفلسطينية لكي تسهل متابعته و علاجه و الحد من انتشاره.

الخصوصية: أن هذا البحث يتم تحت اشراف لجنة هلسنكي المحلية لاخلاق البحث العلمي بجامعة القدس و التي تتابع الجانب الأخلاقي و الخصوصية العالية في التعاطي مع المعطيات الواردة في الاستبيان حيث يتم ترميز هذه المعطيات و جدولتها دون الاشارة تلميحا و لا تصريحا الى صاحبها أو ما يدل عليه من قريب أو بعيد.

الأستمرار في المشاركة: الاستمرار في المشاركة طوعي و يحق للمشاركة عدم الإستمرار في أي وقت

الأطلاع على نتائج البحث: يحق للمشاركة الاطلاع على نتائج البحث بالاشارة الى ذلك في الاستبيان.

استخدام المعطيات: يحق للباحثين استخدام هذه المعطيات الواردة في الاستبيان لأبحاث أخرى في جامعة القدس ما لم يطلب المشارك عكس ذلك.

لقد تلقيت فكرة كافية عن موضوع البحث و قامت الباحثة بالاجابة على كل استفساراتي المتوقعة و ليس لدي مزيد من الأسئلة و بتوقيعي هذا أقر على موافقتي الطوعية في هذا البحث.

الأسم :.....رقم الهاتف .....

البريد الاكتروني:..... التاريخ:.....