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Impediments to the Historical Development of the Clinical Pap Test in the United States: Their Relevance in Optimizing Cervical Cancer Screening in the State of Qatar

Nikolaos Chantziantoniou
University of Nebraska Medical Center

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**IMPEDIMENTS TO THE HISTORICAL DEVELOPMENT OF THE
CLINICAL PAP TEST IN THE UNITED STATES: THEIR
RELEVANCE IN OPTIMIZING CERVICAL CANCER
SCREENING IN THE STATE OF QATAR**

by

Nikolaos Chantziantoniou

A DISSERTATION

Presented to the Faculty of
the University of Nebraska Graduate College
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

Medical Sciences Interdepartmental Area Graduate Program
(Preventive & Societal Medicine)

Under the Supervision of Professor Amber D. Donnelly

University of Nebraska Medical Center
Omaha, Nebraska

August, 2019

Supervisory Committee:

Denise H. Britigan, Ph.D.

Stanley J. Radio, MD

Maheswari S. Mukherjee, Ph.D.

R. Marshall Austin, MD, Ph.D.

Eleanor G. Rogan, Ph.D.

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Through the University of Nebraska Medical Center, this dissertation aims to uncover the impediments that obstructed progress towards the development, acceptance, and application of the clinical Pap test in societal and preventive medicine in the United States of America. It is hoped that knowledge gained from the North American experience may be strategically considered in the contemporary clinical setting of the State of Qatar to optimize cervical cancer prevention through improved Pap test screening, and advance the assault against cervical cancer to rein in this disease burden upon women.

It is also my hope that this work will immortalize the substantive contributions to societal medicine that humanity has inherited from Dr. George N. Papanicolaou and from his wife, Andromache Papanicolaou.

In memory of my late father, and in this very effort to honor his astuteness, these sentiments and acknowledgments comprise the initial texts of this dissertation.

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ABSTRACT

IMPEDIMENTS TO THE HISTORICAL DEVELOPMENT OF THE CLINICAL PAP TEST IN THE UNITED STATES: THEIR RELEVANCE IN OPTIMIZING CERVICAL CANCER SCREENING IN THE STATE OF QATAR

Nikolaos Chantziantoniou, Ph.D.

University of Nebraska Medical Center, 2019

Supervisor: Amber D. Donnelly, Ph.D.

Three hundred surveys listing 31 questions were distributed amongst women and men at Sidra Medicine, Doha, State of Qatar, to assess knowledge and perceptions of: Cervical cancer (CxCa); preventive Pap test screening; Human Papilloma Virus (HPV) vaccination; and, need for population-based screening. Survey questions captured categorical statistical data through four categories: (1) Socio-demographic; (2) Healthcare Services; (3) Health Literacy; and, (4) Self-efficacy and Perceptions.

Hypothesis 1: 12 survey questions pertaining to CxCa and Pap testing revealed 8 statistically-significant dependencies; notably, 70% of respondents were aware of CxCa; however, 31.8% were unaware that CxCa may be curable; 33.7% were unaware of the Pap test; and, 35.2% were unaware that HPV vaccination may protect against CxCa.

Hypothesis 2: Two survey questions pertaining to screening practice revealed no statistically-significant dependencies; however, 67.4% of respondents strongly agreed for establishment of population-based screening in Qatar. **Hypothesis 3:** Three salient parallels were revealed between the Qatar and US clinical experiences: (1) Greater than

60% of symptomatic women in Qatar presented with Stage II/III CxCa in 2014, relative to 60% of women in the US with inoperable disease before 1957; (2) Estimated CxCa death rates in Qatar are 26.7%, relative to 32.2% in the US; and, (3) The burden of CxCa was under-estimated prior to emergence of death registries and epidemiologic data in the US in 1914 and 1952 respectively, relative to 2014 in Qatar.

Impediments to Pap test development and application in the US stemmed from macro-dynamics (i.e., societal, economic, political situations); and, reactive micro-dynamics (i.e., professional conflicts, skepticism, conceptualization of cervical precancer). Pap test screening practices in the State of Qatar may be optimized through:

- (1) *Tumor Registry for inclusion of precancer cases to ascertain actual CxCa incidence;*
- (2) *Organized screening with initial call to screening for asymptomatic women deemed at risk; and,*
- (3) *Reallocation of financial resources to support expanded screening for all women.*

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LIST OF ABBREVIATIONS

| | |
|--------|--|
| ACS | American Cancer Society |
| AGC | Atypical glandular cells |
| ASCC | American Society for the Control of Cancer |
| ASC-H | Atypical squamous cells – cannot rule out HSIL |
| CAP | College of American Pathologists |
| CDC | Centers for Disease Control and Prevention |
| CIS | Carcinoma in situ |
| CMC-NY | Cornell Medical College, New York |
| CxCa | Cervical cancer |
| DC | Diagnostic Cytopathology |
| EMENA | Extended Middle East and North Africa |
| HMC | Hamad Medical Corporation |
| H&E | Hematoxylin and Eosin |
| HPV | Human Papilloma Virus |
| HSIL | High-grade squamous intraepithelial lesion |
| ICO | Institut Catala d'Oncologica |
| IRB | Institutional Review Board |

| | |
|---------|---|
| KFSH&RC | King Faisal Specialist Hospital & Research Center |
| LSIL | Low-grade squamous intraepithelial lesion |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| Pap | 'Papanicolaou' |
| PHCC | Primary Health Care Corporation |
| QCS | Qatar Cancer Society |
| QID | Qatar Identification Number |
| QMoPH | Qatar Ministry of Public Health |
| US | United States of America |
| VFSM | Vaginal Fluid Smear Method |
| WFA | Women's Field Army |
| WHO | World Health Organization |

CHAPTER 1: INTRODUCTION AND DISSERTATION FUNDAMENTALS

Introduction

The clinical (morphology-based) Papanicolaou (Pap) test is a medical procedure applied to ideally detect precancerous (i.e., precursor) lesions of the uterine cervix through cytological grading of abnormal epithelial cells. A plethora of literature in the cytopathology and public health bibliographies establish the clinical Pap test as being the first effective cancer prevention tool in the history of medicine (Chang, 1999; Austin & Chantziantoniou, 2014; El-Mazny, 2014). However, the global impact of the Pap test in preventive medicine varies depending on its availability, accessibility, promotion, endorsement, and uptake.

Since the early experimental work conducted by Dr. George Nicholas Papanicolaou at Cornell Medical College, New York (CMC-NY) that ultimately conceived gynecological cytopathology starting in 1917, and more formally since 1928, 29 years transpired before the clinical Pap test was understood, optimized and field tested, and deployed in screening service in the United States of America (US) by 1957 (Christopherson & Scott, 1977; Chantziantoniou, 2014¹; Cibas & Ducatman, 2014; Chantziantoniou, 2017). In those intervening 29 years various scientific and non-scientific factors disrupted or utterly impeded the evolutionary course of the Pap test from the experimental setting through to population-based clinical practice in the US.

It is impractical to speculate upon the ramifications to society or to public health that may have compounded over time due to those impediments disrupting progress to effective cervical cancer (CxCa) management. Nevertheless, detailed knowledge of those impediments, of their impact, and how they were overcome, may hold relevance when considered to optimize contemporary Pap test screening systems that may be underperforming.

The efficacy of the Pap test remains a testament to a favorable balance between its technical and procedural simplicity, and its far-reaching clinical benefits. Historically, during specific timeframes in the US, system imbalances led to conflicts that were gradually overcome with advancing knowledge of the disease's preinvasive phases, and the Pap test's potential in differentiating them from frank carcinoma. Despite advanced automation in modern cytopathology, the Pap test remains a simple medical procedure whereby cells from ecto- and endo-cervical epithelia may be salvaged and processed to facilitate methodical, cytological grading. In stark contrast to its simplicity, however, was a complex evolutionary warren that continues to elicit speculation in society and in diagnostic medicine (Foltz & Kelsey, 1978; Reagan, 1997; Dickey, 2001; Lowy, 2010). The collective dynamics remain in a state of transition. They also continue to influence the Pap test's scope of practice both in the US and in other nations. As a result, the Pap test's scope of practice globally is inconsistent, as also are the public health ramifications arising from its varied application to manage CxCa (Gustafsson, Ponten, Zack, & Adami, 1997).

Since its promotion by the American Cancer Society (ACS) starting in 1948, the Pap test has steadily and significantly reduced the incidence and mortality rates of CxCa in the US by revealing occult, eradicable precancerous lesions (Koss, 1993; Casper & Clarke, 1998; Michalas, 2000; American Cancer Society, 2017¹). The impact of the Pap test globally has been similarly favorable, but typically in developed nations deploying systematic, population-based Pap test screening programs with adequate patient call and recall as dictated through enforced rescreening guidelines and robust patient-case registries (Christopherson & Scott, 1977; Koss, 1989; Habbema, De Kok, & Brown, 2012; Vaccarella, Lortet-Tieulent, Plummer, Franceschi, & Bray, 2013; Cibas & Ducatman, 2014). In contrast, in developing and in resource-poor regions, where Pap test uptakes may be inaccessible, opportunistic or utterly unavailable, advanced CxCa at diagnosis continues to pose major public health priorities associated with disparaging clinical and societal outcomes (Garner, 2003; Lowy, 2010).

As CxCa is currently regarded a preventable disease in adequately-screened women, cases presenting with advanced-stage malignancy at diagnosis may serve as surrogates reflecting screening disparities or system underperformances (Chang, 1999; Garner, 2003; Gorin, Gauthier, Hay, Miles, & Wardle, 2008). Therefore, system underperformance may be appraisable through such cases as the natural progression of asymptomatic precursor lesions through to infiltrating disease may span numerous years (Garner, 2003). Hence, with optimal population-based Pap test screening coupled with strategic patient call and recall and colposcopy, sufficient opportunities may be

exploited to identify and ablate lesions when still precancerous. Hallmarks of effective screening are therefore repeated Pap test sampling and timely ablation of intraepithelial lesions. However, opportunistic screening systems are typically reactive to suspicious symptomatology and not governed by initial patient call to screening or surveillance strategies (Seoud, 2013; Alemrayat, Abu-Abbas, Al-Naemi, AlTwaishi, Saibi, Zaheer, Khattab, & Adnan, 2018).

Despite the success of CxCa prevention through Pap test screening in the US and in other industrialized nations, not all global regions deploy like practices for the surveillance of precancer in asymptomatic women deemed at risk for developing this disease (Gustafsson, Ponten, Zack, & Adami, 1997).

As discussed in Chapter 3, at the time of this writing, the State of Qatar has not implemented a formal, organized, national population-based Pap test screening program for CxCa prevention for all resident women inclusive of strategic patient call and recall. Although, Pap test sampling is available through various public and private medical providers in Qatar. Creditably, through the Qatar Ministry of Public Health (QMoPH), the Primary Health Care Corporation (PHCC), and the Qatar Cancer Society (QCS), the State has recently invested extensively to support remarkable campaigns to increase public awareness of CxCa, and to encourage women to actively seek Pap test sampling opportunities. Nevertheless, Pap test uptakes in the State of Qatar remain opportunistic following guidance based on the low prevalence of CxCa in this clinical

setting (QMoPH National Cancer Framework, 2017; Sancho-Garnier, Khazraji, Cherif, Mahnane, Hsairi, El Shalakamy, Osgul, Tuncer, Jumaan, & Seoud, 2013; Seoud, 2013).

The State of Qatar is a member country of the Extended Middle East and North Africa (EMENA) region (Seoud, 2013). According to Sancho-Garnier et al. (2013), essentially all member territories and countries of the EMENA region deploy opportunistic Pap test screening in public and private medicine, mainly reactive to presenting symptoms. Consequently, according to Sancho-Garnier et al. (2013), and more recently to Alemrayat et al. (2018), the majority of cervical cancers in the EMENA countries are initially diagnosed when clinically advanced.

Cervical cancer ranks as the 5th most common malignancy in women in the State of Qatar according to the Institut Catala d'Oncologica (ICO) (Institut Catala d'Oncologica, 2017²). The ICO has also published an estimated annual CxCa burden of 15 cases for Qatar; whereas, four cases would prove fatal, reflecting an estimated annual death rate of 26.7% (Institut Catala d'Oncologica, 2017²). In line with these estimates, the *Qatar National Cancer Registry 2014* report (Appendix A) published by the *National Cancer Program*, QMoPH, revealed that of the 18 cases of CxCa registered in 2014, greater than 60% of those cases harbored Stage II/III disease at presentation (QMoPH National Cancer Program, 2014).

As the contemporary experience in Qatar is not unlike the historical experience of CxCa presentation and diagnosis in the US prior to expansion of Pap test screening by 1957, this parallel runs central throughout this dissertation. This parallel also poses an

opportunity for detailed study of its public health and epidemiologic elements. The State of Qatar is a relatively small country with a small female clinical population deemed at risk for developing CxCa; and, is serviced by premier tertiary medical institutions with accredited Diagnostic Cytopathology (DC) operations. The State is modern and developed (Institut Catala d'Oncologica, 2017²).

The parallels between the historical-US and contemporary-Qatar experiences pertaining to CxCa presentation and diagnosis led to the presumptions, research aims, and hypotheses herein considered.

Dissertation Fundamentals - Presumptions

The intents and purposes of this dissertation are conceptually based upon the overarching epidemiological dictum that disease in general, and CxCa notwithstanding, is not randomly distributed throughout humanity (Gordis, 2014). It is presumed, therefore, that prevalence and clustering of CxCa globally may manifest specific commonalities. Commonalities may involve risk factors; Human Papilloma Virus (HPV) subtypes and potential co-infections; CxCa etiology and pathobiology; symptoms at presentation; behavioral attitudes reflecting perceived etiology and likely prevention and cure; women's perceptions of barriers to screening; cultural norms and prohibitions; and, ultimately, the organizational infrastructures that either promote or compromise availability, access, or uptake of Pap test sampling (Chang, 1999; Garner, 2003).

It is from these core presumptions that a detailed understanding of the historical impediments in the US experience may indeed provide insights to guide the designing

of CxCa screening practices in non-US regions. Insights from the US model may guide optimization of existing screening practices by facilitating identification of shortcomings or inadequacies. Likewise, historical insights may address modern public health challenges stemming from rapid technological change, life-style and societal attitudes, financial disparities, and the cultural norms typifying conservative societies, as those characteristic of the EMENA region.

Dissertation Fundamentals - Literature Review

A methodical review of the pertinent cytopathology and public health literature was conducted to support an analysis and categorization of the factors that impeded the historical development, acceptance, and application of the clinical Pap test in the US (Chapter 2).

The literature review also involved a supplementary analysis of chronologically-relevant personal correspondences of Dr. George N. Papanicolaou. It also included a review of pertinent literature in the Greek bibliography to glean obscure perspectives that may embellish the overall understanding of impediments to the development of the clinical Pap test (Diamantis & Magiorkinis, 2012 – *translated from Greek*).

Dissertation Fundamentals - Aims And Hypotheses

The principal aim of this dissertation involved the generation of original, relevant health promotion data to facilitate transformation of existing opportunistic screening practices into more effective population-based Pap test screening programs for CxCa in the State of Qatar.

Overarching Hypothesis

It is hypothesized that women and men in the State of Qatar have adequate health literacy of CxCa; however, they may lack commensurate awareness of disease prevention possible through Pap test screening and HPV vaccination; and, that they would support the establishment of a formal Pap test screening program for all resident women in this nation. It is also hypothesized that, based on likely similarities of CxCa extent at presentation and diagnosis between the contemporary Qatar experience and the historical US experience prior to clinical Pap test screening, insights gained from the US model may provide actionable considerations to facilitate optimization of Pap test screening practices in the State of Qatar, and potentially in other countries in the EMENA region.

Dissertation Aim 1

Evaluate the degree of health literacy in women and men in the State of Qatar of CxCa; of Pap test screening, and of its benefits and uptakes; and, of HPV vaccination.

To evaluate the degree of health literacy in women and men pertaining to CxCa, the disease prevention benefits possible through Pap test screening, and those through HPV vaccination in the State of Qatar, specific questions are incorporated in a needs-assessment survey to generate supporting Socio-demographics, Healthcare Services, Health Literacy, and, Self-efficacy & Perceptions data (Appendix B).

Hypothesis

It is hypothesized that the majority of women and men in the State of Qatar have adequate health literacy of CxCa; however, they lack commensurate awareness of the disease prevention benefits possible through Pap test screening and HPV vaccination.

Dissertation Aim 2

Evaluate the degree of support in women and men in the State of Qatar for the establishment of a formal Pap test screening program for all women.

To evaluate the degree of support by women and men in the State of Qatar for the establishment of a formal Pap test screening program for all women, specific questions are incorporated in a needs-assessment survey to generate supporting socio-demographic and self-efficacy & perceptions statistical data (Appendix B).

Hypothesis

It is hypothesized that the establishment of a formal Pap test screening program for CxCa for all women in the State of Qatar is strongly supported by women and men.

Dissertation Aim 3

Evaluate possible similarities of extent of CxCa at presentation and diagnosis between the contemporary Qatar experience and the historical experience in the US prior to the introduction of clinical population-based Pap test screening in 1957.

To evaluate possible similarities of extent of CxCa at presentation and diagnosis between the contemporary Qatar experience and the historical US experience prior to

Pap test screening, pertinent literature reviews were conducted to ascertain historical information. To facilitate comparisons, equivalent epidemiological data for CxCa arising from the State of Qatar was researched and correlated.

Hypothesis

It is hypothesized that the extent of CxCa at presentation and diagnosis in the historical US experience, prior to the introduction of clinical population-based Pap test screening in 1957, bears similarities with the current experience of CxCa presentation in the State of Qatar mainly due to opportunistic Pap test uptakes.

CHAPTER 2: HISTORICAL IMPEDIMENTS TO THE DEVELOPMENT OF THE CLINICAL PAP TEST ARISING FROM MACRO- AND MICRO-DYNAMICS IN THE US

Chapter 2 details the salient macro- and micro-dynamics that historically impacted upon the evolution of the clinical Pap test in 20th century US. The literature reviews revealed a wide range of factors that influenced the development of the clinical Pap test. This Chapter describes events occurring primarily between 1900 and 1957. This period represents the experience arising from the detection and diagnosis of CxCa prior to robust Pap test screening in the US starting in 1957. The salient impediments revealed through this period were stratified through specific categories and timeframes, and summarized in subsequent sub-sections and tables in this Chapter (Tables 1-9).

The literature revealed that establishment of the clinical Pap test, and by extension gynecological DC, was not a phenomenon occurring in isolation of major historical milestones. These entities were rooted in various facets of history, in the emerging burden of cancer, and in the societal and public health apprehensions and priorities that ensued. They also stemmed from the changing cultural fabric of the US along with prevailing economic and political situations since 1900. They were likewise influenced by events occurring during and immediately following the two World Wars. The overall saga was complex. For the purposes of this dissertation, the following sub-sections were structured to elucidate the most impactful events in an effort to sustain historical and scientific coherence.

Knowledge Of Foundational Events In Diagnostic Cytopathology

Knowledge of the foundational events in DC was formed from information collated from a wide array of literary sources. Pertinent information in the DC and public health bibliographies was reviewed, as were relevant narratives in the medical and political history bibliographies. Accounts from individuals being either confidantes of Dr. Papanicolaou, close professional associates, relatives, moderate or staunch critics of him or of the cytologic method were also reviewed. In addition, Papanicolaou's statements through his personal correspondences in English and Greek were correlated. All materials were cross-checked to build the overall experience through utmost contextual and chronological relevance.

Impediments To The Development Of The Clinical Pap Test Arising From Historical Macro-Dynamics

Macro-dynamics reflected greater forces that either directly or indirectly influenced the inception, development, and application of the clinical Pap test in the US. These dynamics were primarily due to societal, economical, and political developments over the course of time. Although they revolved outside the realm of DC, they predisposed reactive micro-dynamics within the discipline. From a practical perspective, macro-dynamics were inevitable. They were external forces that characterized an evolving American society; hence, may be regarded historical milestones.

Cervical Cancer In The US In The Early-1900s

Epidemiological data pertaining to CxCa incidence *per se* from the early-1900s is practically unavailable. From information referring to death registries, it became evident that mortality due to CxCa changed remarkably between 1900 and 1957, when Pap test screening practices started to make an impact in disease prevention throughout the US.

Accounts referring to the burden of CxCa in the early-1900s appear mainly in secondary-source works by medical historians. Although devoid of specific epidemiological detail, these works described the impact of CxCa, and the attitudes and fears elicited in both women and clinicians. These works underscored the sensitivities and stigmatization associated with this disease throughout the wider dimensions of American society. Such accounts also referred to racial differences seen in CxCa mortality at the turn of the 20th century.

Remarkable descriptions of the overall impact of cancer in the US were organized in a book, entitled *The Secret History Of The War On Cancer* (2007), by Devra Davis. One poignant statement in Davis' book notably embodied the essence of CxCa at the start of the 20th century. According to Davis (2007):

“At the start of the twentieth century, cervical cancer was a death sentence, and often a secret one. It was not unusual for women to go to their graves never knowing what was wrong.”

In the early-1900s, CxCa posed particular challenges that tried the patient and her clinician equally. Amid the most prominent of difficulties was its detection. And,

this was hampered by human attitudes and sensitivities at a time when the disease was regarded a societal menace that inexorably led to silent, painful deaths in relatively young women indiscriminately (Gardner, 2006; Skloot, 2010).

Detection Of Cervical Cancer In The Early-1900s

Research by Lowy (2010) revealed that the vaginal speculum was developed in the early 19th century. Using the speculum, gynecologists gained visual access to the uterine cervix and, after shining light upon it, assessed its gross anatomy with the naked eye. This practice allowed gynecologists to raise clinical suspicions and target exploratory biopsies. This in turn helped anatomical pathologists correlate the ensuing histopathologic findings with the gross, clinical cervical features (Lowy, 2010). Based on such correlations, in 1908, a German physician, Dr. Walther Schauenstein, advocated that the naked eye may adequately inspect the cervix to distinguish a healthy cervix from one that may be cancerous. The healthy cervix “looks soft, pink and rosy”, whereas the diseased cervix appears “gray and full of pus” (Davis, 2007).

Visual inspection of the cervix with clinical correlation of its gross appearance thus became the standard-of-practice in the US. This practice led to early speculations of the disease’s genesis. At the turn of the 20th century, doctors associated CxCa with sexual habits as Jewish women and nuns demonstrated the lowest rates of the disease. They also related the disease to multi-parity and, likely, to cervical trauma during childbirth (Olson, 1989). But unlike other human ailments, the perceptions of CxCa and of its likely etiology transposed the disease onto broader societal contexts in the early-1900s.

Collectively, these dynamics had a profound effect upon clinicians required to not only discover the disease, but to also understand it, and to deliver effective care to all women impartially. According to Davis (2007):

“Doctors had long known that cervical cancer did not arise overnight. But it was accepted as an inevitable result of some poorly understood deficiency, perhaps a moral one. Disease of any kind was seen as a result of not trying hard enough to be good enough. Then, as now, far more black women got the disease and died of it. The fact that this ailment was uniquely a women’s disease that disproportionately affected those then called “coloreds” combined to make cervical cancer less than a high priority for doctors.”

Cervical cancer posed additional barriers for both patients and clinicians given its anatomical origin. The intimacies arising from this disease along with its outcomes relative to other malignancies in women made CxCa a unique clinical challenge, and one often avoided leading to grave consequences. Both the disease in women and its detection by doctors were embedded within a web of societal attitudes, mutually-perceived taboos and embarrassment, and both implicit and explicit prohibitions (Gardner, 2006; Skloot, 2010). According to Davis (2007):

“More accessible forms of cancer might produce visible or palpable lesions, lumps and bumps that, once found and recognized, gave doctors a fighting chance to cut out the growth and arrest the disease. But the cervix, the most common locus of cancer at the beginning of the last century, was a private place

whose means of access was closed to all eyes. At a time when women felt shame at the mere mention of their genitals, the topic of cancer of their private parts was not considered appropriate for public discussion.”

Yet, CxCa could not remain overlooked. The clinical detection of the disease and its treatment posed foremost dilemmas in society and in medicine. These priorities obliged gynecologists to nonetheless align their efforts against the disease applying the standard practice: Advocating visual inspections of the uterine cervix in search of obvious lesions in women. In the early-1900s radical hysterectomy was the mainstay procedure for treatment of CxCa with an associated surgical mortality rate of 20% (Olson, 1989).

The overall problem of CxCa was neither trivial in society, nor in medicine. The predecessor organization to the modern ACS, the American Society for the Control of Cancer (ASCC), was formed precisely in response to these emerging priorities.

Establishment Of The American Society For The Control Of Cancer

The ASCC was established in 1913 in response to the problems arising from the management of CxCa when initially diagnosed in advanced stages (Greenwald, Cullen, & McKenna, 1987; American Cancer Society, 2017²).

The ASCC was formed by a group of businessmen and gynecologists in New York City with the founding mission to: “*Fight Cancer With Knowledge*” (Holleb, 1988; Davis, 2007; American Cancer Society, 2017²). The ASCC promoted the then standard-of-practice: CxCa may be visually detected with the naked eye, confirmed through biopsy,

and managed through hysterectomy (Holleb, 1988; Davis, 2007). However, the founding members of the ASCC had no illusions of the imminent challenge pertaining to cervical visualization. Dr. James S. Ewing served the founding committee of the ASCC.

According to Davis (2007), in an effort to promote the principles of CxCa detection and diagnosis, the ASCC had a “simple aim”:

“...to persuade physicians to learn how to look at the cervix and persuade women to allow regular exams... It never has been easy to get women to take their clothes off and lie...with their feet in cold metal stirrups. A leading ASCC pathologist, James Ewing, ruefully conceded in 1926 that even if doctors became convinced of its value, the prospects for persuading women to undergo this exam twice a year were slim and daunting. It was not clear at the time whether it was harder to find physicians who understood the value of performing the exam or to persuade women of its value.”

Linear Model Of Cervical Carcinogenesis

In the early 20th century in the US, it was surmised that malignant disease progressed linearly starting from a physiological normal (Croswell, Ransohoff, & Kramer, 2010). The linear model of carcinogenesis thus emerged. Based on this theory, CxCa developed incrementally through progressive pathobiological phases. Therefore, CxCa could be hypothetically eliminated through periodic inspections of the cervix for apparent symptomatology however trivial (Croswell, Ransohoff, & Kramer, 2010; Olson, 1989). Throughout the 1920s, the American Medical Association recommended periodic

health examinations in search for subtle anatomical changes in the uterine cervix (Croswell, Ransohoff, & Kramer, 2010). The ASCC, and its descendant organization the ACS, adopted authoritative roles in promoting such practices. The development of the colposcope in 1924 by Dr. Hans Von Hinselmann produced additional tools to support this clinical model (Olson, 1989). The early rationalization of medical *screening* for apparent CxCa thus emerged in the US.

Mortality From Cancer And Other Malignant Tumors - In The Registration Area Of The United States 1914

Within the first year of its mandate, in 1914, in its inaugural attempt to generate knowledge of cancer, the ASCC collaborated with the *Department Of Commerce, United States of America, Bureau Of The Census*, to produce a detailed registry of deaths throughout the US based on estimated population growth; cancer type; patient age group; gender; and, State of residence. In the mammoth publication that ensued under the directorship of Sam L. Rogers in 1916, entitled *Mortality From Cancer And Other Malignant Tumors - In The Registration Area Of The United States 1914*, death rate statistics were organized spanning the years 1900 through 1914 (Department Of Commerce, Bureau Of The Census, 1916). From the data published, when comparing figures specifically from the terminal-end years of 1900 and 1914; for: (a) the estimated population growth; (b) the crude deaths due to all cancer types in women and men; and (c) the deaths specifically due to cancer of the 'female genital organs', the differences in magnitude over the course of the 14 registration years were: 2.14 fold; 2.70 fold; and, 3.02 fold respectively.

The trend in the number of deaths due to all cancer types in those 14 years out-paced estimated US population growth. Meanwhile, the trend in deaths specifically due to gynecological cancer out-paced the trends of all cancers combined for the same period.

As it were, during the first 14 years of the 20th century in the US, CxCa posed an anomaly evidently set upon an unnerving, perhaps geometric trajectory.

Enigmatic problems like CxCa along with other undesirable human ailments formed the bedrock fundamentals of the Eugenics movement in the US. It was during World War I, and thereafter, that the Eugenics movement flourished across the nation (Davis, 2007). The impact of the Eugenics movement in the US was extensively researched in a book, entitled *War Against The Weak – Eugenics And America's Campaign To Create A Master Race* (2003), by Edwin Black. According to Black (2003):

“During the war years, eugenic organizations proliferated in America. Like-minded citizens found ethnic solace and self-vindication in the idea of biological superiority. The Race Betterment Foundation was among the leading eugenic organizations that sprouted around the country...In 1914, Dr. Kellogg organized the First Race Betterment Conference in Battle Creek, Michigan. The conference's purpose was to lay the foundations for the creation of a super race...”

Coincidentally, it was also in September 1914 that Dr. George N. Papanicolaou took employment at CMC-NY, starting the research work that ultimately led to the establishment of the clinical Pap test and its application in CxCa screening (Carmichael,

1973; Chantziantoniou, 2014¹). The reactive micro-dynamics and the ensuing impediments specific to Papanicolaou's work at CMC-NY are described in subsequent sub-sections in this Chapter.

Cancer In The US And Impact Of The Great Depression

The literature likewise revealed that the historical juxtaposition between the development of the clinical Pap test and specific events occurring during the Great Depression was not coincidental.

The Great Depression, spanning a 12-year period from 1929 to 1941, was undoubtedly the most challenging period in US history nested economically and politically between two major World Wars (Amadeo, 2018). It was during the Great Depression that extraordinary shifts emerged in epidemiology and in public health, and consequently in ensuing societal attitudes (Turnock, 2012). These shifts were widely impactful, not just within the realms of science and medicine, and public health (Tapia Granados & Diez Roux, 2009; Amadeo, 2018).

Since the beginning of the 20th century, and throughout the Great Depression, life expectancy in the US was gradually increasing in pace with incrementally-efficacious treatment for infectious diseases (Armstrong, Conn, & Pinner, 1999). The threat of death from cancer eventually surpassed that likely from communicable disease by the time the Depression started dissipating in 1941. Cancer usurped all other ailments, becoming the foremost public health priority coupled with societal distress; casting a profound sense of despair and hopelessness upon patients and clinicians alike.

In 1928, against the backdrop of mounting economical and societal decline, and increasing burden due to advanced CxCa, Papanicolaou introduced the vaginal fluid smear method (VFSM) as being an effective *diagnostic test* to detect the disease. Conclusions drawn from his research at CMC-NY were reported through a presentation, entitled *New Cancer Diagnosis*, delivered in the 3rd Race Betterment Conference organized for eugenicists (Papanicolaou, 1928). As Papanicolaou's discoveries clashed with then standard-of-practice for CxCa detection, his proposals were dismissed by the medical community as being clinically unnecessary (Papanicolaou-Kokkori, 2008; Naylor, 1988). This setback was highly adverse and most unfortunate throughout Papanicolaou's career, but also for the detection and management of CxCa at the start of the Depression. Due to this failure, Papanicolaou ceased working towards refining the diagnosis of CxCa through the cytologic method, and this disruption led to the 'lost decade of cytopathology' (Chantziantoniou, Donnelly, Mukherjee, Boon, & Austin, 2017). The significance of these events in the overall evolution of the clinical Pap test is detailed in subsequent sub-sections in this Chapter.

In 1929, as the Depression deepened, Dr. Clarence Cook Little directed the ASCC (Davis, 2007). Due to the widespread economic decline, the ASCC faced financial difficulties alongside dismal fundraising campaigns and unable to sustain its objective: To manage the control of cancer. Nonetheless, the intensifying impact of CxCa in the US by 1930 exerted considerable pressure upon the organization to act and to project servant leadership command. According to Davis (2007):

“By then more than 140,000 Americans were dying of cancer each year, and the disease had become the nation’s second leading cause of death after heart disease. The sobering fact was that more women than men were dying of cancer and usually from cancers of the cervix, stomach and breast.”

Cervical Cancer Burden In The US In The 1930s

Knowledge of the incidence and burden of CxCa in the 1930s was mainly ascertained retrospectively from cross-referenced information appearing in the more recent DC bibliography proper, mainly in publications after 1941.

In the 1930s, cervical and uterine cancers in the US caused the highest death burden of all cancers in women exerting a heavy societal toll of life-years-lost (Casper & Clarke, 1998; Cibas & Ducatman, 2014). Prior to cytologic screening, CxCa was conventionally discovered through opportunistic biopsy, as classical symptoms secondary to advancing disease (i.e., pelvic pain, abnormal bleeding, and discharge) prompted women to seek the care of a gynecologist. Epidemiological and biographical research by Olson (1989) revealed that in 1931, CxCa was predominantly seen in poorer women during the Depression years. Coupled with unfavorable surgical success rates, a key parameter that emerged in the 1930s was *time*, exemplifying a sense of urgency posed by presenting symptoms and the need for prompt medical intervention to facilitate relief and treatment. Time became the essence for CxCa control. As well, time became the ASCC’s signature political edict (Davis, 2007).

By 1931, time was relatable with CxCa cure outcomes. This relationship was reflected in 1945 by Meigs, Graham, Fremont-Smith, Janzen, & Nelson (1945):

“Early, accurate diagnosis of cancer of the female genital tract has long been the goal of gynecologists. Ewing states that in 1931, 14,464 women died of cancer of the uterus or 12 per cent of all cancer deaths were due to this type...Ewing arrived at figures of an average of 10 per cent approximate 5 year cures for uterine cancer. He calculated that the possible cure under ideal conditions, i.e., intelligent public, skillful and experienced specialists, and modern equipment, would be 40 per cent. The discrepancy between the possible rate of cure and of actual cure bears a direct relationship to the time at which diagnosis is established and treatment instituted.”

To simplify the apparent relationship between timely intervention and possible cure for CxCa, with extent of disease at time of intervention, Meigs, Graham, Fremont-Smith, Kapnick, & Rawson (1943) stated:

“Cancer of the cervix and body of the uterus is a curable condition. Early diagnosis and treatment are prerequisites for cure...Approximately the same statement is given for carcinoma of the cervix by Todd who reports that from the onset of abnormal bleeding the chance of cure decreases 3.24 per cent a week. The average time from the onset of symptoms to operation is stated to be 7.5 months. Eleven of a hundred women with cancer of the cervix reach the surgeon in the early (operable) stage; 29 in the stage of so called “border-line operability”;

60 are totally inoperable when treatment is begun...Delay is thus responsible for a majority of deaths from cervical cancer, a delay to which both patient and physician contribute.”

An understanding of the shared contributions and impact of advanced CxCa at presentation and diagnosis in the 1930s, and how this disease tormented patients and clinicians alike, is herein relevant. But given the aims of this dissertation, these associations ought to be viewed from broader perspectives to reveal their influence throughout the wider dimensions of societal medicine. These perspectives included yet another parameter: The *extent* of disease at presentation. According to Davis (2007):

“By the time its physical tracks could be felt, the illness had often been brewing for more than a decade. The warning signs of bleeding, shortness of breath and pain – then touted as the indications of cancer – were not at all clear in the disease’s early stages. After all, women have been bleeding, sometimes uncomfortably, for as long as the species has existed. By the time the strange discharges, unstoppable cramps, and relentless full-belly feeling were evident, the cancer was unstoppable.”

The evolution of gynecological DC was thus inextricable from two enduring parameters: *Time* and *Bleeding*. The clinical significance of these factors became gradually apparent alongside incremental scientific advancements that led, ultimately, to an understanding of the disease’s natural progression and pathobiology, and how best to manage them depending on available tools. Indeed, it ought to be emphasized

that the association of HPV in cervical carcinogenesis was not known until 1978 (Syrjanen, 2017). In the 1930s, the importance of *Time* and *Bleeding* likewise stemmed from greater historical and societal situations. Abundant scientific and lay literature substantiated the revolutionary advances that characterized the 20th century in North America and elsewhere. In the US particularly, significant technological innovations rapidly transformed medicine and the methods applied to diagnose and treat disease against a backdrop of unprecedented scientific, political, and socio-economical changes.

Amid these dynamics, the extent of public knowledge of the classical symptoms of CxCa became another important variable in an effort to discover cancer as early as possible. The ASCC took these challenges seriously in order to defend the touted urgency for timely disease detection. For the ASCC, sufficient public literacy became a governing organizational objective.

The health literacy campaigns developed in the US to disseminate knowledge of cancer and of its symptoms were researched in a book, entitled *Early Detection – Women, Cancer, And Awareness Campaigns In The Twentieth-Century United States* (2006), by Kirsten E. Gardner.

The Women's Field Army

In an effort to deliver on the expectations posed upon the ASCC, Dr. Clarence C. Little considered an unprecedented idea in 1933. He wanted to disseminate knowledge of cancer to the general public to gain its allegiance in the effort to discover the disease early and, by doing so, raise needed funds. He approached the General Women's

Federation seeking assistance. Dr. Marjorie B. Illig, a radiologist, was the serving Chair of the Federation's Public Health Division. Little's proposal to her was the formation and mobilization of a women's group to spread knowledge of cancer (Gardner, 2006; Davis, 2007).

The General Women's Federation was then active in spreading public health information throughout the US. The organization encouraged its members to educate the public of medical services still available throughout the Depression years, but to also protest the ongoing budget cuts to healthcare (Gardner, 2006).

Little's proposal gained Illig's support and materialized in 1936. It led to a robust public health awareness expedition: The Women's Field Army (WFA) (American Cancer Society, 2017²). The women's movement adopted para-military hierarchies and marched strategically under the motto: *'Cancer Thrives On Ignorance. Fight It With Knowledge'*. According to Davis (2007):

"At its peak the army numbered over 2 million. Set up as the ASCC's public education arm and fielding battalions in every State, WFA members marched door-to-door collecting money and handing out pamphlets. They organized public events...to raise money and generally spread the word about cancer..."

Dr. Illig supported the WFA given her professional experiences and convictions pertaining to CxCa in the mid-1930s. According to Davis (2007):

“As a radiologist, she had seen dozens of young women whose x-rays revealed abdomens riddled with spreading white blotches of disease. Illig explained to her colleagues at the federation that doctors could identify subtle abnormalities of the cervix long before cancer showed up on x-rays. Women’s lives could be saved if they would show up for regular physical exams. The suggestion that early detection could prevent deaths provided a radical and hopeful solution for a problem that had come to be fatalistically accepted. If women could be mobilized against this devastating disease, the world would be better off.”

The WFA was established in the mid-west States by 1937 (Gardner, 2006). Based in Cedar Rapids, the Iowa WFA phalanx organized various projects relying on the prominence of Dr. Arthur Wright Erskine, a local physician. Collaborating with Erskine, the Iowa WFA produced various educational materials for dissemination throughout the mid-west States. As radio was the mainstay technology by which to reach the public widely, their initiatives included live broadcasts in an effort to reach households dispersed throughout the rural farming landscapes. And it was through these initiatives that Erskine uncovered another impediment to the timely detection of CxCa: The geographic vastness of the mid-west US, and the varied urban and rural population clustering throughout the heartland States. According to Gardner (2006):

“The Iowa WFA, female activists, and Erskine expressed concern about teaching female cancer awareness in rural areas, with scattered populations of women. Unlike urban areas, Erskine argued, “there are geographic, economic, and

perhaps psychological conditions in our state, and in other rural states” that might interfere with early detection efforts. Iowa cancer activists recognized that many people would not want to travel to remote urban cancer centers for treatment: “They get homesick and discouraged and abandon treatment before they should. In practice, therefore, the great majority of patients with cancer must now, and for some time to come, be treated in or near their communities. We must do the best we can with what we have.” Through the medical lens, Erskine realized that local treatment facilities might be inferior to centralized, better-equipped urban centers, but he also considered the unique behavioral tendencies of his target population. Less superior treatment was better than no treatment.”

Nevertheless, with increased public awareness of cancer because of the WFA, with expanded organizational exposure, and with the imperative to fight the disease as early as possible, the ASCC faced potent public relations predicaments. Davis (2007) stated:

“Folks began to believe the claim that early detection was the key to treating the disease, but such claims raised serious questions. Why were cancer rates increasing when more people were seeing their doctors sooner? Why was so little real progress being made against finding and treating the disease? Why were more and more women dying of cervical cancer? Significant numbers were beginning to question what “cancer control” really meant.”

The National Cancer Act Of 1937

Despite the expanded general awareness of cancer, the worsening patterns between population growth and mortality trends *due* to cancer became profoundly alarming throughout the late-1930s.

In response, US Congress was compelled to enact the National Cancer Act of 1937 (Holleb, 1988; National Cancer Institute, 2016). The Act, signed into law by President Franklin D. Roosevelt, created the National Cancer Institute (NCI) from an allocation of \$750,000 accompanied by ambitious aims during a period in US history marked by devastating economic and societal setbacks. The NCI became the foremost research organization in the US Public Health Service (Habbema, De Kok, & Brown, 2012). Amongst the initial mandates of the NCI was the redistribution of an additional \$700,000 in the form of research grants cascaded to scientists through affiliated governmental organizations (Holleb, 1988; National Cancer Institute, 2016). The underlying intent of the Act was to stimulate research and development and training, to unravel the causes of cancer, its diagnosis, its effective treatment, and eradication.

The National Cancer Act of 1937 was enacted in the depths of the Great Depression (Amadeo, 2018). The Act therefore symbolized a stark paradox between the magnitude of the public health urgency posed by increasing burdens of cancer, and the funding seemingly necessary to rein in this plight upon humanity during the severest financial recession in US history.

In 1939, following a change in prospects at CMC-NY, the 'lost decade' of DC ended. Papanicolaou was then encouraged to revive his work on CxCa working in collaboration with Dr. Herbert F. Traut, a gynecological oncologist at CMC-NY.

By 1941, as the Depression ended, Papanicolaou and Traut had transformed the previously-dismissed VFSM from a *diagnostic test* into a *screening test* accompanied by an awareness of its secondary disease-prevention potential (Papanicolaou & Traut, 1941). However, the method's resurrection and transformation through to the clinical Pap test in 1948 occurred following specific events stemming, in large part, from the National Cancer Act of 1937, and bold advocacy demonstrated by the ACS. These events are detailed in dedicated subsequent sub-sections in this Chapter.

What facilitated this shift in prospects was primarily the urgency posed by increasing deaths due to CxCa and, secondarily, by the conceptualization of cervical precancer arising from Papanicolaou's and Traut's work in 1941. As such, another worrisome paradox began to emerge for the ASCC that contrasted increasing deaths due to invasive CxCa with the possible cures for precancer through VFSM detection. However, the screening test remained under scrutiny; notably, it lacked a characteristic, unambiguous diagnostic nomenclature to allow alignment with the diagnostic language of anatomical pathology. But perhaps more importantly in 1941, the VFSM lacked widespread consensus as to what would be its *true* role in the burgeoning medicine of CxCa detection and control (Koss, 1989).

Despite the imperfections, the cytologic method offered promising clinical advantages at a most opportune time. The VFSM offered an alternative by which to detect and ablate precancerous lesions through timely intervention; an alternative that may arrest the natural biology of the disease towards invasive cancer. Papanicolaou's simple procedure thus offered far-reaching clinical benefits, not merely the detection of advanced disease through vaginal secretion analysis. The cytologic method lessened the detriments of *time*, the urgency due to presenting symptoms, and the grave consequences typical of delayed surgery. This alternative appealed to gynecologists facing the sensitivities and therapeutic challenges of advanced, oftentimes inoperable CxCa in their patients in the early-1940s.

Against a background of escalating enthusiasm in gynecological DC, Papanicolaou and Traut's monograph, entitled *Diagnosis Of Uterine Cancer By The Vaginal Smear* (1943), published by The Commonwealth Fund, became a cornerstone for the subsequent events that led towards the establishment of the clinical Pap test (Papanicolaou & Traut, 1943). Their monograph formed the catalyst for ongoing technical and procedural advancements, but also for the realization of population-based cytologic screening for cervical precancer in asymptomatic women (Boon & Chantziantoniou, 2013).

Rebranding Of The American Society For The Control Of Cancer Into The American Cancer Society

One year after Papanicolaou and Traut's epic monograph in 1943, the ASCC was obliged to respond to pressing developments. It was rebranded as the American Cancer

Society in 1944 because of the initiatives commanded by Mrs. Mary Woodard Lasker, and of her convictions and political influence.

Mary W. Lasker was a wealthy, prominent philanthropist dismayed by the lack of progress in research and apparent inaction by the ASCC to address the growing threat of cancer. Noting the ASCC's limited cash flow and chronic inability to uphold its mission, she actively raised \$4 million for the organization demanding, in return, major restructuring of its constitution (Holleb, 1988).

Mary Lasker transformed the ASCC into an authoritative, agile organization supported by astonishing financial leverage during the depths of World War II. She thus became an influential member on the ACS Board. Following her command, ACS policymakers espoused funding for cancer research as so dictated by Mary Lasker: That, "...out of every \$4 raised the organization would spend \$1 on research" (Davis, 2007; American Cancer Society, 2017²).

Due to Mary Lasker's enterprises the ASCC reemerged in 1944 as the emboldened ACS, poised to tackle the mounting problem of ineffective cancer control in the US. The re-profiling of the ASCC coincided favorably with Papanicolaou's work at CMC-NY and with the ongoing developments in the cytologic methods (Hinsey, 1962). It was following these specific dynamics that barriers impeding the acceptance and use of the VFSM started to weaken following the extensive research work in DC funded by the ACS. The ACS honored the National Cancer Act's intents and purposes, and became

a staunch supporter of Papanicolaou's work (Hinsey, 1962; Koss, 1993; Papanicolaou-Kokkori, 2008).

Amid growing interest in the VFSM in 1945, the ACS was compelled to review its public awareness and advocacy policies to assess organizational alignment with the rapidly changing societal and medical developments in the US as World War II ended. Its Board then deemed the WFA as being utterly unfitting in a post-war period. Being a quasi-military operation predominantly made up of amateurs and activists with little formal education in medicine or cancer, the ACS Board decided the WFA be disbanded to mitigate likely bruising public relations quandaries (Davis, 2007).

Alternatively, in 1946, to disseminate scientific knowledge formally, the ACS inaugurated its intramural program for epidemiological research responding to a 5-fold increase in lung cancer in the US during the Great Depression years (Thun, Calle, Rodriguez, & Wingo, 2000). The intramural program was designed to track cancer incidence trends, risk factors, screening methods, and treatment statistics. However, it was not until 1952, and henceforth, that the ACS published *Cancer Facts And Figures* annually to include data for CxCa (Thun, Calle, Rodriguez, & Wingo, 2000).

The timing of the ACS's *Cancer Facts And Figures* for CxCa in 1952 was not immaterial. It followed two significant events in the evolutionary timeline of the clinical Pap test, both occurring in 1951: The death of Mrs. Henrietta Lacks to CxCa; and, auspicious preliminary outcomes arising from the Memphis and Shelby County,

Tennessee, trial sponsored by the NCI - a direct consequence of the National Cancer Act of 1937.

Death Of Henrietta Lacks To Cervical Cancer: The HeLa Cell Line

The story of Henrietta Lacks was detailed in a remarkable book, entitled *The Immortal Life Of Henrietta Lacks* (2010), by Rebecca Skloot.

Henrietta Lacks was an African-American woman that died from advanced CxCa at Johns Hopkins Hospital, Baltimore, on October 4, 1951. Although her clinical course may have been similar to that of other women dying of CxCa at that time, her case proved extraordinary and scientifically significant.

Henrietta Lacks had noticed abnormal vaginal bleeding, and self-felt a nodule in her uterine cervix. Appropriately, upon visual inspection, her local physician noted the nodule but suspected it was syphilitic. When Henrietta's tests returned negative for syphilis, she was led to a gynecologist at the Johns Hopkins Hospital. A cervical biopsy confirmed she had infiltrating squamous CxCa (Skloot, 2010). However, her cancer proved highly malignant and was widely extensive at diagnosis. Henrietta Lacks, a young mother of five children, succumbed to CxCa 31 years old.

Skloot (2010) described Henrietta Lacks' suffering in vivid detail. In the context of this dissertation, her book also manifested the attitudes and bleak realities of advanced CxCa prevailing in the early-1950s. According to Skloot (2010):

"...Henrietta told her doctors several times that she thought the cancer was spreading, that she could feel it moving through her, but they found nothing

wrong with her. “The patient states that she feels fairly well,” one doctor wrote in her chart, “however she continues to complain of some vague lower abdominal discomfort...No evidence of recurrence. Return in one month.”

There’s no indication that Henrietta questioned him; like most patients in the 1950s, she deferred to anything her doctors said. This was a time when “benevolent deception” was a common practice – doctors often withheld even the most fundamental information from their patients, sometimes not giving them any diagnosis at all. They believed it was best not to confuse or upset patients with frightening terms they might not understand, like *cancer*. Doctors knew best, and most patients didn’t question that...Especially black patients in public wards.”

The case of Henrietta Lacks altered the history of medicine as malignant cells from her cervix were removed just months before her death without her knowledge or permission. This was done to salvage cells for cancer research based on cell cultures. Unlike other cell cultures of malignant cells that follow finite cell division cycles, Henrietta Lacks’ cells continue dividing *in vitro* through to this day. They are biologically immortal. Her cells are otherwise scientifically known as: The HeLa cell line. Her CxCa cells have facilitated revolutionary advancements in vaccine development, virology, oncology, and chemotherapy due to their immortality allowing research to be conducted and repeatedly validated. Nonetheless, along with the infamous Tuskegee syphilis experiment in the US (Brown, 2017), Henrietta Lacks’ case led to the

establishment of the Discipline of Medical Ethics, and its ramifications in the conduct of modern medical research globally (Skloot, 2010).

The overall impact of CxCa in 1951 in the US, with a glimpse of the impediments to Pap test uptakes, was also alluded to by Skloot (2010):

“At that point, more than 15,000 women were dying each year from cervical cancer. The Pap smear had the potential to decrease that rate by 70 percent or more, but there were two things standing in its way: first, many women – like Henrietta – simply didn’t get the test; and, second, even when they did, few doctors knew how to interpret the results accurately, because they didn’t know what the various stages of cervical cancer looked like under the microscope. Some mistook cervical infections for cancer and removed a woman’s entire reproductive tract when all she needed was antibiotics. Others mistook malignant changes for infection, sending women home with antibiotics only to have them return later, dying from metastasized cancer. And even when doctors correctly diagnosed precancerous changes, they often didn’t know how those changes should be treated.”

Dr. Richard Wesley TeLinde was a gynecological surgeon amongst the medical team attending to Henrietta Lacks at Johns Hopkins Hospital. He was then actively involved in the US-wide debate of: “What qualified as cervical cancer, and how best to treat it” (Skloot, 2010). Pertaining to DC, anatomical pathology, and surgical treatment

of CxCa, the following narrative embodied the state of gynecological healthcare in the US in the early-1950s (Skloot, 2010):

“In 1951, most doctors in the field believed that invasive carcinoma was deadly, and carcinoma in situ wasn’t. So they treated the invasive type aggressively but generally didn’t worry about carcinoma in situ because they thought it couldn’t spread. TeLinde disagreed – he believed carcinoma in situ was simply an early stage of invasive carcinoma that, if left untreated, eventually became deadly. So he treated it aggressively, often removing the cervix, uterus, and most of the vagina. He argued that this would drastically reduce cervical cancer deaths, but his critics called it extreme and unnecessary...TeLinde presented his argument about carcinoma in situ to a major meeting of pathologists in Washington, D.C., and the audience heckled him off the stage.”

The Memphis And Shelby County, Tennessee, Trial For Cervical Carcinoma In Situ

The Memphis and Shelby County, Tennessee, clinical trial was launched in 1951 to test the VFSM’s potential to identify carcinoma in situ (CIS) in asymptomatic women, and to distinguish this lesion from invasive CxCa in symptomatic women (Dunn & Sprunt, 1955). The study was among the first population-based trials in the history of gynecological DC to assess a *screening test*, not a *diagnostic test*. The trial was authorized and funded by the NCI and produced promising results in favor of VFSM-based screening for early CxCa in asymptomatic women. Moreover, the Memphis and Shelby

County trial produced important epidemiological data reflecting that local, clinical population.

The Memphis and Shelby County trial was furthermore significant as it considered societal attitudes, professional attitudes, and the deployment of a non-medical workforce to analyze the arising volumes of smears, instead of pathologists who only reviewed abnormal smears brought to their attention. As such, the Memphis and Shelby County trial tested and introduced a model by which to analyze and report VFSM cases for the detection of cervical precancer.

The Memphis trial had four objectives (Dunn & Sprunt, 1955): "(1) To determine whether periodic vaginal exfoliative cytology as a screening procedure can be used to diagnose cancer in the preinvasive stage; (2) To accumulate data for determining age-specific incidence and prevalence rates for both preinvasive and invasive cervical cancer; (3) To estimate the frequency with which vaginal cytology needs to be applied to be effective as a case-finding procedure; and (4) To determine whether, through this case-finding procedure, cervical cancer can become largely a curable disease."

Dunn and Sprunt (1955) emphasized that, in this trial, "cytology is used for screening; it is not competing with the tissue study for relative accuracy in final diagnosis." Controversy and suspected professional encroachment between DC and cervical biopsy were pervasive in 1951. And these conflicts became increasingly more acute alongside the growing volumes of cervical smears generated through screening, and the monetary returns affected due to reduced billing for cervical biopsies.

Nevertheless, the Memphis and Shelby County trial also revealed gaps in public literacy despite the extensive awareness campaigns conducted by the ACS, by its predecessor the ASCC since 1913, and by the robust WFA. According to Dunn and Sprunt (1955):

“It soon became evident that the public was not overly conscious of cancer as a personal problem, and that more aggressive educational measures were needed. Yet it was necessary that publicity should not antagonize practicing physicians since their cooperation is a necessary part of the project...

Any apprehension about the public’s over-consciousness of cancer has been completely dispelled. Enlightenment and motivation have become the leitmotifs of the publicity program in the effort to reach women individually through every possible medium, until they accept the fact that they can have cervical cancer, and that the cytology examination is a means of detecting this cancer in a curable stage.”

The political push-back exerted upon the cytologic method and its alleged potential to detect cervical precancer in the early-1950s, were also manifested through the Memphis trial. According to Dunn and Sprunt (1955):

“In a few instances, skeptics have put the cytology program to the test by submitting specimens from known or clinically obvious cases. There are no known instances in which the cytology examination has failed under these circumstances.”

The American Cancer Society At 75: Despair To Hopefulness, And Cancer Prevention

By 1988, the ACS had undergone a notable metamorphosis since its simple beginnings. Commenting upon the significant organizational changes since 1913, the Senior Vice President for Medical Affairs at the ACS, Dr. Arthur I. Holleb (1988) stated:

“From this vantage point we can say we have had a good 75 years at the wheel of change...Change in the way that cancer is understood by the medical profession and the public as a group of more than 100 diseases, a growing number of which are now clearly curable. Change in the focus of the patient from despair to hopefulness for increased length of life and improved quality of life. And change to the idea that cancer *prevention*, at home and in the workplace, is an achievable goal for a broad spectrum of the population.”

The American Cancer Society At 100: Increasing Life Expectancy In The US, And Burden Of Cervical Cancer

In 2013, as the ACS celebrated its centennial, reflecting upon lingering epidemiological realities, Stobbe (2013) commented in the *Daily Herald* (New York):

“Back in 1913 when it [*the ACS*] was formed, cancer was a lesser threat for most Americans. The biggest killers then were flu, pneumonia, tuberculosis, and stomach bugs. At the time when average life expectancy was 47, few lived long enough to get cancer...Cancer became the nation’s no. 2 killer in 1938, a ranking it has held ever since.”

The above excerpt from the feature article by Stobbe (2013) was predated through more explicit epidemiological detail by Dr. Charles S. Cameron, the serving Medical and Scientific Director of the ACS in 1956. Cameron stated (1956):

“In certain countries – especially the United States – cancer seems to be getting more prevalent, but the amount of its increase approximately parallels the lengthening span of life in those countries. In 1900, the death-rate from cancer in the United States was 64 per 100,000; a baby boy could expect to live to be 48 years old and a baby girl could anticipate 51 years of life. Today, the life expectancy of males is 68 years, and of women 72 years. But these added years have not been won without paying a price – for the cancer death rate in U.S.A. is now 147 per 100,000.”

Dr. Cameron’s speculations sustained their legitimacy since 1956. Pertaining specifically to CxCa deaths in the US for the period spanning 1999 through to 2015, the Centers for Disease Control and Prevention (CDC) validated Cameron’s deductions by declaring (Centers for Disease Control and Prevention, 2017):

“While rates of cancer diagnoses and cancer deaths continue to decline each year, the number of new cases and deaths are going up. This happens because the size of our population is growing and aging each year.”

To conclude this account of macro-dynamics and arising impediments, despite efficacious screening systems deployed to identify cervical precancerous lesions and facilitate their timely ablation, the burden of CxCa is anticipated to increase

proportionately with global population growth. In addition, the global discipline of CxCa control may be vulnerable to societal, economic, political, and epidemiological changes.

Impediments To The Development Of The Clinical Pap Test Arising From Historical Micro-Dynamics

In large part, the development of the clinical Pap test was a derivative of inevitable, impactful public health and historical macro-dynamics that orbited around the realm of DC in the first half of the 20th century in the US in the context of CxCa. The reactive discipline-specific micro-dynamics that impacted from within the realm of DC were substantially more complex, but equally important. They in turn led to various impediments related to Papanicolaou's aspirations, his work, his professional qualifications, and the conflicts that ensued following the introduction of the VFSM and its proposed deployment in clinical screening service. Micro-dynamics also emerged due to specific individuals that nonetheless played significant roles; either by contributing towards the developmental evolution of the clinical Pap test, or by obstructing it.

Dr. George N. Papanicolaou: PhD Research, Employment At Cornell Medical College, New York

Relevant to DC and the assessment of cellular morphology through microscopy, Papanicolaou's graduate studies proved exceptionally important.

George N. Papanicolaou was born on May 13, 1883, in Kymi, Greece. His father, Dr. Nicholas A. Papanicolaou, was a physician and a prominent politician (Carmichael,

1973). Although George's early study interests were philosophy and the violin, he abided by his father's wishes and enrolled into medical school at the University of Athens in 1898. In 1904, he graduated with honors at the age of 21. His knowledge of anatomy, clinical symptoms, and disease proved invaluable throughout his career at CMC-NY. These foundations assured the contentious concepts he introduced and crafted in DC were credible, and not clinically irrelevant (Carmichael, 1973; Boon & Chantziantoniou, 2013; Chantziantoniou, 2014¹).

Nonetheless, Papanicolaou remained uninterested in practicing medicine and eventually refused to work as such in the family clinic in Kymi (Papanicolaou-Kokkori, 2008). Instead, he painfully gained his father's support to pursue PhD studies in Germany to study philosophy and the biological sciences (Carmichael, 1973; Boon & Chantziantoniou, 2013; Chantziantoniou, 2014¹). In the first decade of the 20th century, the role of chromosomes in Mendelian genetics and the fundamentals of Darwinian biology for trait inheritance were the prominent subject matters for research and study. These sciences were irresistible for Papanicolaou. These sciences were also the pillars of Eugenics ideology (Black, 2003).

In the spring of 1907, Papanicolaou attended studies at the University of Jena, in Germany, under the renowned Ernst Haeckel. Within his first semester he doubted the suitability of his program. He thereafter relocated to Freiburg, Germany, to study under the mentorship of August Weisman. But after another six months he was convinced that he belonged in the Zoological Institute of Munich, to study under the distinguished

Professor Richard Hertwig. The Zoological Institute of Munich was then regarded the eminent academic center for biological and zoological research (Carmichael, 1973; Papanicolaou-Kokkori, 2008).

One activity assigned to Papanicolaou's initial studies at the Institute was termed: "Fertility day". During such studies, he and his classmates observed the process of fertilization and cell division in sea urchin cells under the microscope. These phenomena were enthralling and proved life-changing for Papanicolaou. It was then he chose to devote his life to biological research and not to the service of medicine *per se* (Papanicolaou-Kokkori, 2008). Papanicolaou was assigned the doctorate research topic of differentiation and determination of sex in *Daphnides*.

Shortly after obtaining his PhD degree in 1910, Papanicolaou returned to Kymi. There he struggled between his personal desire to pursue biological research and his father's pleas he practice medicine in Kymi to promote the family clinic. Papanicolaou stood adamant against this proposition. On September 15, 1910, he married Andromache Mavroyeni, the daughter of a prominent military official in Greece, and the couple journeyed immediately to France in pursuit of suitable employment opportunities (Chantziantoniou, 2014³). Fortuitously between 1911 and 1912 Papanicolaou worked as a marine zoologist at the Oceanographic Museum in Monaco, and accompanied Prince Albert I of Monaco on Mediterranean expeditions to classify marine species. After the death of his mother, Papanicolaou and Andromache returned to Greece, and he was soon thereafter enlisted in the Greek military to provide medical

support in the Balkan War in 1912 (Papanicolaou-Kokkori, 2008; Boon & Chantziantoniou, 2013).

During his Balkan War service Papanicolaou befriended Greek-American volunteers that spoke to him of the promise of opportunity in the far off land of the US. These acquaintances convinced Papanicolaou that what he longed for was to pursue biological research in the United States of America; a new life, and the opportunity to achieve what it was that he was destined for (Boon & Chantziantoniou, 2013; Chantziantoniou, 2014²). Despite opposition from their respective families, on October 19, 1913, Dr. George N. Papanicolaou and his wife, Andromache, landed in New York, and registered as newly-arriving immigrants to the US. Papanicolaou was then 30 years old (Carmichael, 1973; Papanicolaou-Kokkori, 2008).

Coincidentally, it was also in 1913 that the ASCC was established in response to the growing problem of CxCa in the US.

Soon after their arrival to New York, Dr. Papanicolaou and Andromache faced inevitable problems, and the need for employment became imperative. Shortly thereafter Papanicolaou met with the distinguished zoologist and Nobel Laureate at Columbia University, Dr. Thomas Hunt Morgan, seeking his advice. In 1913, Morgan had published a book, entitled *Heredity And Sex*, in which he incorporated data from Papanicolaou's PhD thesis (Carmichael, 1973; Chantziantoniou, 2014¹). This coincidence worked in Papanicolaou's favor as Morgan genially referred him to Dr. William James

Elser, of the Department of Pathology and Bacteriology, at the New York Hospital. Elser promptly hired Papanicolaou as part-time laboratory technician (Koss, 2000).

Noting Papanicolaou's skills and passion for biological research, Elser brought Papanicolaou to the attention of Dr. Charles Rupert Stockard at CMC-NY for possible employment in a formal research setting. Stockard hired Papanicolaou as Instructor of Anatomy in September 1914. Andromache Papanicolaou was thereafter permitted to volunteer as laboratory assistant alongside her husband to manage the technical work arising from his research starting in November 1914 (Carmichael, 1973; Chantziantoniou, 2014¹).

It was also in 1914 that "negative eugenics" practices prevailed across the US to address undesirable human diseases such as CxCa; a disease perceived to be associated with societal immorality; and, one likely genetically transmissible (Black, 2003).

Development Of The Experimental Vaginal Fluid Smear Method In Lower Mammals (1915-1920)

When Papanicolaou joined CMC-NY in 1914, Stockard was researching the genetic transmission of acquired chromosomal aberrations to Guinea pig progeny. Chromosomal impairments were induced in Guinea pigs through exposure to alcohol vapors. Laboratory animals were bred in controlled studies to assess the inheritance of alcohol-induced chromosomal damage against the resulting congenital anomalies (Carmichael, 1973). Given the large colony of experimental Guinea pigs at CMC-NY, Papanicolaou launched a research study assessing the biology of sex differentiation

through X and Y chromosome analysis. Both Stockard's and Papanicolaou's research was mutually dependent on chromosomal analysis in mitotically-active cells in Guinea pig ovaries at ovulation (Koss, 2000).

Papanicolaou had to surgically harvest ovaries precisely at ovulation. As the time of ovulation was unapparent, an excessive number of laboratory animals were sacrificed without scientific advantage. Papanicolaou considered that these mammals menstruated, although feebly. He also considered if vaginal secretions, however miniscule, may perhaps reveal clues to help him pinpoint time of ovulation. To acquire vaginal fluids, he obtained a nasal speculum and, using a pipette, blindly collected vaginal fluids from animals every day over a course of months. Fluids were smeared onto glass slides, air-dried, stained with Hematoxylin and Eosin (H&E), and microscopically examined for repeating cellular characteristics (Chantziantoniou, Donnelly, Mukherjee, Boon, & Austin, 2017).

Using this simple method Papanicolaou observed epithelial cell alterations that reflected cyclical ovarian and hormonal physiology. Based on their observations, Stockard and Papanicolaou defined the Guinea pig oestrous cycle and revealed time of ovulation precisely. These findings were published in an obscure 3-page report in *Science* in 1917 (Stockard & Papanicolaou, 1917¹). Concerned that the scientific significance of their research may not be represented by 3 pages, Papanicolaou republished their data in greater detail also in 1917 in the *American Journal Of Anatomy* (Stockard & Papanicolaou, 1917²). The follow-up 58-page report triangulated epithelial

cell cytomorphology with ovarian and uterine histology, and introduced terms and concepts that transcended into modern DC practice (Boon & Chantziantoniou, 2013; Chantziantoniou, Donnelly, Mukherjee, Boon, & Austin, 2017; Chantziantoniou, 2017).

Transformation Of The Experimental Vaginal Fluid Smear Method Into The Clinical VFMS In Women (1920-1948)

In 1920, being also a trained physician, Papanicolaou questioned whether the epithelial cell changes noted in the Guinea pig experimental model may possibly occur in the human model. However, not being a licensed clinician in New York, he had no access to women to test this curiosity. It was in 1920 that he started applying the very same method on Andromache. He collected a sample daily and analyzed the epithelial cells in her vaginal secretions. This practice lasted 21 years, till 1941, from which exercise Papanicolaou perfected the Pap stain method (Chantziantoniou, Donnelly, Mukherjee, Boon, & Austin, 2017). It was from Andromache's cells that baseline 'typical' gynecological cytomorphology was established, forming the contrast against the morphology of 'atypical', malignant cells arising from CxCa (Boon & Chantziantoniou, 2013).

In 1925, Papanicolaou started analyzing vaginal fluids collected from other women in the New York Hospital under a special professional arrangement. Some of those women were being followed for cervical pathology. As such, in 1925, he encountered malignant cells arising from CxCa. These encounters sparked a new chapter in Papanicolaou's career that ultimately led to the development of the clinical Pap test (Chantziantoniou, 2014¹).

With gained confidence in the cytologic method and in his abilities to identify malignant cells exfoliated from CxCa, Papanicolaou embarked on a journey in 1928 to propose the clinical VFSM as being an effective *diagnostic test* to confirm cervical cancer through a presentation, entitled *New Cancer Diagnosis* (Papanicolaou, 1928). His discoveries were utterly disregarded by the medical community accompanied by overt resistance even hostility (Papanicolaou-Kokkori, 2008; Naylor, 1988). The notion that the VFSM could become an alternative to cervical biopsy was sharply contested by his peers. According to Davis (2007):

“...in the 1930s, the medical world was not moved by Papanicolaou’s work, and women, black and white, continued to die at alarming rates.”

After the dismissal of the clinical VFSM following Papanicolaou’s *New Cancer Diagnosis* presentation, he scaled back his research work on CxCa succumbing to a sense of failure, and to what he feared the most in life: Embarrassment and professional ridicule (Koss, 1973; Papanicolaou-Kokkori, 2008). Papanicolaou attributed his failure to the poor staining of malignant cells that simply did not impress pathologists (Casper & Clarke, 1998). This belief sparked a campaign for Papanicolaou to perfect a stain for CxCa cells that lasted until just before his death in 1962 (Chantziantoniou, Donnelly, Mukherjee, Boon, & Austin, 2017).

However, his 1928 presentation was also perceived as being inspired by the then raging negative Eugenics movement in the US (Casper & Clarke, 1998; Austin & Chantziantoniou, 2014). The initial framing of Papanicolaou’s discoveries alongside

nuances of Eugenics ideology in the lay press was incongruent with the importance of the revolutionary work that ultimately established gynecological DC (Chantziantoniou, 2014¹).

The clinical VFSM was evidently perceived as being a method through which to identify and weed-out cancer patients for the generation of a well-bred elite race; one immune to cancer, presumably leading to societal betterment (Carmichael, 1973; Casper & Clarke, 1998). Papanicolaou's presentation was delivered in the 3rd Race Betterment Conference in Battle Creek Michigan, on January 4, 1928 (Cameron, 1962). That conference was a conclave of "negative" eugenicists envisioning population control through human sterilization and other tactics. It was not a formal medical meeting to address the mounting challenges posed by a worrisome malignancy in women (Papanicolaou, 1928; Casper & Clarke, 1998; Black, 2003; Austin & Chantziantoniou, 2014).

Four days after Papanicolaou's 1928 Battle Creek presentation, an article appeared in the *Buffalo Evening News* on January 8, 1928, by Watson Davis, entitled *Cancer Diagnosing System Discovered* (Chantziantoniou, 2014²). Davis stated (Davis, 1928):

"The discovery was made as a byproduct of fundamental work on the nature of sex in women, following successful investigations of the sexual cycle of guinea pigs and other animals, the same method of research were applied to women in health and disease with results that promise to confer real blessings upon the

human race just as soon as they are developed and taboos are overcome to allow their application.”

Davis’ article manifested Eugenics undertones and alluded to “taboos” or to prohibitions pertaining to the acceptance and application of the VFSM.

In 1928, Papanicolaou’s chairman, Dr. Charles R. Stockard, was an active and prominent participant in the Eugenics campaign through his teachings and research at CMC-NY (Casper & Clarke, 1998). Likewise, the director of the ASCC in 1929, Dr. Clarence C. Little pioneered research in targeted breeding and genetic experiments in laboratory mice at Harvard University. Little proposed that the experience arising from the experimental mouse model may also be applied to humans. He participated in the Eugenics movement in the US, and although immigration laws then protected the “American gene pool from defectives, he urged sterilization of the mentally and criminally deficient” (Davis, 2007).

Another prominent eugenicist in the US was the zoologist, Dr. Charles Benedict Davenport, a Harvard graduate (Black, 2003). The core mantra of the eugenicists was the control of human defects thus the menace they posed upon society; and, therefore, protection of the purity of American society. According to Black (2003):

“Several principle areas of scholarly investigation were identified from the worthy realms of geophysics, astronomy and plant biology. Now another scientific endeavor would be added: negative eugenics. The program would quickly become known as “the practical means of cutting off defective germ-

plasm” and would embrace a gamut of remedies from segregation to sterilization to euthanasia. The radical human engineering program would sprint not from the medical schools and health clinics of America, but from the pastures, barns and chicken coops – because the advocates of eugenics were primarily plant and animal breeders.”

Therefore, any relationship perceived between Davenport, a zoologist and prominent eugenicist, and Papanicolaou, a former zoologist researching sex differentiation in Guinea pig breeding experiments at CMC-NY, could easily cloud the scientific significance of the VFSM, or its relevance in diagnostic medicine and CxCa management.

During the ‘lost decade’ that followed his 1928 Battle Creek presentation, Papanicolaou experimented with staining techniques and developed medical procedures and hormonal cytopathology in collaboration with Dr. Ephraim Shorr, an endocrinologist, and avid researcher at CMC-NY (Casper & Clarke, 1998; Chantziantoniou, 2014¹). To achieve workable tools by which to indirectly assay circulating hormones, Papanicolaou engineered dyes and colors to act as markers of varied epithelial cell origin, maturity, and viability. Along with these objectives, he also experimented with wet fixation and staining protocols to improve the visualization of CxCa cells in smears believing that this problem led to his professional demise (Chantziantoniou, Donnelly, Mukherjee, Boon, & Austin, 2017). Despite the 1928 Battle Creek setback, Papanicolaou’s curiosity and interest in CxCa and its diagnosis never

eased - neither did encouragement from his wife and laboratory assistant, Andromache (Mary) Papanicolaou, for him to stay the course (Hinsey, 1962; Chantziantoniou, 2014³).

As it were, in 1939, Papanicolaou's professional prospects changed utterly when Dr. Joseph Clarence Hinsey became Chairman of the Department of Anatomy at CMC-NY following the passing of Stockard. After reviewing Papanicolaou's professional portfolio, Hinsey was particularly impressed by Papanicolaou's *New Cancer Diagnosis* presentation and saw potential in the VFSM. But he also saw weakness. Hinsey urged Papanicolaou to reinstate his research work channeling his efforts towards the prevention of CxCa, not solely its diagnosis (Papanicolaou-Kokkori, 2008). The following excerpt reflected Hinsey's recollections of their encounters in 1939 (Hinsey, 1962):

"His first paper on this subject was presented to the Third Race Betterment Conference and was published in its proceedings in 1928...It was met with indifference and skepticism. He said: "I failed to create much faith among my colleagues in the practicability of this procedure." The prevailing opinion, expressed to him by one of the outstanding pathologists of the time, was that "since the uterine cervix was accessible to diagnostic exploration by biopsy, a relatively simple procedure, the use of a cytologic examination was superfluous." Others less persistent and dedicated might have given up but "Pap", encouraged by Mary, continued."

Hinsey was amply cognizant of the background macro-socio-political developments in the US following the National Cancer Act enactment in 1937, and assertively leveraged financial support for Papanicolaou's work from The Commonwealth Fund, and subsequently from the ACS. Until 1941, Papanicolaou's work had been supported through CMC-NY; thereafter, The Commonwealth Fund provided an initial grant of \$1,800, while their total support had amounted to \$124,000 by 1952 (Hinsey, 1962). Also according to Hinsey (Hinsey, 1962):

"He [*Papanicolaou*] came to me one day to get approval for a grant of some \$4,000 from one of the pharmaceutical firms to support a project in endocrinology. He was somewhat taken back when I urged him not to take it, but instead to devote all his time to developing his cytologic method for diagnosis of early cancer in the reproductive tracts of women. I told him then how I had been impressed by his work first reported in 1928. He told me of his previous disappointments and his fears about securing adequate support and sufficient clinical material. The American Cancer Society was not then as vigorous as it is today and the Federal programs for research support had not been begun. I assured him of my whole hearted support and we both agreed that he should proceed step-wise, (1) to develop the method and establish its validity, (2) to train others to use it, (3) then to educate the profession and the public as to what it had to offer."

Hinsey was visionary, and administratively savvy. He foresaw potential but also specific impediments to Papanicolaou's progress. He realized Papanicolaou lacked

medical credentials in the US thus had no access to patients; he also lacked formal training in anatomical pathology thus had neither qualifications nor authority in the field; also, that he needed ample clinical material for analysis with tissue correlation to test and validate his work. In light of these vulnerabilities, against a backdrop of pervasive skepticism, Hinsey brokered the collaboration of Dr. Herbert F. Traut, a gynecological oncologist at CMC-NY with knowledge in anatomical pathology. Papanicolaou and Traut's synergy, and their epic publications in 1941 and in 1943, manifested in the renaissance of gynecological DC (Papanicolaou & Traut, 1941; Boon & Chantziantoniou, 2013). Their works created a sensation, thrusting the discipline of DC into the formal arena of CxCa diagnostic medicine in the US (Papanicolaou-Kokkori, 2008). These dynamics also created resistance and opposition.

Hinsey's decision-making was the spark that catalyzed the subsequent course of events that led to the establishment of the clinical Pap test in 1948, and to its deployment in screening practice in the US since 1957. In a short article published in the *Journal Oncologia*, in memory of Papanicolaou's life and career, entitled *Necrologia – Obituary For George N. Papanicolaou, M.D., Ph.D.*, Traut referred to additional impediments in the backdrop of World War II (Traut, 1963):

“As the material from pathological specimens became available, and the vaginal smears matched with the observations from this material, it became probable that the vaginal smear might adequately represent the presence of early cancer. However, it took a number of years, approximately six, before there was enough

data accumulated so that the collaborators could make a definite statement with regard to the reliability of vaginal smears as an indication of the growth of cancerous changes. The paper, read before the New York Obstetrical-Gynecological Society in 1938, by Papanicolaou and Traut, was the first contribution announcing these possibilities. The studies were not readily acceptable to pathologists in general, and the idea was not grasped with great vigor, partly because it appeared at the time when the United States were involved in World War II, and had many other matters to consider.”

Nevertheless, Papanicolaou and Traut’s publications and the VFSM appealed to weary gynecologists facing the problem of advanced CxCa in their patients in the mid-1940s. Among them were two prominent gynecologists: Dr. J. Ernest Ayre (Montreal, Canada), and Dr. Joe V. Meigs (Boston, US). Ayre and Meigs promptly adopted and tested the method in their respective clinical practices. Their contributions eventually redefined the clinical VFSM and formalized the concept of early detection of cervical precancer and its surgical ablation. Collectively, Ayre and Meigs entrenched the feasibility of prevention of advanced disease through systematic screening in asymptomatic women (Hinsey, 1962; Traut, 1963; Stewart, 1971; Hutter, 1981; Koss, 1993).

After World War II, being a gynecological surgeon, Meigs modified the practice of radical hysterectomy for advanced CxCa and his methods led to a significant decrease in surgical mortality rates from near 20% to 1% (Olson, 1989). Furthermore,

epidemiological evidence in the mid-1940s then associated higher rates of CxCa with married or widowed women, rekindling the suspicion of disease causality through sexual activity (Olson, 1989).

Yet, the VFSM, and the cytologic method it embodied, required procedural overhauling to offer attractive, undeniable advantages to both gynecologists and pathologists. In this regard, Ayre's resourcefulness proved invaluable.

J. Ernest Ayre was a gynecologist turned cytopathologist, and a staunch proponent of Papanicolaou's work and of the VFSM. Ayre's hybrid skillsets afforded him unique advantages. As a cytopathologist, he naturally related with malignant cells arising from CxCa, the target disease of the VFSM. Meanwhile, as a former gynecologist, Ayre understood the reservations voiced by his clinical colleagues accustomed to confirming the disease visually and through conventional biopsies. Attempting to reconcile these polarities, and to render the VFSM more attractive to gynecologists, Ayre proposed a modification in Papanicolaou's simple test in a key publication, entitled *A Simple Office Test For Uterine Cancer Diagnosis*, appearing in the *Canadian Medical Association Journal*, in 1944 (Ayre, 1944).

In essence, Ayre identified major deficiencies in Papanicolaou's method of blind vaginal pool fluid collection through a pipette. He thus redefined the VFSM making it a two-smear test performed under direct cervical visualization. He wanted the test to be successful but also simple enough for any clinician to perform in the office setting, anywhere, without prerequisite gynecological specialization. In so doing, cervical

sampling could then become ubiquitous, performed by family physicians throughout the US, not unlike a blood test. This innovation vastly expanded the scope of practice and outreach for the screening VFSM. Ayre proposed that under direct cervical visualization, a standard smear be prepared from vaginal pool secretions as proposed by Papanicolaou to include exfoliated epithelial cells from the vaginal and external cervical surfaces. Thereafter, another dedicated smear could be prepared from mucus sampled directly from the cervical external os to include exfoliated cells from the transformation zone and endocervical canal (Ayre, 1944).

In 1946, Ayre reported his success in detecting cervical precancer using the two-smear modification (Ayre, 1946). But as it was subsequently questioned if his approach may miss lesions adjacent to the cervical os on the ecto-cervix, Ayre developed the eponymous Ayre spatula to sample the outer epithelial circumference of the cervix and internal os (Ayre, 1947). The spatula smear Ayre termed: "surface biopsy", contending it would make the procedure "more rapid and more efficient" (Ayre, 1951). Ayre's intuitive choice of terminology conjoined the disciplines of gynecology and DC for the sampling and screening for cervical precancer through the modified clinical VFSM.

Ayre's work also targeted particular impediments to the deployment of the VFSM. According to Ayre (1944):

"The statement that uterine cancer may be accurately diagnosed by the vaginal or cervical os smear probably arouses an initial skepticism in the minds of many. The idea at first glance perhaps appears somewhat far-fetched. It may be the

impression of some that the vaginal smears consist only of vaginal epithelial cells scraped off from the vaginal mucosa, and that the diagnosis of cancer is attempted from the morphological and staining characteristics of the vaginal cells themselves. It is difficult to conceive how any diagnosis of uterine cancer could be made from a study of these cells alone. When one considers, however, that the vaginal secretions contain not only vaginal cells but also cells thrown off from the cervix, the endometrium, and the tubal epithelium, the horizon of the diagnostic possibilities might appear to be broadened."

Ayre defended the two-smear VFSM as follows (Ayre, 1944):

"Uterine cancer annually takes a toll of 26,000 lives in the United States. There has been little improvement in these statistics during the last 20 years. According to the findings of Bigelow and Lombard, the average time lost in uterine cancer cases from the first signs of bleeding to the time of operation is almost eight months. Therefore, delay in diagnosis is a major factor in maintaining the high mortality rate. So often when the patient in the menopausal age presents herself with irregular bleeding the physician finds it impossible to differentiate between the more frequent menopausal changes and a beginning malignant growth.

A simple office test which may be taken by any physician when the first signs of spotting are reported should be of great value speeding up the diagnosis. It is relatively easy to diagnose cancer clinically, once the growth is advanced, but it

is not so simple when there is nothing abnormal palpable or visible to be found.

This is the stage when diagnosis would allow more certain cure.”

In 1947, in Iowa, Dr. Arthur W. Erskine also adopted the VFSM but ensured it stayed locally accessible as an office test as previously advocated by Ayre, rather than it being administered solely through distant urban medical clinics. Erskine’s approach proved transformational in the evolution of Pap test screening. According to Gardner (2006):

“Such local commitment, experience, and activism, coupled with women’s traditional philanthropy, made the Iowa ACS a breeding ground for new programs. While the national ACS debated the best way to proceed with the vaginal smear as a screening tool for the population at large, locally the Iowa ACS embarked on a small and specific study that would determine the test’s effect in this community...

It was Erskine who first convinced the Iowa ACS to subsidize a local study of the Pap smear. The ACS donated \$12,000 to the program, which started in 1947 when personnel at the Gynecology Department of the State University of Iowa City performed vaginal smears on all women over thirty years of age who were admitted to the hospital. In addition, physicians performed vaginal smears on all female residents of the two state mental hospitals. Clinicians collected a total of 5,214 smears and from these diagnosed 200 cancer cases.

By 1948, preliminary results of the Iowa study confirmed the effectiveness of the Pap smear as an effective screening tool. Cancer activists in Cedar Rapids proposed an expansion of the Pap study to include routine tests in both Cedar Rapids hospitals and private offices in the area. Vaginal smears could be collected in any location, cells could be fixed to slides there, and then slides could be transported to a central cytology lab in Iowa City for final reading. The Iowa ACS approved the proposal, and in 1948 Cedar Rapids became the first city in Iowa, and one of the first cities in the United States, to begin mass screening of women using Pap smears.

The Iowa study would ultimately serve as a model for a national program for cervical cancer screening.”

The favorable reports produced by Ayre and Meigs demonstrating clinical progress and the outcomes from Erskine’s initiatives gave the national ACS the traction it needed. The ACS capitalized upon these post-World War II dynamics to reconsider its approach. It encouraged deployment of the clinical VFSM in diagnostic medicine disregarding skepticism amongst pathologists.

As World War II had ended, and as American society yearned for a sense of victory and enlightenment, the ACS achieved a much needed signature triumph in public health and in societal medicine: The alleged defeat of CxCa. Collectively, these developments were effective in raising the levels of national optimism following the setbacks of World War II and Pearl Harbor, alongside the political and financial weight

of the National Cancer Act of 1937, that of Mrs. Mary W. Lasker, and that of the repositioned ACS.

The Clinical Pap Test (1948 Henceforth)

It was under the directorship of the astute Dr. Charles S. Cameron that the national ACS coined the term *Pap test* for the clinical VFSM in 1948.

The ACS then actively funded major educational meetings to disseminate knowledge, and boldly promoted the Pap test into screening service to mitigate the growing number of unnecessary deaths due to lacking or delayed sampling (Koss, 1993). Cameron served the ACS as its Medical and Scientific Director from 1948 to 1958 (Davis, 2007). That was the most critical decade in the history of DC, and the last decade of Papanicolaou's career at CMC-NY (Boon & Chantziantoniou, 2013). Nonetheless, despite the energy projected by the ACS during the 1950s, advanced CxCa reemerged as a profound dilemma in the US. Accounts of deaths due to purportedly preventable CxCa, such as that of Henrietta Lacks in 1951, stoked societal distress not unlike that experienced in the 1930s during the Great Depression, and in the 1940s prior to the understanding of cervical precancer. Referring specifically to CxCa in the early-1950s, Hendrix stated (The Washington Post, 2017):

“...when Lacks, a mother of five, was being treated in East Baltimore during the Truman era, it was an illness clouded in secrecy, shame and dread.”

In post-World War II US society characterized by advancing modernization and life-style changes, premature deaths in young women due to supposedly preventable

CxCa became a source of awkwardness for the ACS. This was particularly poignant for Charles Cameron. He needed to foster a paradigm shift to eternalize the notion that CxCa had indeed been successfully defeated through availability of the Pap test. To achieve this, he altered the direction and organizational culture of the ACS.

Until the mid-1950s, the ACS had focused essentially all its efforts towards identifying a cure for cancer, a “downstream approach”; Cameron then advocated that, instead, energy ought to be invested towards cancer prevention, an “upstream approach” (Casper & Clarke, 1998). The paradigm shift that Cameron envisaged started to materialize riding on the positive outcomes from the Memphis and Shelby County trial, and Erskine’s accomplishments in Iowa.

On October 24, 1952, the *New York Times* published a poignant article, entitled *Cancer Care Seen Saving More Lives – Up To 100,000 A Year Forecast By Dr. C. S. Cameron In Full Use Of Detection Centers*. The article not only revealed the political and professional push-back Cameron faced, it also communicated his frustration. However, it also introduced his concept of specialized medical centers that would be dedicated to detect thus prevent cancer, and his justification for them. Cameron’s assertion was based upon Ayre’s proposition of the “simple office test” (Ayre, 1944). In the context of this dissertation, the *New York Times* article warrants complete reproduction as follows (New York Times, 1952):

“Dr. Charles S. Cameron, medical and scientific director of the American Cancer Society, predicted yesterday that 75,000 to 100,000 persons could be saved

annually if physicians and clinics gave each of their patients a six-point cancer check-up. The examination would include the following danger areas: skin, oral cavity, female generative tract, breast, rectum and lung with the lung requiring the further check of an x-ray.

Dr. Cameron told the thirty-ninth annual meeting of the society at the Park Sheraton Hotel that its cancer detection programs were coolly received by individual doctors and local medical groups. He said the cancer detection center idea was criticized as threatening to dislocate the traditional doctor-patient relationship. Another program to promote cancer detection in the doctor's office in cooperation with state or county medical societies, he added, also had "hardly encouraging results".

Dr. Cameron reported that in some localities where doctors were asked to provide cancer detection examination service, five out of six doctors indicated their unwillingness to cooperate.

In his annual report he defended the early detection principle, replied to criticism of the cancer detection center by holding that it served to establish direct relations between private physicians and patients and urged reappraisal of the program to make the doctor's office a detection center.

He proposed a new program for detecting cancer early by centering upon the 3,500,000 persons receiving social security, all of whom are over 65 years old. Dr. Cameron said 500,000 of these people would die of cancer if present rates held.

Observing that 3,500,000 persons could be examined once yearly or oftener by 100,000 doctors, he maintained that such a program could save 75,000 to 100,000 lives.

He suggested that the society might embark on a five-year plan for this special segment of the public. He contended that if the precision weapons designed to detect early cancer could not produce measurable results in five years there would be reason to reconsider the validity of all cancer control."

Four years after Cameron's ultimatum to the ACS, in an effort to quell lingering skepticism and societal anxiety, without belittling the plight that cancer posed upon humanity, Cameron stated (Cameron, 1956):

"Incurable cancer, then, need no longer be a sentence to unremitting agony. Medical science is steadily making it possible for more patients with cancer, even though it cannot be cured, to live longer, to live more fully, and to enjoy greater comfort. But these are not always easy to come by. They require all the ingenuity and resourcefulness the doctor has. They call for understanding, persistence, and gentle firmness on the part of the family. And they call for determination in the patient to fight a good fight."

Being the Medical and Scientific Director of the ACS in 1956, Cameron's statements were calculated. The responsibility perceived to be shared between clinician and patient in the war against cancer was undeniable. But Cameron's rhetoric inferred beyond that relationship: He alluded to the unique responsibility that the ACS and the

medical establishment at large also shared in that war. Cameron likewise alluded to the fervor and clinical significance of the developments then occurring in DC overall.

Along with Hinsey, Cameron was equally aware of the politics impeding the Pap test's development and deployment, and was fretful of ongoing delays particularly when *time* was a proven determinant of the likely success or failure of CxCa management. Time was a predictable variable to delays in diagnosis and treatment. In turn, delays were a predictable variable to extent of disease at presentation and diagnosis. These key, interrelated elements were detailed by Davis, from which the following remarks about Cameron's frustrations are reproduced (Davis, 2007):

"Cameron's outrage over delays in using the Pap smear in medicine finally boiled over in 1956...Women were dying while doctors debated who should be in charge and proposed ever more elaborate studies on the issue. At the 1956 annual ACS meeting, Cameron demanded that the board of directors stop stalling and put the Pap test into place nationwide. "I hold that we need not wait for more evidence; that there is enough evidence", he declared; "that there is enough evidence on hand to justify taking the position – women over 40, vaginal smear twice a year. Can we justify any longer delaying a vigorous campaign to press the use of the smear? ...My conscience and the opinion of those with the widest experience in its use say no."

The emergence of cervical precancer from Papanicolaou's and Traut's work had decisively transformed the role of the VFSM. Likewise, its diagnostic potential in

gynecology gained the trust and buy-in from most gynecologists. Conversely, in anatomical pathology, skepticism and opposition prevailed. At issue was the underlying proposition of non-infiltrating cervical precancer (i.e., carcinoma in situ).

Although the concept of cervical CIS was described by another prominent gynecologist in New York, Dr. Isidor Clinton Rubin, in 1910 (Olson, 1989), this concept sparked a controversy amongst leading pathologists as to if cervical precancer was indeed cancer. That is, was treated cervical intraepithelial precancerous disease truly cured CxCa? The prospect of cervical precancer challenged the core tenets and then understanding *of* cancer - being, exclusively and conceptually, an invasive, progressive, irreversible disease (Stewart, 1971; Hutter, 1981; Koss, 1993).

These controversies resurfaced intensely in 1951 when Henrietta Lacks presented with advanced CxCa and soon thereafter died of it age 31; after never having a cervical smear test although it was available since 1941, when she was 21 (Skloot, 2010). Lacks' case projected worrisome inadequacies in societal and diagnostic medicine overall that could have conceivably affected, and taken the life of, any woman. Collectively, these issues posed contentious impediments that lingered beyond Papanicolaou's death in 1962, well into the late-1970s. This debate lingered until the HPV-associated etiology of CxCa was unraveled, and high-grade squamous intraepithelial lesion (HSIL) became a formal diagnostic, clinical, and therapeutic entity (Hutter, 1981; Koss, 1993; Syrjanen, 2017).

The indiscriminate menace of CxCa and its widespread societal ramifications in humanity were underscored in an article in *The Washington Post*, entitled *When Henrietta Lacks Had Cervical Cancer, It Was A 'Death Sentence'. Her Cells Would Help Change That*, by Steve Hendrix, published on April 22, 2017. According to Hendrix (The Washington Post, 2017):

“One month after Lacks was buried, another woman whose name would live forever was wheeled into an operating room to be treated for cervical cancer, and she didn’t even know it. Eva Peron, the glamorous and powerful wife of Argentinian President Juan Peron, was never told she had the disease.

Evita thought she was having a procedure by a leading Buenos Aires surgeon to stop some cervical bleeding. Instead, after she was anesthetized, George Pack, a cancer specialist from New York who had been flown secretly to South America, entered the O.R. and performed a radical hysterectomy.

There was such a taboo around cancer that many doctors didn’t want to use the C-word at all, lest the patient lose hope – or commit suicide – at a time when cancer seemed always to lead to a coffin.

With Peron, of course, politics and power also played a role in the secrecy. But even when the surgery failed to stop the cancer, and she went into a painful decline, she was kept in the dark.

Peron and Lacks fell to cervical cancer right at the beginning of a new age in fighting the disease. The biggest breakthrough was the introduction of a remarkably effective test for pre-cancerous cells developed by a Greek-born violin player and doctor named George Papanicolaou. His simple “pap smear”, which allowed doctors to treat and cure the cancer before it became established, was just coming into general use as a screening tool when Lacks fell ill.

Cervical cancers are now considered one of the more treatable malignancies, but not everywhere. In poor areas, where screening and treatment remain out-of-reach for many women, it’s still 1951.”

In 1956, due to his growing frustration, Cameron produced a book aimed for the general public but to also implicitly press the medical establishment for unacceptable behavior in its efforts to control cancer in the US. His book was written to increase layman’s awareness of cancer and to arouse action in seeking medical attention early. Cameron’s book framed *time* as being the key determinant between possible cure or death from cancer, entitled *The Truth About Cancer* (1956), Cameron stated (1956):

“The woman who is wise enough to play it safe, then, will insist on a careful examination of her pelvis twice a year – no matter how strong and healthy she seems to be. Do you doubt the wisdom of this procedure? Then just compare the curability of cancer of the uterus in very early, moderately advanced stages with its curability in late stages: Treatment of very early cancer of the uterus will cure 70% per cent or more. About 35 per cent of the moderately advanced cases,

which is the condition in which most women with the disease are first seen by the doctor, can be cured. And of the late and extensive cases, fewer than 10 per cent can be saved.”

As the clinical Pap test was being increasingly deployed into service, Cameron’s book in 1956 alluded to unfavorable odds for 5-year survivals from advanced cervical cancer despite the availability of the clinical VFSM since 1941 and improved surgical procedures developed by Meigs (Olson, 1989). Cameron aimed to persuade the general public to exercise self-empowerment and advocacy through increased knowledge of cancer and of its symptoms. Cameron transferred ownership and political leverage to the public and, particularly, to the patient. His commentaries also aimed to subtly off-set the lagging medical establishment as screening practices for CxCa were being frustratingly deliberated in the US in the latter-1950s primarily due to widespread skepticism and inaction. Nonetheless, in the absence of promising therapies, and due to poor long-term survival outcomes for all cancer patients, the disease remained dreaded as an indiscriminate hindrance to societal betterment throughout the US (Cameron, 1956).

As screening services were being implemented throughout the US, other impediments promptly emerged. A prominent issue became the lack of laboratories and therefore the lack of expertise to manage the growing volumes of smears that were being prepared as a result of increased health literacy. Secondly, pathologists remained resistant as not accustomed to grading abnormal cells appearing singly or in groups on

glass slides using unfamiliar stains (Boon & Chantziantoniou, 2013). Thirdly, neither reporting nomenclature nor therapeutic approach was consistent throughout the US. And, fourthly, the deployment of low-paid, non-medical cytologists to read the cumbersome smears became yet another matter of contention (Casper & Clarke, 1998). As the majority of screening cytologists were women, the overall system became imbalanced with engendered polarities: Most pathologists were men, and most screening cytologists were women. These situations led to serious problems for the burgeoning clinical Pap test and for the ACS struggling to establish it through Cameron's insistence (Casper & Clarke, 1998).

Furthermore, the expanding screening system for early detection of a dreaded woman's cancer, supported by women cytologists, for the benefit of all women, rekindled the gender sensitivities surrounding the woman-physician relationship in the context of CxCa. Sensitivities implied: Could male doctors truly understand and prioritize the defeat of cervical cancer in all women? (Casper & Clarke, 1998).

In a commemorative article published in the *Journal Of The American Medical Association* in 1962, entitled *Dedication Of The Papanicolaou Cancer Research Institute*, Cameron summed-up the salient accomplishments arising from Papanicolaou's 50-year journey in research and in CxCa diagnosis and prevention (Cameron, 1962):

"He devised a means of identifying cancer of the uterus in the presymptomatic stage and thereby placed beyond 80% the curability of the second most fatal cancer in women...He defined with superb precision carcinoma in situ of the

uterine cervix and demonstrated that the smear will discover the precursor to invasive cancer before it can be seen with the naked eye and when it can be eradicated in 100% of cases. By these 2 achievements he has provided the means of delivering women from the threat of death by uterine cancer...

He has provided science with a precision system of investigation which makes possible the detailed analysis of cellular morphologic changes – in transition from wholly normal to the frankly neoplastic – and thereby he has opened to scientists a new avenue of the study of mechanisms of carcinogenesis.”

Nevertheless, CIS altered the epidemiology and understanding of CxCa. It also impacted on screening practice, the concepts of cervical pathobiology, and how these parameters may ultimately yield the control of CxCa.

Screening Principles And World Health Organization Targets

Preclinical CxCa prompted reassessment of the linear model of cervical carcinogenesis considered in the 1920s. By the late 1960s, sufficient knowledge of CxCa had been garnered through Pap test screening whereby the fundamentals of medical ‘screening’ required reformulation. It became evident that screening for cervical precancer in asymptomatic women was synonymous with CxCa prevention. That is, by detecting the intraepithelial entity, the invasive entity may be negated through intervention. The Pap test was therefore aligned for the preclinical entity; although, it could detect either entity. The complexities of CxCa gradually challenged the theory of linear carcinogenesis. This was due to the regressive nature of some cervical lesions

relative to progressive lesions that quickly led to invasive disease although variably, and not inevitably between patients. The inability for the profession to explain these phenomena was problematic. But they did nonetheless manifest yet another mysterious dimension of CxCa.

These developments compelled the WHO to formulate its *Principles and Practice of Screening for Disease* in 1968 (Crowell, Ransohoff, & Kramer, 2010). The WHO's principles aimed to guide the development of screening methods. The WHO's criteria follow (Crowell, Ransohoff, & Kramer, 2010):

- The condition sought should be an important health problem.
- There should be an accepted treatment for patients with recognized disease, and treatment should be better at an earlier stage.
- Facilities for diagnosis and treatment should be available.
- There should be a recognizable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be an agreed-upon policy on whom to treat as patients.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.

- Case-finding should be a continuing process and not a “once and for all” project.

From a contemporary lens, both the nature of CxCa and the experience generated by Pap test screening collectively aligned with the criteria set out by the WHO in 1968. But outcomes arising from the intensifying screening practices throughout the US since the mid-1950s revealed an even greater complexity for CxCa prevention stemming from the subjective, interpretive nature of the Pap test itself, and its inherent diagnostic error rates. These problems of course played into the hands of myopic skeptics, but they also influenced future design and application of screening practices, and screening interval guidelines.

Eventually, the Pap test resolved the very issue that obstructed its establishment in 1928: That cervical CIS was a lesion typically unapparent for biopsy; therefore, biopsy alone may be insufficient to negate CxCa. This reality was repeatedly cautioned by Ayre since 1944 (Ayre, 1944). This outcome governed the foundations for prospective cytologic screening. Effective precancer surveillance, and ensuing disease prevention, commanded that the Pap test and cervical biopsy become one in purpose: Mutually-dependent.

Sequential (Two-Stage) Testing Model For Cervical Cancer Prevention Through Screening

Due to its preclinical phase and invasive phase, CxCa was branded a two-phase disease (Crowell, Ransohoff, & Kramer, 2010; Skloot, 2010; Gordis, 2014). This

characterization and the complement formed between the Pap test and biopsy led to the Sequential Two-Step Testing model for CxCa screening. According to Gordis (2014):

“In sequential or two-stage screening, a less expensive, less invasive, or less uncomfortable test is generally performed first, and those who screen positive are recalled for further testing with a more expensive, more invasive, or more uncomfortable test, which may have greater sensitivity and specificity. It is hoped that bringing back for further testing only those who screen positive will reduce the problem of false positives.”

The Sequential Two-Stage Testing model manifested the basis for Pap test screening. From the effort to identify a subgroup of women in a given population, two additional factors emerged: (a) Classification of individuals at risk for developing this disease; and (b) Qualification of disease prevention through screening (Gordis, 2014). Therefore, with definition of the at risk subgroup, the benefits of screening may be maximized; and as the Pap test could detect preclinical disease in asymptomatic women, it was destined to serve as a tool for secondary disease prevention.

Reports by Foltz and Kelsey (1978), Greenwald, Cullen and McKenna (1987), and Foulks (1998), methodically described the incremental expansion of the theoretical and practical essentials pertaining to Pap test screening for CxCa. But with expanding screening practices throughout the US, previously unforeseen epidemiological limitations soon emerged. These problems were due to biases produced from screening, as they impacted upon the calculation of *actual* incidence or prevalence rates of disease.

The dominant biases were: Healthy volunteer bias; Lead-time bias; and, Over-diagnosis bias (Crowell, Ransohoff, & Kramer, 2010).

It is nonetheless important to impress that the eventual acceptance of the clinical Pap test by 1957 was a direct result of its transformation from the 1928 VFSM prototype driven by key modifications incorporated into the method, and into the organizational infrastructure supporting and promoting Pap test screening. Major improvements included the dedicated Papanicolaou staining method (Chantziantoniou, Donnelly, Mukherjee, Boon, & Austin, 2017); the Ayre two-smear VFSM and office test, and the subsequent Ayre collection spatula (Ayre, 1944; Ayre, 1947); conceptualization of precancerous (i.e., carcinoma in situ) cervical lesions (Meigs, 1947; Ayre & Ayre, 1949; Ayre, 1949; Papanicolaou & Koprowska, 1951; Koss & Durfee, 1956; Ayre, 1961); method verification through large population trials such as the Iowa Cedar Rapids project, and the Memphis and Shelby County study with corroboration from prominent institutions (Dunn & Sprunt, 1955; Gardner, 2006); women's advocacy and empowerment (Reagan, 1997); and, the establishment of a low-paid, non-medical workforce trained to analyze the growing numbers of smears arising from expanding screening practices (Casper & Clarke, 1998).

Promotion And Endorsement Of Pap Test Screening In The US

In 1957, despite the ongoing achievements, the control of CxCa remained dismal. The ACS was left with little alternative but to once again bolster the significance of *time*, to push ahead with Pap test screening endorsement.

Television had then supplanted radio as being the prominent technology by which to reach the public throughout the vastness of the US. To reemphasize the significant impact of *time* in the diagnosis and management of CxCa, and to highlight accrued knowledge for the lay public, the ACS commissioned a television documentary in 1957 narrated by the prominent gynecologist, Dr. Joe V. Meigs. The program was titled: *Time And Two Women*. The transcript of that documentary, along with specific photos and images of gynecological anatomy, was also published in the *Journal Of The American Medical Association* by Meigs in 1957 (Meigs, 1957). The Abstract from that publication follows (Meigs, 1957):

“Seeking to motivate women to adopt the lifesaving habit of health checkups, this film was released as a part of a broad education program which will be undertaken in communities where technical facilities are available for interpreting vaginal smears, and where the county medical societies approve use of this film. The uterine cancer cell examination, the “Pap” smear, is explained in an effort to alert women to the urgency of early detection of uterine cancer. The film deals with diagnosis of cancer of the uterus with special emphasis on cytology and dramatizes the fate of two women: one who ignored warning signals and saw her doctor too late and the other whose early cervical cancer was detected in the course of a periodic checkup.”

Although the transcript alluded to possibly inadequate infrastructure throughout the US, and to reluctance by some county medical establishments to air the

documentary, it may be stated that subsequent to 1957, the clinical Pap test was arguably understood, established, and decisively set upon a US-wide course of deployment supported by remarkable health literacy and promotion, and the vested interests of the ACS. According to Gardner (2006):

“The history of the vaginal smear offers one illustration of the technological innovations that redefined female cancers in the second half of the twentieth century. As scientists, practitioners, female patients, and cancer activists sought ways to detect cancer as early as possible, screening technology gained impressive financial and academic support that shaped cancer awareness advocacy. Undoubtedly, Mary Lasker’s influence and emphasis on funding cancer research contributed to the promotion of the Pap smear in U.S. culture. Although cancer educators waited until the late 1950s to launch a cervical cancer screening awareness campaign, the evolution of the technology and the scientific responses to cancer screening dated back to the early twentieth century.”

Dr. George N. Papanicolaou: Personal Letters, Character, Aspirations, And Professional Conflicts

Papanicolaou’s sensitivities may be appreciated through his major (i.e., larger) publications listing laborious narratives describing preceding work by his peers (Chantziantoniou, 2014¹). This may be evident in the publications through which he introduced novel methods or concepts; such as: The introduction and role of the experimental VFSM in Guinea pigs (Stockard & Papanicolaou, 1917²), and the application of the VFSM in women along with inception of the Papanicolaou staining

method (Papanicolaou, 1933). To him, the more novel and potentially controversial the concept, the more support it demanded. Papanicolaou structured commensurate scientific evidence upon which to frame his observations, hypotheses, and conclusions.

Papanicolaou's intuitive style of writing may also be appreciated in his personal correspondences that were reviewed for this dissertation. During the difficult period when he was trying to convince his father of what he wanted in life and why, Papanicolaou composed letters mirroring a 'scientific' defense. Laborious correspondences were exchanged between 1907 and 1910 designed to debate yet frame his preferences and counter-arguments against the prospect of him practicing medicine. The similarities between his personal and scientific writings are striking; revealing Papanicolaou's ability to precisely organize and set, and communicate convincing propositions (Papanicolaou-Kokkori, 2008).

After reviewing the pertinent English and Greek literature, and Papanicolaou's personal correspondences in the context of this dissertation, it may be argued that his character remained unchanged throughout life. Since boyhood, Papanicolaou yearned to understand and to champion the forces of nature (Carmichael, 1973; Boon & Chantziantoniou, 2013; Chantziantoniou, 2014¹). He frequently and purposely put himself in perilous situations to test his determination and resilience (Papanicolaou-Kokkori, 2008). Throughout life, he also remained awestruck by the rhythmic vitality and demise of cells and living organisms in nature's Kingdoms. These grand aspirations and dilemmas drove his decision-making throughout life, transcending into the passion,

energy, and determination encoded within the fabric of his scientific work in DC. These aspirations allowed him to dare curiosity and failure, to surpass defeats, but also to intuitively organize observations into articulate scientific deductions.

It is important to reiterate that although Dr. George N. Papanicolaou held a Medical Doctor degree from the University of Athens, he was not a practicing clinician in the US. Neither had he pursued formal training in anatomical pathology. Throughout his 43-year career at CMC-NY, he was employed in the Department of Anatomy working in the research and academic arenas. His career's work at CMC-NY was upheld by his post-graduate PhD degree from the University of Munich. Papanicolaou was not a formal anatomical pathologist.

Understandably, Papanicolaou's work on the diagnosis of CxCa inevitably led to various professional conflicts. These conflicts manifested into impediments due to him lacking qualifications thus authority in the field of anatomical pathology (Koss, 1973). He was never oblivious of the realities however, nor viewed the risks as being trivial (Carmichael, 1973). Papanicolaou's sensing of controversial concepts in DC as being potential obstacles to his progress was highly intuitive.

Papanicolaou's character and aspirations were important throughout his career, affording him the necessary tools by which to overcome and navigate past contentious issues, and what seemed oftentimes as impassable obstacles. Nevertheless, his career's journey was neither painless nor straightforward and support, through various forms, was necessary to sustain momentum in the development of the clinical Pap test and DC.

Papanicolaou sustained a life-long fear of embarrassment and of insecurity in general (Carmichael, 1973; Papanicolaou-Kokkori, 2008). In the professional setting, he was particularly sensitive to producing work that may attract ridicule from pathologists; and particularly when his conceptualizations over-extended onto their realms of authority (Koss, 1973). These problems became most profound in 1943 and in 1951 when Papanicolaou introduced his concepts of CIS in gynecological and pulmonary cytopathology respectively, and the existence of dyskaryotic cells.

Dr. George N. Papanicolaou: Dyskaryotic Cells Pathognomonic Of Cervical Precancer

The cytomorphology of the dyskaryotic cells Papanicolaou asserted as being pathognomonic of non-infiltrating cancer became another major impediment. The topic of dyskaryotic cells was a highly contentious issue in cervical DC in the mid-1950s. Dr. Leopold G. Koss was an enduring skeptic of Papanicolaou's propositions. In 1956, Koss and Grace R. Durfee stated (Koss & Durfee, 1956):

“The cellular abnormalities characterizing koilocytotic atypias, of course, have been noticed before. They fall into Papanicolaou's category of superficial, intermediate, and parabasal cell dyskaryosis. This classification of abnormal cells is of didactic value only, since pathologic findings clearly indicate that large atypical cells may be found at all levels of the epithelium.”

The matter of dyskaryotic cells became an extraordinary flashpoint. These cells posed a challenge squarely on pathologists accustomed to reading histologic sections, as they struggled to assimilate with the cytomorphology of exfoliated, oftentimes single

epithelial cells in smears arising from CIS (Foote & Li, 1948; Carson & Gall, 1953; Ayre & Scott, 1961; Johnson, Easterday, Gore, & Hertig, 1964; Hutter, 1981). Despite the opposition, and lack of authority, Papanicolaou stood adamant to the proposed diagnostic value of dyskaryotic cells. His posturing was not always welcome, and this led to conflicts with prominent pathologists. But unlike pathologists, Papanicolaou had the advantage of not being bound by cells in histologic sections, nor by H&E staining. This matter led to various confrontations and was exceptional enough that it captured entirely the texts and discussions of *Symposium A* published in the maiden issue and volume of *Acta Cytologica* in 1957 (Koprowska, 1997; Bibbo, 2011; Chantziantoniou, 2017).

Divides Of Authority Between Papanicolaou's Experimental Work And Clinical Practice

Throughout the saga of the clinical Pap test, Papanicolaou's wife and closest associates helped him persevere and stay the course. Andromache, Hinsey, Traut, Cameron, Hashime Muryama, Dr. Andrew A. Marchetti, and Dr. Irena Koprowska were equally as conscious of his character and risks, and from their own personal efforts allayed Papanicolaou's weaknesses facilitating incremental progress (Hinsey, 1962; Marchetti, 1969; Carmichael, 1973; Koprowska, 1997).

From all the historical dynamics, perhaps, Hinsey's thoughtfulness and administrative stances resolved the majority of impediments. Hinsey's decision to broker the collaboration between Papanicolaou and Traut (and later to include the gynecologist, Dr. Andrew A. Marchetti) proved critical in bridging the divides of

authority between Papanicolaou's experimental work and clinical practice (Carmichael, 1973). This was imperative for progress. Their synergy, and their publications describing the cytomorphology of cervical CIS, cemented a bond between the VFSM and beleaguered gynecologists facing the dire challenges of advanced CxCa, and family physicians eager for guidance. Hinsey successfully managed the tethering between experimental laboratory methods with the clinical management of a dreaded malignancy in women. Traut's involvement in that historical juncture was crucial. Like Ayre, Traut understood the language of anatomical pathology; he also understood the histological patterns of CxCa, and he readily assimilated with the respective dyskaryotic cells scattered in smears arising from those cancers. Being a gynecologist, Traut also understood the problems posed by occult cervical precancer in asymptomatic women, and the urgencies and surgical challenges posed by advanced cancer in symptomatic women. Traut successfully entrenched the clinical relevance of Papanicolaou's work in preventive medicine; something Papanicolaou almost certainly may not have been able to achieve solely. However, the triangulation between subjective DC, anatomical pathology, and clinical gynecological oncology, did not materialize with ease. Koss stated the following in 2010 (Koss, 2010):

"Dr. Pap himself was a rather insecure diagnostician. Instead of using clear terminology to describe his findings, he used classes; he subdivided his smears into classes from I to V because he felt safer if he used the term "Class III" rather than saying the smear was suspicious of cancer.

It became quite evident to me that there were some serious problems with that technique, that the people who were interpreting smears, such as Dr. Pap, had really no idea of the underlying pathology. The pathologists on the other hand, had a very vague idea of what cytology could offer. It became clear to me from the beginning that there ought to be someone who would know both areas of diagnosis and could combine them. Ultimately, I wrote a number of books, which were attempting to explain or to clarify the relationship of the techniques for the benefit of mankind.”

It must also be emphasized that development of gynecological cytopathology through its arduous evolutionary course was a testament of Papanicolaou’s personality. Our understanding of his nature, and of its pertinence during this saga, may be formed as gleaned from his personal letters, and from various remarks and accounts communicated by his closest associates and relatives, but also from his critics (Hinsey, 1962; Koss, 1963; Koss, 1973; Koss, 1983; Koprowska, 1997; Papanicolaou-Kokkori, 2008).

Overall, he was a patient, sentimental, soft-spoken man; although, one reserved, and painfully steadfast in his convictions and decisions. No matter the hardship, he was determined to pursue what he regarded logical, scientifically sound, and beneficial to humanity. Papanicolaou was also naturally intelligent and briskly aware of imminent risk or opportunity. He was introverted and overly cautious, oftentimes difficult to be understood (Koss, 1973; Koprowska, 1997). Nonetheless, although his attributes and

dynamism occasionally reared interpersonal conflicts with various colleagues, they also ultimately governed his overall sense of vision, and sense of purpose.

In the late-1940s, supported by the ACS, Papanicolaou, Traut, and Marchetti, were actively speaking in various academic and professional forums to disseminate knowledge of cervical DC and the value of the clinical Pap test in preventing disease. After all, dissemination of knowledge was one of the mutually-agreed upon recommendations posed to Papanicolaou by Hinsey in 1939 (Hinsey, 1962). Following one such meeting, Marchetti recollected as follows (Marchetti, 1969):

“At the greater number of these meetings it was the pathologists who were the most vehement in stating that Dr. “Pap’s” smear was a superfluous procedure when the more reliable biopsy of the cervix was already available for cancer diagnosis. I could sense that during a discussion the then current point of view of the pathologists would hurt Dr. “Pap” very much. The few times that I presented the subject I would conclude by stating that the cytologic smear of the cervix and vagina in screening for cancer would eventually become as important as the peripheral blood smear in diagnosing hematologic disease. This conclusion, I suspect, gave heart to Dr. “Pap” when he made his concluding remarks, since he knew I believed it. That conviction, in my humble judgement, remains unchanged. Indeed, if facilities for cytologic screening were made available to every woman on the universe and if all women were willing to take advantage of

these facilities, currently I am ready to state that death from carcinoma of the cervix, in two or three decades, would become unacceptable.”

Marchetti’s narrative embodied the essence of the overall micro-dynamics in DC prior to 1957 when Papanicolaou retired from CMC-NY. More importantly, however, Marchetti’s convictions were prophetic as CxCa has indeed become a preventable disease through effective Pap test screening. And, as a result, deaths due to advanced CxCa may appropriately be regarded as being proxies of suboptimal Pap test uptakes, or of underperforming screening systems (Foltz & Kelsey, 1978; Koss, 1989; Dickey, 2001).

Salient Impediments To The Development Of The Clinical Pap Test In The US, Categorized And Stratified For Two Salient Timeframes: 1928-1941 And 1941-1957

This sub-section organizes the salient historical impediments to the development of the clinical Pap test in the US.

Evolutionary Timeframes Of Pap Test Development

Papanicolaou and Traut reintroduced the VFSM to the medical community in 1941 as being an effective method by which to detect precancerous lesions of the uterine cervix through an epic paper, entitled *The Diagnostic Value Of Vaginal Smears In Carcinoma Of The Uterus* (Papanicolaou & Traut, 1941; Austin & Chantziantoniou, 2014). Their descriptions of CIS became a formative turning point in the evolution of gynecological DC and defined a pivotal historical reference focus. As the clinical Pap test evolved over a period of 29 years (i.e., 1928-1957), it appeared prudent to organize the

associated impediments to its development as stratified before and after 1941. For the intents and purposes of this dissertation, the two timeframes are defined as follows:

- ***Timeframe 1 (1928-1941)***: Introduction of the clinical Vaginal Fluid Smear Method as a *diagnostic test for advanced cervical cancer*
- ***Timeframe 2 (1941-1957)***: Reintroduction of the clinical Vaginal Fluid Smear Method as a *screening test for cervical precancer*

The salient historical impediments to the overall development of the clinical Pap test from 1928 through to 1957, before and after 1941, were summarized specifically through nine categories and dedicated Tables:

1. Socio-economic factors
2. Socio-political factors
3. Socio-behavioral factors
4. Cervical cancer: burden, diagnosis, treatment, and prognosis
5. Method imperfections, and interruptions
6. Method framing, public awareness, and advocacy
7. Clinical application, and validation
8. Infrastructure, and human resources
9. Dr. Papanicolaou: vulnerabilities, professional qualifications, and conflicts

Tables Summarizing The Salient Historical Impediments

Tables 1 through 9 summarizing the salient historical impediments to the overall development and application of the clinical Pap test follow:

TABLE 1: Salient impediments to the development of the clinical Pap test in the United States due to *socio-economic* factors, stratified before and after 1941.

| Impediments: <i>Socio-economic factors</i> | |
|--|--|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ Great Depression: widespread economic and societal declines, curtailed medical services ▪ Underfunding: ASCC unable to invest towards the control of CxCa ▪ Papanicolaou's work in CxCa detection not supported at CMC-NY thus underfunded ▪ Higher rates of CxCa linked with poorer women ▪ Lack of funding to support research in overall cancer control | <ul style="list-style-type: none"> ▪ World War II ▪ Papanicolaou's work in CxCa detection was underfunded at CMC-NY until 1944 when the ASCC was rebranded and espoused allocation of research funds |

TABLE 2: Salient impediments to the development of the clinical Pap test in the United States due to *socio-political* factors, stratified before and after 1941.

| Impediments: <i>Socio-political factors</i> | |
|--|---|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ Disruptions due to Great Depression, societal decline ▪ Perceived association between VFSM and negative Eugenics movement ▪ 3rd Race Betterment Conference; not a medical conference ▪ VFSM deemed unnecessary by pathologists, gynecologists ▪ Perceived encroachment by VFSM on conventional cervical biopsy ▪ Lacking support for Papanicolaou's work in CxCa diagnosis by Stockard at CMC-NY ▪ Societal expectations for cancer control unmet by the ASCC | <ul style="list-style-type: none"> ▪ Disruptions due to World War II ▪ Unmet societal expectations for effective cancer control; inaction by the ASCC to control CxCa till its rebranding in 1944 ▪ Skepticism and resistance to the VFSM by pathologists ▪ The Womens Field Army deemed inappropriate, disbanded ▪ Papanicolaou lacking professional credentials and authority in anatomical pathology ▪ Questioned role of the clinical Pap test in diagnostic medicine |

TABLE 3: Salient impediments to the development of the clinical Pap test in the United States due to *socio-behavioral* factors, stratified before and after 1941.

| Impediments: <i>Socio-behavioral factors</i> | |
|--|---|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ Etiology and pathobiology of CxCa unknown; dreaded disease leading to certain death ▪ Societal distress, anxiety, hopelessness ▪ Stigmatization from CxCa ▪ Societal sensitivities, taboos ▪ Lacking health literacy; diagnostic information withheld from women ▪ Lacking women’s sense of susceptibility to CxCa ▪ Lacking women’s self-empowerment ▪ Delayed diagnosis and treatment of CxCa ▪ Inadequate doctors’ engagement, commitment, and buy-in | <ul style="list-style-type: none"> ▪ Etiology and pathobiology of CxCa unknown; mysterious, dreaded disease ▪ Societal distress, anxiety ▪ Stigmatization from CxCa ▪ Societal sensitivities, taboos ▪ Lacking health literacy; diagnostic information withheld from women ▪ Lacking women’s sense of susceptibility to CxCa ▪ Lacking women’s self-empowerment ▪ Delayed diagnosis and treatment of CxCa ▪ Inadequate doctors’ engagement, commitment, and buy-in |

TABLE 4: Salient impediments to the development of the clinical Pap test in the United States due to *cervical cancer burden: diagnosis, treatment, and prognosis*, stratified before and after 1941.

| Impediments: <i>Cervical cancer burden: diagnosis, treatment, and prognosis</i> | |
|--|---|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ Death rates due to cancer increasing ▪ CxCa burden out-paced population growth ▪ Diagnosis of CxCa through visual inspection of cervix with biopsy confirmation ▪ Treatment solely through radical hysterectomy with surgical mortality rates at 20% ▪ Poor prognosis due to delayed detection of advanced disease at presentation, 60% inoperability ▪ Pathologists, gynecologists unaware of cervical precancer | <ul style="list-style-type: none"> ▪ CxCa death rates increasing despite availability of VFSM due to inaction towards prophylactic screening ▪ Unfavorable 5-year survival rates due to advanced cancer at delayed presentation and time of surgical intervention ▪ Inconsistent treatment for CxCa ▪ Disagreement about cervical CIS, its qualification, and how to treat it |

TABLE 5: Salient impediments to the development of the clinical Pap test in the United States due to *VFSM imperfections, and interruptions*, stratified before and after 1941.

| Impediments: <i>VFSM imperfections, and interruptions</i> | |
|--|---|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ Disruptions due to Great Depression, lost decade of cytopathology ▪ VFSM smears cumbersome to read due to excessive blood, necrosis ▪ Poor staining due to air drying, H&E ▪ Pathologists lacking skill sets to grade single, dyskaryotic cells in smears ▪ Opposition to VFSM by pathologists; method deemed unnecessary relative to conventional biopsy ▪ Lacking correlative diagnostic nomenclature with anatomical pathology ▪ Gynecologists and pathologists not engaged | <ul style="list-style-type: none"> ▪ Disruptions due to WWII following the Great Depression ▪ Questioned role of the VFSM in preventive medicine ▪ VFSM perceived as being unnecessary relative to conventional cervical biopsy ▪ Opposition by pathologists ▪ Pathologists resistant to concept of cervical CIS, and diagnostic value of dyskaryotic cells ▪ Resistance to VFSM screening for CxCa by medical establishment ▪ Lacking health literacy throughout the US |

TABLE 6: Salient impediments to the development of the clinical Pap test in the United States due to *VFSM method framing, public awareness, and advocacy*, stratified before and after 1941.

| Impediments: VFSM framing, public awareness, and advocacy | |
|--|--|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ 3rd Race Betterment Conference; not a formal medical meeting ▪ Perceived association between VFSM and negative Eugenics movement ▪ Unfavorable initial framing of the VFSM in lay press ▪ Lacking public awareness of VFSM benefits ▪ Women lacking sense of susceptibility to CxCa ▪ ASCC underfunded, leading to diminished political influence ▪ VFSM not endorsed by ASCC ▪ Geographic vastness of the US, compromised health literacy | <ul style="list-style-type: none"> ▪ Lacking awareness of CxCa etiology, pathobiology, and precancer ▪ Lacking public awareness of VFSM benefits ▪ Women lacking sense of susceptibility to CxCa ▪ Concern of alienating women, physicians, and pathologists ▪ Reluctance to adopt the ‘simple office test’ proposed by Ayre ▪ Reluctance by some States to participate in improving health literacy of CxCa |

TABLE 7: Salient impediments to the development of the clinical Pap test in the United States due to *VFSM clinical application, and validation*, stratified before and after 1941.

| Impediments: <i>VFSM clinical application, and validation</i> | |
|--|--|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ VFSM dismissed by pathologists, gynecologists ▪ Population-based trials lacking due to Depression, lost decade of cytopathology, and skepticism ▪ VFSM imperfections; lacking technical optimization, suboptimal staining ▪ VFSM unattractive to gynecologists due to lacking knowledge of cervical precancer ▪ VFSM unattractive to pathologists due to lacking skill sets in grading single abnormal cells in smears using unfamiliar stains | <ul style="list-style-type: none"> ▪ Widespread resistance to VFSM application by pathologists ▪ Population-based trials lacking till 1947 (Erskine) and 1951 (Memphis and Shelby County trial) ▪ Political push-back against CxCa screening as a ‘simple office test’, or through cancer detection centers ▪ Disagreement amongst clinicians of CxCa screening practice; inaction, deliberations of Pap test application ▪ Lacking infrastructure; laboratories, expertise, workforce to sustain screening system expansion and smear analysis |

TABLE 8: Salient impediments to the development of the clinical Pap test in the United States due to *infrastructure, and human resources*, stratified before and after 1941.

| Impediments: <i>Infrastructure, and human resources</i> | |
|---|--|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ Lacking knowledge and infrastructure to support the newly-introduced VFSM ▪ Lacking support by Stockard at CMC-NY for VFSM clinical testing ▪ Lacking scientific foundations by which to support the VFSM at CMC-NY ▪ Lacking professional multi-disciplinary collaborations at CMC-NY till 1939 | <ul style="list-style-type: none"> ▪ Lacking infrastructure to support organized CxCa screening ▪ Lacking skilled personnel (i.e., pathologists and screening cytologists) ▪ Lacking US-wide adoption of Pap test screening |

TABLE 9: Salient impediments to the development of the clinical Pap test in the United States due to *Dr. Papanicolaou's vulnerabilities, professional qualifications, and conflicts* stratified before and after 1941.

| Impediments: <i>Dr. Papanicolaou: vulnerabilities, professional qualifications, and conflicts</i> | |
|---|---|
| Timeframe 1 (1928-1941) | Timeframe 2 (1941-1957) |
| <ul style="list-style-type: none"> ▪ Perceived relationship between Papanicolaou and negative Eugenics movement ▪ Papanicolaou not a licensed clinician; lacked qualifications and authority in anatomical pathology; concepts questioned, dismissed by pathologists ▪ The lost decade of cytopathology ▪ Papanicolaou's perceptions of failure, inability to solely perfect the VFSM ▪ Lacking professional multi-disciplinary collaborations at CMC-NY | <ul style="list-style-type: none"> ▪ Papanicolaou not a licensed clinician ▪ Papanicolaou lacking qualifications and authority in anatomical pathology ▪ Papanicolaou's concepts questioned, dismissed by pathologists ▪ Papanicolaou's diagnostic terminology (i.e., Dyskaryotic cells, Pap Class Reporting system) incongruent with diagnostic language of anatomical pathology leading to push-back ▪ Lacking support from CMC-NY for Papanicolaou's work |

CHAPTER 3: CERVICAL CANCER BURDEN, EPIDEMIOLOGICAL EXPERIENCE, CLINICAL PAP TEST UPTAKES, AND HEALTH PROMOTION IN THE STATE OF QATAR

Pap Test Uptakes In The Extended Middle East And North Africa Region

Practically all the nations that comprise the Extended Middle East and North Africa (EMENA) geographic region have not adopted organized, national population-based Pap test screening programs for the secondary prevention of CxCa in the asymptomatic female population; nor strategically in women deemed at risk for developing this disease. In the EMENA region, Pap test uptakes are overwhelmingly opportunistic (Seoud, 2013; Sancho-Garnier et al., 2013).

Opportunistic Pap test sampling may be defined as: The uptake of Pap test cervical sampling services as the clinical opportunity warrants (Gustafsson, Ponten, Zack, & Adami, 1997). Opportunistic screening systems typically do not involve an initial patient call to screening or recall.

Essentially all nations and territories in the EMENA region deploy opportunistic screening practices in their public and private healthcare sectors (Sancho-Garnier et al., 2013). However, most of the wealthier nations in this region, notably the Gulf Arab States, and Saudi Arabia, operate standard-of-practice tertiary medical institutions, most of which serve patients through premier diagnostic laboratory services modeled after American practices and accredited by the College of American Pathologists (CAP).

As the Pap test is not widely deployed for population-based screening in the EMENA region, it is instead utilized as a diagnostic test to rule out or rule in CxCa in response to presenting, suspicious symptomatology. Consequently, nearly all cervical cancers in this region are initially detected through opportunistic Pap test sampling. And, as was the situation in the early 20th century in the US, the majority of cervical cancers diagnosed in the EMENA region are characteristically in advanced stages at diagnosis (Sancho-Garnier et al., 2013; Alemrayat et al., 2018). In such clinical settings, opportunistic Pap test sampling may also be defined as being optional; not strategically or formally advocated for disease detection or prevention in the at risk, asymptomatic clinical population.

In the context of public health and women's welfare in the EMENA region however, the impact of advanced CxCa poses potentially devastating, highly impactful societal detriments. This holds particularly true in the predominantly conservative, traditional societies that are characteristic of this region largely based on matriarchically-structured cultural norms, and the considerable societal importance placed upon female fertility (Seoud, 2013; Jumaan, Ghanem, Taher, Braikat, AlAwaidy, & Dbaido, 2013).

It is important to nonetheless emphasize the remarkable health promotion initiatives and campaigns undertaken in the State of Qatar to increase health literacy for CxCa, and particularly since 2014. Major initiatives conducted mainly through the QMoPH, the PHCC, and the QCS are listed in chronological sequence in subsequent sub-sections in this Chapter.

Global Cervical Cancer Burden

Cervical Cancer Burden In Resource-Poor, Developing Global Regions

According to World Health Organization (WHO) estimates, over one million women globally have CxCa although unaware of their disease. Most of these women in developing nations face no prospect of access to Pap testing or to gynecological services (Cibas & Ducatman, 2014; World Health Organization, 2014). These women comprise a population sub-set harboring preclinical disease and, therefore, the most likely beneficiaries of secondary disease prevention through Pap test screening.

According to the Institut Catala d'Oncologica (ICO), 527,624 new cases of CxCa were diagnosed worldwide in 2012; whereas, 265,672 proved fatal (Institut Catala d'Oncologica, 2017¹). These data equate into a global death rate of 50.3% for *new* cases alone. However, 230,158 of those fatal cases (86.6%) occurred in low- to middle-income developing nations due to financial or screening disparities (Institut Catala d'Oncologica, 2017¹).

Alarmingly, in the absence of secondary preventative screening, the death rate due to CxCa in resource-poor nations is projected to increase by 25% within the next decade (Consul, Agrawal, Sharma, Bansal, Gutch, & Jain, 2012).

In 2017, according to the ICO World Report (ICO, 2017¹), CxCa ranked as the 4th leading type of cancer in women globally, and the 2nd most common cancer in women in the 15-44 years age group globally.

Cervical Cancer Burden In The US

Of the half million new cases of CxCa anticipated globally and annually according to the WHO (World Health Organization, 2014), the ACS estimated that 13,170 of those cases will be registered in the US for the year 2019; whereas, 4,250 of those women would die of their disease (World Health Organization, 2014; Limmer, LoBiondo, & Dains, 2014; American Cancer Society, 2018). These ACS estimates suggest a 32.2% US-specific death rate due to CxCa in modern clinical practice.

Importantly, the 13,170 new cases expected in the US for 2019 equate to nearly 2.5% of the total global burden of new cases estimated by the WHO and the ACS (World Health Organization, 2014; American Cancer Society, 2018).

Cervical Cancer Burden And Management In The State Of Qatar

The State of Qatar is a sovereign nation amongst the Gulf Arab States, and a member country of the EMENA region (Seoud, 2013). Qatar is also assigned to the greater geographic region of Western Asia by the ICO (Institut Catala d'Oncologica, 2017²).

Qatar is an affluent sea-fairing Arab State forming a small Peninsula jutting acutely into the Persian Gulf from the eastern flank of the greater Saudi Arabian heartland. The State of Qatar boasts a modern, hospitable, educated society, although one embedded in the fabric of a traditional, conservative, Bedouin culture as is characteristic of most Gulf Arab States (Qatar Ministry of Foreign Affairs, 2019). The State of Qatar has experienced an unprecedented economic boom in the past 40 years

resulting in remarkable multi-sector modernization (Qatar Ministry of Economy and Commerce, Oxford Business Group, 2019). Qatar is currently in the midst of massive infrastructure development in the run-up to the FIFA World Cup event in 2022. The healthcare sector has similarly expanded medical services in tandem with these national developments.

According to information published by the World Population Review, pertaining to Qatar and to the US, the population of Qatar was estimated to be 2.7 million in July 2018, relative to 327 million for the US in February 2018 (World Population Review, 2018¹; World Population Review, 2018²). In Qatar, women comprised 25.09% of the entire population, estimated to be 676,137 (World Population Review, 2018¹). In 2018, the minority of these women were Qatari nationals, and the majority expatriate women residing in Qatar originating from various countries, predominantly from Asia.

Accordingly, the population pyramid of Qatar is significantly skewed towards males. The vast majority of the male population comprises an expatriate, blue-collar migrant workforce employed in the infrastructural megaprojects. The female population is characterized by a primary age group component of 30-34 years, followed by a secondary component of 35-39 years (Institut Catala d'Oncologica, 2017²).

Of the entire female population in Qatar in 2017, 481,127 women (71.1%) were over the age of 15 and deemed at risk for developing CxCa according to the ICO (Institut Catala d'Oncologica, 2017²).

Accessing Pap Test Sampling In The State Of Qatar

Access to Pap test sampling is currently available through private and public healthcare providers in the State of Qatar (QMoPH Guide To Healthcare Services In Qatar General Adult Population, 2018).

The public healthcare system is robust and multi-tiered. The *Qatar Primary Health Care Corporation* (PHCC) (www.phcc.qa) operates 26 community-based healthcare centers strategically located throughout the nation based on population density. The community-based centers provide a wide range of primary care services acting as the first contact of consultation for non-emergent patients. Depending on the medical concern, patients may either undergo treatment locally or be referred to larger centers in the capital city, Doha, for additional investigations and treatment.

The largest public tertiary hospital in Qatar is the Hamad Medical Corporation (HMC) in Doha (www.hamad.qa). The HMC was established in 1979 through Emiri decree as a not-for-profit healthcare organization. The HMC currently integrates 12 specialist hospitals and provides comprehensive standard-of-practice medical services to accommodate patients that could not be treated in the community-based setting. The HMC houses the largest, comprehensive DC service in Qatar managing the vast majority of Pap test cases (approximately 10,000 cases annually) arising from the public system, predominantly cases received from PHCC centers. The HMC DC service is modeled after American (i.e., Bethesda) guidelines for the reading and reporting of gynecological

Pap test cases, as also dictated through the College of American Pathologists (CAP) inclusive of HPV reflex genotyping for high-risk HPV.

Expatriate residents in Qatar that have a Qatar Identification number (QID) may access medical services at PHCC centers or HMC and settle a nominal deductible fee. Medical consultations, treatment, and pharmacological prescriptions are heavily subsidized by the State. Emergency medical services are provided without fee throughout Qatar.

Another major establishment in Doha is Sidra Medicine (www.sidra.org). Sidra Medicine is a private, fee-for-service, ultramodern academic Women's and Children's hospital. Sidra Medicine is affiliated with CMC-NY, through the Cornell Medical College-Qatar campus located in the Education City complex adjacent to Sidra Medicine. The DC service at Sidra was launched in February 2018. The Sidra DC service is likewise modeled after American and CAP accreditation guidelines, inclusive of HPV reflex genotyping.

Current Pap Test Uptake Practice In The State Of Qatar

At the time of this writing, the State of Qatar has not implemented a formal, organized, national population-based Pap test screening program for cervical cancer prevention for all asymptomatic resident women inclusive of initial patient call to screening or recall. Through guidance from the QMoPH, PHCC, and the QCS, the State is currently providing opportunistic Pap testing services due to the low prevalence of this disease (discussed in greater detail in Chapter 6).

Cervical Cancer Epidemiology In The State Of Qatar

Cervical Cancer Rates In The State Of Qatar

According to the *Human Papillomavirus And Related Disease Report For Qatar* in 2017 (Institut Catala d'Oncologica, 2017²), CxCa ranks as the 5th most common cancer in women in the State of Qatar, and the 6th most common cancer in women in the 15-44 years age group.

Also according to the ICO (Institut Catala d'Oncologica, 2017²), the State of Qatar had a crude incidence rate of 3.2 cases per 100,000 for CxCa (relative to 3.8 cases for Western Asia); and a crude mortality rate of 0.9 cases per 100,000 (relative to 1.6 cases for Western Asia). Recent studies by Sathian, van Teijlingen, & Rajesh (2018) report an age-standardized incidence and death rate for CxCa in Qatar as being: 5.1 and 2.4 per 100,000 respectively. In comparison, the age-standardized incidence and death rates for CxCa in the US for the period spanning 2011-2015 were: 7.6 and 2.3 per 100,000 respectively according the American Cancer Society (2018).

Cervical Cancer Registry, Presentation, And Diagnosis In The State Of Qatar

Under the auspices of the *Qatar National Cancer Program*, the *National Cancer Registry* initiative was launched at HMC in 2012 to record prevalence statistics from cancer cases (A.A. Hmaidan; personal communication, March 21, 2016). Prevalence statistics prior to 2012 were computed from case studies based on treatment course and outcomes, hence regarded potentially inaccurate. As such, epidemiologically-accurate

cancer statistics became available in Qatar from 2012 henceforth through the *National Cancer Program*.

From 1970-2015, in Qatari women, 61 invasive CxCa cases and 18 CIS cases were experienced totaling 79 cases; whereby, 77.2% were invasive cases, and 22.8% were precancerous cases. In the same timeframe, in expatriate women, 178 invasive CxCa cases and 32 CIS cases were experienced totaling 210 cases; whereby, 84.8% were invasive cases, and 15.2% were precancerous cases.

The *National Cancer Registry, Cancer Incidence 2014* report (Appendix A) (QMoPH National Cancer Program, 2014) revealed that 18 cases of CxCa were registered in 2014 along with 17 cases of CIS of the cervix. The report also declared that of the 18 cases of invasive cervical cancer registered, 28% of these cases were in Qatari women while the remainder 72% of cases were in non-Qatari, expatriate women. Also, importantly, that greater than 60% of all the CxCa cases registered in 2014 were subsequently shown to harbor Stage II/III disease at histologic diagnosis; and, that these cases produced a bimodal pattern of prevalence distribution based on two peak age groups: 40-44, and 60-64 years. The clinical and demographic data of CxCa cases arising from the contemporary Qatar setting closely align with ICO World Report estimates. The ICO (Institut Catala d'Oncologica, 2017²) published an anticipated annual CxCa burden of 15 cases for Qatar; four of which may be fatal, reflecting an estimated death rate of 26.7% annually.

Cervical Cancer Health Literacy And Healthcare Promotion In The State Of Qatar

Sidra Medicine Symposium: The 1st Century Of Gynecological Cytopathology, The Pap Test – Then, Now And The Future

The author took employment at Sidra Medicine starting in November 2013. In line with the *National Cancer Registry, Cancer Incidence 2014* report (QMoPH National Cancer Program, 2014), the Sidra DC Section and the Department of Pathology organized a dedicated symposium to raise awareness of CxCa, Pap test screening practices, and vaccination for HPV. The symposium, entitled *The 1st Century Of Gynecological Cytopathology, The Pap test – Then, Now And The Future*, was conducted on December 07, 2014 (Appendix C, D, and E). The symposium was open to all stakeholders affiliated with the detection and management of CxCa in the State of Qatar. Attendees included clinicians, diagnostic cytologists, and representatives from the QMoPH. The symposium and its outcomes were widely acknowledged in the local English and Arabic language press and web-based media.

Following the Sidra Medicine symposium in 2014, the author was invited to participate in an *ad-hoc* committee at the QMoPH to explore the prospect of organized CxCa screening in the State of Qatar. The author's participation ended in March 2016.

Guidelines For Cervical Cancer Screening In The State Of Qatar

In 2016, the QMoPH, through its *National Cancer Program*, published draft guidelines for the management of CxCa inclusive of screening practice in a report, entitled *Guidelines For Cervical Cancer Screening In The State of Qatar* (QMoPH National

Cancer Program, 2016¹) (Appendix F). The guidelines produced *General Principles* suggesting:

“All eligible and asymptomatic women aged 25 to 64 years and sexually active should be invited for routine cervical screening at given age ranges and screening intervals:

- Women aged 25 to 49 years should be screened every 3 years;
- Women aged 50 to 64 years should be screened every 5 years.”

Moreover:

“Depending on the cervical screening result, human papillomavirus test (HPV test) will be conducted.”

The *General Principles* also recommended that women ought to give consent to Pap test sampling after being adequately educated of the risks and benefits of screening.

Nevertheless, in due course, the QMoPH decided that CxCa management through Pap test population-based screening with patient call and recall shall remain under consideration as a work-in-progress. Shortly thereafter, the author was advised that given the relatively low incidence rates recorded for this disease in this geographically-small clinical setting, Pap test uptakes were to remain opportunistic in the State of Qatar (V.V. Recreo; personal communication, March 17, 2016).

Guideline For Suspected Cancer Referral In The State Of Qatar

Also in 2016, the QMoPH, through its *National Cancer Program*, published its draft guidelines for clinicians to follow a referral process for suspected cancer patients,

entitled *Guideline For Suspected Cancer Referral In The State Of Qatar* (QMoPH National Cancer Program, 2016²) (Appendix G). The guidelines were based on a flow-chart guiding the management of patients depending on presenting symptoms, and suspected cancer type; whereas:

“The suspected cancer referral guidelines have been produced with the assistance of a multidisciplinary group of clinicians to provide a comprehensive overview of the suspected cancer patient’s journey from referral to timely diagnosis and treatment.”

The purpose of the guidelines was to assure least possible delays in cancer diagnosis and treatment. The proposed *Patient Referral Pathway* included a flow chart, entitled *Urgent Suspicion Of Cancer*. The referral pathway proposed clinical examinations and diagnostic investigations be conducted within 48 hours of patient presentation; and, that definitive treatment be initiated within 14 days of diagnosis. Such initiatives are highly extraordinary.

Specifically for suspected gynecological cancers (i.e., cervical, endometrial and ovarian cancers), the clinical criteria for clinicians to apply the 48-hour *Urgent Suspicion Of Cancer* pathway follow:

- Post-menopausal bleeding
- Abnormal high grade cervical smear (HSIL, ASC-H, AGC)
- Suspicious mass
- Suspicious imaging

- Radiological findings strongly suspicious of invasive malignancy

Similarly, the clinical criteria for a patient's referral within 14 days for additional investigations follow:

- LSIL
- Irregular bleeding in a woman on hormone replacement therapy
- Purulent vaginal discharge
- Bloodstained vaginal discharge
- Inter-menstrual bleeding
- Post-coital bleeding
- Persistent abdominal distention/bloating
- Abdominal/pelvic pain
- Feeling full quickly and/or having difficulty eating (loss of appetite)

Qatar Cancer Society Awareness Campaign For Cervical Cancer: "Be Well"

In January 2017, the QCS launched an extensive health awareness campaign, entitled *Be Well* (Qatar Cancer Society, 2017) (Appendix H). The campaign ran throughout the month of January 2017 to raise awareness of CxCa, of its symptoms, of its potential prevention through Pap test screening, and to ultimately encourage women to "check out the Pap smear." The campaign also included lectures and workshops conducted by authorized officials. The article posted on January 11, 2017, in the QatarIsBooming website (www.qatarisbooming.com), stated:

“...cervical cancer often does not cause symptoms until it is advanced, so it is important to start the early detection tests regularly even when you feel healthy, and in Qatar: you can do the Pap test in Primary Health Care Center (Women’s Health Clinic).”

National Health Strategy 2018-2022

In 2018, the QMoPH published the *National Health Strategy 2018-2022*, under the subtitle, *Our Health Our Future* (QMoPH National Health Strategy 2018-2022, 2018) (Appendix I). The national strategy stipulated an increased but comprehensive effort for the early detection of disease and its possible prevention through improved health education and best-practice services for cancer treatment. The ultimate target of the strategy, through to 2022, was a 15% reduction in premature mortality due to chronic diseases such as cancer (QMoPH National Health Strategy 2018-2022, 2018).

National Clinical Guidelines For The State Of Qatar (2nd Edition)

In April 2017, in the run-up to the *National Health Strategy 2018-2022*, the QMoPH had published its 2nd edition clinical guidelines, entitled *National Clinical Guidelines For The State Of Qatar – 2nd Edition* (Appendix J). The QMoPH capitalized upon the extensive internet connectivity and mobile phone networks installed throughout the State to provide practice guidelines for all registered clinicians through dedicated websites, apps, and e-medicine platforms. The rationale of the guidelines follows (QMoPH National Clinical Guidelines For The State Of Qatar – 2nd Edition, 2017):

“The majority of healthcare practitioners working in Qatar have been trained overseas. As we draw upon the advantages brought forward by the diverse set of specialized skills, languages and perspectives in patient and peer interactions, it is also of utmost importance to acknowledge that this may innately contribute to a significant variation in the standard of care provided.

The National Clinical Guidelines project started in April 2015. Initially, through consultations with stakeholders, the MoPH NCG team mapped the processes for guideline development and localization by different organizations across Qatar’s health economy. The gaps between current practice in Qatar and the international best practice approach were identified and accordingly a model for guideline development was agreed and established.”

Qatar Ministry Of Public Health Infographic: “What Is Cervical Cancer?”

Also in 2017, the QMoPH produced a public health infographic, entitled *What Is Cervical Cancer* (Appendix K(a) and K(b)). The 2-page fold-out brochure illustrated salient information about CxCa: Its global incidence; its etiology; what is HPV; the symptoms of CxCa and of HPV infection; how women may protect themselves from HPV and CxCa; the purpose of HPV vaccination; and, encouragement for women to seek medical care (QMoPH *What Is Cervical Cancer*, 2017).

HPV Vaccination Protection In The State Of Qatar

In February 2018, the QMoPH announced its endorsement and immediate roll-out of the national vaccination program for HPV (Sathian, van Teijlingen, & Rajesh,

2018; QMoPH Health Protection & Communicable Disease, 2018). The program advocated prompt availability of the HPV vaccine throughout the State to facilitate protection and primary prevention of CxCa. The program proposed that HPV vaccination be made available to females and males age 12 to 26.

Opportunities For Healthcare Promotion Research

Along with the myriad of initiatives and health literacy campaigns conducted in the State of Qatar since 2014, the introduction of HPV vaccination in 2018 manifested an unprecedented potential for effective CxCa control. As such, these developments posed a unique opportunity for research to assess current public awareness of CxCa, of the Pap test, and, of perceptions and attitudes towards HPV vaccination. Similarly, to assess likely public support for a formal population-based CxCa screening program for all resident women through a needs-assessment survey offered to both women and men.

In addition to the knowledge gained from the historical development of the Pap test in the US, such survey-based data may reveal gaps to guide the consideration of tailored cytopathology and gynecology services at Sidra Medicine in keeping with the governmental initiatives and long-term healthcare ambitions for the State. Such research data may also aid in the optimization of existing CxCa management philosophies and practices in the State of Qatar to mitigate the number of women presenting with advanced disease at diagnosis.

Through a collaborative research team effort at Sidra Medicine, a needs-assessment survey was strategically designed to test for these opportunities. Relevant

survey-based research designs were reviewed for the development of the needs-assessment survey: (Kahn, Chiou, Allen, Goodman, Perlman, & Emans, 1999; Badrinath, Ghazal-Aswad, Osman, Deemas, & McIlvenny, 2004; Lyva, Byrd, & Tarwater, 2006; Denny & Wright, 2009; Fernandez, Diamond, Rakowski, Gonzales, Tortolero-Luna, Williams, & Morales-Campos, 2009; Guvenc, Akyuz, & Acikel, 2010; Tanner-Smith & Brown, 2010; Ma, Gao, Fang, Tan, Feng, Ge, & Nguyen, 2013; Jaglarz, Tomaszewski, Kamzol, Puskulluoglu, & Krzemieniecki, 2014; Lee & Carvallo, 2014; Ebu, Mupepi, Siakwa, & Sampelle, 2015; Glanz, Rimer, & Viswanath, 2015; Interis, Anakwenze, Aung, & Jolly, 2016).

The structure of the survey, along with its questions and responses, and their rationale, are listed in Chapters 4 and 5 respectively.

CHAPTER 4: NEEDS-ASSESSMENT SURVEY MATERIALS AND METHODS

Preceding Survey-Based Research In The State Of Qatar

To uncover relevant, preceding survey-based research from the State of Qatar, a PubMed search was conducted using the following four key terms inclusively: *Cervical + Cancer + Survey + Qatar*. The search revealed one indexed survey-based study by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) reporting findings arising from a needs-assessment project conducted in 2008 reflecting women participants visiting PHCC centers in Qatar. Two other studies were also revealed from the PubMed search reporting epidemiological data arising from Qatar, but not from needs-assessment surveys. A Google search using the same key terms inclusively revealed a second survey-based study by Alali, Salem, Elmahdi, Alkubaisi, Alwahedi, Taher, Yousuf, Aljaber, & Mostafa (2016) not indexed in PubMed. These two survey-based exercises analyzed responses exclusively from women participants.

It is the author's belief that this dissertation comprises the third survey-based exercise conducted in the State of Qatar; although, it was the first to assess perceptions and magnitude of support for a formal, national Pap test screening program for all resident women; from both women and men participants.

Needs-Assessment Survey Design

The needs-assessment survey research protocol was composed following guidelines from the National Institutes of Health (NIH) (National Institutes of Health, 2018). The research protocol, survey questions, and responses were produced collaboratively in both English and Arabic, and submitted to the Sidra Institutional Review Board (IRB) Ethics Committee for consideration on November 02, 2017. Following two revisions, the research study was formally approved by the Sidra IRB on December 11, 2018, under protocol number: MoPH-Sidra-IRB-099. The distribution of 300 surveys commenced on December 28, 2018, and ended on April 03, 2019. The Sidra IRB approval stipulated that survey distribution be conducted within the Sidra Medicine caption area.

The survey was voluntary, self-reported, and anonymous as no personal identification information was requested or recorded. Invited participants were women or men, either visitors or patients accessing gynecological services at Sidra Medicine, or interested employees. The survey was exclusively in hard-copy format. After participants' completion of the survey, all surveys were enclosed in dedicated envelopes and subsequently organized to support data capture.

The Sidra IRB committee dictated the final wording of the survey questions and responses in both the English and Arabic survey versions to sustain cultural sensitivity and the societal norms of the State of Qatar. Specific wording nonetheless aimed to uphold the intent and rationale of the questions as direct translations from English to

Arabic were not always appropriate or comprehensible. The Sidra IRB committee also approved a *Leaflet* to accompany the surveys to welcome the respondents and provide an introduction to the aims of the research effort. The *Leaflet*, produced in both English and Arabic, also functioned to document participants' consent to survey participation, with an attestation of their age not being under 18 years. Given the laws and stipulations applicable to medical practice and research in the State of Qatar, an exclusion criterion was imposed such that the survey would not be made available to participants younger than 18 years of age.

Needs-Assessment Survey Questions, Responses, And Rationale

The needs-assessment survey was considered through a collaborative research team effort (see Acknowledgments) and consisted of 31 questions. The English version of the survey, in its entirety, appears in Appendix B. The survey questions were worded with relevance to the current practices for CxCa management in the State of Qatar, and took into account preceding survey-based research. The overall intent was to produce robust data reflecting the views and opinions of women and men, to support services development at Sidra Medicine, and ongoing, follow-up research and academic work.

Needs-Assessment Survey Questions And Data Categories

The needs-assessment questions and responses were designed to capture information based on four broad data categories: (1) Socio-demographic; (2) Healthcare Services; (3) Health Literacy; and, (4) Self-efficacy and Perceptions.

The breakdown of questions (i.e., variables) incorporated into the four data categories follows:

- Category 1: Socio-demographic (Questions 1-8, and 31)
- Category 2: Healthcare Services (Questions 9-11)
- Category 3: Health Literacy (Questions 12-20)
- Category 4: Self-efficacy and Perceptions (Questions 21-30)

Needs-Assessment Survey Questions

The needs-assessment survey questions, responses, and their specific rationale follow:

Question 1**Nationality.**

- Qatari
- Middle Eastern
- Asian
- European
- North American
- South American
- African
- Other

Rationale: Question 1 aimed to capture socio-demographic data based on:

Nationality. The intent was to produce a breakdown of the nationalities arising from all respondents to facilitate correlation with the proportionality of nationalities amongst all residents currently in the State of Qatar. Such data may elucidate population representation.

Question 2**Gender.**

- Female
- Male

Rationale: Question 2 aimed to capture socio-demographic data based on:

Gender. The intent was to facilitate stratification of the entire data set based on gender.

Question 3**Age group (Years).**

- Under 20
- 20-29
- 30-39
- 40-49
- 50-59
- Over 60

Rationale: Question 3 aimed to capture socio-demographic data based on: *Age group (years)*. This question aimed to capture age-related data from all respondents based on six age-group categories. The intent was to reveal distributions particularly from women to allow correlations with preceding epidemiological data arising from Qatar as published by the QMoPH (QMoPH National Cancer Program, 2014) in the context of CxCa. This question would also facilitate the exclusion of participants younger than age 20.

Question 4**Highest education level.**

- Middle School
- High School
- University
- Other

Rationale: Question 4 aimed to capture socio-demographic data based on: *Highest education level*. This question aimed to capture the extent of education from all respondents to facilitate correlations with population-based statistics arising from the State of Qatar.

Question 5**Marital status.**

- Never married
- Married
- Divorced
- Widowed

Rationale: Question 5 aimed to capture socio-demographic data from all respondents based on: *Marital status*. This question would also facilitate correlation with previously-reported studies, and statistics arising from the State of Qatar.

Question 6**Marriage duration.**

- Under 5
- 5-10
- 10-20
- Over 20
- Not applicable

Rationale: Question 6 aimed to capture socio-demographic data from all respondents based on: *Marriage duration* (in periods of years).

Question 7**Employment status.**

- Employed
- Unemployed
- Other

Rationale: Question 7 aimed to capture demographic data from all respondents based on: *Employment status*. The intent was to reveal extent of likely financial independence amongst respondents.

Question 8

You have health insurance coverage?

- Yes
- No

Rationale: Question 8 aimed to capture socio-demographic data from all respondents based on: *Health insurance coverage*.

Question 9

You had a Pap test before?

- Yes
- No
- Not applicable

Rationale: Question 9 aimed to capture healthcare services data based on: *Pap test uptake*. This question aimed to assess the likelihood of Pap test uptakes from all women respondents; allowing subsequent exclusion of male respondents.

Question 10

If you had a Pap test before, when was it performed?

- 1-3 years ago
- 4-6 years ago
- Over 6 years ago

Rationale: Question 10 aimed to capture healthcare services data based on: *Years duration since previous Pap test*. This question aimed to assess time-frames of preceding Pap test uptakes from all women respondents; allowing subsequent exclusion of male respondents. These data may correlate with the screening intervals currently recommended by the QMoPH based on age-group.

Question 11

Did you, or any member of your family have cervical cancer before?

- Yes
- No
- Don't know

Rationale: Question 11 aimed to capture healthcare services data based on:

History of cervical cancer in family member. This question aimed to assess awareness of CxCa from all respondents.

Question 12

Cervical cancer may be preventable.

- Yes
- No
- Don't know

Rationale: Question 12 aimed to capture health literacy data based on: *Knowledge*

of cervical cancer preventability. This question aimed to assess awareness pertaining to the possible prevention of CxCa from all respondents.

Question 13

You are aware of the Pap test smear cytologic method.

- Yes
- No

Rationale: Question 13 aimed to capture health literacy data based on: *Awareness*

of the Pap test smear cytologic method. This question aimed to assess public awareness pertaining to the Pap test smear cytologic method from all respondents.

Question 14

Where did you hear of the Pap test smear cytologic method for the first time?

- Relatives, friends
- Gynecologist
- Mass media (newspaper, internet, television)
- Family physician
- Nurse
- Other
- Not applicable

Rationale: Question 14 aimed to capture health literacy data based on: *Source of knowledge of the Pap test smear cytologic method*. This question aimed to assess the predominant sources of information regarding the Pap test cytologic method from all respondents.

Question 15

You have knowledge of cervical cancer.

- Yes
- No

Rationale: Question 15 aimed to capture health literacy data based on: *Knowledge of cervical cancer*. This question aimed to assess knowledge pertaining to CxCa from all respondents.

Question 16

Early detection of cervical cancer is important for effective treatment.

- Yes
- No
- Don't know

Rationale: Question 16 aimed to capture health literacy data based on: *Importance of early detection of cervical cancer for effective treatment*. This question aimed to assess awareness pertaining to the importance of early detection of CxCa to facilitate effective treatment for all respondents.

Question 17

Regular Pap tests may protect you from cervical cancer.

- Yes
- No
- Don't know

Rationale: Question 17 aimed to capture health literacy data based on: *Knowledge of protection afforded through regular Pap test uptakes*. This question aimed to assess awareness pertaining to likely disease prevention through protection availed by regular Pap test uptakes from all respondents; allowing subsequent exclusion of male respondents.

Question 18

Cervical cancer may be curable.

- Yes
- No
- Don't know

Rationale: Question 18 aimed to capture health literacy data based on: *Curability of cervical cancer*. This question aimed to assess awareness pertaining to the likely curability of CxCa from all respondents.

Question 19

Vaccination for the Human Papilloma Virus protects against cervical cancer and other HPV-associated cancers.

- Yes
- No
- Don't know

Rationale: Question 19 aimed to capture health literacy data based on: *Knowledge of protection for HPV-associated cancers, and cervical cancer, through HPV vaccination*. This question aimed to assess awareness pertaining to the likely protections offered through HPV vaccination for the development of CxCa and other HPV-associated cancers from all respondents.

Question 20

Menopausal women need a Pap test.

- Yes
- No
- Don't know

Rationale: Question 20 aimed to capture health literacy data based on: *Knowledge of need of Pap testing for menopausal women*. This question aimed to assess knowledge pertaining to the need for Pap testing by menopausal women from all respondents. This question may reveal significant findings as the peak incidence of CxCa in the State of Qatar occurs in the 60-64 years age group as published by the QMoPH (National Cancer Program, 2014).

Question 21

More information is needed to improve your knowledge of cervical cancer.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 21 aimed to capture self-efficacy and perceptions data based on: *Need for additional information to improve participant's knowledge of cervical cancer*. This question aimed to assess self-efficacy and agreement/support reflecting the need for additional health literacy pertaining to CxCa from all respondents.

Question 22

Regular Pap tests are a good health practice.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 22 aimed to capture self-efficacy and perceptions data based on: *Degree of good health practice through regular Pap testing*. This question aimed to assess self-efficacy and agreement/support of the perceived value embedded in regular Pap test uptakes as being a good health practice from all respondents.

Question 23

Getting a Pap test performed is too difficult.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 23 aimed to capture self-efficacy and perceptions data based on: *Difficulty of getting a Pap test performed*. This question aimed to assess degree of self-efficacy and agreement/support of the likely difficulty in getting a Pap test performed from all respondents; allowing subsequent exclusion of male responders. This question may reveal perceptions of barriers to Pap testing specifically in women.

Question 24

You would recommend a Pap test to your family, friends, and colleagues.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 24 aimed to capture self-efficacy and perceptions data based on: *Recommendation of the Pap test for family, friends, and colleagues*. This question aimed to assess degree of self-efficacy and agreement/support of the respondent to recommend the Pap test to family, friends, and colleagues from all respondents. This question may also reveal a reflection of overall knowledge of CxCa and of Pap testing, and of perceived barriers to Pap test uptakes.

Question 25

Getting a Pap test is a valued investment for good healthcare.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 25 aimed to capture self-efficacy and perceptions data based on: *Value of investment in a Pap test for good healthcare*. This question aimed to assess degree of self-efficacy and agreement/support of the perceived value of investment embedded in the Pap test for good health from all respondents.

Question 26

You would support a Pap test screening program for cervical cancer.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 26 aimed to capture self-efficacy and perceptions data based on: *Support for a screening program for cervical cancer*. This question aimed to assess degree of self-efficacy and agreement/support for a Pap test screening program from all respondents.

Question 27

A formal Pap test screening program for cervical cancer should be established for all women in the State of Qatar.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 27 aimed to capture self-efficacy and perceptions data based on: *Support for the establishment of a formal screening program for cervical cancer for all resident women in the State of Qatar*. This question aimed to assess degree of self-efficacy and agreement/support for the establishment of a formal, national Pap test screening program for all resident women in the State of Qatar from all respondents.

Question 28

You know where to go to get a Pap test performed.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 28 aimed to capture self-efficacy and perceptions data based on: *Knowledge as to where to get a Pap test performed.* This question aimed to assess degree of self-efficacy and agreement/support for knowledge as to where to get a Pap test performed in the State of Qatar from all respondents; allowing subsequent exclusion of male responders.

Question 29

A Pap test has no value for you.

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 29 aimed to capture self-efficacy and perceptions data based on: *Value of a Pap test for the respondent.* This question aimed to assess degree of self-efficacy and agreement/support as to if the Pap test has or has not value for the respondent, from all respondents; allowing subsequent exclusion of male responders.

Question 30

If a self-test for cervical cancer was available you would prefer it?

- Strongly agree
- Agree
- Undecided
- Disagree
- Strongly disagree

Rationale: Question 30 aimed to capture self-efficacy and perceptions data based on: *Support (i.e., preference) for a self-test for cervical cancer if available*. This question aimed to assess degree of self-efficacy and agreement/support as to the preference for a self-test for CxCa if available from all respondents; allowing subsequent exclusion of male responders. This question may also reveal a reflection of perceived barriers to Pap test uptakes.

Question 31

If employed, are you employed in the healthcare sector?

- Yes
- No

Rationale: Question 31 aimed to capture socio-demographic data based on: *Employment in the healthcare sector*. This question aimed to assess likely employment in the healthcare sector from all respondents allowing correlation with data from preceding survey-based research conducted in the State of Qatar.

CHAPTER 5: NEEDS-ASSESSMENT SURVEY RESULTS

Needs-Assessment Survey Data Set

Three-hundred surveys were distributed, completed, and retrieved for this study using either the English or Arabic hard-copy versions depending on participants' preference. Completed surveys were organized and registered as per date of data capture, and sequentially numbered 001 to 300.

Needs-Assessment Survey Data Set Analysis

Responses from all surveys were transcribed into a dedicated Excel spreadsheet designed with columns and drop-down menus to coincide with all survey questions and responses. The complete data set from the spreadsheet was imported electronically into a dedicated file using the R version 3.5.1 software (The R Foundation[®]) for the generation of contingency tables, figures representing data through bar plots, and for bivariate and multi-factorial statistical computations (Diez, Barr, & Cetinkaya-Rundel, 2015).

The entire data set was analyzed through three levels of statistical analysis. As the survey produced exclusively categorical data, every question was considered a variable for statistical associations. Calculations for standard deviations, confidence intervals, and mean were not applicable.

Firstly, all data counts (i.e., responses) from all answered questions were represented as being a proportion of the total data set of 300 surveys to produce a

Percent Response Rate, as: $[(n_ / 300) \text{ Response Rate: } _ \%]$ for each question (i.e., variable). This was done to reflect questions possibly left unanswered by respondents. Thereafter, responses were analyzed through univariate categorical data analyses calculating the counts and frequencies against the total number of responses captured for every specific question.

Secondly, every question (i.e., variable) was subjected to bivariate correlations to reveal dependencies against all other variables based on category. This was achieved using a G-test analysis, a robust version of the Chi-Square test. Bivariate analyses produced a matrix revealing the p-values reflecting associations between variables for the entire data set. The p-value threshold for statistical significance in this study was set at $p < 0.05$.

Thirdly, multi-factorial analyses were attempted using Multiple Correspondence analysis and clustering techniques in an effort to reveal the contributing influence towards the dependencies throughout the data set for any one variable. However, these multivariate analyses did not produce computations or graphics with sufficient definition to contribute additional, meaningful statistical information, and were therefore not incorporated in this dissertation.

All data analyses were performed using R version 3.5.1 software (The R Foundation®).

Needs-Assessment Survey Data Set Organization

Responses arising from each question were tabulated as counts (n) and frequencies (%) in dedicated Tables stratified by *Gender*. The Tables demonstrated the complete array of responses for all 31 questions for the entire 300 survey data set. Percent values were rounded to 3 significant figures.

The entire survey data set was tabulated through nine Tables (Table 10-18). The Tables demonstrated survey questions sequentially and descriptively (in italics), with all response options as counts (n) and frequencies (%), and this data was thereafter segregated through stratification by *Gender*.

The p-values generated from the bivariate statistical analyses were organized in five Tables (Table 19-23). These Tables demonstrated matrices of p-values to reveal statistically significant associations between variables as organized in the four categories: Socio-demographic, Healthcare Services, Health Literacy, and Self-efficacy & Perceptions. Significant p-values were highlighted using bold font.

Needs-Assessment Survey Limitations

Listed below are conceivable limitations arising from this survey-based research work given its design and clinical context. As a result of these limitations and their likely impact, potentially unreliable data or conclusions may have been proposed. Where applicable, these limitations were rationalized and addressed in the remarks and interpretations as appearing per survey question (i.e., variable) in the dissertation

Discussion (Chapter 6). The intent was to alert the readership of the likely impact posed by the following possible limitations.

- *Survey Comprehension*: As the needs-assessment survey was voluntary, self-reported, and anonymous, it remains impractical to presume that all respondents comprehended equally the survey questions and/or answer options. As such, any possible incomprehension or confusion on the part of the respondent may have led to problematic statistical computations;
- *Language Barriers*: Nearly 81.5% of the 2.7 million people currently residing in the State of Qatar are multi-national expatriates employed through passport-based work permits and originated from essentially all nationalities and regions of the world. It is therefore plausible that a substantial proportion of these expatriates may not have had English or Arabic as their mother languages, or may not have had proficient command of these languages. Language barriers may have impacted on respondents' comprehension of survey questions and answers as alluded to above;
- *Percent Response Rates*: Percent Response Rate calculations intended to demonstrate the percentage of respondents that answered every question in the 300 distributed surveys. It is plausible that questions left unanswered may have reflected *Survey Comprehension* or *Language Barriers* limitations as argued above. However, the *Percent Response Rates* may also effectively represent the potential extent and thus impact of these limitations. Also,

Percent Response Rates may reflect conservative cultural norms obstructing respondents' willingness to answer questions that may have been perceived as being sensitive;

- *Employment In The Healthcare Sector:* As this survey-based research was conducted in Sidra Medicine given Sidra IRB stipulations, 54.1% of survey respondents indicated being employed in the healthcare sector (Table 18; Question 31). It is plausible that healthcare employees may demonstrate increased levels of CxCa health literacy compared to the general public by virtue of their employment status in a specialized Women's and Children's hospital; therefore, healthcare employees may not be representative of the general public at large in the State of Qatar. Nevertheless, data was interpreted cautiously herein under the presumption that responses from healthcare workers posed a reasonable representation of the general public;
- *Population Representation:* As an extension of the aforementioned limitation, as this survey research was conducted within Sidra Medicine, inclusive of patients and visitors in a specialized hospital, it is equally plausible that survey respondents may not be representative of the general public at large in the State of Qatar;
- *Incidence Of Cervical Cancer In The State Of Qatar:* The incidence of CxCa in the State of Qatar is reported as being 3.2 cases per 100,000 (Chapters 3 & 6). However, without a dedicated registry system to track and measure actual

incidence rates of CxCa it is plausible that the reported incidence rate is under-estimated. Although this potential limitation is neither avoidable nor challenged in the context of this dissertation, remarks and interpretations put forward in Chapter 6 may need to be considered cautiously;

- *Question 6 (Marriage Duration)*: Given the overlap of years in the answer options for Question 6, data arising from this variable may be erroneous as it poses a delimitation on the part of the researchers. The answer options were nonetheless intended to represent time periods, and this limitation may not be adversely impactful pertaining to the remarks, interpretations or conclusions raised relative to the dissertation hypotheses. Nevertheless, this potential limitation is emphasized accordingly in the dissertation Discussion (Chapter 6). Any additional research work conducted to assess the impact of *Marriage Duration* in the clinical setting of Qatar ought to reconstruct the answer options for Question 6 to avoid time period overlap.

Needs-Assessment Survey Tables For Categorical Data And Statistical Dependencies Analyses

Tables (10 through 23) follow:

TABLE 10: Categorical data from the survey data set for Questions 1-4 including Response Rates. Data presented as counts (n) with corresponding frequencies (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|--|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q1 (n=300/300) Response Rate: 100% | <i>Nationality.</i> | | | n=180 | 60.0% | n=120 | 40.0% |
| | <i>Qatari</i> | 53 | 17.6 | 19 | 10.6 | 34 | 28.3 |
| | <i>Middle Eastern</i> | 46 | 15.3 | 22 | 12.2 | 24 | 20.0 |
| | <i>Asian</i> | 80 | 26.7 | 64 | 35.6 | 16 | 13.3 |
| | <i>European</i> | 38 | 12.7 | 26 | 14.4 | 12 | 10.0 |
| | <i>North American</i> | 13 | 4.34 | 10 | 5.56 | 3 | 2.50 |
| | <i>South American</i> | 2 | 0.67 | 1 | 0.56 | 1 | 0.83 |
| | <i>African</i> | 51 | 17.0 | 28 | 15.6 | 23 | 19.2 |
| | <i>Other</i> | 17 | 5.69 | 10 | 5.56 | 7 | 5.83 |
| Q2 (n=293/300) Response Rate: 97.7% | <i>Gender.</i> | N/A | N/A | n=173 | 59.0% | n=120 | 41.0% |
| Q3 (n=292*/300) Response Rate: 97.7% | <i>Age group (years).</i> | | | n=173 | 59.2% | n=120 | 40.8% |
| | <i>Under 20</i> | (1) | - | - | - | (1) | - |
| | <i>20-29</i> | 89 | 30.5 | 51 | 28.5 | 38 | 31.7 |
| | <i>30-39</i> | 117 | 40.0 | 68 | 39.3 | 49 | 40.8 |
| | <i>40-49</i> | 52 | 17.8 | 35 | 20.2 | 17 | 14.2 |
| | <i>50-59</i> | 27 | 9.20 | 14 | 8.09 | 13 | 10.8 |
| *after exclusion of (1) male under 20 years old | <i>Over 60</i> | 7 | 2.50 | 5 | 2.89 | 2 | 1.67 |
| Q4 (n=293/300) Response Rate: 97.7% | <i>Highest education level.</i> | | | n=173 | 59.0% | n=120 | 41.0% |
| | <i>Middle School</i> | 4 | 1.36 | 2 | 1.15 | 2 | 1.67 |
| | <i>High School</i> | 30 | 10.2 | 17 | 9.82 | 13 | 10.8 |
| | <i>University</i> | 243 | 82.9 | 144 | 83.2 | 99 | 82.5 |
| | <i>Other</i> | 16 | 5.54 | 10 | 5.78 | 6 | 5.00 |

TABLE 11: Categorical data from the survey data set for Questions 5-9 including Response Rates. Data presented as counts (n) with corresponding percentages (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|--|--|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q5 (n=293/300) Response Rate: 97.7% | Marital status. | | | n=173 | 59.0% | n=120 | 41.0% |
| | <i>Never married</i> | 92 | 31.4 | 57 | 32.9 | 35 | 29.2 |
| | <i>Married</i> | 186 | 63.5 | 106 | 61.3 | 80 | 66.7 |
| | <i>Divorced</i> | 11 | 3.75 | 8 | 4.62 | 3 | 2.50 |
| | <i>Widowed</i> | 4 | 1.35 | 2 | 1.16 | 2 | 1.67 |
| Q6 (n=265/300) Response Rate: 88.3% | Marriage duration. (Years) | | | n=165 | 62.2% | n=100 | 37.8% |
| | <i>Under 5</i> | 41 | 15.5 | 28 | 17.0 | 13 | 13.0 |
| | <i>5-10</i> | 66 | 25.0 | 30 | 18.2 | 36 | 36.0 |
| | <i>10-20</i> | 54 | 20.3 | 30 | 18.2 | 24 | 24.0 |
| | <i>Over 20</i> | 33 | 12.5 | 22 | 13.3 | 11 | 11.0 |
| | <i>Not applicable</i> | 71 | 26.7 | 55 | 33.3 | 16 | 16.0 |
| Q7 (n=287/300) Response Rate: 95.7% | Employment status. | | | n=169 | 58.9% | n=118 | 41.1% |
| | <i>Employed</i> | 212 | 73.9 | 132 | 78.1 | 80 | 67.8 |
| | <i>Unemployed</i> | 63 | 21.9 | 30 | 17.7 | 33 | 27.9 |
| | <i>Other</i> | 12 | 4.20 | 7 | 4.14 | 5 | 4.24 |
| Q8 (n=288/300) Response Rate: 96.0% | You have health insurance coverage? | | | n=170 | 59.0% | n=118 | 41.0% |
| | <i>Yes</i> | 229 | 79.5 | 142 | 83.5 | 87 | 73.7 |
| | <i>No</i> | 59 | 20.5 | 28 | 16.5 | 31 | 26.3 |
| Q9 (n=286/300) Response Rate: 95.3% | You had a Pap test before? | | | n=168 | 58.7% | n=118 | 41.3% |
| | <i>Yes</i> | 105 | 36.7 | 82 | 48.8 | 23 | 19.5 |
| | <i>No</i> | 149 | 52.0 | 79 | 47.0 | 70 | 59.3 |
| | <i>Not applicable</i> | 32 | 11.3 | 7 | 4.17 | 25 | 21.2 |

TABLE 12: Categorical data from the survey data set for Questions 10-13 including Response Rates. Data presented as counts (n) with corresponding percentages (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|--|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q10 (n=104/300) Response Rate: 34.7% | <i>If you had a Pap test before, when was it performed?</i> | | | n=82 | 78.8% | n=22 | 21.2% |
| | 1-3 years ago | 74 | 71.1 | 59 | 71.9 | 15 | 68.2 |
| | 4-6 years ago | 21 | 20.2 | 17 | 20.7 | 4 | 18.2 |
| | Over 6 years ago | 9 | 8.70 | 6 | 7.32 | 3 | 13.6 |
| Q11 (n=286/300) Response Rate: 95.3% | <i>Did you, or any member of your family have cervical cancer before?</i> | | | n=168 | 58.7% | n=118 | 41.3% |
| | Yes | 10 | 3.49 | 8 | 4.76 | 2 | 1.69 |
| | No | 266 | 93.0 | 153 | 91.1 | 113 | 95.7 |
| | Don't know | 10 | 3.51 | 7 | 4.17 | 3 | 2.54 |
| Q12 (n=288/300) Response Rate: 96.0% | <i>Cervical cancer may be preventable.</i> | | | n=170 | 59.0% | n=118 | 41.0% |
| | Yes | 242 | 84.0 | 142 | 83.5 | 100 | 84.7 |
| | No | 3 | 1.00 | 3 | 1.76 | 0 | 0.00 |
| | Don't know | 43 | 15.0 | 25 | 14.7 | 18 | 15.3 |
| Q13 (n=288/300) Response Rate: 96.0% | <i>You are aware of the Pap test smear cytologic method.</i> | | | n=170 | 59.0% | n=118 | 41.0% |
| | Yes | 191 | 66.3 | 123 | 72.4 | 68 | 57.6 |
| | No | 97 | 33.7 | 47 | 27.6 | 50 | 42.4 |

TABLE 13: Categorical data from the survey data set for Questions 14-16 including Response Rates. Data presented as counts (n) with corresponding percentages (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|---|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q14 (n=280/300) Response Rate: 93.3% | <i>Where did you hear of the Pap test smear cytologic method for the first time?</i> | | | n=171 | 61.0% | n=109 | 39.0% |
| | <i>Relatives, friends</i> | 46 | 16.4 | 25 | 14.6 | 21 | 19.2 |
| | <i>Gynecologist</i> | 72 | 25.7 | 46 | 26.9 | 26 | 23.9 |
| | <i>Mass media (newspaper, internet, television)</i> | 41 | 14.6 | 27 | 15.8 | 14 | 12.8 |
| | <i>Family physician</i> | 16 | 5.71 | 14 | 8.18 | 2 | 1.83 |
| | <i>Nurse</i> | 5 | 1.89 | 4 | 2.34 | 1 | 0.92 |
| | <i>Other</i> | 52 | 18.6 | 26 | 15.2 | 26 | 23.9 |
| | <i>Not applicable</i> | 48 | 17.1 | 29 | 17.0 | 19 | 17.4 |
| Q15 (n=290/300) Response Rate: 96.7% | <i>You have knowledge of cervical cancer.</i> | | | n=173 | 59.7% | n=117 | 40.3% |
| | <i>Yes</i> | 203 | 70.0 | 135 | 78.0 | 68 | 58.1 |
| | <i>No</i> | 87 | 30.0 | 38 | 22.0 | 49 | 41.9 |
| Q16 (n=290/300) Response Rate: 96.7% | <i>Early detection of cervical cancer is important for effective treatment.</i> | | | n=173 | 59.7% | n=117 | 40.3% |
| | <i>Yes</i> | 271 | 93.4 | 159 | 91.9 | 112 | 95.7 |
| | <i>No</i> | 1 | 0.40 | 1 | 0.57 | 0 | 0.00 |
| | <i>Don't know</i> | 18 | 6.20 | 13 | 7.51 | 5 | 4.27 |

TABLE 14: Categorical data from the survey data set for Questions 17-19 including Response Rates. Data presented as counts (n) with corresponding percentages (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|--|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q17 (n=286/300) Response Rate: 95.3% | <i>Regular Pap tests may protect you from cervical cancer.</i> | | | n=169 | 59.0% | n=117 | 41.0% |
| | Yes | 243 | 84.9 | 146 | 86.4 | 97 | 82.9 |
| | No | 8 | 2.79 | 6 | 3.55 | 2 | 1.71 |
| | Don't know | 35 | 12.3 | 17 | 10.1 | 18 | 15.4 |
| Q18 (n=290/300) Response Rate: 96.7% | <i>Cervical cancer may be curable.</i> | | | n=172 | 59.3% | n=118 | 40.7% |
| | Yes | 190 | 65.5 | 116 | 67.4 | 74 | 62.7 |
| | No | 8 | 2.70 | 6 | 3.48 | 2 | 1.69 |
| | Don't know | 92 | 31.8 | 50 | 29.1 | 42 | 35.6 |
| Q19 (n=287/300) Response Rate: 95.7% | <i>Vaccination for the Human Papilloma Virus protects against cervical cancer and other HPV-associated cancers.</i> | | | n=170 | 59.2% | n=117 | 40.8% |
| | Yes | 180 | 62.7 | 123 | 72.3 | 57 | 48.7 |
| | No | 6 | 2.10 | 2 | 1.17 | 4 | 3.41 |
| | Don't know | 101 | 35.2 | 45 | 26.5 | 56 | 47.9 |

TABLE 15: Categorical data from the survey data set for Questions 20-22 including Response Rates. Data presented as counts (n) with corresponding percentages (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|--|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q20 (n=281/300) Response Rate: 93.7% | <i>Menopausal women need a Pap test.</i> | | | n=169 | 60.1% | n=112 | 39.9% |
| | Yes | 194 | 69.0 | 124 | 73.3 | 70 | 62.5 |
| | No | 8 | 2.80 | 6 | 3.55 | 2 | 1.78 |
| | Don't know | 79 | 28.2 | 39 | 23.1 | 40 | 35.7 |
| Q21 (n=286/300) Response Rate: 95.3% | <i>More information is needed to improve your knowledge of cervical cancer.</i> | | | n=169 | 59.1% | n=117 | 40.9% |
| | Strongly agree | 147 | 51.4 | 89 | 52.7 | 58 | 49.6 |
| | Agree | 117 | 40.9 | 65 | 38.5 | 52 | 44.4 |
| | Undecided | 12 | 4.21 | 10 | 5.92 | 2 | 1.71 |
| | Disagree | 10 | 3.49 | 5 | 2.95 | 5 | 4.27 |
| | Strongly disagree | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Q22 (n=286/300) Response Rate: 95.3% | <i>Regular Pap tests are a good health practice.</i> | | | n=169 | 59.1% | n=117 | 40.9% |
| | Strongly agree | 196 | 68.5 | 118 | 69.8 | 78 | 66.7 |
| | Agree | 72 | 25.1 | 41 | 24.2 | 31 | 26.5 |
| | Undecided | 15 | 5.24 | 7 | 4.14 | 8 | 6.83 |
| | Disagree | 2 | 0.70 | 2 | 1.18 | 0 | 0.00 |
| | Strongly disagree | 1 | 0.46 | 1 | 0.59 | 0 | 0.00 |

TABLE 16: Categorical data from the survey data set for Questions 23-25 including Response Rates. Data presented as counts (n) with corresponding percentages (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|---|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q23 (n=284/300) Response Rate: 94.7% | <i>Getting a Pap test performed is too difficult.</i> | | | n=168 | 59.2% | n=116 | 40.8% |
| | <i>Strongly agree</i> | 19 | 6.70 | 11 | 6.55 | 8 | 6.89 |
| | <i>Agree</i> | 36 | 12.7 | 27 | 16.1 | 9 | 7.75 |
| | <i>Undecided</i> | 85 | 29.9 | 50 | 29.7 | 35 | 30.2 |
| | <i>Disagree</i> | 116 | 40.8 | 64 | 38.1 | 52 | 44.8 |
| | <i>Strongly disagree</i> | 28 | 9.90 | 16 | 9.52 | 12 | 10.3 |
| Q24 (n=285/300) Response Rate: 95.0% | <i>You would recommend a Pap test to your family, friends, and colleagues.</i> | | | n=169 | 59.3% | n=116 | 40.7% |
| | <i>Strongly agree</i> | 177 | 62.1 | 109 | 64.5 | 68 | 58.6 |
| | <i>Agree</i> | 89 | 31.6 | 50 | 29.6 | 39 | 33.6 |
| | <i>Undecided</i> | 17 | 5.96 | 9 | 5.32 | 8 | 6.89 |
| | <i>Disagree</i> | 1 | 0.35 | 0 | 0.00 | 1 | 0.86 |
| | <i>Strongly disagree</i> | 1 | 0.35 | 1 | 0.59 | 0 | 0.00 |
| Q25 (n=288/300) Response Rate: 96.0% | <i>Getting a Pap test is a valued investment for good healthcare.</i> | | | n=169 | 58.7% | n=119 | 41.3% |
| | <i>Strongly agree</i> | 177 | 61.5 | 104 | 61.5 | 73 | 61.3 |
| | <i>Agree</i> | 95 | 33.0 | 57 | 33.7 | 38 | 31.9 |
| | <i>Undecided</i> | 13 | 4.51 | 7 | 4.14 | 6 | 5.04 |
| | <i>Disagree</i> | 2 | 0.69 | 1 | 0.59 | 1 | 0.84 |
| | <i>Strongly disagree</i> | 1 | 0.30 | 0 | 0.00 | 1 | 0.84 |

TABLE 17: Categorical data from the survey data set for Questions 26-28 including Response Rates. Data presented as counts (n) with corresponding percentages (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|--|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q26 (n=287/300) Response Rate: 95.7% | <i>You would support a Pap test screening program for cervical cancer.</i> | | | n=168 | 58.5% | n=119 | 41.5% |
| | <i>Strongly agree</i> | 196 | 68.3 | 116 | 69.0 | 80 | 67.2 |
| | <i>Agree</i> | 81 | 28.2 | 45 | 26.8 | 36 | 30.3 |
| | <i>Undecided</i> | 10 | 3.50 | 7 | 4.17 | 3 | 2.52 |
| | <i>Disagree</i> | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| | <i>Strongly disagree</i> | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Q27 (n=286/300) Response Rate: 95.3% | <i>A formal Pap test screening program for cervical cancer should be established for all women in the State of Qatar.</i> | | | n=168 | 58.7% | n=118 | 41.3% |
| | <i>Strongly agree</i> | 193 | 67.4 | 116 | 69.0 | 77 | 65.3 |
| | <i>Agree</i> | 78 | 27.2 | 46 | 27.4 | 32 | 27.1 |
| | <i>Undecided</i> | 14 | 5.40 | 6 | 3.60 | 8 | 6.77 |
| | <i>Disagree</i> | 1 | 0.35 | 0 | 0.00 | 1 | 0.85 |
| | <i>Strongly disagree</i> | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| Q28 (n=282/300) Response Rate: 94.0% | <i>You know where to go to get a Pap test performed.</i> | | | n=165 | 58.5% | n=117 | 41.5% |
| | <i>Strongly agree</i> | 88 | 31.2 | 59 | 35.8 | 29 | 24.8 |
| | <i>Agree</i> | 84 | 29.8 | 47 | 28.5 | 37 | 31.6 |
| | <i>Undecided</i> | 53 | 18.8 | 27 | 16.4 | 26 | 22.2 |
| | <i>Disagree</i> | 34 | 12.0 | 21 | 12.7 | 13 | 11.1 |
| | <i>Strongly disagree</i> | 23 | 8.20 | 11 | 6.67 | 12 | 10.3 |

TABLE 18: Categorical data from the survey data set for Questions 29-31 including Response Rates. Data presented as counts (n) with corresponding frequencies (%) stratified by *Gender*.

| Question | Description | Count | Frequency | Women | | Men | |
|---|---|-------|-----------|-------|-----------|-------|-----------|
| | | | | Count | Frequency | Count | Frequency |
| Q29 (n=284/300) Response Rate: 94.7% | <i>A Pap test has no value for you.</i> | | | n=167 | 58.8% | n=117 | 41.2% |
| | <i>Strongly agree</i> | 6 | 2.10 | 2 | 1.19 | 4 | 3.42 |
| | <i>Agree</i> | 12 | 4.22 | 5 | 2.99 | 7 | 5.98 |
| | <i>Undecided</i> | 25 | 8.80 | 11 | 6.58 | 14 | 11.9 |
| | <i>Disagree</i> | 103 | 36.3 | 58 | 34.7 | 45 | 38.5 |
| | <i>Strongly disagree</i> | 138 | 48.5 | 91 | 54.5 | 47 | 40.2 |
| Q30 (n=283/300) Response Rate: 94.3% | <i>If a self-test for cervical cancer was available you would prefer it?</i> | | | n=168 | 59.4% | n=115 | 40.6% |
| | <i>Strongly agree</i> | 123 | 43.4 | 73 | 43.5 | 50 | 43.5 |
| | <i>Agree</i> | 88 | 31.0 | 49 | 29.2 | 39 | 33.9 |
| | <i>Undecided</i> | 46 | 16.2 | 29 | 17.3 | 17 | 14.8 |
| | <i>Disagree</i> | 23 | 8.10 | 15 | 8.92 | 8 | 6.96 |
| | <i>Strongly disagree</i> | 3 | 1.30 | 2 | 1.19 | 1 | 0.87 |
| Q31 (n=279/300) Response Rate: 93.0% | <i>If employed, are you employed in the healthcare sector?</i> | | | n=161 | 57.7% | n=118 | 42.3% |
| | <i>Yes</i> | 151 | 54.1 | 93 | 57.7 | 58 | 49.2 |
| | <i>No</i> | 128 | 45.9 | 68 | 42.3 | 60 | 50.8 |

TABLE 19: Bivariate analysis matrix revealing dependencies expressed through p-values between Socio-demographic variables (Q1-8, 31) in Category 1, and Health Services variables (Q9-11) in Category 2 (significant p-values appear in bold font).

| | Category 1: Socio-demographic Variables | | | | | | | | |
|---|---|--------------------|--------------------|--------------------------------|-----------------------|--------------------------|--------------------------|----------------------------------|--------------------------------------|
| Category 2: | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q31 |
| Healthcare Services Variables | <i>Nationality</i> | <i>Gender</i> | <i>Age group</i> | <i>Highest education level</i> | <i>Marital status</i> | <i>Marriage duration</i> | <i>Employment status</i> | <i>Health insurance coverage</i> | <i>Employed in healthcare sector</i> |
| Q9 <i>Had a Pap test before</i> | 0.00000012 | 0.000000006 | 0.000000008 | 0.03798 | 0.00000004 | 0.0000032 | 0.000018 | 0.9377 | 0.0003357 |
| Q10 <i>If had a Pap test before, when was it performed</i> | 0.5665 | 0.6679 | 0.8776 | 0.08175 | 0.3181 | 0.03648 | 0.3497 | 0.1781 | 0.4238 |
| Q11 <i>Family history of CxCa</i> | 0.5512 | 0.2526 | 0.8759 | 0.4913 | 0.593 | 0.4116 | 0.1158 | 0.08225 | 0.5599 |

TABLE 20: Bivariate analysis matrix revealing dependencies expressed through p-values between Socio-demographic variables (Q1-8, 31) in Category 1, and Health Literacy variables (Q12-16) in Category 3 (significant p-values appear in bold font).

| | Category 1: Socio-demographic Variables | | | | | | | | |
|--|---|-----------------|------------------|--------------------------------|-----------------------|--------------------------|--------------------------|----------------------------------|--------------------------------------|
| Category 3: | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q31 |
| Health Literacy Variables | <i>Nationality</i> | <i>Gender</i> | <i>Age group</i> | <i>Highest education level</i> | <i>Marital status</i> | <i>Marriage duration</i> | <i>Employment status</i> | <i>Health insurance coverage</i> | <i>Employed in healthcare sector</i> |
| Q12 <i>CxCa may be preventable</i> | 0.6504 | 0.203 | 0.5918 | 0.8562 | 0.1113 | 0.3495 | 0.09697 | 0.4663 | 0.0001159 |
| Q13 <i>You are aware of the Pap test cytologic method</i> | 0.03766 | 0.009553 | 0.1407 | 0.06513 | 0.9244 | 0.1719 | 0.1989 | 0.004242 | 0.0000065 |
| Q14 <i>Where did you hear of the Pap test method before</i> | 0.1212 | 0.1059 | 0.04087 | 0.1308 | 0.002733 | 0.02039 | 0.1255 | 0.4708 | 0.0005167 |
| Q15 <i>You have knowledge of CxCa</i> | 0.000022 | 0.000304 | 0.1206 | 0.3161 | 0.8381 | 0.7295 | 0.1249 | 0.03714 | 0.0003576 |
| Q16 <i>Early detection of CxCa is important for effective treatment</i> | 0.7644 | 0.3042 | 0.517 | 0.3228 | 0.4728 | 0.5452 | 0.8334 | 0.1369 | 0.0004853 |

TABLE 21: Bivariate analysis matrix revealing dependencies expressed through p-values between Socio-demographic variables (Q1-8, 31) in Category 1, and Health Literacy variables (Q17-20) in Category 3 (significant p-values appear in bold font).

| | Category 1: Socio-demographic Variables | | | | | | | | |
|--|---|------------------|------------------|--------------------------------|-----------------------|--------------------------|--------------------------|----------------------------------|--------------------------------------|
| Category 3: | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q31 |
| Health Literacy Variables | <i>Nationality</i> | <i>Gender</i> | <i>Age group</i> | <i>Highest education level</i> | <i>Marital status</i> | <i>Marriage duration</i> | <i>Employment status</i> | <i>Health insurance coverage</i> | <i>Employed in healthcare sector</i> |
| Q17 <i>Regular Pap tests may protect you from CxCa</i> | 0.5621 | 0.2776 | 0.3541 | 0.6093 | 0.4012 | 0.3052 | 0.07667 | 0.08415 | 0.02428 |
| Q18 <i>CxCa may be curable</i> | 0.004244 | 0.3612 | 0.8374 | 0.9297 | 0.3412 | 0.3456 | 0.01827 | 0.1408 | 0.0000623 |
| Q19 <i>Vaccination for HPV protects against CxCa and other HPV-associated cancers</i> | 0.0000026 | 0.0002238 | 0.3403 | 0.6515 | 0.2085 | 0.0273 | 0.1814 | 0.4581 | 0.003599 |
| Q20 <i>Menopausal women need a Pap test</i> | 0.01045 | 0.05802 | 0.8842 | 0.2837 | 0.8848 | 0.09809 | 0.07443 | 0.4436 | 0.02444 |

TABLE 22: Bivariate analysis matrix revealing dependencies expressed through p-values between Socio-demographic variables (Q1-8, 31) in Category 1, and Self-efficacy & Perceptions variables (Q21-25) in Category 4 (significant p-values appear in bold font).

| | Category 1: Socio-demographic Variables | | | | | | | | |
|---|---|---------------|------------------|--------------------------------|-----------------------|--------------------------|--------------------------|----------------------------------|--------------------------------------|
| Category 4: | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q31 |
| Self-efficacy & Perceptions Variables | <i>Nationality</i> | <i>Gender</i> | <i>Age group</i> | <i>Highest education level</i> | <i>Marital status</i> | <i>Marriage duration</i> | <i>Employment status</i> | <i>Health insurance coverage</i> | <i>Employed in healthcare sector</i> |
| Q21 <i>Information is needed to improve your knowledge of CxCa</i> | 0.09256 | 0.2262 | 0.04504 | 0.5698 | 0.01028 | 0.02365 | 0.2134 | 0.8437 | 0.2293 |
| Q22 <i>Regular Pap tests are good for health practice</i> | 0.4393 | 0.3629 | 0.1502 | 0.4466 | 0.5316 | 0.8438 | 0.1016 | 0.342 | 0.238 |
| Q23 <i>Getting a Pap test performed is too difficult</i> | 0.5385 | 0.3088 | 0.1085 | 0.2865 | 0.1268 | 0.04028 | 0.7795 | 0.7002 | 0.8119 |
| Q24 <i>You would recommend a Pap test to family, friends</i> | 0.4181 | 0.4246 | 0.07992 | 0.7831 | 0.6696 | 0.514 | 0.04067 | 0.1035 | 0.1419 |
| Q25 <i>Getting a Pap test done is a valued investment</i> | 0.6466 | 0.7317 | 0.4497 | 0.6395 | 0.6208 | 0.7334 | 0.1147 | 0.3275 | 0.7594 |

TABLE 23: Bivariate analysis matrix revealing dependencies expressed through p-values between Socio-demographic variables (Q1-8, 31) in Category 1, and Self-efficacy & Perceptions variables (Q26-30) in Category 4 (significant p-values appear in bold font).

| | Category 1: Socio-demographic Variables | | | | | | | | |
|--|---|---------------|------------------|--------------------------------|-----------------------|--------------------------|--------------------------|----------------------------------|--------------------------------------|
| Category 4: | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q31 |
| Self-efficacy & Perceptions Variables | <i>Nationality</i> | <i>Gender</i> | <i>Age group</i> | <i>Highest education level</i> | <i>Marital status</i> | <i>Marriage duration</i> | <i>Employment status</i> | <i>Health insurance coverage</i> | <i>Employed in healthcare sector</i> |
| Q26 <i>You would support a Pap test screening program for CxCa</i> | 0.09911 | 0.6406 | 0.1715 | 0.05745 | 0.331 | 0.5249 | 0.09047 | 0.6946 | 0.6357 |
| Q27 <i>A formal screening program should be established, all women in Qatar</i> | 0.795 | 0.3409 | 0.6989 | 0.8102 | 0.6961 | 0.8417 | 0.2855 | 0.8942 | 0.4663 |
| Q28 <i>You know where to go to get a Pap test performed</i> | 0.003118 | 0.2504 | 0.2983 | 0.1304 | 0.1847 | 0.2102 | 0.6531 | 0.6023 | 0.2191 |
| Q29 <i>A Pap test has no value for you</i> | 0.06362 | 0.07646 | 0.1012 | 0.2248 | 0.3868 | 0.01878 | 0.4397 | 0.9227 | 0.343 |
| Q30 <i>If a self-test for CxCa was available you would prefer it</i> | 0.3133 | 0.886 | 0.3237 | 0.699 | 0.1174 | 0.2863 | 0.09273 | 0.4196 | 0.2823 |

Needs-Assessment Survey Data Set Representation

The entire survey data set was represented through 16 Figures. Each Figure included 2 bar plots separated by a line for definition where possible.

Figure 1 represented responses from survey questions 1 and 2 as illustrated in dedicated univariate bar plots. *Gender* was utilized as the stratification determinant thereafter for all questions (i.e., Questions 3-31).

Responses from survey questions 3 through 31 were represented in dedicated composite bar plots with data stratification between women and men based on counts, and contrasted by grey-scale colors (Figures 2-16).

Needs-Assessment Survey Data Set Figures

Figures (1 through 16) follow:

FIGURE 1: Two bar plots representing Socio-demographic survey data captured for Questions 1 and 2 reflecting the breakdown of response counts; all respondents, for *Nationality* and *Gender*.

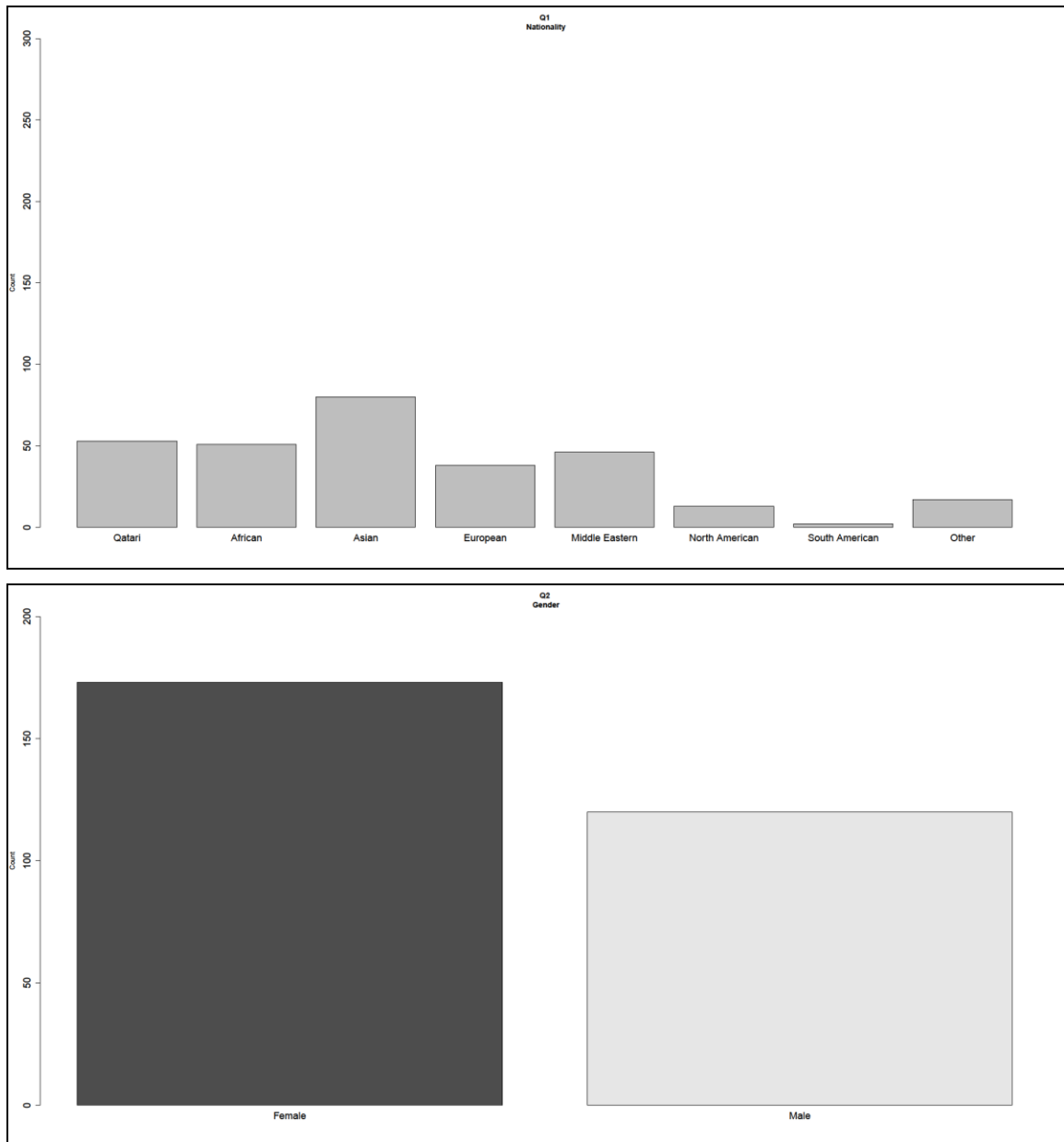


FIGURE 2: Composite figure of 2 bar plots representing Socio-demographic survey data captured for Questions 1 and 3 reflecting the breakdown of response counts; all respondents, for *Nationality* and *Age Group* respectively stratified by *Gender*.

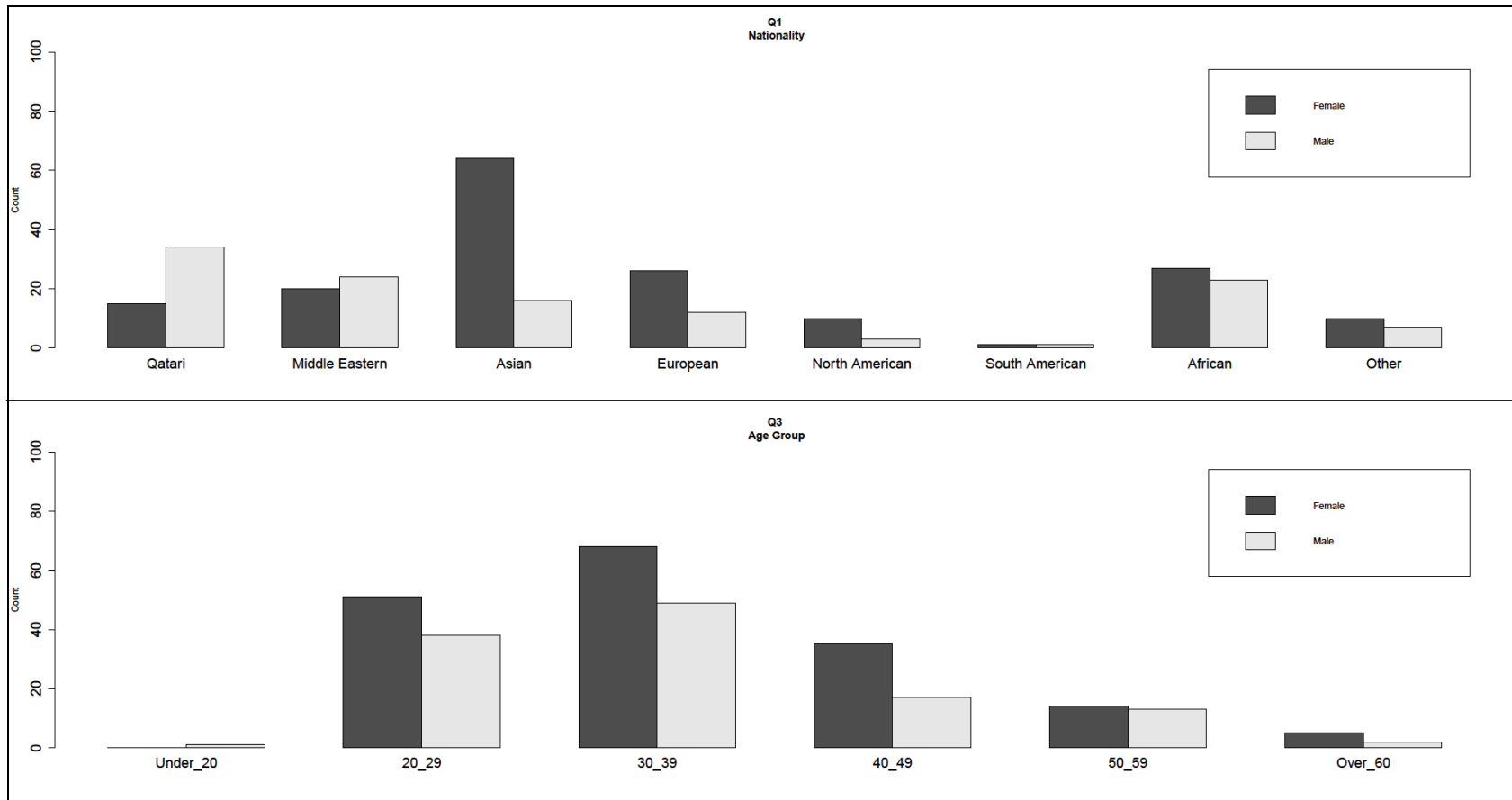


FIGURE 3: Composite figure of 2 bar plots representing Socio-demographic survey data captured for Questions 4 and 5 reflecting the breakdown of response counts; all respondents, for *Highest Education Level* and *Marital Status* respectively stratified by *Gender*.

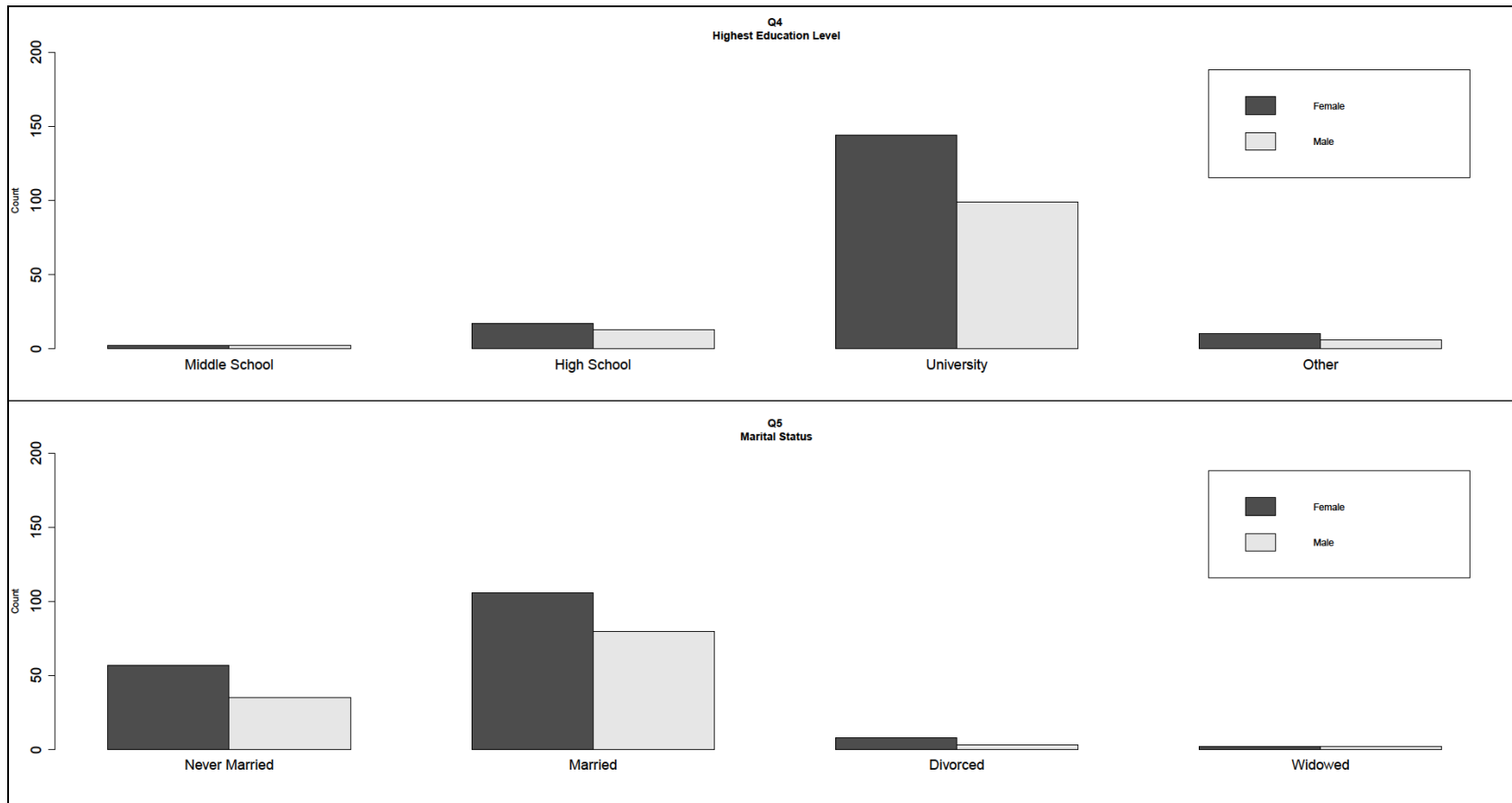


FIGURE 4: Composite figure of 2 bar plots representing Socio-demographic survey data captured for Questions 6 and 7 reflecting the breakdown of response counts; all respondents, for *Marriage Duration* and *Employment Status* respectively stratified by *Gender*.

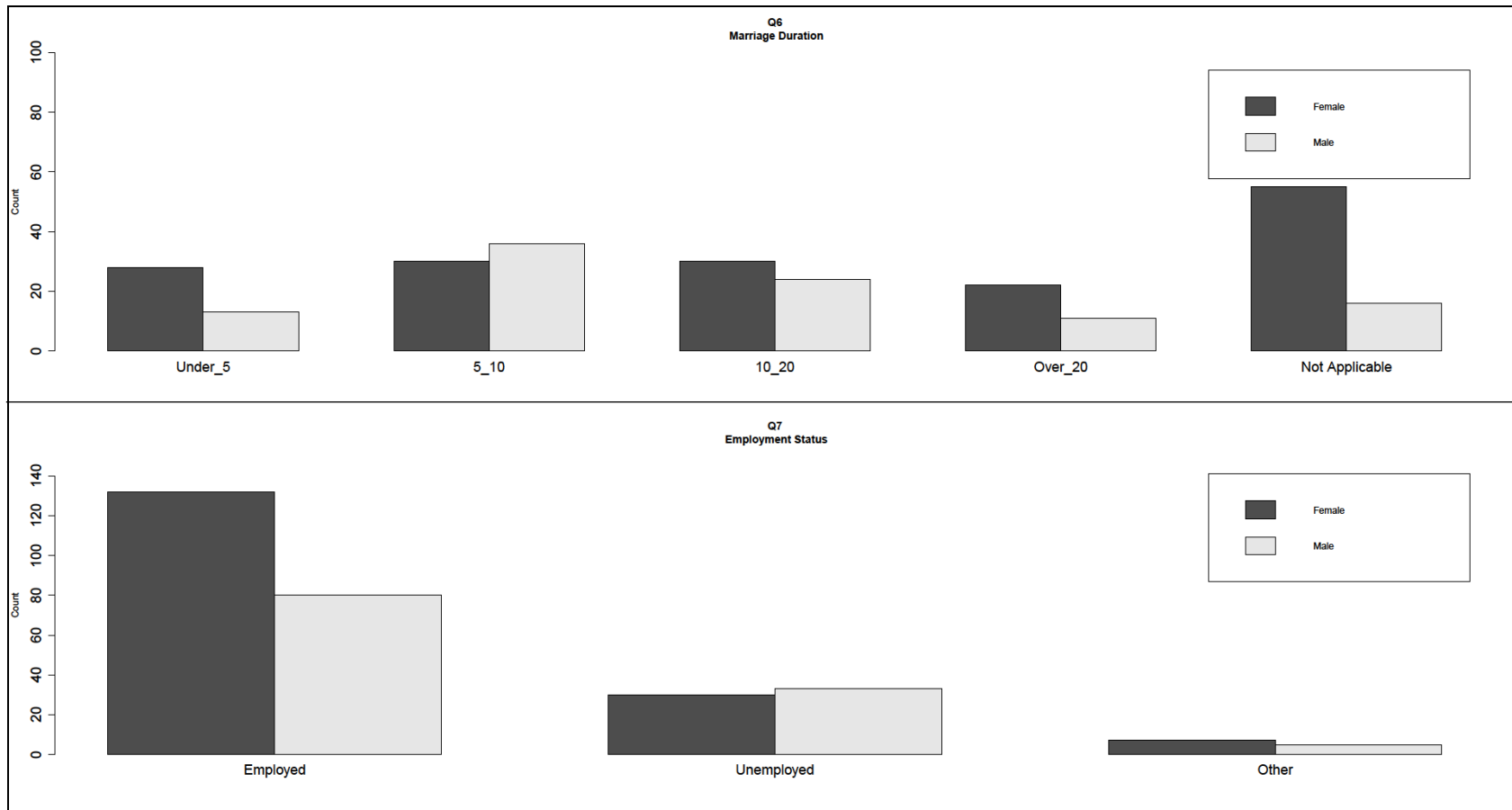


FIGURE 5: Composite figure of 2 bar plots representing Socio-demographic and Healthcare Services survey data captured for Questions 8 and 9 reflecting the breakdown of response counts; all respondents, for *Health Insurance Coverage* and *Pap test Uptake* respectively stratified by *Gender*.

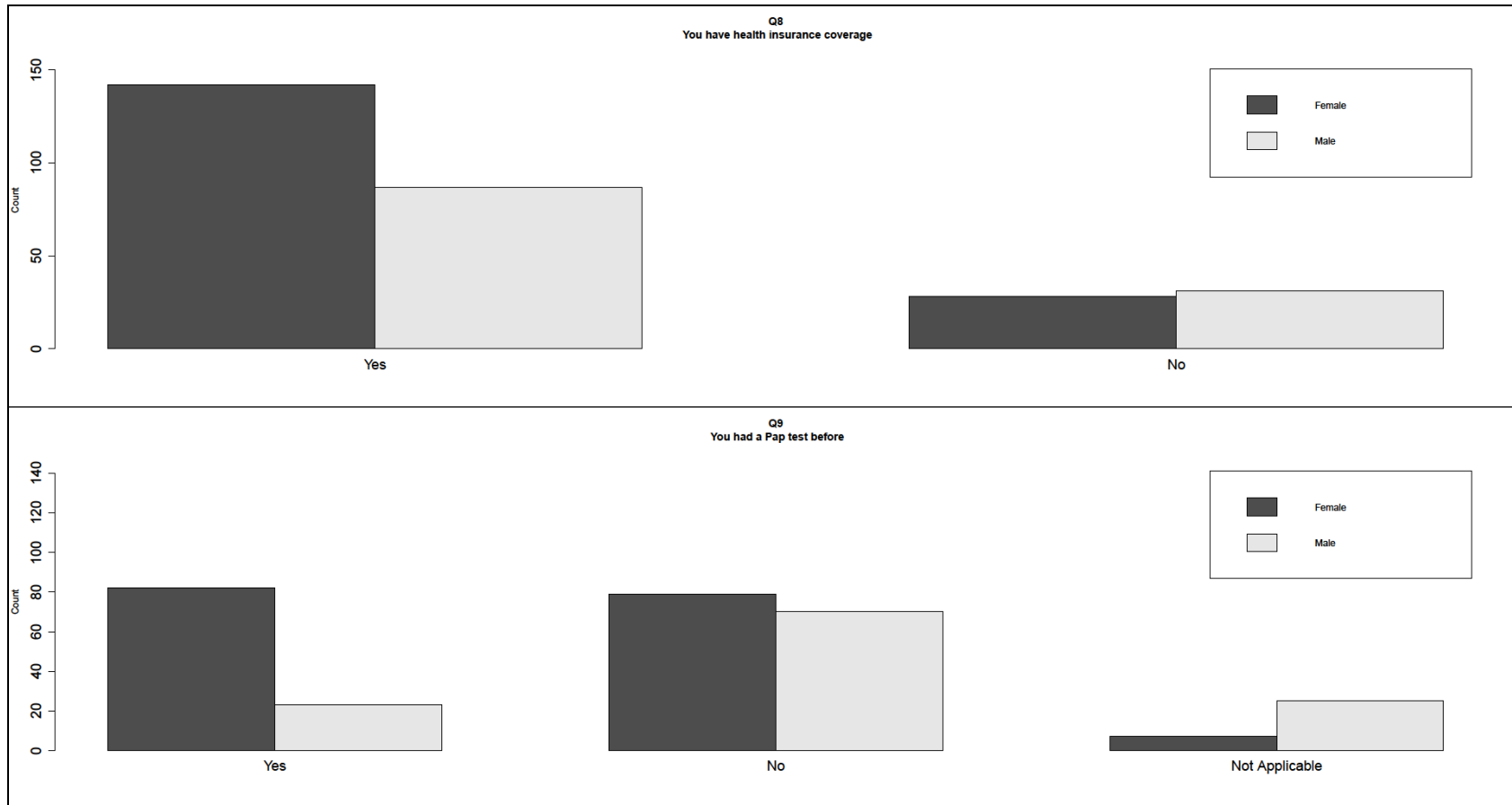


FIGURE 6: Composite figure of 2 bar plots representing Healthcare Services survey data captured for Questions 10 and 11 reflecting the breakdown of response counts; all respondents, for *Preceding Pap test* and *Family history of Cervical Cancer* respectively stratified by *Gender*.

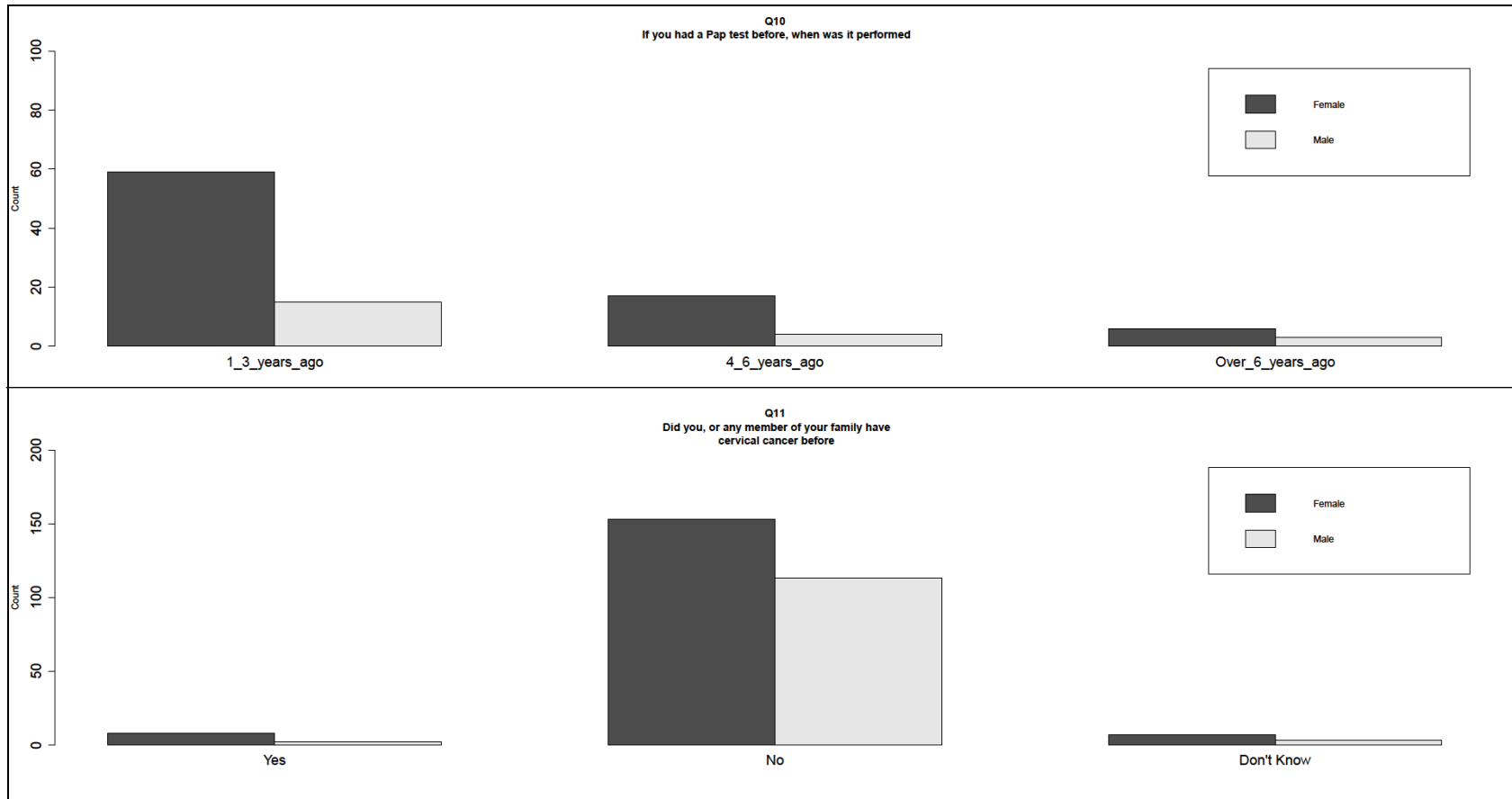


FIGURE 7: Composite figure of 2 bar plots representing Health Literacy survey data captured for Questions 12 and 13 reflecting the breakdown of response counts; all respondents, for *Cervical cancer preventability* and *Pap test smear awareness* respectively stratified by *Gender*.

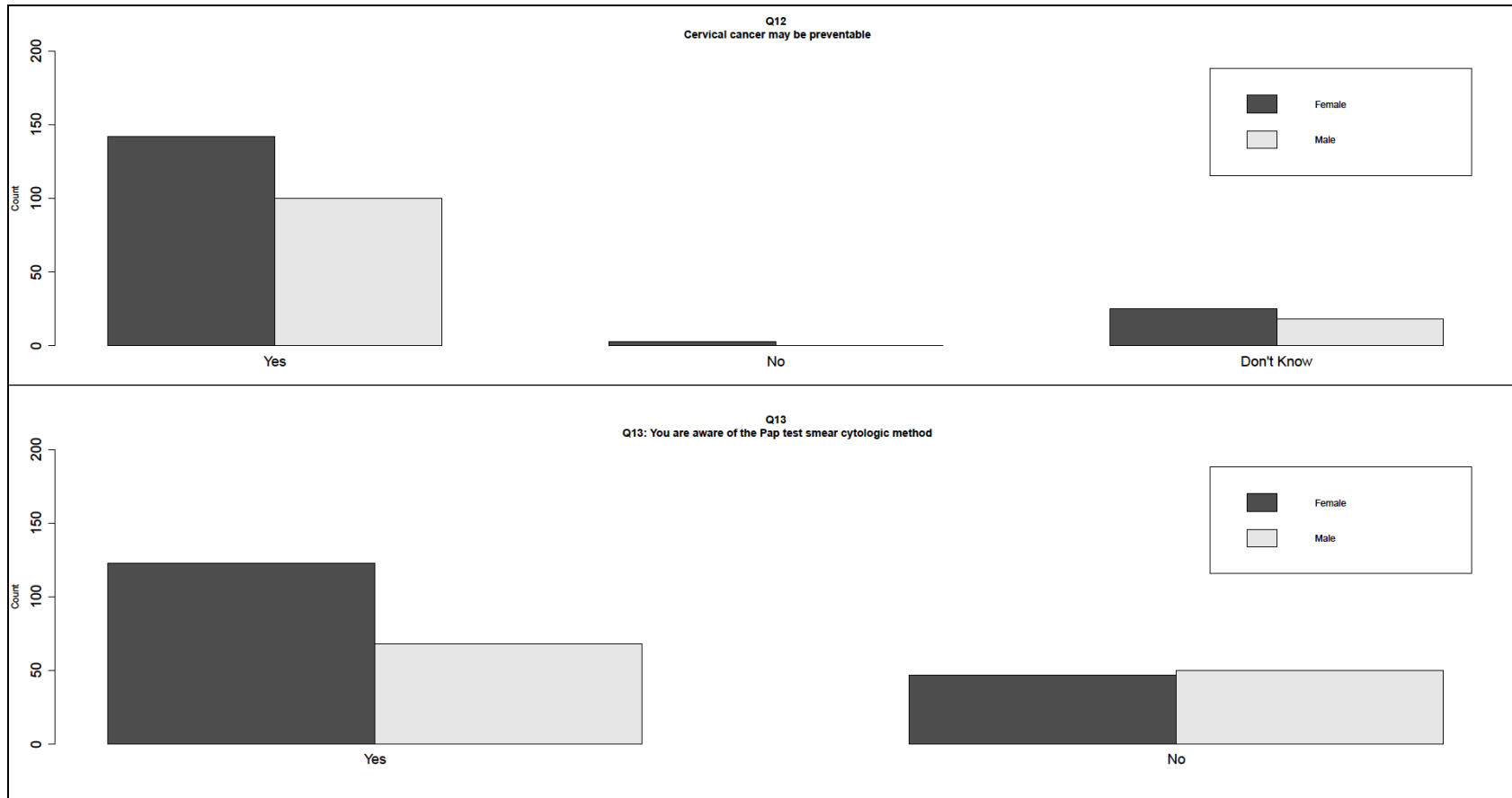


FIGURE 8: Composite figure of 2 bar plots representing Health Literacy survey data captured for Questions 14 and 15 reflecting the breakdown of response counts; all respondents, for *Initial Pap test knowledge* and *Knowledge of cervical cancer* respectively stratified by *Gender*.

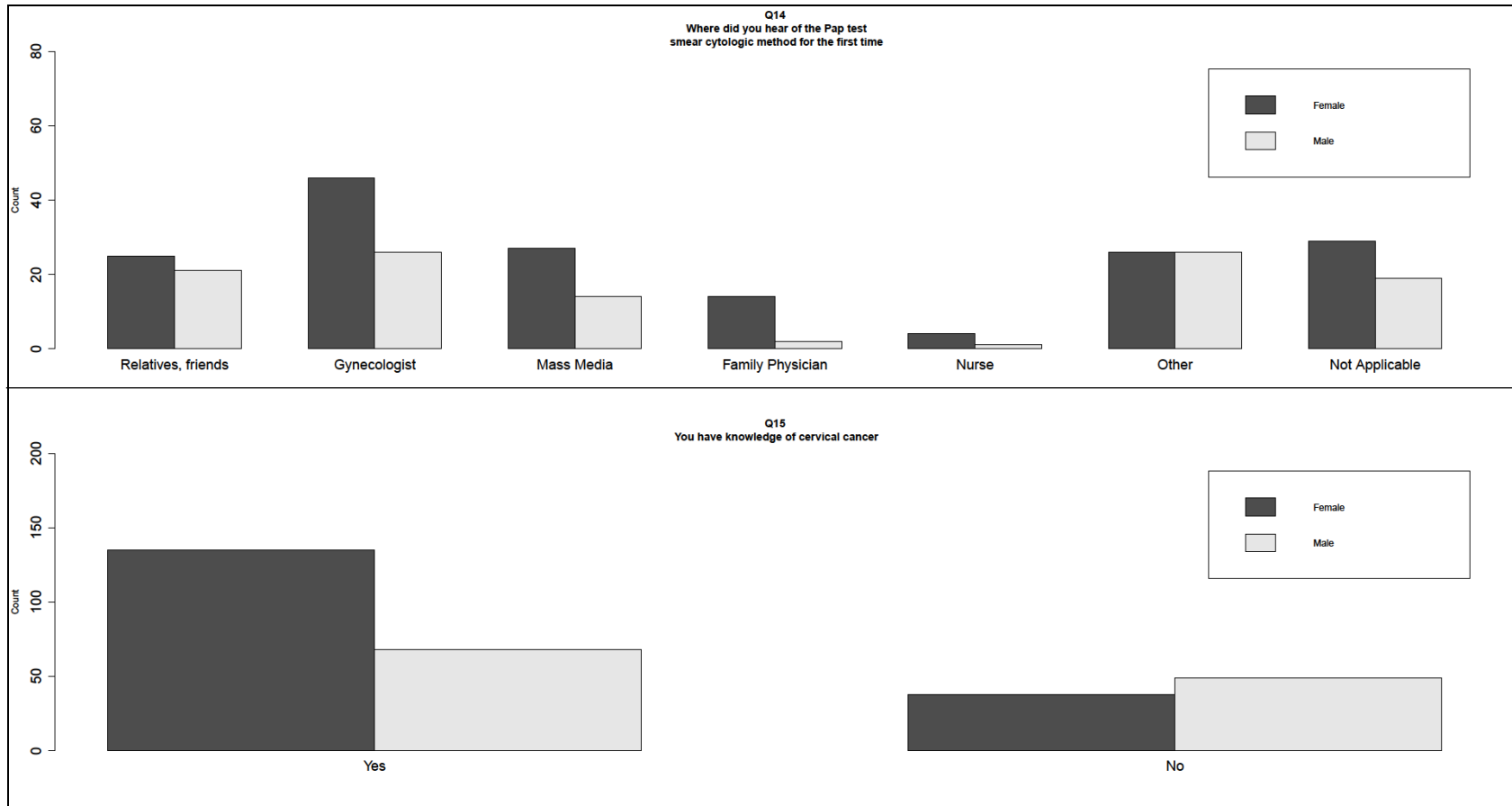


FIGURE 9: Composite figure of 2 bar plots representing Health Literacy survey data captured for Questions 16 and 17 reflecting the breakdown of response counts; all respondents, for perceived *Importance of early cervical cancer detection* and *Protection through regular Pap tests* respectively stratified by *Gender*.

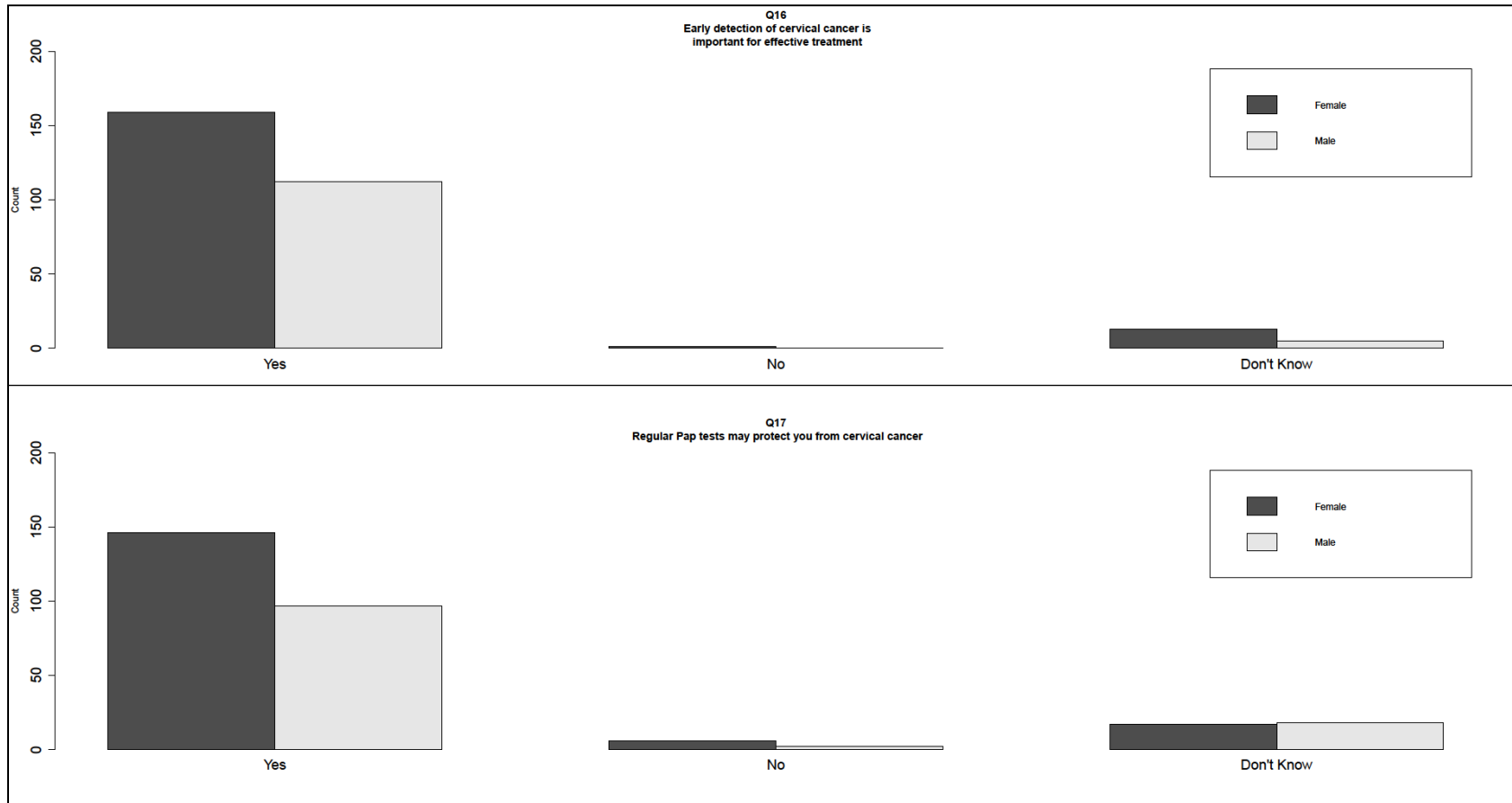


FIGURE 10: Composite figure of 2 bar plots representing Health Literacy survey data captured for Questions 18 and 19 reflecting the breakdown of response counts; all respondents, for perceived *Cervical cancer curability* and *HPV vaccination protection* respectively stratified by *Gender*.

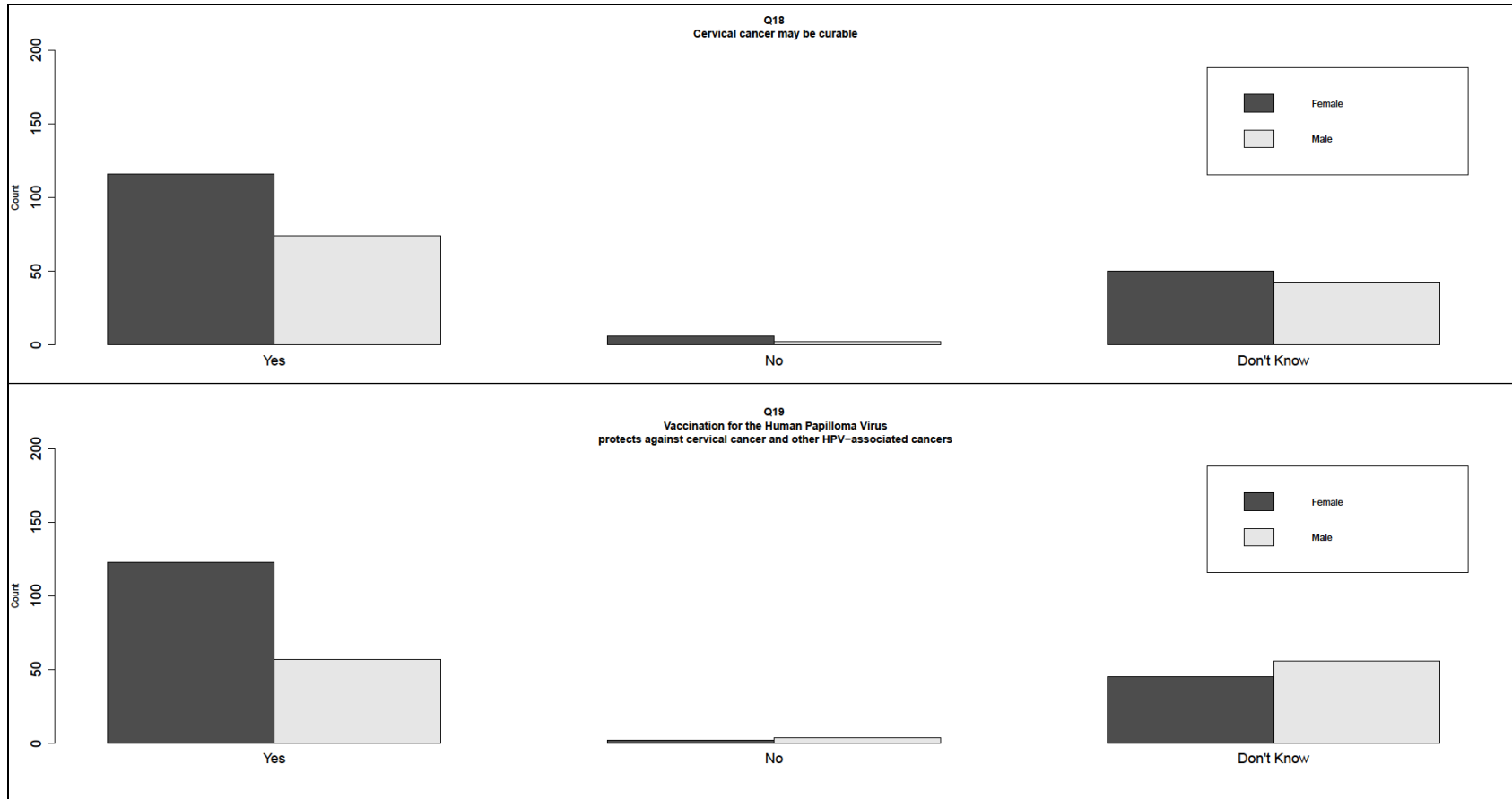


FIGURE 11: Composite figure of 2 bar plots representing Health Literacy and Self-efficacy & Perceptions survey data captured for Questions 20 and 21 reflecting the breakdown of response counts; all respondents, for perceived *Need of Pap testing for menopausal women* and *Need for additional information regarding cervical cancer* respectively stratified by Gender.

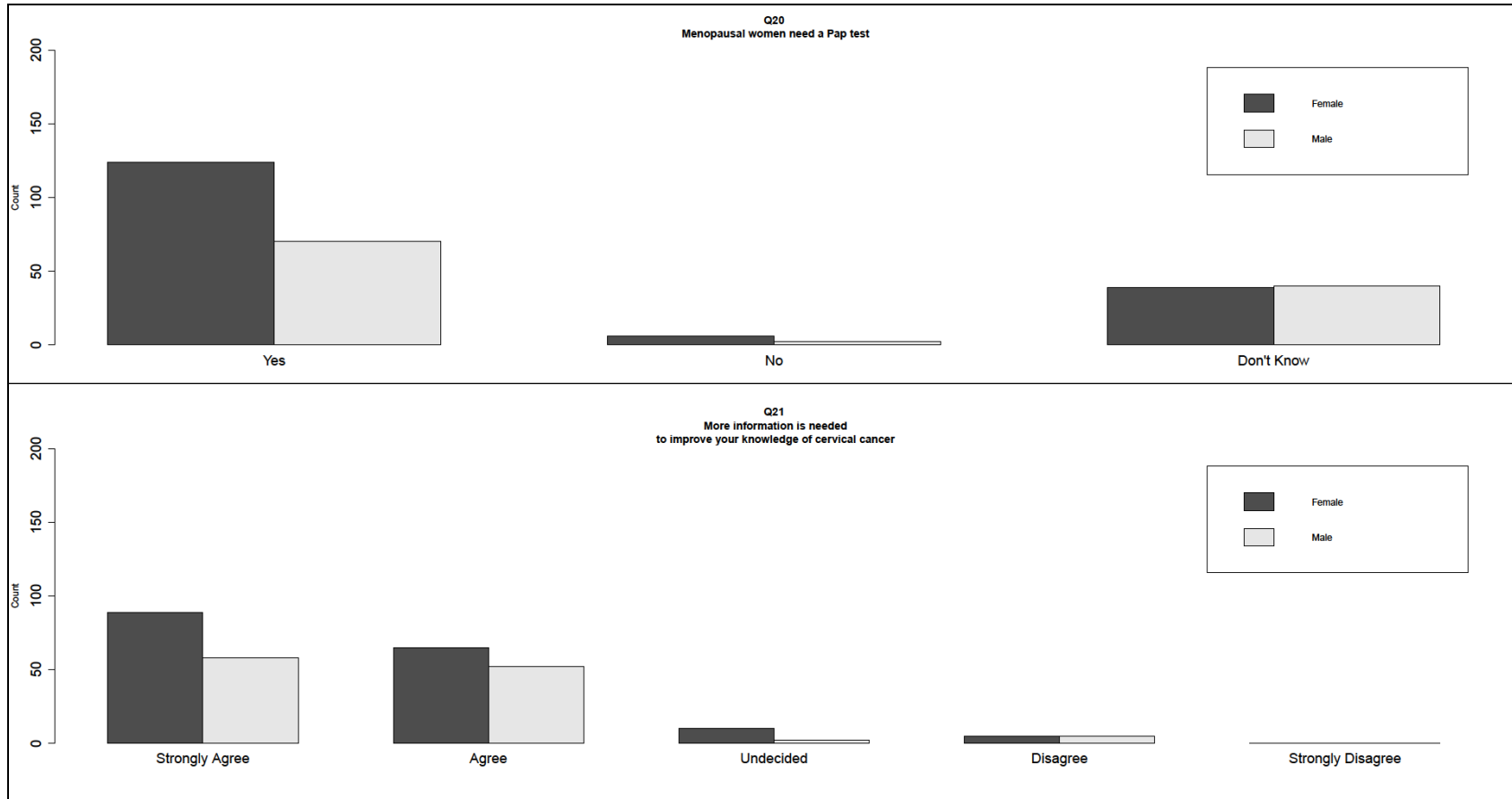


FIGURE 12: Composite figure of 2 bar plots representing Self-efficacy & Perceptions survey data captured for Questions 22 and 23 reflecting the breakdown of response counts; all respondents, for perceived *Value of Pap testing* and *Difficulty in getting a Pap test performed* respectively stratified by *Gender*.

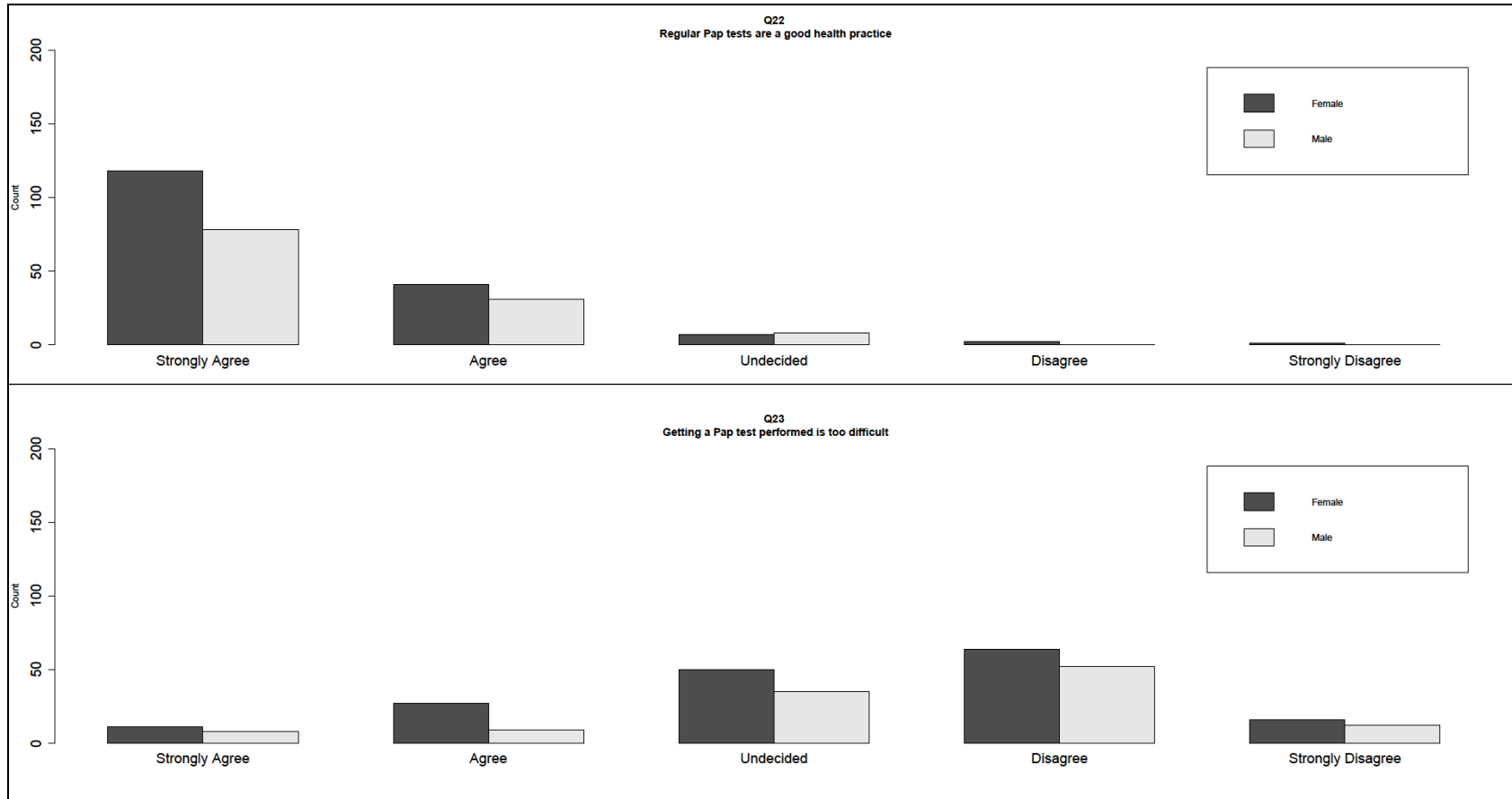


FIGURE 13: Composite figure of 2 bar plots representing Self-efficacy & Perceptions survey data captured for Questions 24 and 25 reflecting the breakdown of response counts; all respondents, for *Willingness to recommend the Pap test to others* and *Perceived healthcare value of a Pap test* respectively stratified by *Gender*.

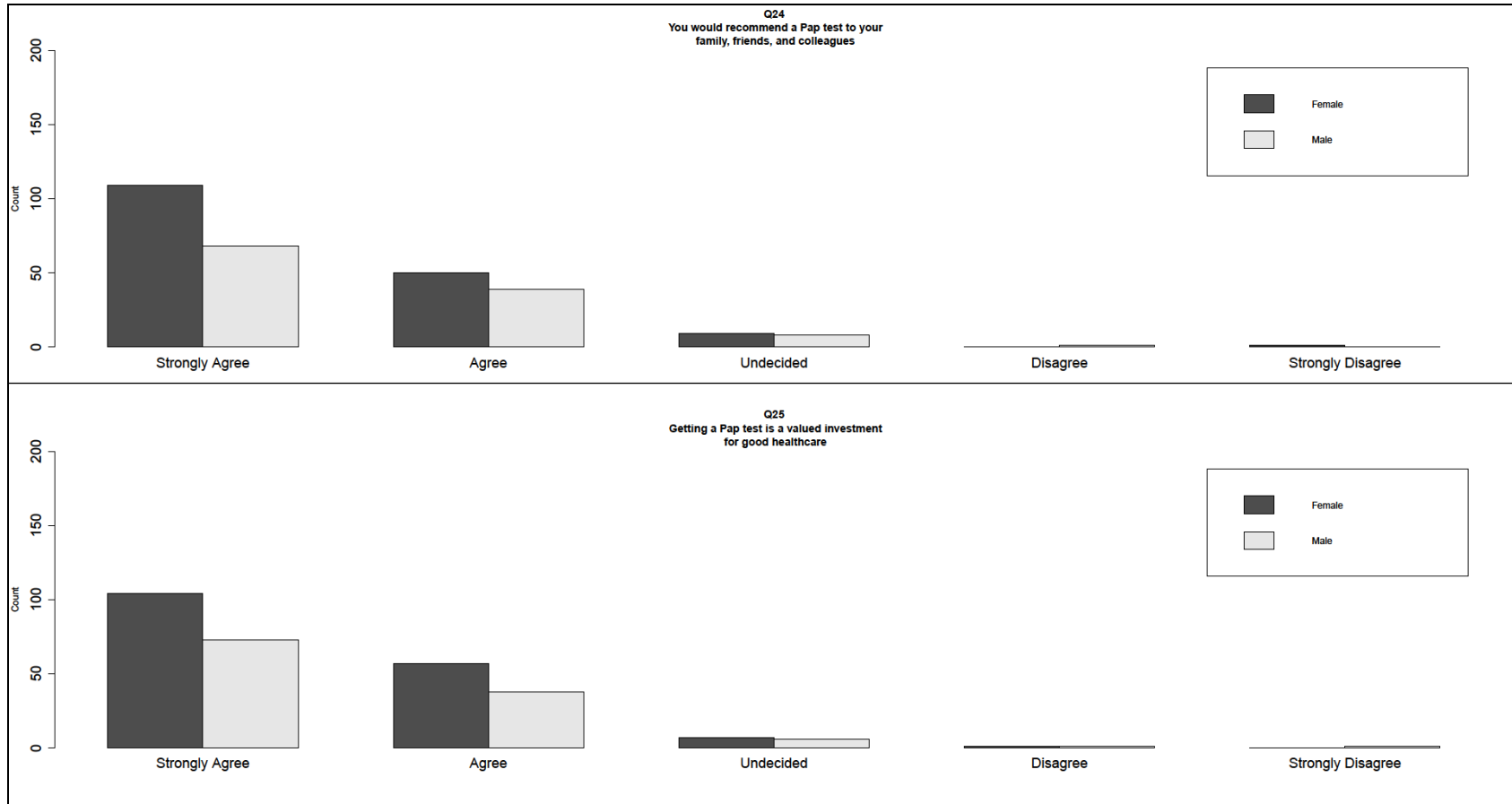


FIGURE 14: Composite figure of 2 bar plots representing Self-efficacy & Perceptions survey data captured for Questions 26 and 27 reflecting the breakdown of response counts; all respondents, for *Support for a Pap test screening program* and *Support for a formal Pap test screening program for all resident women in the State of Qatar* respectively stratified by Gender.

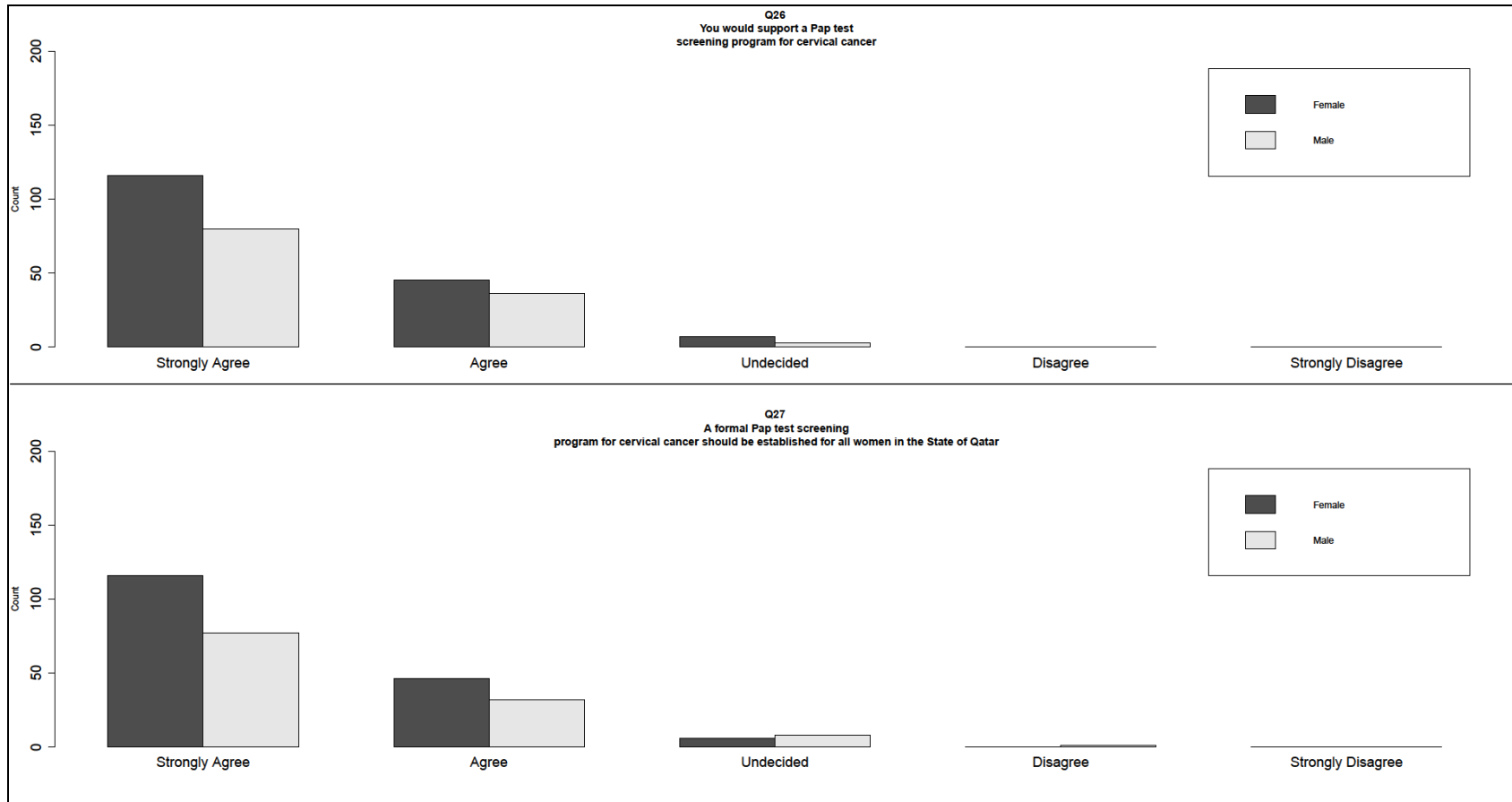


FIGURE 15: Composite figure of 2 bar plots representing Self-efficacy & Perceptions survey data captured for Questions 28 and 29 reflecting the breakdown of response counts; all respondents, for *Knowledge of where to go to get a Pap test performed* and *Perceived personal value of a Pap test* respectively stratified by Gender.

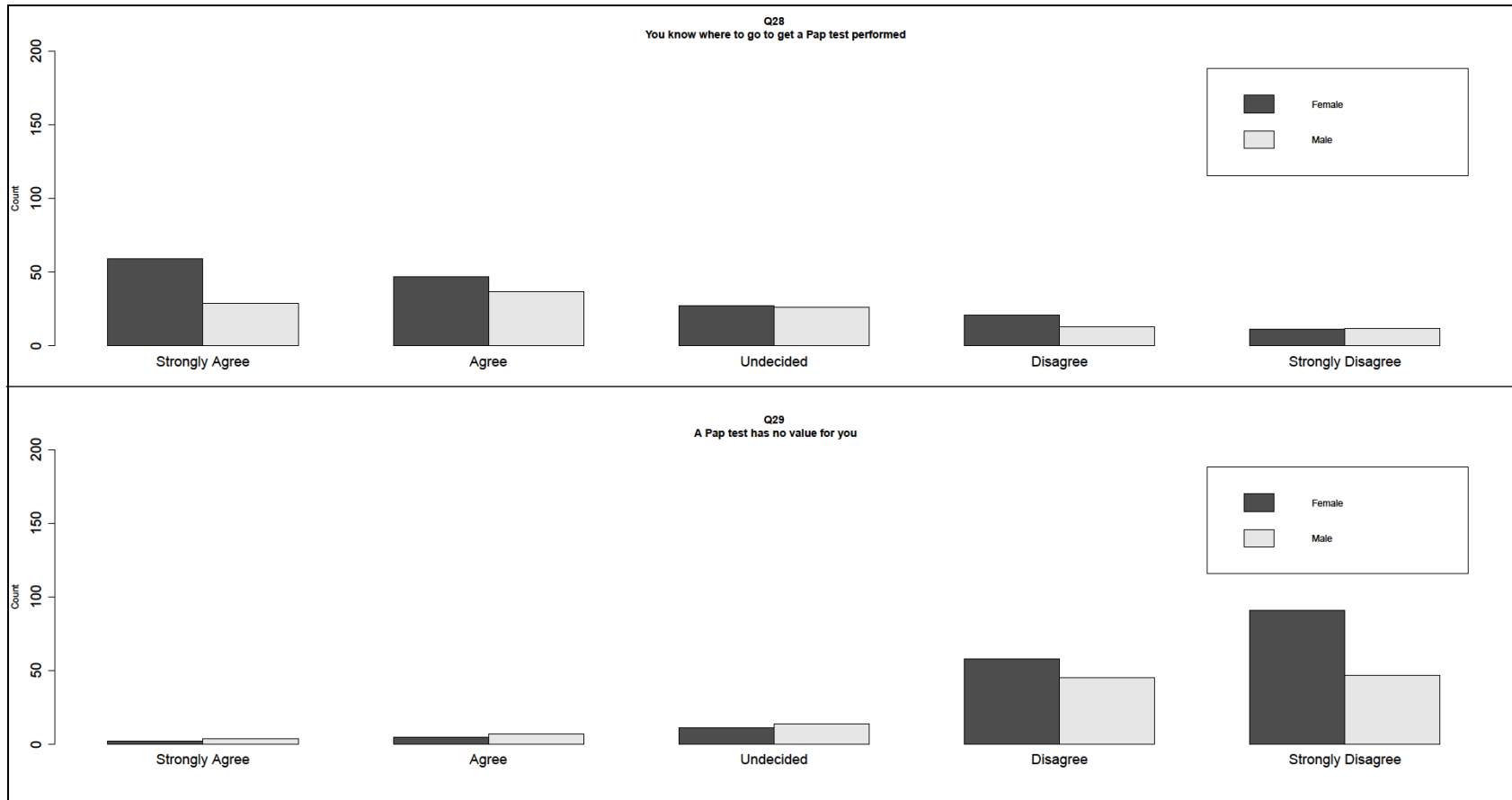
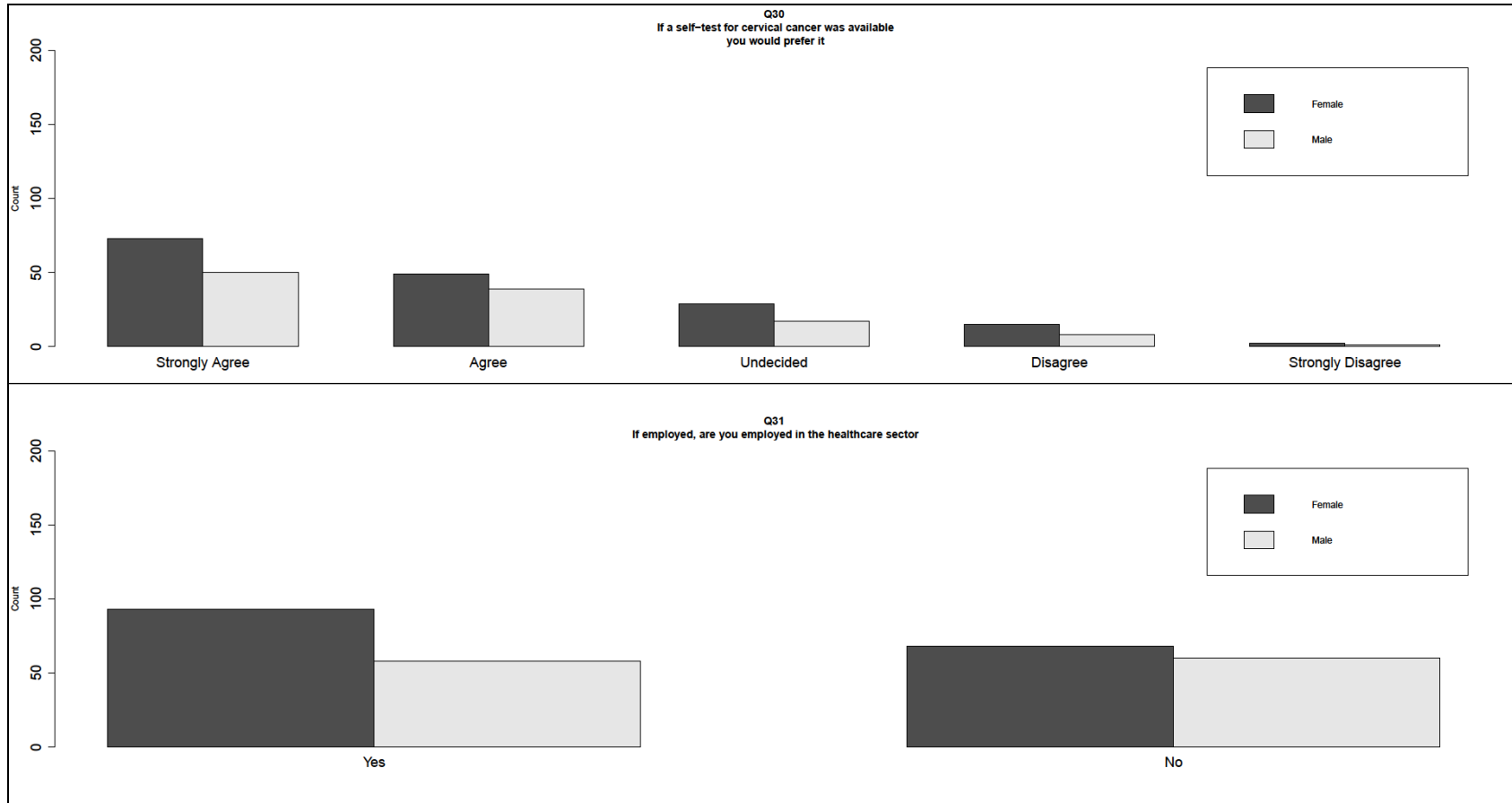


FIGURE 16: Composite figure of 2 bar plots representing Self-efficacy & Perceptions and Socio-demographic survey data captured for Questions 30 and 31 reflecting the breakdown of response counts; all respondents, for *Support and preference for possible self-testing for cervical cancer* and for *Employment in the healthcare sector* respectively stratified by Gender.



CHAPTER 6: DISCUSSION AND CONCLUSIONS

No other diagnostic test for cancer has impacted upon the intimacies of women's healthcare and social welfare to a greater extent than that of the Pap test in the history of medicine (Foltz & Kelsey, 1978; Greenwald, Cullen, & McKenna, 1987; Casper & Clarke, 1998). While the clinical Pap test remains perfect and paradoxically imperfect given various limitations, it has a proven legacy for saving lives since its deployment in the US in 1957 (Koss, 1989; Gordis, 2014). According to Cibas and Ducatman (2014), nearly 90% of women in the US claim to have had a Pap test within a preceding 3 year period. Notably, the WHO has cautioned that less than 5% of women in developing, resource-poor nations had, or may ever have, a Pap test (Sherris, Herdman, & Elias, 2001). This striking incongruity is at the heart of this research effort.

The experience arising from 62 years of systematic Pap test screening in various developed nations since 1957 is incontestable (Habbema, De Kok, & Brown, 2012). As CxCa is now widely considered a preventable disease, Garner (2003) alleged that any woman presenting with advanced CxCa ought to be viewed as a surrogate indicator of failed screening practice. A complementary report by Suba and Raab (2004) pertaining to Pap test sampling in developing nations, stated that failures in CxCa screening may be attributable to programmatic shortfalls rather than to technical limitations inherent in the Pap test. Consequently, a paradigmatic reconsideration of priorities may be

universally warranted to yield improved access to screening hence to improved clinical benefits.

It is hoped that insights brought forward from the historical experience in the US, coupled with emerging technologies both in medicine and through global modernization, may alleviate Pap test uptake disparities to facilitate equitable CxCa control. Similarly, that data and conclusions drawn from this research may facilitate optimization of existing Pap test sampling practices in the State of Qatar. The ultimate objective would be a reduction in the number of women presenting with advanced CxCa at diagnosis in this small clinical setting.

Insights Brought Forward From The Historical Development Of The Clinical Pap Test In The United States

In the first 57 years of the 20th century, both anticipated and unforeseen situations influenced the evolutionary course of the VFMSM from its experimental prototype through to its clinical deployment as the refined Pap test. Despite the various dynamics, it was political will prompted by the burden of CxCa, its detection, and its ramifications in women's welfare that drove the evolutionary saga of the Pap test from 1928 through to 1957, and henceforth.

Significance Of Cervical Cancer Definition Through Carcinoma In Situ

The most significant milestone was conceptualization and detection of cervical precancer proposed by Papanicolaou and Traut in 1941. However, it ought to be reiterated that CxCa was a mysterious disease in 1928 when Papanicolaou introduced

the *diagnostic* VFSM in the Battle Creek conference. CxCa assumed definition with the emergence of CIS, but this also led to unforeseen challenges. Preclinical, cervical CIS posed a hermaphroditic phenomenon in the mid-1940s: On the one hand, it enticed gynecologists with a *screening* tool by which to detect and ablate asymptomatic disease and effectively prevent invasive cancer; from the other hand, it antagonized surgeons and pathologists perceiving professional threats and challenges to medical tenets and practices. History has witnessed the commendable efforts by various individuals and organizations to resolve these dilemmas. The recognition of dyskaryotic cells purportedly pathognomonic of cervical precancer using unfamiliar cytologic smears and stains was a major, understandable challenge to conventional anatomical pathology. Yet, in the overall timeline of events, it was cervical precancer that reformed the prospects for Papanicolaou, for the Pap test, and for the management and control of CxCa in the US, and in other developed nations.

Papanicolaou and Traut's foundational monograph in 1943 produced a tangible target for the medical establishment. That target had been elusive until 1943 even though cervical CIS was a recognized entity in anatomical pathology. But what wasn't recognized was how to identify CIS, when still preclinical, using a non-invasive method. The new target facilitated the revelation of early CxCa in asymptomatic women through use of the VFSM. This target transcended into the basis for CxCa prevention through Pap test screening. Papanicolaou and Traut's work also facilitated novel concepts in the

epidemiology of CxCa. Through CIS, the preclinical and latent phases of the disease became measurable targets diagnostically and therapeutically from 1941 henceforth.

It may be reasonable to speculate that neither the success of the Pap test in preventive medicine, nor the modern institution of gynecological cytopathology, may have materialized had it not been for the cytologic detection and clinical impact of cervical precancer. Cervical precancer demarcated a critical threshold for public health surveillance and disease control.

Significance Of Organizational Policy, Promotion, And Advocacy

Macro-dynamics revealed the importance of formal organizational advocacy and policy prompted by political will, along with allocation of commensurate human and financial resources to address societal threats such as CxCa. Ironically, Papanicolaou's introduction of the diagnostic VFSM through his *New Cancer Diagnosis* presentation in 1928 coincided with profound, distractive priorities in the US: The Great Depression; an increasing burden and death rate due to cancer; and the Eugenics campaign calculating the eradication of unwanted human ailments through avant-garde tactics. The overall backdrop to Papanicolaou's 1928 presentation was complex and unaccommodating. During the 1920s, the dreaded disease that oftentimes led to indiscriminate silent deaths in women was a scientific oddity. Understandably, CxCa elicited adverse attitudes of hopelessness, fatalism, and stigmatization in both society and medicine. And the overall nature and intimacies of CxCa along with its anatomy and possible detection aroused prohibitions trying both women and their clinicians. The ASCC had anticipated these

challenges at its onset in 1913 but struggled to resolve them. The evolution of policymaking and advocacy in parallel with the momentum generated from the Pap test's development was critical.

The contributions by Ayre, Meigs, and Erskine were most timely by the late-1940s. They offered the reenergized ACS a convenient opportunity to demonstrate servant leadership and assuredly claim the defeat of CxCa. This triumph in preventive medicine spawned optimism towards the effective control of other cancers based on emerging theories of carcinogenesis. These outcomes revealed the importance of sponsorship, promotion, and professional collaboration to bring about efficacious methods.

Significance Of Method Framing

The seemingly failed presentation by Papanicolaou in 1928 revealed the importance of proper framing for a novel concept in medicine, to project its relevance and facilitate its acceptance. In the author's opinion, Papanicolaou's setback reflected a lack of judgement and leadership on the part of Stockard in sanctioning Papanicolaou's presentation in the sidelines of a formal negative Eugenics conference; arguably an inappropriate venue to posit a potentially significant advancement in diagnostic medicine.

The 'lost decade of cytopathology' that followed Papanicolaou's failure led to an incalculable compounding effect on public health and lives lost due to a likely 10-year

postponement of screening practices for CxCa in the US. The sheer cost to humanity may never be amply grasped.

Significance Of Political Commitment And Financial Resources

Cancer in general and its alarming trends during the 1930s threatened political stability in the US in the lead-up to World War II. This reality prompted enactment of the National Cancer Act in 1937. The Act created unprecedented energy backed by funding to support cancer research through the NCI, to mitigate threats to society posed by cancer. But it was not until Dr. Joseph C. Hinsey capitalized upon these collective dynamics in 1939 to bring the Act's intents and purposes to bear for the eventual prevention of CxCa. The National Cancer Act and the organizations it spawned revealed the importance of policy, advocacy, mission, commitment, and financial reinforcement; all driven by societal priorities and mainstream public demands. It was the culmination of these dynamics through Hinsey's administrative directives that revived Papanicolaou's potential, mitigated his vulnerabilities, and decisively ushered the renaissance of gynecological cytopathology through the detection of cervical CIS by the cytologic method.

Significance Of Field Testing And Method Modeling

The NCI-sponsored Memphis and Shelby County trial field tested the VFSM's potential to discriminate between cervical precancer and invasive disease cytologically. Cervical precancer became the essence for the control of CxCa as proposed through a prominent government-funded clinical study. The Memphis trial demonstrated how

prevalence of CxCa may only be appreciated when non-infiltrating and progressive epithelial lesions are taken into account as being integral elements of the same disease; as was also proposed by TeLinde attending to Henrietta Lacks in 1951 (Skloot, 2010). This archetype in epidemiological reasoning further challenged the classical tenets of cancer and its purported obligatory invasiveness. Nevertheless, the Memphis study produced an actionable model for population-based Pap test screening through cervical precancer. Under Dr. Charles Cameron's directorship, the ACS could not but boldly exploit the scientific momentum and endorse the Pap test for prompt deployment in population-based screening starting in 1957.

It is also speculated by the author that the timing of the ACS's decision to launch Pap test screening in 1957 coincided intentionally with Papanicolaou's retirement from CMC-NY. The ACS presumably assessed that sufficient experience was at hand to proceed with screening expansion. And, not doing so would have placed the ACS within an unwarrantable predicament. Societal and women's empowerment in the late-1950s reinforced the ACS's decision making.

Significance Of Professional Collaboration And Perception

Micro-dynamics arose predominantly from 1939 onwards following Hinsey's initiatives. They reflected the actions and reactions emerging from within a medical system coming to terms with the novelty of cervical precancer, its qualification, its detection, and its ablation, and its likely relevance in the control of other cancers with presumptive preclinical phases. Constructive forces reflected promoters such as

Papanicolaou, Mary Lasker, Hinsey, Ayre, Meigs, Erskine, Marchetti, and Cameron; organizations such as US Congress, The Commonwealth Fund, and the ACS; also, the driving expectations posed by society at large prompting political and organizational advocacy and commitment. Disruptive forces reflected push back from pathologists, surgeons, and other facets of the medical establishment that perceived impending professional insecurities, encroachment, challenges to medical basics, and threats to authority. Micro-dynamics also manifested the complex nuances arising from multi-disciplinary professional collaborations toiling to establish a novel method in diagnostic medicine, and to bridge the gaps between varying perceptions, authorities, and skill-sets.

Significance Of Adequate Health Literacy And Sense Of Disease Susceptibility

Notably, the Memphis and Shelby County trial also revealed concerning gaps in health literacy, and therefore restressed the importance of improved public awareness of CxCa and of its symptoms if the disease was to be rendered controllable. The Memphis trial also demonstrated the importance of clinicians' participation and commitment, to actively promote Pap test utilization. Ultimately, the Memphis trial recommended that every woman be made aware that she may develop CxCa in her lifetime, regardless of age or societal eminence. An unwavering sense of susceptibility amongst women appeared critical for adequate acceptance of the Pap test.

Finally, despite extensive health literacy campaigns conducted by the ASCC, the WFA, and the ACS by 1951, the Memphis trial concluded that knowledge of CxCa, and

of the benefits possible through Pap testing remained insufficient in that clinical setting. Cameron's initiatives through the ACS and through his personal publications aimed to increase the public's sense of self-empowerment in seeking medical attention early, and to encourage its active participation to facilitate improved cure rates. His aim was to offset a lagging medical establishment by transferring empowerment to the public. This empowerment continues to govern the scope of the Pap test in the US, and elsewhere through to modern practice.

Low Incidence Of Cervical Cancer And Screening Policy In The State Of Qatar

Based on the *National Cancer Framework*, currently in effect in the State of Qatar for the period 2017 through to 2022, published by the QMoPH (QMoPH National Cancer Framework, 2017) (Appendix L), the official position of the Ministry pertaining to cervical cancer screening is the following:

“Cervical cancer screening currently operates within Qatar on an opportunistic basis due to the relatively low prevalence of the disease. A situational analysis to understand the evidence base for the adoption of a national population-based cervical cancer screening service in Qatar is currently under evaluation between screening service providers and the MOPH.”

The QMoPH's position is based upon the low prevalence of CxCa in the State of Qatar. This position may be argued given the State's modest society and conservative cultural norms pertaining to sexual behavior. However, with opportunistic screening, the risk for incidence under-estimation is potentially substantial. Under-estimation of

the *actual* incidence of disease may undermine the currently-enforced strategy. As stated in Chapter 2, due to widespread, mature screening practices in the US since 1957, the incidence of CxCa was *reduced* to 7.6 per 100,000 as calculated for the period 2011 through 2015 by the ACS (American Cancer Society, 2018). In contrast, with opportunistic screening practices in the State of Qatar the incidence was 3.2 per 100,000 in 2017 (Institut Catala d'Oncologica, 2017²).

Given the importance of accurate assessment of *actual* CxCa incidence for the State of Qatar, the disease's preclinical and clinical phases ought to be assessed collectively. That is, cases of cervical CIS ought to be included in the incidence calculations, and therefore in the formal deliberations towards screening practice design, as was also proposed by TeLinde and the Memphis trial in 1951 (Dunn & Sprunt, 1955; Skloot, 2010). Sherris, Herdman, & Elias (2001) support the concept that CIS cases and invasive CxCa cases ought to be viewed as elements of the same disease, and therefore taken equally into account epidemiologically, and particularly in clinical settings utilizing opportunistic screening practices.

Recent efforts by the WHO calling to action the elimination of CxCa globally through increased screening and HPV vaccination have inspired development of mathematical models predicting the eventual elimination of the disease over a course of 50 years, from 2020 to 2069 (Simms, Steinberg, Caruana, Smith, Lew, Soerjomataram, Castle, Bray, & Canfell, 2019). Although the incidence threshold by which CxCa may be regarded eliminated remains undetermined, Simms et al. (2019) have proposed two

thresholds to guide public health initiatives: (1) Under 6 new cases per 100,000, to reflect a rare disease; and, (2) Under 4 new cases per 100,000, to reflect an eliminated disease. Should these mathematical models prove valid, then CxCa in the State of Qatar is arguably both rare and eliminated; however, such arguments rest upon the accuracy of *actual* incidence determination. It is surmised by the author, that in the background of opportunistic screening with lacking surveillance of actual intraepithelial and invasive disease in the entire female population at large, the incidence rate for CxCa may be potentially inaccurate hence misleading. The potentially under-estimated incidence of CxCa in Qatar is an inevitable limitation in this study.

Moreover, should organized Pap test screening practices be eventually introduced in the State of Qatar, the actual incidence of CxCa may likely increase simply due to expanded sampling and the revelation of preclinical, intraepithelial lesions as HSIL. A similar phenomenon was reported following increased sampling of papillary thyroid cancer nodules due to improved imaging and diagnostic fine needle aspiration biopsy methods (Gordis, 2014).

Data Analyses, Remarks, And Interpretations

Tables 10-18 tabulate the categorical data for all variables arising from this research. Tables 19-23 tabulate the p-values computed from the bivariate statistical analyses between the variables comprising Category 1 (Socio-demographic variables) and all other survey variables (questions) throughout Categories 2, 3 and 4, to test for

dependency. Socio-demographic variables are utilized as the reference for likely dependency consistently with all other survey variables throughout Tables 19-23.

The following sub-sections discuss the salient categorical results from this study per variable and category. Also, the statistically significant associations with all other variables were discussed with p-value insertions. Proposed remarks and interpretations were supported by relevant published literature where available. It is emphasized that p-values reflected statistically significant differences between correlated variables. However, as the questions in this survey listed several answer options, follow-up, and targeted research may be required to delve into the data set to explore likelihood of significance between specific questions and answers. Such detailed analyses would be beyond the scope of this dissertation relative to the hypotheses raised herein.

Interpretation Of Socio-Demographic Research Data (Questions: 1-8, 31)

Category 1 incorporated survey Questions 1-8, and 31, in an effort to generate Socio-demographic data. Tables 10, 11 and 18 reflect categorical data captured for all variables from all participants; and likewise, thereafter stratified by *Gender*. These data were represented through Figures 1-5, and 16.

Q1 Nationality.

Percent Response Rate: 100%, from 300 surveys. Table 10 and Figures 1 and 2 represent the breakdown of *Nationality* from all participants in this study. Figure 1 represents the distribution of nationalities for all respondents inclusive; Figure 2 represents the

nationalities of all respondents stratified by *Gender*. Tables 19-23 represent the bivariate analyses and matrices of p-values.

These data produced statistically significant associations between *Nationality* and: *Pap test uptakes* ($p=0.00000012$); *Awareness of the Pap test cytologic method* ($p=0.03766$); *Knowledge of CxCa* ($p=0.000022$); *CxCa curability* ($p=0.004244$); *Perceived protection through HPV vaccination* ($p=0.0000026$); *if Menopausal women require a Pap test* ($p=0.01045$); and *Knowledge of where to get a Pap test performed in Qatar* ($p=0.003118$).

These overall findings suggest that statistically significant differences exist between respondents based on *Nationality*, in Healthcare Services (Q9-11), Health Literacy (Q12-20), and Self-efficacy & Perceptions (Q21-30).

Remarks:

The largest proportion of all respondents by nationality, were Asian. Respondents with Asian nationality produced the primary proportion of 26.7% of all nationalities; followed by a secondary proportion from Qatari nationals of 17.6%; followed by a tertiary proportion with African nationality of 17.0%. Of all Asian respondents, 80% were women.

The distribution of nationalities in this study suggested a representative sampling of the various nationalities of residents currently in the population of the State of Qatar. According to the World Population Review report for Qatar for 2018 (World Population Review, 2018¹), the dominant population component was reflected by Asian

expatriates (i.e., Indian (24%), Nepali (16%), Filipino (11%), Bangladeshi/Sri Lankan (16%)) collectively comprising 67% of the entire 2.7 million population of Qatar. The 17.6% of Qatari respondents in this study correlated satisfactorily with the national Qatari population in 2018, then 15% of the entire population of Qatar.

The most significant association was noted between *Nationality* and *Pap test uptakes* ($p=0.00000012$). Given the dominance of Asian women respondents in this study relative to all other nationalities (26.7%), it is likely that these women reflected the greater variability for Pap test uptakes. Moreover, of the women respondents in this study that indicated never been Pap tested, 48.1% had also indicated being of Asian nationality. These findings may facilitate targeted health promotion initiatives in Qatar based on residents' nationalities.

Relevant Research:

Survey-based research conducted by Ma et al., (2013) to study the perceptions of Vietnamese American women to undergo a Pap test, concluded that 53% of the respondents reported ever having a Pap test. The study reported that the most impactful health promotion behavioral changes, through the Health Belief Model, occurred after an increased sense of susceptibility to developing CxCa. However, the dominant barriers to having a Pap test were embarrassment, believing a Pap test was not required if feeling well, and, not understanding what is being done during a Pap test.

Another survey-based study by Lee & Carvallo (2014) studied the perceived barriers of Asian American women to undergoing a Pap test. Their study concluded that

the most impactful parameters to influence self-efficacy and a sense of susceptibility to CxCa were: marital status and misbeliefs. Women revealed misperceptions of what is 'healthy' in the absence of symptoms, and lacking knowledge of CxCa and of Pap test screening regardless of education; educated women lacked knowledge of CxCa screening.

Similar survey-based studies conducted in South Ghana by Ebu, Mupepi, Siakwa, & Sampelle (2015), reported that 68.4% of respondent women had never heard of CxCa; 93.6% had no knowledge of risk factors; and 97.7% had no knowledge of the Pap test.

The significant associations between nationality and Pap test uptakes will be discussed below in greater detail in the section for Q9.

Q2 Gender.

Percent Response Rate: 97.7%, from 293 of 300 surveys. Table 10 and Figure 1 represent the *Gender* distribution from all respondents in this survey. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

From 293 respondents, 173 (59.0%) were women, and 120 (41.0%) were men.

These data produced statistically significant associations between *Gender* and: *Pap test uptakes* ($p=0.000000006$); *Awareness of the Pap test cytologic method* ($p=0.009553$); *Knowledge of CxCa* ($p=0.000304$); and *Perceived protection through HPV vaccination* ($p=0.0002238$). However, no significant associations between *Gender* and Category 4 variables reflecting Self-efficacy & Perceptions were revealed.

These overall findings suggest that statistically significant differences exist between respondents based on *Gender*, in Healthcare Services (Q9-11) and in Health Literacy (Q12-20).

Remarks:

These data suggested a relatively balanced representation of public views through the female and male participants in this research. The lack of significant statistical associations with Category 4 variables reflecting Self-efficacy & Perceptions may also be realized through Figures 11-16 illustrating the relatively equivalent response counts between women and men recorded in this study without prominent differences.

Q3 Age group (Years).

Percent Response Rate: 97.7%, from 292 of 300 surveys. Table 10 and Figure 2 represent the *Age group* distributions from all respondents, also stratified by *Gender*. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

The 97.7% Response Rate was calculated after exclusion of 1 survey from a male respondent claiming an age of less than 20. This adjustment complied with the exclusion criterion stipulated by the Sidra IRB.

These data produced statistically significant associations between respondents' *Age group* and: *Pap test uptakes* ($p=0.000000008$); *Where information was received of the Pap test* ($p=0.04087$); and *Perceived need for additional information to improve knowledge of CxCa* ($p=0.04504$).

These overall findings suggest that statistically significant differences exist between respondents based on *Age group*, in Healthcare Services (Q9-11), in Health Literacy (Q12-20), and in Self-efficacy & Perceptions (Q21-30).

Remarks:

The largest proportion of age group for all respondents was the 30-39 year age group comprising 40.0% of all respondents. Of these, women accounted for 58.0%. The second largest age group proportion was the 20-29 year age group comprising 30.5% of all respondents; whereas 57.3% were women. The distribution of age groups (Figure 2) suggested a satisfactory representation of the population currently in the State of Qatar; as in 2018, according to the ICO (Institut Catala d'Oncologica, 2017²), the primary age group of all women was 30-34 years, followed by a secondary age group of 35-39 years.

The primary age group of all men in Qatar in 2018 was 25-29 years, followed by a secondary age group of 35-39 years. The data arising from this research correlated with the population pyramid for Qatar being skewed towards males; representing the relatively large population proportion comprising young expatriate men employed in the State's megaprojects as discussed in Chapter 3.

The highly statistically significant association noted between *Age group* (Q3) and the variable *Had a Pap test before?* (Q9) warranted particular consideration. From the total of 173 women that participated in this study (Table 10), 79 (45.6%) claimed never having a Pap test. This group of women showed a primary age group of 20-29 years, followed by a secondary age group of 30-39 years. Practically, when combined, these women

comprised a near 40-year age bracket. As the bimodal peak ages of CxCa cases with Stage II/III disease at presentation in Qatar were 40-44 and 60-64 years in 2014 (QMoPH National Cancer Program, 2014), the 30-39 year respondent women, that never had a Pap test, may represent a cohort at increased risk for developing CxCa. The significance of these observations will be discussed in greater detail in a subsequent sub-section in this Chapter.

Relevant Research:

Research by Kahn, Chiou, Allen, Goodman, Perlman, & Emans (1999) studied the relationship between beliefs about Pap smears and compliance for follow-up instructions in adolescents. Their study concluded that strategies to provide adequate health literacy, and the implementation of an appointment reminder system, improved Pap test uptakes in adolescents. These collaborators also suggested that healthcare promotion initiatives ought to be age-group specific.

Q4 Highest education level.

Percent Response Rate: 97.7%, from 293 of 300 surveys. Table 10 and Figure 3 represent the *Highest education level* distributions from all respondents, also stratified by *Gender*. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

These data produced statistically significant associations between respondents' *Highest education level* and: *Pap test uptakes* ($p=0.03798$); however, no associations with any of the Category 3 variables, or Category 4 variables were revealed. Yet, a relatively

weak statistical dependency was noted between *Highest education level* and: *Support for a Pap test screening program for CxCa* (Q26) ($p=0.05745$).

These overall findings suggest that statistically significant differences exist between respondents based on *Highest education level*, in Healthcare Services (Q9-11).

Remarks:

The largest proportion of education level revealed from all respondents and between genders was that of *University level*. From 293 participants, 243 (82.9%) indicated a university level education; when stratified by gender, women (83.2%) and men (82.5%) indicated a university level education essentially equally. These findings correlated with demographic vital statistics arising from the State of Qatar as published by the ICO. According to the ICO (Institut Catala d'Oncologica, 2017²), the overall adult literacy rate from the entire Qatar population age 15 and older in 2017 was 97.8%. Moreover, the secondary school enrollment rate from the entire Qatar population was 94.5%. Overall, the population in Qatar boasts high levels of education and literacy.

Nevertheless, these overall findings were surprising given the relatively high literacy rates amongst residents in Qatar according to the ICO (Institut Catala d'Oncologica, 2017²), relative to the alarming proportion of respondent women in this study claiming never having a Pap test (47.0%). These findings may facilitate targeted health promotion initiatives in Qatar based on education levels.

Relevant Research:

The relationship between Pap test uptakes and women's education levels in Qatar have been researched by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011). Their study also reported the statistically significant dependency noted between education level and Pap test uptake. They concluded that knowledge of CxCa and of the Pap test was inadequate in women less than 30 years of age, and in those women with lower education levels. Their research also revealed that knowledge of CxCa was significantly greater in women with a University degree education.

Q5 Marital status.

Percent Response Rate: 97.7%, from 293 of 300 surveys. Table 11 and Figure 3 represent the *Marital status* distributions from all respondents, also stratified by *Gender*. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

The data produced statistically significant associations between respondents' *Marital status* and: *Pap test uptakes* ($p=0.00000004$); *Where information was received of the Pap test* ($p=0.002733$); and *Perceived need for additional information to improve knowledge of CxCa* ($p=0.01028$).

These overall findings suggest that statistically significant differences exist between respondents based on *Marital status*, in Healthcare Services (Q9-11), Health Literacy (Q12-20), and Self-efficacy & Perceptions (Q21-30).

Remarks:

The largest proportion of marital status revealed from all respondents and between genders was that of *Married*. From 293 participants, 186 (63.5%) indicated being married; when stratified by gender: women (61.3%) and men (66.7%) indicated as being married. The data also revealed respondents never before married. From all respondents, 92 (31.4%) indicated never been married; when stratified by gender: women (32.9%) and men (29.2%) indicated never been married.

The most significant association was noted between *Marital status* and *Pap test uptakes* ($p=0.00000004$). This association is discussed in detail in this Chapter, in the subsection describing the subset of married women never before having a Pap test.

Relevant Research:

Consistent with this dissertation, Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) also reported a relationship between marital status and awareness of CxCa and of Pap test screening.

Q6 Marriage duration.

Percent Response Rate: 88.3%, from 265 of 300 surveys. Table 11 and Figure 4 represent the *Marriage duration* distributions from all respondents, also stratified by *Gender*. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

These data produced statistically significant associations between respondents' *Marriage duration* and: *Pap test uptakes* ($p=0.0000032$); *When was the previous Pap test performed* ($p=0.03648$); *Where did you hear of the Pap test method before* ($p=0.02039$); *Perceived protection from HPV vaccination* ($p=0.0273$); *Perceived need for additional information to improve knowledge of CxCa* ($p=0.02365$); *Perception that getting a Pap test done is too difficult* ($p=0.04028$); and *Perceived no value of the Pap test* ($p=0.01878$).

These overall findings suggest that statistically significant differences exist between respondents based on *Marriage duration*, in Healthcare Services (Q9-11), Health Literacy (Q12-20), and Self-efficacy & Perceptions (Q21-30). However, as marriage duration is a potential limitation in this study, conclusions ought to be considered cautiously.

Remarks:

Although Q6 posed a limitation in this study, the largest proportion of marriage duration revealed from all respondents and between genders was that of *Not applicable*: 71 (26.7%). The second largest proportion was for 5-10 years, followed by 10-20 years. From 265 participants, 66 (25.0%) indicated being married 5-10 years; when stratified by gender: women (18.2%) and men (36.0%) indicated being married 5-10 years. Likewise, 18.2% of respondent women indicated being married 10-20 years.

That 26.7% of the respondents in this study (and 33.3% of women) selected *Not applicable* for Q6 was surprising. The relatively large component of *Not applicable* may possibly reflect reluctance by some respondents to disclose marriage durations. These

findings may also reflect the cultural norms characteristic of a conservative society as the one in the State of Qatar.

Relevant Research:

Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) researched women's attitudes in Qatar and likewise reported an association between marriage duration and Pap test uptakes. Their research revealed a greater awareness of CxCa particularly amongst women married for greater than 15 years, and in women with greater parity. However, survey-based research by Alali et al., (2016) reported that increasing parity was regarded amongst the risk factors for CxCa development in Qatar.

Q7 Employment status.

Percent Response Rate: 95.7%, from 287 of 300 surveys. Table 11 and Figure 4 represent the *Employment status* distributions from all respondents, also stratified by *Gender*. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

These data produced statistically significant associations between respondents' *Employment status* and: *Pap test uptakes* ($p=0.000018$); *CxCa may be curable* ($p=0.01827$); and *Recommendation of the Pap test to family and friends* ($p=0.04067$).

These overall findings suggest that statistically significant differences exist between respondents based on *Employment status*, in Healthcare Services (Q9-11), Health Literacy (Q12-30), and Self-efficacy & Perceptions (Q21-30).

Remarks:

The largest proportion of employment status revealed from all respondents and between genders was that of *Employed*. From 287 participants, 212 (73.9%) indicated being employed; when stratified by gender: women (78.1%) and men (67.8%) indicated being employed.

The highly significant association noted between *Employment status* and *Pap test uptakes* ($p=0.000018$) was remarkable as amongst the women that indicated never been Pap tested in this study, 83.5% had health insurance coverage through employment. These findings are discussed in greater detail in a subsequent sub-section in this Chapter.

Relevant Research:

Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) reported greater knowledge of CxCa in employed women in Qatar, and particularly in women with a University degree education. Their findings are consistent with the associations revealed through this research.

Q8 You have health insurance coverage?

Percent Response Rate: 96.0%, from 288 of 300 surveys. Table 11 and Figure 5 represent the *Health insurance coverage* distribution from all respondents, also stratified by *Gender*. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

These data produced no dependencies with variables in Category 2 reflecting Healthcare Services; however, significant associations were noted with *Awareness of the cytologic method* ($p=0.004242$); and *Knowledge of CxCa* ($p=0.03714$). No dependency with variables in Category 4 reflecting Self-efficacy & Perceptions was revealed.

These overall findings suggest that statistically significant differences exist between respondents based on *Health insurance coverage*, in Health Literacy (Q12-20).

Remarks:

From 288 respondents, 229 (79.5%) indicated having health insurance coverage; whereas, 20.5% of respondents did not. Of the genders: 83.5% of women and 73.7% of men indicated having insurance coverage.

The significant associations noted between *Health insurance coverage* and awareness of the cytologic method ($p=0.004242$) and of CxCa ($p=0.03714$) was remarkable as 83.5% of women participants may have access to Pap testing and therefore awareness, although, this study revealed that 45.7% of women participants claimed never been Pap tested. These findings suggest that lacking *Health insurance coverage* may be a barrier to Pap test uptakes. These findings may further support development of population-based screening practices in Qatar

Q31 If employed, are you employed in the healthcare sector?

Percent Response Rate: 93.0%, from 279 of 300 surveys. Table 18 and Figure 16 represent the *Employment in the healthcare sector* distribution from all respondents, also stratified by

Gender. Tables 19-23 represent the bivariate analyses conducted and matrices of p-values.

These data produced significant associations between *Employment in the healthcare sector* and: *Previous Pap test uptake* ($p=0.0003357$); *CxCa may be preventable* ($p=0.0001159$); *Awareness of the Pap test cytologic method* ($p=0.0000065$); *Where information of the Pap test was heard* ($p=0.0005167$); *Knowledge of CxCa* ($p=0.0003576$); *Knowledge of importance of early detection of CxCa for treatment* ($p=0.0004853$); *Regular Pap tests may protect from CxCa* ($p=0.02428$); *CxCa may be curable* ($p=0.0000623$); *Perception of protection from HPV vaccination* ($p=0.003599$); and *Perceptions if Menopausal women need a Pap test* ($p=0.02444$). No dependencies with variables in Category 4 reflecting Self-efficacy & Perceptions were revealed.

These overall findings suggest that statistically significant differences exist between respondents based on *Employment in the healthcare sector*, in Healthcare Services (Q9-11), and Health Literacy (Q12-20).

Remarks:

From 279 respondents, 151 (54.1%) indicated being employed in the healthcare sector; whereas, 128 (45.9%) of respondents were not. Of the genders: 57.7% of women and 49.2% of men indicated being employed in the healthcare sector. These findings reveal relatively balanced survey participation by women and men employed in the healthcare sector, or elsewhere.

Although participants' likely employment in the healthcare sector may be a potential limitation in this study, the aforementioned statistical associations may suggest that healthcare sector employees continue to lack sufficient awareness of CxCa and of the Pap test not unlike the greater population of women in the State of Qatar. These findings may reflect conservative cultural norms universal amongst women in this nation.

Relevant Research:

Survey-based research by Alali et al., (2016) in Qatar studying the attitudes of women employed in PHCC centers as clinical staff reported that 42.2% of these women had a Pap test before, and that the most impactful determinant was a sense of embarrassment and of being noticed by their colleagues.

Interpretation Of Healthcare Services Research Data (Questions: 9-11)

Q9 You had a Pap test before?

Percent Response Rate: 95.3%, from 286 of 300 surveys. Table 11 and Figure 5 represent the distribution of responses from all respondents for Q9, also stratified by *Gender*. Table 19 represents the bivariate analyses conducted and matrices of p-values.

These data produced statistically significant associations with 8 of the 9 variables in Category 1 reflecting Socio-demographic variables (Q1-9, 31).

This variable demonstrated remarkable statistically significant associations with all Socio-demographic variables except for *Health insurance coverage*. These data suggest

that statistically significant differences exist between respondents based on Pap test uptakes throughout the variables reflecting socio-demographic attributes of all respondents.

Remarks:

From 286 respondents, 105 (36.7%) indicated having a Pap test before; whereas, 149 (52.0%) of respondents had not, and 32 (11.3%) indicated *Not Applicable*. Of the genders: 48.8% of the women had a Pap test, and 47.0% had not. These outcomes are considered to be epidemiologically important and warranted detailed analysis. The significance of women not having a Pap test before is discussed in a subsequent subsection in this Chapter.

The sub-set of 19.5% of men that claimed to have had a Pap test before embody a study limitation and may be regarded a surrogate of Health Literacy inadequacies. Arguably, any lacking awareness of CxCa or of the Pap test may have led to confusion in either women or men respondents. It is speculated that these men had confused the Pap test as being some other test they may have had, that may also have sounded alike phonetically, either through the English or Arabic language.

This potential limitation may have been intensified given the variable nationalities of the survey respondents and their likely mother languages that may have been other than English or Arabic.

Relevant Research:

The findings arising from this study are consistent with survey-based research by Alali et al., (2016). In their research, they assessed knowledge of CxCa and of the Pap test amongst women employed in PHCC centers in Qatar. Their findings revealed that 42.2% of respondent women indicated having a Pap test. The most impactful barrier was embarrassment (17.3%), followed by inadequate knowledge of CxCa (14.8%), and that 94.5% of the participating women would prefer a female physician. These findings were also corroborated by research from Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) reporting that 39.4% of the respondent women had a Pap test; likewise, studies by Metwali, Al Kindi, Shanbleh, Al Akshar, & Sarhan (2015) assessing women in the United Arab Emirates, discovered that amongst 212 participating women, 37.2% had a Pap test.

Q10 If you had a Pap test before, when was it performed?

Percent Response Rate: 34.7%, from 104 of 300 surveys. Table 12 and Figure 6 represent the distribution of responses from all respondents for Q10, also stratified by *Gender*. Table 19 represents the bivariate analyses conducted and matrices of p-values.

These data produced one statistically significant association with 1 Category 1 variable reflecting Socio-demographics: *Marriage duration* ($p=0.03648$). However, as *Marriage duration* is a potential limitation in this study this association needs to be considered cautiously.

Remarks:

From 104 respondents, 74 (71.1%) indicated having a Pap test in the preceding 1-3 years; whereas, 21 (20.2%) of respondents had a Pap test in the preceding 4-6 years, and 9 (8.70%) over 6 years prior. Of the genders, 82.0% of the respondents were women; whereas, 71.9% of which had a Pap test within 1-3 years, 20.7% within 4-6 years, and 7.32% over 6 years prior.

The relatively low Response Rate for this survey question reflected the responses predominantly from women. As such, that 71.9% of women that have had a Pap test had it in the preceding 1-3 years correlated with the currently-enforced guidelines by the QMoPH recommending that women aged 25-49 years should be screened every 3 years (QMoPH National Cancer Program, 2016¹).

Relevant Research:

Survey-based research by Alali et al., (2016), assessing women employed in PHCC centers in Qatar, reported that 9.0% had adequate knowledge of their eligibility for Pap test sampling and an awareness of the recommended screening intervals as endorsed by the QMoPH.

Similar survey-based research by Fernandez et al., (2009) studied the relationship between self-efficacy and Pap test uptakes in low-income Mexican American women. Their study reported that higher self-efficacy correlated with the likelihood of recent Pap testing amongst these women. In contrast, research by Denny & Wright (2009) reported

a 4.22-fold increase in the risk for developing CxCa in women that had a preceding Pap test greater than 4-6 years prior.

Q11 Did you, or any member of your family have cervical cancer before?

Percent Response Rate: 95.3%, from 286 of 300 surveys. Table 12 and Figure 6 represent the distribution of responses from all respondents for Q11, also stratified by *Gender*. Table 19 represents the bivariate analyses conducted and matrices of p-values.

These data produced no statistically significant associations with Category 1 variables reflecting Socio-demographics.

Remarks:

From 286 respondents, 10 (3.49%) indicated having a family history of CxCa; whereas, 266 (93.0%) of respondents indicated no family history, and 10 (3.49%) did not know. That 93.0% of respondents claimed no family history of CxCa likely reflected the low prevalence of this disease as published for the clinical setting of the State of Qatar, or, arguably, a lacking awareness of the disease. However, another limitation in this study is possible under-estimation of CxCa incidence in Qatar, which may impact public perceptions of extent of disease at large.

Relevant Research:

No pertinent research pertaining to this question could be identified arising from Qatar.

Interpretation Of Health Literacy Research Data (Questions: 12-20)

Q12 Cervical cancer may be preventable.

Percent Response Rate: 96.0%, from 288 of 300 surveys. Table 12 and Figure 7 represent the distribution of responses from all respondents for Q12, also stratified by *Gender*. Table 20 represents the bivariate analyses conducted and matrices of p-values.

These data produced 1 statistically significant association with Category 1 variables reflecting Socio-demographics: *Employment in the healthcare sector* (p=0.0001159).

These overall findings suggest that statistically significant differences exist between respondents based on CxCa being possibly preventable, amongst survey participants employed in the healthcare sector, or otherwise. However, as employment in the healthcare sector is a potential limitation in this study, this association may be potentially unreliable.

Remarks:

From 288 respondents, 242 (84.0%) indicated that CxCa may be preventable; whereas, 3 (1.00%) of respondents said no, and 43 (15.0%) did not know. That 84.0% of respondents claimed that CxCa may be preventable may reflect adequate awareness of CxCa. However, that 15% of respondents did not know suggested insufficient knowledge of CxCa preventability.

Relevant Research:

In survey-based research in Qatar by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011), they asked a related question: “Is it possible to detect CxCa with the Pap test smear before symptoms appear?” Their study revealed that 62.4% of the participating women agreed that the Pap test may detect CxCa early, compared to 37.6% that disagreed.

Q13 You are aware of the Pap test smear cytologic method.

Percent Response Rate: 96.0%, from 288 of 300 surveys. Table 12 and Figure 7 represent the distribution of responses from all respondents for Q13, also stratified by *Gender*. Table 20 represents the bivariate analyses conducted and matrices of p-values.

These data produced 4 statistically significant associations with Category 1 variables reflecting Socio-demographics: *Nationality* ($p=0.03766$); *Gender* ($p=0.009553$); *Health insurance coverage* ($p=0.004242$); and *Employment in the healthcare sector* ($p=0.0000065$).

These overall findings suggest that statistically significant differences exist between respondents based on awareness of the cytologic method, in Health Services (Q9-11).

Remarks:

From 288 respondents, 191 (66.3%) indicated awareness of the cytologic method; whereas, 97 (33.7%) of respondents indicated no awareness. That 33.7% of respondents

indicated not having an awareness of the Pap test cytologic method is relevant to the hypotheses in this dissertation. These findings suggest insufficient knowledge of the cytologic Pap test method overall; accordingly, 27.6% of women respondents indicated no knowledge of the Pap test cytologic method. Furthermore, this variable revealed a statistically significant association between women's nationality, health insurance coverage, and whether employed in the healthcare sector or not.

Relevant Research:

These data are consistent with research outcomes from work by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011). Their research revealed that 76% of surveyed women in Qatar indicated having adequate knowledge of the Pap test smear method; although, levels of health literacy decreased significantly in women recently married, in those under age 30, and in those with lower education levels. Their findings are corroborated by research conducted in the United Arab Emirates by Metwali, Al Kindi, Shanbleh, Al Akshar, & Sarhan (2015). Their work concluded that of 212 women surveyed, 74.5% knew of the Pap test.

Q14 Where did you hear of the Pap test smear cytologic method for the first time?

Percent Response Rate: 93.3%, from 280 of 300 surveys. Table 13 and Figure 8 represent the distribution of responses from all respondents for Q14, also stratified by *Gender*. Table 20 represents the bivariate analyses conducted and matrices of p-values.

These data produced 4 statistically significant associations with Category 1 variables reflecting Socio-demographics: *Age group* ($p=0.04087$); *Marital status*

($p=0.002733$); *Marriage duration* ($p=0.02039$); and *Employment in the healthcare sector* ($p=0.0005167$).

These overall findings suggest that statistically significant differences exist between respondents based on acquisition of knowledge of the Pap test smear method.

Remarks:

From 280 respondents, the largest proportion of responses indicated *Gynecologist*, 72 (25.7%); followed by *Other*, 52 (18.6%), and *Not applicable*, 48 (17.1%). That 26.9% of women heard of the Pap test from a Gynecologist suggests these women may have had a Pap test and therefore received medical consultation. However, the second largest frequency of women's responses (17.9%) indicated *Not applicable*. These findings may also suggest a sub-set of women lacking health literacy for CxCa.

Relevant Research:

Research conducted in Qatar by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) revealed a significant finding: That the majority of women respondents obtained knowledge of CxCa from their social network (i.e., relatives and friends) rather than from physicians. These outcomes may explain the 17.1% of respondents in this study that indicated *Not applicable* for Q14. Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) attributed this surprising finding to the absence of a well-organized screening program in Qatar.

In another study by Badrinath, Ghazal-Aswad, Osman, Deemas, & McIlvenny (2004), assessing the knowledge of CxCa amongst female primary care physicians in the United Arab Emirates, revealed that of the participating 98 physicians, 40.0% reported ever performing a clinical Pap test procedure on their patients. These findings may not only reflect insufficient health literacy amongst clinicians, they may also reflect lacking procedural competencies, and perhaps a lack of Pap test promotion.

Q15 You have knowledge of cervical cancer.

Percent Response Rate: 96.7%, from 290 of 300 surveys. Table 13 and Figure 8 represent the distribution of responses from all respondents for Q15, also stratified by Gender. Table 20 represents the bivariate analyses conducted and matrices of p-values.

These data produced 4 statistically significant associations with Category 1 variables reflecting Socio-demographics: *Nationality* ($p=0.000022$); *Gender* ($p=0.000304$); *Health insurance coverage* ($p=0.03714$); and *Employment in the healthcare sector* ($p=0.0003576$).

The overall findings suggest that statistically significant differences between respondents exist relevant to knowledge of CxCa.

Remarks:

From 290 respondents, the largest proportion of responses indicated knowledge of CxCa, 203 (70.0%); followed by *No knowledge*, 87 (30.0%). That 30.0% of respondents indicated not having knowledge of CxCa is relevant to the hypotheses in this dissertation. These data further suggest that an impactful relationship may exist

between nationality, health insurance coverage, and employment in the healthcare sector between the women and men participants. Given the limitations outlined for this study, in-depth follow-up research may explore specific parameters in these associations to facilitate health promotion initiatives in the State of Qatar.

Relevant Research:

Survey-based research by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) surveying women in Qatar revealed that over 85% of women participants had heard of CxCa, and that knowledge of CxCa increased significantly in women in the 30-49 years age group, in those employed, and in those with a University degree education. Studies by Metwali, Al Kindi, Shanbleh, Al Akshar, & Sarhan (2015) surveying 212 women in the United Arab Emirates revealed that 29% of participating women had knowledge of CxCa.

Q16 Early detection of cervical cancer is important for effective treatment.

Percent Response Rate: 96.7%, from 290 of 300 surveys. Table 13 and Figure 9 represent the distribution of responses from all respondents for Q16, also stratified by *Gender*. Table 20 represents the bivariate analyses conducted and matrices of p-values.

These data produced 1 statistically significant association with Category 1 variables reflecting Socio-demographics: *Employment in the healthcare sector* (p=0.0004853).

These overall findings suggest that statistically significant differences exist between respondents based on importance of early detection of CxCa for effective

treatment and likely employment in the healthcare sector. However, as employment in the healthcare sector is a potential limitation in this study, this association may be unreliable.

Remarks:

From 290 respondents, the largest proportion of responses indicated that early detection of CxCa is important for effective treatment, 271 (93.4%); followed by *No*, 1 (0.40%), and *Don't know*, 18 (6.20%). That 6.20% of respondents indicated that early detection of CxCa was not important is relevant to the hypotheses in this dissertation. Of the women respondents, 7.51% indicated not knowing if early detection of CxCa is important for effective treatment.

Relevant Research:

Survey-based research by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) in Qatar, revealed that 62.4% of participating women agreed that early detection of CxCa is important for effective treatment; whereas, 37.6% of women disagreed.

Q17 Regular Pap tests may protect you from cervical cancer.

Percent Response Rate: 95.3%, from 286 of 300 surveys. Table 14 and Figure 9 represent the distribution of responses from all respondents for Q17, also stratified by *Gender*. Table 21 represents the bivariate analyses conducted and matrices of p-values.

These data produced 1 statistically significant association with Category 1 variables reflecting Socio-demographics: *Employment in the healthcare sector* ($p=0.02428$).

These overall findings suggest that statistically significant differences exist between respondents based on protection through regular Pap tests. However, as employment in the healthcare sector is a limitation in this study, this association may be unreliable.

Remarks:

From 286 respondents, the largest proportion of responses indicated that regular Pap tests may protect from CxCa, 243 (84.9%); followed by *No*, 8 (2.79%), and *Don't know*, 35 (12.3%). That 12.3% of respondents indicated that regular Pap testing does not protect from CxCa is relevant to the hypotheses in this dissertation.

Relevant Research:

Survey-based research by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) in Qatar, revealed that 64.8% of participating women agreed that the Pap test may protect them from CxCa; whereas, 35.2% of women disagreed.

Q18 Cervical cancer may be curable.

Percent Response Rate: 96.7%, from 290 of 300 surveys. Table 14 and Figure 10 represent the distribution of responses from all respondents for Q18, as also stratified by *Gender*. Table 21 represents the bivariate analyses conducted and matrices of p-values.

These data produced 3 statistically significant associations with Category 1 variables reflecting Socio-demographics: *Nationality* (p=0.004244); *Employment status* (p=0.01827); and *Employment in the healthcare sector* (p=0.0000623).

Remarks:

From 290 respondents, the largest proportion of responses indicated that CxCa, may be curable, 190 (65.5%); followed by *No*, 8 (2.70%), and *Don't know*, 92 (31.8%). That 31.8% of respondents indicated no knowledge that CxCa may be curable is relevant to the hypotheses in this dissertation, and considered a significant finding. These findings may facilitate targeted health promotion initiatives in Qatar.

Relevant Research:

Survey-based research by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) in Qatar, revealed that 82.4% of participating women agreed that CxCa may be curable; whereas, 17.6% of women disagreed.

Q19 Vaccination for the Human Papilloma Virus protects against cervical cancer and other HPV-associated cancers.

Percent Response Rate: 95.7%, from 287 of 300 surveys. Table 14 and Figure 10 represent the distribution of responses from all respondents for Q19, also stratified by *Gender*.

Table 21 represents the bivariate analyses conducted and matrices of p-values.

These data revealed: 4 statistically significant associations with Category 1 variables reflecting Socio-demographics: *Nationality* ($p=0.0000026$); *Gender* ($p=0.0002238$); *Marriage duration* ($p=0.0273$); and *Employment in the healthcare sector* ($p=0.003599$).

These overall findings suggest that statistically significant differences exist between respondents based on likely protection through HPV vaccination. However, due to study limitations these associations may be potentially unreliable.

Remarks:

From 287 respondents, the largest proportion of responses indicated that HPV vaccination may protect against CxCa, 180 (62.7%); followed by *No*, 6 (2.10%), and *Don't know*, 101 (35.2%). That 35.2% of respondents indicated no knowledge that HPV vaccination may protect against CxCa is relevant to the hypotheses in this dissertation, and perhaps a major finding as HPV vaccination was recently rolled out in the State of Qatar in February 2018. Of the women respondents, 26.5% indicated no knowledge of protection against CxCa from HPV vaccination.

Nevertheless, despite the study limitations and the recent introduction of HPV vaccination in Qatar, it may take numerous years before the impact of this initiative may be epidemiologically validated. As such, this initiative should not be taken to imply that Pap testing be diminished. Therefore, health promotion for both Pap testing and for HPV vaccination ought to be executed in parallel, and their effectiveness would depend on public awareness and acceptance, and on framing approaches to convey awareness considering the various nationalities of expatriates residing in Qatar.

Relevant Research:

No pertinent survey-based research pertaining to HPV vaccination could be identified arising from Qatar. Nevertheless, a literature search was conducted to uncover studies to correlate with the data generated from this dissertation. That 35.2% of all respondents in this dissertation indicated having no knowledge of HPV vaccination is considered a significant health literacy finding.

Studies by Senapati, Nayak, Kar, & Dwibedi (2017) reported that the risk associated with the potential development of CxCa is HPV genotype specific, and may be linked with HPV genotype co-infections, or multiple infections. Therefore, an awareness of the prevalent HPV genotypes in the Qatar clinical setting would be of epidemiological value as vaccination programs are being implemented. Jumaan, Ghanem, Taher, Braikat, Al Awaidy, & Dbaido (2013) studied the likely prospects and challenges that may arise from HPV vaccination in the EMENA region. Of the barriers that they uncovered, they reported the most impactful may be the relatively poor understanding of CxCa and HPV vaccination amongst parents, physicians, and government officials. Their study concluded that for HPV vaccination to be successful in the EMENA countries, and as physicians are very influential, it is crucial that clinicians are well aware of the target practices in order to promote vaccination.

Jumaan, Ghanem, Taher, Braikat, Al Awaidy, & Dbaido (2013) also emphasized that physicians' awareness of HPV vaccination in the EMENA region is scarce. In a study by Saqer, Ghazal, Barqawi, Babi, AlKhafaji, & Elmekresh (2017) to assess knowledge of HPV vaccination in Sharjah, a United Arab Emirate, revealed that despite the general public's lack of knowledge pertaining to HPV vaccination, parents showed a willingness to vaccinate their daughters if government recommended the practice, and also provided the vaccine. The prevalence of HPV and CxCa in Qatar was studied by Afifi, Altaher, & Abushareeda in 2005. Their studies revealed that HPV infections commenced with early marriage and frequent coitus from early in life, and with

increasing number of pregnancies, and that these parameters are associated with cervical carcinogenesis amongst women in Qatar. Moreover, their studies revealed that older women in Qatar failed to realize that the risk of developing CxCa does not reduce with age; therefore, it is important that they seek cervical sampling accordingly.

Bansal, Elmi, Skariah, Haddad, Abu-Raddad, Al Hamadi, Mohamed-Nady, Affifi, Ghedira, Hassen, Al-Thani, Al-Ansari, & Sultan (2014) studied the distribution of HPV genotypes amongst Arab women in the State of Qatar. Their studies analyzed the prevailing HPV genotypes depending on cytologic findings. Bansal et al., (2014) reported that HPV 16 was the prevalent genotype amongst women with normal cytologic findings, and that HPV 16, 18 and 56 were the most prevalent amongst women with abnormal cytologic findings. Moreover, Bansal et al., (2014) discovered a high prevalence of HPV 81 amongst the low-risk HPV lesions. They claimed these findings are unique to the Arab population in Qatar, and unlike the epidemiology of HPV infection in western nations.

Work by Leader, Weiner, Kelly, Hornik, & Capella (2009) revealed that women may be more receptive to HPV vaccination if it is framed as a tool by which to prevent CxCa, rather than for the prevention for sexually transmitted infections. Moreover, as HPV vaccination is targeted towards adolescents and young adults, the school and academic settings may play a significant role in promoting the uptake of HPV vaccination through improved awareness of CxCa (Desiante, Russo, Giorgino, Caputi,

Battista, Cipriani, & Conversano, 2017). Such an approach would greatly improve the overall knowledge base of CxCa and that of the Pap test in the State of Qatar.

Q20 Menopausal women need a Pap test.

Percent Response Rate: 93.7%, from 281 of 300 surveys. Table 15 and Figure 11 represent the distribution of responses from all respondents for Q20, also stratified by *Gender*.

Table 21 represents the bivariate analyses conducted and matrices of p-values.

These data produced 2 statistically significant associations with Category 1 variables reflecting Socio-demographics: *Nationality* ($p=0.01045$); and *Employment in the healthcare sector* ($p=0.02444$).

These overall findings suggest that statistically significant differences exist between respondents based on menopausal women needing a Pap test, depending on nationality and employment in the healthcare sector although such employment is a potential limitation in the study. As such, the aforementioned associations may be unreliable.

Remarks:

From 281 respondents, the largest proportion of responses indicated that menopausal women need a Pap test, 194 (69.0%); followed by *No*, 8 (2.80%), and *Don't know*, 79 (28.2%). That 28.2% of respondents indicated no knowledge that menopausal women need a Pap test is relevant to the hypotheses in this dissertation. Of the women respondents, 23.1% indicated no knowledge that menopausal women need a Pap test.

It is speculated that such lacking health literacy amongst women may result from equally lacking perceptions of susceptibility to CxCa development.

Relevant Research:

No pertinent survey-based research pertaining to menopausal women and their need for Pap testing could be identified arising from Qatar. It is believed that this dissertation reflects the first such initiative. However, Afifi, Altaher, & Abushareeda (2005) revealed that older women in Qatar were inadequately aware that their risk of developing CxCa does not diminish with age; therefore, it is important they seek cervical sampling accordingly. The data arising from this dissertation are consistent with such findings.

Interpretation Of Self-Efficacy And Perceptions Research Data (Questions: 21-30)

Q21 More information is needed to improve your knowledge of cervical cancer.

Percent Response Rate: 95.3%, from 286 of 300 surveys. Table 15 and Figure 11 represent the distribution of responses from all respondents for Q21, also stratified by Gender.

Table 22 represents the bivariate analyses conducted and matrices of p-values.

These data produced 3 statistically significant associations with Category 1 variables reflecting Socio-demographics: *Age group* ($p=0.04504$); *Marital status* ($p=0.01028$); and *Marriage duration* ($p=0.02365$).

These overall findings suggest that statistically significant differences exist between respondents based on need for additional CxCa information, relevant to age

group, marital status, and marriage duration; although marriage duration is a potential limitation in this study, hence the association may be unreliable.

Remarks:

From 286 respondents, the largest proportion of responses indicated *Strongly agree*, 147 (51.4%); followed by *Agree*, 117 (40.9%). That 92.3% of respondents indicated *Strongly agree + Agree*, is relevant to the hypotheses in this dissertation. Of the women respondents, 52.7% indicated strong agreement for additional information about CxCa.

Relevant Research:

No pertinent research identified.

Q22 Regular Pap tests are a good health practice.

Percent Response Rate: 95.3%, from 286 of 300 surveys. Table 15 and Figure 12 represent the distribution of responses from all respondents for Q22, also stratified by *Gender*.

Table 22 represents the bivariate analyses conducted and matrices of p-values.

These data produced no statistically significant associations with Category 1 variables reflecting Socio-demographics.

However, these findings may represent women's perceptions of beneficial health protection through regular Pap testing; perhaps Pap test rhythmicity is perceived positively. Nevertheless, of the women respondents in this study, 4.14% were undecided. These findings may facilitate targeted health promotion initiatives in Qatar.

Remarks:

From 286 respondents, the largest proportion of responses indicated *Strongly agree*, 196 (68.5%); followed by *Agree*, 72 (25.1%). That 93.7% of respondents indicated *Strongly agree + Agree*, is relevant to the hypotheses in this dissertation. Of the women respondents, 69.8% indicated strong agreement.

Relevant Research:

Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) posed a related question in their survey: "Is early detection of CxCa good for treatment outcome?" Their study reported that 64.8% of the surveyed women agreed with this question, whereas, 35.2% disagreed.

Q23 Getting a Pap test performed is too difficult.

Percent Response Rate: 94.7%, from 284 of 300 surveys. Table 16 and Figure 12 represent the distribution of responses from all respondents for Q23, also stratified by *Gender*. Table 22 represents the bivariate analyses conducted and matrices of p-values.

These data produced 1 statistically significant association with Category 1 variables reflecting Socio-demographics: *Marriage duration* ($p=0.04028$). However, marriage duration is a limitation in this study and the association may be unreliable.

Remarks:

From 284 respondents, the largest proportion of responses indicated *Strongly disagree*, 116 (40.8%); followed by *Undecided*, 85 (29.9%). That 40.8% of respondents

indicated *Strongly disagree*, is relevant to the hypotheses in this dissertation. However, of the women respondents, 38.1% indicated disagreement, but 6.55% strongly agreed that getting a Pap test performed is too difficult. These findings may suggest that 6.55% of women faced overwhelming barriers to Pap test uptakes.

Relevant Research:

Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) posed a related question in their survey: "If you were told that a Pap test is a simple, painless and good for early detection of CxCa, would you like to have one?" Their study reported that 85.8% of the surveyed women agreed with this question, whereas, 14.2% disagreed

Q24 You would recommend a Pap test to your family, friends, and colleagues.

Percent Response Rate: 95.0%, from 285 of 300 surveys. Table 16 and Figure 13 represent the distribution of responses from all respondents for Q24, also stratified by *Gender*.

Table 22 represents the bivariate analyses conducted and matrices of p-values.

These data produced 1 statistically significant association with Category 1 variables reflecting Socio-demographics: *Employment status* ($p=0.04067$).

These overall findings suggest that employed women, being likely more health literate of CxCa, may be more willing to recommend the Pap test to other women.

Remarks:

From 285 respondents, the largest proportion of responses indicated *Strongly agree*, 177 (62.1%); followed by *Agree*, 89 (31.6%). Of the women respondents, 64.5%

strongly agreed to recommend the Pap test to family, friends, and colleagues; however, 5.32% of respondent women were undecided, although none disagreed.

Relevant Research:

No pertinent research identified.

Q25 Getting a Pap test is a valued investment for good healthcare.

Percent Response Rate: 96.0%, from 288 of 300 surveys. Table 16 and Figure 13 represent the distribution of responses from all respondents for Q25, also stratified by *Gender*.

Table 22 represents the bivariate analyses conducted and matrices of p-values.

These data produced no statistically significant associations with Category 1 variables reflecting Socio-demographics.

Overall findings may suggest positive perceptions amongst women for the likely investment value in Pap testing.

Remarks:

From 288 respondents, the largest proportion of responses indicated *Strongly agree*, 177 (61.5%); followed by *Agree*, 95 (33.0%). That 94.4% of respondents indicated *Strongly agree + Agree*, is relevant to the hypotheses in this dissertation. Of the women respondents, 61.5% strongly agreed that the Pap test is a valued investment.

Relevant Research:

No pertinent survey-based research pertaining to value of investment in a Pap test could be identified arising from Qatar. It is believed that this dissertation reflects the first such initiative.

Q26 You would support a Pap test screening program for cervical cancer.

Percent Response Rate: 95.7%, from 287 of 300 surveys. Table 17 and Figure 14 represent the distribution of responses from all respondents for Q26, also stratified by *Gender*. Table 23 represents the bivariate analyses conducted and matrices of p-values.

These data produced no statistically significant associations with Category 1 variables reflecting Socio-demographics.

These overall findings suggest equivalent perceptions of screening practice for CxCa amongst women and men in the State of Qatar.

Remarks:

From 287 respondents, the largest proportion of responses indicated *Strongly agree*, 196 (68.3%); followed by *Agree*, 81 (28.2%). That 96.5% of respondents indicated *Strongly agree + Agree*, is relevant to the hypotheses in this dissertation. The frequencies of support for a screening program between women and men respondents were essentially equal: 69.0% and 67.2% respectively. These findings reflecting public support may facilitate targeted health promotion initiatives in Qatar.

Relevant Research:

No pertinent survey-based research pertaining to public support for a Pap test screening program for CxCa could be identified arising from Qatar. It is believed that this dissertation reflects the first such initiative and data.

Q27 A formal Pap test screening program for cervical cancer should be established for all women in the State of Qatar.

Percent Response Rate: 95.3%, from 286 of 300 surveys. Table 17 and Figure 14 represent the distribution of responses from all respondents for Q27, also stratified by *Gender*.

Table 23 represents the bivariate analyses conducted and matrices of p-values.

These data produced no statistically significant associations with Category 1 variables reflecting Socio-demographics.

These overall findings suggest equivalent perceptions of screening practice for CxCa amongst women and men in the State of Qatar.

Remarks:

From 286 respondents, the largest proportion of responses indicated *Strongly agree*, 193 (67.4%); followed by *Agree*, 78 (27.2%). That 94.8% of respondents indicated *Strongly agree + Agree*, is relevant to the hypotheses in this dissertation. The frequencies of support for a screening program between women and men respondents were essentially equal: 69.0% and 65.3% respectively. These findings demonstrated strong support amongst women and men respondents that the State of Qatar ought to establish

a formal screening program for all resident women. These findings reflecting public support may facilitate targeted health promotion initiatives in Qatar.

Relevant Research:

No pertinent survey-based research pertaining to public support for the establishment of a formal Pap test screening program for CxCa for all women in the State of Qatar could be identified arising from Qatar. It is believed that this dissertation reflects the first such initiative and data.

Q28 You know where to go to get a Pap test performed.

Percent Response Rate: 94.0%, from 282 of 300 surveys. Table 17 and Figure 15 represent the distribution of responses from all respondents for Q28, also stratified by *Gender*.

Table 23 represents the bivariate analyses conducted and matrices of p-values.

These data produced 1 statistically significant association with Category 1 variables reflecting Socio-demographics: *Nationality* (p=0.003118).

These overall findings suggest that statistically significant differences exist between respondents based on Nationality, relevant to knowledge of where to get a Pap test performed.

Remarks:

From 282 respondents, the largest proportion of responses indicated *Strongly agree*, 88 (31.2%); followed by *Agree*, 84 (29.8%). That 61.0% of respondents indicated *Strongly agree + Agree*, is relevant to the hypotheses in this dissertation. However, of the

women respondents, 16.4% were undecided, 12.7% disagreed, and 6.67% strongly disagreed to knowing where to get a Pap test performed. These findings likely reflected inadequacies in healthcare services availability and health literacy in general.

Relevant Research:

Survey-based research by Alali et al., (2016) revealed that 94.5% of respondent women in Qatar preferred female physicians to male clinicians; and survey research by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) revealed that 55.4% of clinical staff employed in PHCC centers in Qatar would agree to see gynecologists in well women's clinics. Nonetheless, data from this dissertation revealed that 16.4% of respondent women were undecided as to where to get a Pap test performed. This is regarded a significant finding.

Q29 A Pap test has no value for you.

Percent Response Rate: 94.7%, from 284 of 300 surveys. Table 18 and Figure 15 represent the distribution of responses from all respondents for Q29, also stratified by *Gender*. Table 23 represents the bivariate analyses conducted and matrices of p-values.

These data produced 1 statistically significant association with Category 1 variables reflecting Socio-demographics: *Marriage duration* ($p=0.01878$). However, Marriage duration is a potential limitation in this study and the association may be unreliable.

Remarks:

From 284 respondents, the largest proportion of responses indicated *Strongly disagree*, 138 (48.5%); followed by *Disagree*, 103 (36.3%). That 84.9% of respondents indicated *Strongly disagree + Disagree*, is relevant to the hypotheses in this dissertation. Of the women respondents, 54.5% indicated strong disagreement; however, 6.58% were undecided. These overall findings likely reflect inadequacies in Self-efficacy & Perceptions, and Health literacy, and may facilitate targeted health promotion initiatives in Qatar.

Relevant Research:

No pertinent survey-based research pertaining to public perceptions of personal value gained from a Pap test could be identified arising from Qatar. It is believed that this dissertation reflects the first such initiative and data. Nonetheless, survey-based research by Alali et al., (2016) revealed that 57.8% of respondent women in Qatar did not perceive that they were at risk for developing CxCa therefore a Pap test was not a priority for them.

Q30 If a self-test for cervical cancer was available you would prefer it?

Percent Response Rate: 94.3%, from 283 of 300 surveys. Table 18 and Figure 16 represent the distribution of responses from all respondents for Q30, also stratified by *Gender*. Table 23 represents the bivariate analyses conducted and matrices of p-values.

These data produced no statistically significant associations with Category 1 variables reflecting Socio-demographics.

These overall findings may be reflective of cultural norms in a conservative society as that in the State of Qatar.

Remarks:

From 283 respondents, the largest proportion of responses indicated *Strongly agree*, 123 (43.4%); followed by *Agree*, 88 (31.0%). That 74.6% of respondents indicated *Strongly agree + Agree* for a preference for self-testing for CxCa is an important finding. Of the women respondents, 43.5% strongly agreed, and 29.2% agreed. These findings led to a combined 72.6% agreement from women respondents that they would prefer a self-sampling approach if available.

Relevant Research:

No pertinent survey-based research pertaining to self-testing for CxCa could be identified arising from Qatar. As HPV vaccination was recently rolled out in the State of Qatar in February 2018, a literature search was conducted to uncover studies to correlate with the data generated from this dissertation relevant to self-testing

In the US, Des Marais, Zhao, Hobbs, Sivaramam, Barclay, Brewer, & Smith (2018) studied the likely acceptance of home self-collection of samples for HPV and sexually transmitted infections. Their studies revealed that most participants (93.6%) indicated not having difficulties in understanding the method and purpose of self-collection, and that 96.3% of the participating women showed a willingness to apply this method. Related cross-sectional studies by Chen, Hsieh, Chou, & Tzeng (2014) attempted to

determine likelihood of women in Taiwan to apply self-sampling methods for HPV to screen for CxCa. Their studies concluded that outreach efforts to promote self-sampling for HPV ought to target women that have had a Pap test, who perceive themselves as being susceptible to both HPV infection and CxCa, and women who declare a willingness to apply the method.

Gupta, Palmer, Bik, Cardenas, Nunez, Kraal, Bird, Bowers, Smith, Walton, Goddard, Almonacid, Zneimer, Richman, & Apte (2018) concluded that self-sampling for HPV is a method potentially well suited to mitigate barriers such as embarrassment, and particularly for women not participating in screening programs. It is surmised that in the clinical setting of Qatar, self-testing methods may overcome various barriers to Pap test sampling either perceived or experienced by women. Bais, van Kemenade, Berkhof, Verheijen, Snijders, Voorhorst, Babovic, van Ballegooijen, Helmerhorst, & Meijer (2006) concluded that cervicovaginal self-sampling using brushes may be an effective alternative method to protect women that may not respond to calls for Pap test sampling.

Particular Consideration: Sub-Set Of Married Women In The State Of Qatar Never Before Having A Pap Test

The highly statistically significant association ($p=0.000000008$) revealed from this research between the variables: *Age group* (Q3) and *Had a Pap test before?* (Q9) warranted particular consideration and critical analysis. This association defined a sentinel group

of women respondents that had never had a Pap test. An effort was launched to filter through the data to uncover the likely barriers, and potential epidemiological impact.

This sub-set of women respondents that claimed never before having a Pap test was particularly relevant to the basis of this research work. As such, the aforementioned association was regarded as being epidemiologically significant and likely to yield impactful insights relative to the hypotheses posed through this dissertation.

To explore this association in greater detail, categorical data captured specifically from these women respondents were sorted and analyzed to initially determine their ages. From the total of 173 women that participated in this study (Table 10), 79 (45.7%) claimed never to have had a Pap test. This group of women produced a primary age group of 20-29 years (53.2%), followed by a secondary age group of 30-39 years (30.4%). For practicality, combined, these women formed a sub-set of respondents accounting for 45.7% of all the women that participated in this survey-based research.

The age range of this sub-set of women may be epidemiologically significant particularly in the clinical setting of the State of Qatar. As the bimodal peak ages of CxCa cases presenting with Stage II/III disease in Qatar in 2014 were 40-44 and 60-64 years respectively (QMoPH National Cancer Program, 2014), this sub-set of respondent women that never had a Pap test may represent a cohort of women with preclinical CxCa; whereby, their progressing cervical pathobiology may be asymptomatic, and therefore not clinically suspected. In theory, based on the discussions in Chapter 3, such women may align clinically with the one million women globally that are unaware of

their cervical disease as estimated by the WHO (World Health Organization, 2014). Thus, it may be these very women that would benefit the most from optimized Pap test screening practices in the State of Qatar. Likewise, an increased sense of disease susceptibility through targeted health promotion may also encourage these women particularly to actively seek medical care, as was concluded by the Memphis and Shelby County trial in 1951.

Analysis of additional categorical data specifically sorted from this sub-set of respondent women revealed the following parameters; that: 82.2% had a University level education; 83.5% had health insurance coverage; and, that their nationalities were Asian, African, and Qatari by decreasing frequencies (i.e., 48.1%, 18.9% and 12.7% respectively).

More importantly, however, of these 79 women, 35 (44.3%) were married, and 42 (53.2%) were never married. When analyzed in greater detail, this differential produced valuable epidemiological insights.

The 53.2% of these 79 women that were neither married nor Pap test screened correlated with the clinical recommendations enforced in the State of Qatar. Currently, it is recommended that Pap test services be made available to women aged 25 to 64, and when sexually active, according to the *Guidelines For Cervical Cancer Screening In The State of Qatar* (QMoPH National Cancer Program, 2016¹) (Appendix F). Therefore, Pap testing in these unmarried women would be discouraged by the medical establishment, unless they are symptomatic, reflecting the hallmarks of opportunistic screening.

However, the 44.3% of these 79 respondent women that were married and sexually active and not Pap tested, posed a unique opportunity for methodical review. These married women may be at greater risk for developing CxCa than the women never married. This presumption may be valid as these women could have been Pap test screened given the current guidelines, but were not. It was prudent to conduct a methodical data analysis to explore the responses arising from this specific sub-set of 35 respondent women.

The analysis revealed the following categorical data reflecting Healthcare services, Health literacy, and Self-efficacy & Perceptions, as indicated by the respondent 35 women:

- 20.0% had no health insurance coverage (Q8);
- 31.4% had no awareness of the Pap test cytologic method (Q13);
- 22.9% had no knowledge of CxCa (Q15);
- 11.4% had no knowledge that early detection of CxCa is important for effective treatment (Q16);
- 14.2% had no knowledge that regular Pap tests may protect for CxCa (Q17);
- 28.6% did not know that CxCa may be curable (Q18);
- 31.4% did not know that HPV vaccination may protect against CxCa (Q19);
- 48.5% strongly agreed to needing additional information of CxCa (Q21);
- 17.1% agreed that getting a Pap test is too difficult (Q23);

- 85.7% strongly agreed + agreed that a formal screening program be established in the State of Qatar for all women (Q27);
- 34.2% agreed to knowing where to go to get a Pap test performed (Q28);
- 42.9% strongly disagreed that a Pap test has no value for them (Q29);
- 77.1% strongly agreed + agreed that they would prefer a self-test for CxCa if this option was available.

If the frequencies revealed from this sub-set of women respondents may be taken as being representative, then their extrapolation onto the entire population of women in the State of Qatar in 2018, may potentially reflect 45.7% of 676,137 women, equating to 308,994 women in Qatar never before having a Pap test (World Population Review, 2018¹). And similarly, 44.3% of these 308,994 women may potentially equate to 136,884 women in Qatar that may be married, eligible to receive a Pap test, but not being Pap test screened unless symptomatic. Such plausible realities may also explain, at least partially, the purportedly relatively low prevalence of CxCa in the State of Qatar largely due to opportunistic screening practice.

From the remarkable data that emerged reflecting this specific sub-set of respondent women, preliminary findings arising from this research were described in an Abstract/ePoster, and submitted for publication and presentation in the International Academy of Cytology Congress in Sydney, Australia, May 5-9, 2019 (Appendix M).

Conclusions Arising From Dissertation Aims

In this section, salient data and figures are converged in an effort to support the hypotheses raised in this dissertation; and based on this discussion, to propose Opportunities for Improvement with relevance to the clinical setting in the State of Qatar.

Dissertation Aim 1

Dissertation Aim 1 proposed an evaluation of the degree of health literacy in women and men in the State of Qatar of CxCa; of Pap test screening and of its benefits and uptakes; and, of HPV vaccination. Based on Dissertation Aim 1, it was hypothesized that:

The majority of women and men in the State of Qatar have adequate health literacy of CxCa; however, they lack commensurate awareness of the disease prevention benefits possible through Pap test screening and HPV vaccination.

The overall data captured from this needs-assessment research upheld the hypothesis put forward. From the entire data set reflecting the views of women and men, the following was revealed relevant to Hypothesis 1:

Health Literacy Of Cervical Cancer:

- Q12 (*CxCa may be preventable*): Yes (84%), Don't know (15%) (Table 12, Figure 7)
- Q15 (*You have knowledge of CxCa*): Yes (70%), No (30%) (Table 13, Figure 8)

- Q16 (*Early detection of CxCa is important for treatment*): Yes (93.4%), Don't know (6.2%) (Table 13, Figure 9)
- Q18 (*CxCa may be curable*): Yes (65.5%), Don't know (31.8%) (Table 14, Figure 10)
- Q21 (*More information is needed about CxCa*): Strongly agree (51.4%) (Table 15, Figure 11)

Health Literacy Of Pap Test Screening:

- Q13 (*You are aware of the Pap test cytologic method*): Yes (66.3%), No (33.7%) (Table 12, Figure 7)
- Q17 (*Regular Pap test may protect you against CxCa*): Yes (84.9), Don't know (12.2%) (Table 14, Figure 9)
- Q20 (*Menopausal women need a Pap test*): Yes (69%), Don't know (28.2%) (Table 15, Figure 11)
- Q22 (*Regular Pap tests are a good health practice*): Strongly agree (68.5%) (Table 15, Figure 12)
- Q25 (*Getting a Pap test is a valued investment*): Strongly agree (61.5%) (Table 16, Figure 13)
- Q28 (*Know where to get a Pap test done*): Strongly agree (31.2%) (Table 17, Figure 15)

Health Literacy Of HPV Vaccination:

- Q19 (*HPV vaccination may protect against CxCa*): Yes (62.7%), Don't know (35.2%) (Table 14, Figure 10)

Of the aforementioned 12 survey questions, 8 revealed statistically significant associations with respondents' likely employment in the healthcare sector. These findings emphasized the impact of differences in health literacy between individuals that work in healthcare, arguably more medically literate, compared to those that did not. Overall, the data suggests that women and men in the State of Qatar are generally aware of CxCa (70% of all respondents indicated *Yes*); however, a commensurate awareness of the disease prevention benefits possible through Pap test screening and HPV vaccination was relatively lower; whereas, 66.3% of respondents indicated an awareness of the Pap test cytologic method; and 62.7% of respondents indicated an awareness of HPV vaccination benefits. Nevertheless, while these frequencies reflecting *awareness* may appear relatively similar, the indications by respondents reflecting *no awareness* are more significant; whereas, 31.8% of respondents did not know that CxCa may be curable, as compared with 33.7% of respondents that did not know of the Pap test; and 35.2% of respondents that did not know HPV vaccination may protect against CxCa.

Therefore, if indeed 33.7% of the general public in Qatar has no awareness of the Pap test, then this may translate to essentially 1/3 of the female population at risk for

developing CxCa also not knowing the benefits of Pap test sampling. This reality may be deemed alarming.

These differences in awareness may be explained by the relatively high degree of academic literacy amongst the public in Qatar and the astonishing initiatives by the QMoPH and the QCS to raise awareness of CxCa overall, and, by the lack of organized screening in Qatar. As Pap test screening is neither endorsed as a population-based disease prevention tool, nor recommended equivalently for all women deemed at risk for developing this disease, a differential of awareness potentially exists between the public's knowledge of the disease, and its knowledge of the methods through which to detect it and protect one's self from it.

Relative to Dissertation Aim 1, and the arising hypothesis, another remarkable finding was the identification of the sub-set of married women that never had a Pap test. Given their specific ages ranging between 20 and 39 years of age, these women likely comprise a cohort at highest risk for developing CxCa. This research revealed that of these specific women: 22.9% indicated no knowledge of CxCa; compared with 31.4% that indicated no awareness of the Pap test; and, also 31.4% that indicated no awareness of the disease prevention benefits possible through HPV vaccination. Moreover, 48.5% of these specific women indicated a need to acquire additional knowledge of CxCa.

Therefore, while this dissertation demonstrated adequate health literacy amongst women and men in Qatar for CxCa, it also revealed relatively lacking commensurate

health literacy for disease prevention benefits possible through Pap test cytopathology and HPV vaccination.

Dissertation Aim 2

Dissertation Aim 2 proposed an evaluation of the degree of support in women and men in the State of Qatar for the establishment of a formal Pap test screening program for all women. Based on Dissertation Aim 2, it was hypothesized that:

The establishment of a formal Pap test screening program for CxCa for all women in the State of Qatar is strongly supported by women and men.

The overall data captured from the needs-assessment research upheld the hypothesis put forward. From the entire data set reflecting the views of women and men, the following was revealed relevant to Hypothesis 2:

Support For Population-Based Cervical Cancer Screening In The State Of Qatar:

- Q26 (*You would support a Pap test screening program*): Strongly agree (68.3%), Strongly disagree (0.00%) (Table 17, Figure 14)
- Q27 (*A formal Pap test screening program for cervical cancer should be established for all women in the State of Qatar*): Strongly agree (67.4%), Strongly disagree (0.00%) (Table 17, Figure 14)

Although neither of the aforementioned questions revealed notable statistically significant dependencies with other variables, the data suggests that women and men in the State of Qatar strongly support the establishment of a formal CxCa screening

program for all women. Of all respondents, 67.4% strongly agreed with this proposition.

In contrast, from the sub-set of married women that had never before had a Pap test, 85.7% strongly agreed + agreed to the establishment of a formal screening program.

Therefore, this dissertation demonstrated strong support by women and men respondents for the establishment of a formal Pap test screening program for CxCa for all women in the State of Qatar.

Dissertation Aim 3

Dissertation Aim 3 proposed an evaluation of possible similarities of extent of CxCa at presentation and diagnosis between the contemporary Qatar experience and the historical experience in the US prior to the introduction of clinical population-based Pap test screening in 1957. Based on Dissertation Aim 3, it was hypothesized that:

The extent of CxCa at presentation and diagnosis in the historical US experience, prior to the introduction of clinical population-based Pap test screening in 1957, bears similarities with the current experience of CxCa presentation in the State of Qatar mainly due to opportunistic Pap test uptakes.

The data that was reviewed and correlated relevant to Dissertation Aim 3, revealed various parallels between the historical experience in the US and the contemporary experience in the State of Qatar pertaining to CxCa management, and upheld the hypothesis put forward.

Opportunistic Cervical Sampling:

Arguably, the detection of CxCa during the 1920s and 1930s in the US, and in the modern Qatar setting, aligned with opportunistic cervical sampling. In the US, symptomatic women received a reflex biopsy; in Qatar they received a reflex Pap test. In either situation, disease identification was prompted by clinical symptoms raising the suspicion of CxCa. However, what is unique from this parallel between the US and the Qatar experiences is that the potential benefits from systematic Pap test screening were unknown in the 1920s and 1930s.

Advanced-Stage Cervical Cancer At Presentation:

The alarming priorities due to CxCa experienced in contemporary developing regions are not unlike the presentation and burden of disease experienced in the US prior to formalization of Pap test screening in the late-1950s. A striking parallel between the historical experience in the US and the contemporary Qatar experience was the 60% of inoperable CxCa cases at presentation and diagnosis during the mid-1940s in the US (Meigs, Graham, Fremont-Smith, Kapnick, & Rawson, 1943). Those outcomes were remarkably similar with the 60% of cases presenting with Stage II/III CxCa in Qatar primarily because of opportunistic screening in 2014 (QMoPH National Cancer Program, 2014).

Also, Meigs, Graham, Fremont-Smith, Janzen, & Nelson (1945) reported that despite best practice in 1945, the possible cure rate for CxCa was 40%; implying, that the

death rate would likely have been essentially 60%. These findings form another possible parallel with the contemporary Qatar experience of advanced disease at presentation.

Death Rates Due To Cervical Cancer:

Despite the aforementioned likely death rates from CxCa in the mid-1940s in the US, the death rate in modern practice as a result of Pap test screening practices has fallen to a 32.2% US-specific death rate according to the ACS (American Cancer Society, 2018). Currently in Qatar, from the 15 CxCa cases estimated annually by the ICO, the estimated death rate from CxCa is at 26.7% (Institut Catala d'Oncologica, 2017²). The literature reviews conducted for this dissertation did not reveal a plausible scenario to explain this parallel; however, as 72% of the CxCa cases in Qatar are seen typically in expatriate women, it is likely that these women repatriate to their homelands post-diagnosis for treatment, and may be therefore lost to follow-up.

Cervical Cancer Case Registries:

In 1914, the ASCC collaborated with the *Department Of Commerce, United States of America, Bureau Of The Census*, to produce a detailed registry of deaths throughout the US based on estimated population growth; cancer type; patient age group; gender; and, State of residence. This initiative produced a mammoth publication listing numbers of deaths; it was essentially a death registry. However, it was not until 1952, and henceforth, that the American Cancer Society published *Cancer Facts And Figures* annually to include data for CxCa (Thun, Calle, Rodriguez, & Wingo, 2000). This was prompted by the Memphis trial that recommended tracking of CIS. The ACS's *Cancer*

Facts And Figures not only tracked death rates, it also tracked actual incidence rates based on robust data collection and analysis.

Currently in Qatar, the *National Cancer Registry* initiative was launched at HMC in 2012 to record prevalence statistics from cancer cases (A.A. Hmaidan; personal communication, March 21, 2016). Prevalence statistics prior to 2012 were computed from case studies based on treatment course and outcomes, hence regarded potentially inaccurate. As such, epidemiologically-accurate cancer statistics became available in Qatar from 2012 henceforth through the *National Cancer Program*. Hence a major part of historical case and death statistics due to CxCa is unavailable. These realities form another parallel between the US and Qatari experiences.

Therefore, epidemiological data reviews and correlations conducted for this dissertation demonstrated various parallels between the historical US experience and the contemporary experience arising from CxCa management in the State of Qatar. It is concluded that these parallels stemmed from the commonality of opportunistic cervical sampling.

Opportunities For Improvement

In this section, the author proposes opportunities for improvement in an effort to optimize existing Pap test cervical sampling practices in the State of Qatar. The below-mentioned proposals arise based on the research outcomes herein described. It is once again prudent to emphasize the remarkable investments allocated towards cytopathology services and the overall initiatives conducted to raise awareness of CxCa

in Qatar. However, data arising from this dissertation revealed major gaps in Health Literacy and in the public's sense of Self-efficacy & Perceptions towards the uptake of Pap test services and HPV vaccination.

Tumor Registry:

Proposed is the development and implementation of a robust Tumor Registry in the State of Qatar for CxCa.

The likely benefits may be potentially significant. Habbema, De Kok, & Brown (2012) described the impact of such a system in the burgeoning screening systems for CxCa in the Netherlands. A Tumor Registry designed to track all cases may also suffice as a registry of all women residing in Qatar age 15 and older, and therefore those women deemed at risk for developing CxCa. As all residents in Qatar have a QID residency number, the Tumor Registry may track all women using the QID system. Such a Registry may also form the platform for organized screening by registering initial call to screening, by tracking adherence to rescreening recommendations based on cytopathologic findings, and by monitoring the follow-up timelines and surgical pathology outcomes arising from pathologic cases.

Such a Tumor Registry would better track intraepithelial and invasive disease, and therefore result in accurate epidemiological statistics inclusive of CIS and invasive CxCa, leading to reliable statistics by which to assess incidence, prevalence, and treatment effectiveness. A Tumor Registry would also track women regardless of transience. It is inevitable that with the large population of expatriate residents in Qatar,

women that may be lost to follow-up would pose a significant limitation in the calculation of actual incidence of CxCa in this small clinical setting. Ultimately, a potential decision to implement systematic Pap test screening in Qatar would rest upon accurate prevalence data. Therefore, a Tumor Registry may prove to be a most significant prerequisite infrastructure for system optimization.

Another potential benefit from a Tumor Registry would be the standardization of diagnostic and therapeutic practices conducted in Qatar between the private and public healthcare providers. Alignment of these disciplines may produce substantial information upon which to consider cervical sampling methods that would be tailored to this clinical environment (Al-Naggar, 2012, Khan & Woolhead, 2015).

A Tumor Registry may also facilitate targeted health literacy through specific apps disseminated throughout the extensive mobile phone networks in Qatar, based on age-group, nationality, and mother language.

Implementation Of Population-Based Screening For All Women:

Data revealed through this dissertation research amply support the design and implementation of population-based Pap test screening in Qatar.

The survey-based research conducted by Al-Meer, Aseel, Al-Khalaf, Al-Kuwari, & Ismail (2011) formed the closest study to the intents and purposes of this dissertation. Their report concluded that the gaps in health literacy that they uncovered were attributable to the lack of organized Pap test screening in Qatar. As such, based on the health literacy gaps revealed through this research, and the overwhelming public

support for such a system as evidenced by the survey respondents, population-based screening ought to be formally considered and implemented.

Another significant justification for Pap test population-based screening in Qatar is the recent implementation of HPV vaccination in this nation. Given the health literacy gaps pertaining to the awareness of HPV vaccination amongst the general public as represented by the respondents in this research, the impact of vaccination may not be fully realized for some time.

Another epidemiological determinant may be the unique prevalence of HPV genotypes in this clinical setting as reported by Bansal, Elmi, Skariah, Haddad, Abu-Raddad, Al Hamadi, Mohamed-Nady, Affifi, Ghedira, Hassen, Al-Thani, Al-Ansari, & Sultan (2014). As HPV 16 was shown to be prevalent in women in Qatar even with normal cytologic findings, continuous Pap test screening may be appropriate to track likely progressive cervical disease.

Whereas the Pap test may not prevent the biological initiation of cervical neoplasia, it may effectively prevent its progression to infiltrating disease by facilitating early detection, leading to timely surgical intervention and effective ablation. Furthermore, HPV vaccination may not protect women already infected, and which are therefore at risk for developing cervical cancer. Therefore, despite the potential for primary disease prevention through HPV vaccination in Qatar, systematic Pap test screening practices seem prudent to provide outreach and coverage for all women

deemed at risk for developing this disease as it may require decades of surveillance before the effect of vaccination is realized in this nation.

Managing Reallocation Of Financial Resources:

It is speculated that with a potential reduction in CxCa cases in the State of Qatar that may arise due to systematic screening, reallocation of saved financial resources may support expanded and financially sustainable Pap test screening (Goldie, Gaffikin, Goldhaber-Fiebert, Gordillo-Tobar, Levin, Mahe & Wright, 2005; Kim, Sharma, O'Shea, Sweet, Diaz, Sancho-Garnier, & Seoud, 2013). Based on studies by Pendrith, Thind, Zaric, & Sarma (2016), mitigation of the 18 cases of advanced CxCa that were reported in 2014 in Qatar, and the associated costs for treatment and follow-up, may have translated into an, albeit conservative, saving of 1.75 million Riyals. Such savings, possible through Pap test screening, and assuming the cost for a Pap test to be 200 Qatari Riyals (i.e., \$54.79 USD), may have supported reallocation of funds to support 8,750 Pap tests.

Although 83.5% of the 170 respondent women that participated in this research indicated having healthcare insurance, the remainder 16.5% of women claimed that they did not. Therefore, a relatively significant proportion of women in the State of Qatar may be facing financial obstacles in seeking and actually getting a Pap test performed.

Based on the overall discussions in Chapter 6, the converged survey-based data and conclusions arising from this dissertation, optimization and transformation of current opportunistic Pap test screening practices to systematic screening for CxCa in

the State of Qatar may be feasible, and particularly given the advanced cytopathology services already in operation at Sidra Medicine and HMC in this small clinical setting.

CHAPTER 7: EPILOGUE

It is an unfortunate contradiction that in the clinical setting of opportunistic screening, any woman ought to present with classical symptoms of invasive disease before the Pap test may have an opportunity to forewarn that she has cervical cancer. It is equally perplexing that in the modern epoch of unprecedented medical experience of cervical cancer and near-complete epigenetic and molecular characterization of this dreaded disease that any woman globally may not be able to undergo at least one episode of cervical sampling to test for likely preclinical disease.

Cervical sampling may take various forms: It may be a classic Pap test, a molecular HPV test, a self-test for HPV, or, simply, visualization of the uterine cervix to inspect for anatomical aberrations through the Schiller's iodine or acetic acid method. Options for secondary prevention of cervical cancer both basic and sophisticated are abundant. HPV vaccination for primary prevention of the disease is also available but requires time to mature, to yield clinical results. However, every effort is ethically required by the medical establishment to avoid the need for tertiary prevention: The radical methods oftentimes necessary to treat advanced cervical cancer, largely resulting from underperforming diagnostic screening practices in preventive and societal medicine.

The author has witnessed the impact of systematic cervical cancer screening in the backdrop of opportunistic screening vividly and definitively through specific career phases in the EMENA region.

After a 14-year career phase at the Health Sciences Center in Winnipeg, Canada, applying North American practices to manage cervical cancer, the author relocated to the King Faisal Specialist Hospital & Research Center (KFSH&RC) in Riyadh, Saudi Arabia, in December 1994. The KFSH&RC catered to the Royal family and employed 6,500 staff. The KFSH&RC had an outreach for nearly 25,000 individuals eligible to avail its medical services. The cytopathology service at KFSH&RC analyzed 8,000 Pap test cases annually. By applying systematic screening practices stipulated through CAP accreditation, none of the women with detected intraepithelial cervical disease developed invasive cancer. Yet, nearly 10 cases of advanced cervical cancer were experienced annually. These women presented to Emergency seeking much delayed care, and originated from outside the cervical sampling outreach of the KFSH&RC.

Subsequently, at King Abdulaziz Medical City hospital, in Riyadh, Saudi Arabia, where the service outreach expanded to over 54,000 individuals, predominantly military personnel and their extended families, intraepithelial disease was likewise managed, and development of invasive cervical cancer was negated successfully. Nevertheless, annually, nearly 12 cases of advanced cervical cancer were experienced; and, none of those women had ever had a Pap test, of any form.

These tertiary hospital experiences clearly distinguished the demarcations between opportunistic and systematic screening practices for cervical cancer. In essence, the screening outreach orbits of these two impressive medical institutions formed pockets of organized screening superimposed, not unlike islands, upon a greater landscape characterized as a sea of opportunistic screening throughout the vast Saudi Arabian heartland. Arguably, incremental expansion of the organized screening orbits would gradually phase out the opportunistic screening landscape; such a scenario would mirror the clinical screening experience in the US that has formed since 1957.

Most of those diseased women that presented to cytopathology declined treatment despite, oftentimes, favorable prognoses depending on disease-stage at diagnosis. The societal impact of cervical cancer in this conservative, matriarchically-structured culture is not only devastating it is also incalculable, due to its compounding ripple effect throughout all strata of society.

At the onset of this research work, it was merely hoped that the uncovered insights, data, and conclusions drawn, may *possibly* serve to optimize screening practice in the State of Qatar. With composition of this Epilogue, it is essentially *assured* that indeed, they may.

In the midst of this experience, insofar as cervical cancer is concerned, there is ample opportunity for political commitment, for revision of clinical philosophies, and for execution of optimized screening practices supported by strategic health promotion

initiatives. And, in the opinion of the author, these convictions have a global relevance, not just for the State of Qatar.

In closing, the author expresses utmost gratitude and extends sincere thanks to the University of Nebraska Medical Center for seeing merit in this scientific work in Preventive and Societal Medicine.

Nikolaos Chantziantoniou

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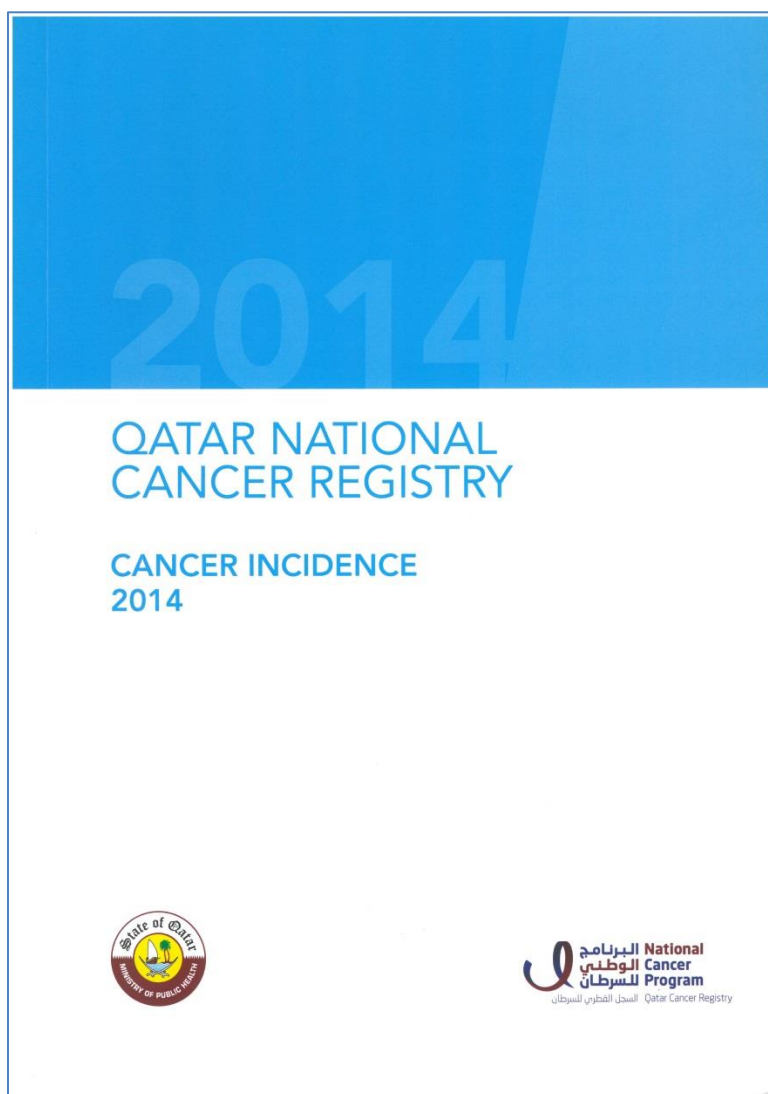
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APPENDICIES

Appendix A: National Cancer Program, Qatar National Cancer Registry 2014 report published by the Qatar Ministry of Public Health.

[<http://www.sidra.org/sidra-marks-international-pathology-day/>]



Appendix B: Needs-Assessment Survey (English version) [Protocol: MoPH-Sidra-IRB-099].



AWARENESS, KNOWLEDGE, AND PERCEPTIONS OF
SCREENING FOR CERVICAL CANCER, AND HUMAN
PAPILLOMAVIRUS VACCINATION IN QATAR

Respondent Number:

ANONYMOUS SURVEY FOR MEN AND WOMEN

| Questions (English) | |
|--|--|
| <p>1 Nationality</p> <ul style="list-style-type: none"> <input type="radio"/> Qatari <input type="radio"/> Middle Eastern <input type="radio"/> Asian <input type="radio"/> European <input type="radio"/> North American <input type="radio"/> South American <input type="radio"/> African <input type="radio"/> Other | |
| <p>2 Gender</p> <ul style="list-style-type: none"> <input type="radio"/> Female <input type="radio"/> Male | |

| | |
|---|--|
| <p>3 Age group (Years)</p> <ul style="list-style-type: none"><input type="radio"/> Under 20<input type="radio"/> 20-29<input type="radio"/> 30-39<input type="radio"/> 40-49<input type="radio"/> 50-59<input type="radio"/> Over 60 | |
| <p>4 Highest education level</p> <ul style="list-style-type: none"><input type="radio"/> Middle School<input type="radio"/> High School<input type="radio"/> University<input type="radio"/> Other | |
| <p>5 Marital status</p> <ul style="list-style-type: none"><input type="radio"/> Never married<input type="radio"/> Married<input type="radio"/> Divorced<input type="radio"/> Widowed | |
| <p>6 Marriage duration (Years)</p> <ul style="list-style-type: none"><input type="radio"/> Under 5<input type="radio"/> 5-10<input type="radio"/> 10-20<input type="radio"/> Over 20<input type="radio"/> Not applicable | |
| <p>7 Employment status</p> <ul style="list-style-type: none"><input type="radio"/> Employed<input type="radio"/> Unemployed<input type="radio"/> Other | |
| <p>8 You have health insurance coverage</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No | |

| | |
|--|--|
| <p>9 You had a Pap test before</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No<input type="radio"/> Not applicable | |
| <p>10 If you had a Pap test before, when was it performed</p> <ul style="list-style-type: none"><input type="radio"/> 1-3 years ago<input type="radio"/> 4-6 years ago<input type="radio"/> Over 6 years ago | |
| <p>11 Did you, or any member of your family have cervical cancer before</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No<input type="radio"/> Don't know | |
| <p>12 Cervical cancer may be preventable</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No<input type="radio"/> Don't know | |
| <p>13 You are aware of the Pap test smear cytologic method</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No | |

| | |
|---|--|
| <p>14 Where did you hear of the Pap test smear cytologic method for the first time</p> <ul style="list-style-type: none"><input type="radio"/> Relatives, friends<input type="radio"/> Gynecologist<input type="radio"/> Mass media (newspaper, internet, television)<input type="radio"/> Family physician<input type="radio"/> Nurse<input type="radio"/> Other<input type="radio"/> Not applicable | |
| <p>15 You have knowledge of cervical cancer</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No | |
| <p>16 Early detection of cervical cancer is important for effective treatment</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No<input type="radio"/> Don't know | |
| <p>17 Regular Pap tests may protect you from cervical cancer</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No<input type="radio"/> Don't know | |
| <p>18 Cervical cancer may be curable</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No<input type="radio"/> Don't know | |

| | |
|---|--|
| <p>19 Vaccination for the Human Papilloma Virus protects against cervical cancer and other HPV-associated cancers</p> <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Don't know | |
| <p>20 Menopausal women need a Pap test</p> <ul style="list-style-type: none"> <input type="radio"/> Yes <input type="radio"/> No <input type="radio"/> Don't know | |
| <p>21 More information is needed to improve your knowledge of cervical cancer</p> <ul style="list-style-type: none"> <input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Undecided <input type="radio"/> Disagree <input type="radio"/> Strongly disagree | |
| <p>22 Regular Pap tests are a good health practice</p> <ul style="list-style-type: none"> <input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Undecided <input type="radio"/> Disagree <input type="radio"/> Strongly disagree | |
| <p>23 Getting a Pap test performed is too difficult</p> <ul style="list-style-type: none"> <input type="radio"/> Strongly agree <input type="radio"/> Agree <input type="radio"/> Undecided <input type="radio"/> Disagree <input type="radio"/> Strongly disagree | |

| | |
|---|--|
| <p>24 You would recommend a Pap test to your family, friends, and colleagues</p> <ul style="list-style-type: none">○ Strongly agree○ Agree○ Undecided○ Disagree○ Strongly disagree | |
| <p>25 Getting a Pap test is a valued investment for good healthcare</p> <ul style="list-style-type: none">○ Strongly agree○ Agree○ Undecided○ Disagree○ Strongly disagree | |
| <p>26 You would support a Pap test screening program for cervical cancer</p> <ul style="list-style-type: none">○ Strongly agree○ Agree○ Undecided○ Disagree○ Strongly disagree | |
| <p>27 A formal Pap test screening program for cervical cancer should be established for all women in the State of Qatar</p> <ul style="list-style-type: none">○ Strongly agree○ Agree○ Undecided○ Disagree○ Strongly disagree | |

| | |
|--|--|
| <p>28 You know where to go to get a Pap test performed</p> <ul style="list-style-type: none"><input type="radio"/> Strongly agree<input type="radio"/> Agree<input type="radio"/> Undecided<input type="radio"/> Disagree<input type="radio"/> Strongly disagree | |
| <p>29 A Pap test has no value for you</p> <ul style="list-style-type: none"><input type="radio"/> Strongly agree<input type="radio"/> Agree<input type="radio"/> Undecided<input type="radio"/> Disagree<input type="radio"/> Strongly disagree | |
| <p>30 If a self-test for cervical cancer was available you would prefer it</p> <ul style="list-style-type: none"><input type="radio"/> Strongly agree<input type="radio"/> Agree<input type="radio"/> Undecided<input type="radio"/> Disagree<input type="radio"/> Strongly disagree | |
| <p>31 If employed, are you employed in the healthcare sector?</p> <ul style="list-style-type: none"><input type="radio"/> Yes<input type="radio"/> No | |
| <p>Thank you for your participation</p> | |

Appendix C: Symposium Compendium (*The 1st Century Of Gynecological Cytopathology, The Pap test – Then, Now And The Future*), conducted December 7, 2014. [<https://www.sidra.org/media/news-room/2014/december/sidra-medical-and-research-center-hosts-symposiu/>]



Appendix D: Symposium Goals and Objectives (*The 1st Century Of Gynecological Cytopathology, The Pap test – Then, Now And The Future*), conducted December 7, 2014. [<https://www.sidra.org/media/news-room/2014/december/sidra-medical-and-research-center-hosts-symposiu/>]

Symposium Goals and Objectives

Goals

- Commemorate the 1st Century of Gynecological Cytopathology; highlighting the early experimental work of Dr. George N. Papanicolaou at Cornell Medical College, New York.
- Commemorate the early clinical scientific work at Cornell that led to the development of the Pap test.
- Commemorate the participation of Cornell, The Commonwealth Fund, The American Cancer Society and the National Cancer Institute for the development of mass screening programs for cervical cancer.
- Present the role and scope of gynecological cytopathology through the screening Pap test.

Objectives

The Symposium aims to raise the audiences' awareness of:

- The early scientific work that led to the development and establishment of the Pap test.
- The contributions of distinguished scientific pioneers: George N. Papanicolaou, Andromache Papanicolaou, Charles Stockard, Herbert Traut, Hashime Murayama, Joseph Hinsey, Charles Cameron.
- The benefits and impact of organized screening systems for cervical cancer.
- The involvement of HPV DNA in the pathobiology and carcinogenesis of cervical cancer.
- Future trends of gynecological cytopathology; in Qatar and the world.

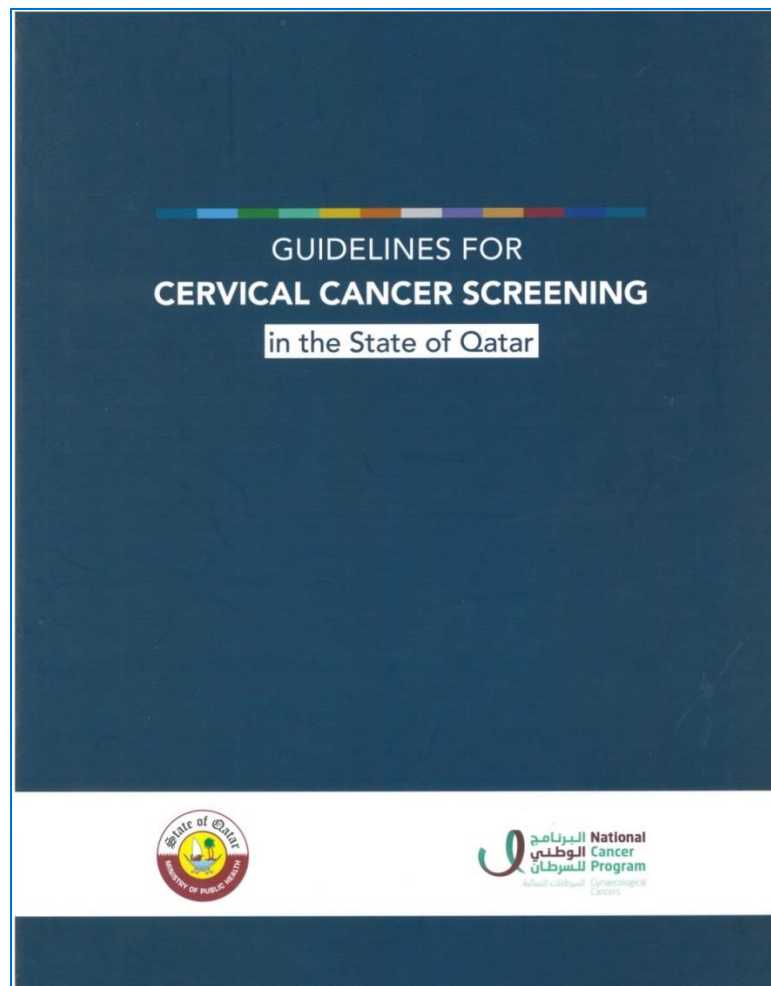


Appendix E: Symposium Program Schedule (*The 1st Century Of Gynecological Cytopathology, The Pap test – Then, Now And The Future*), conducted December 7, 2014. [<https://www.sidra.org/media/news-room/2014/december/sidra-medical-and-research-center-hosts-symposiu/>]

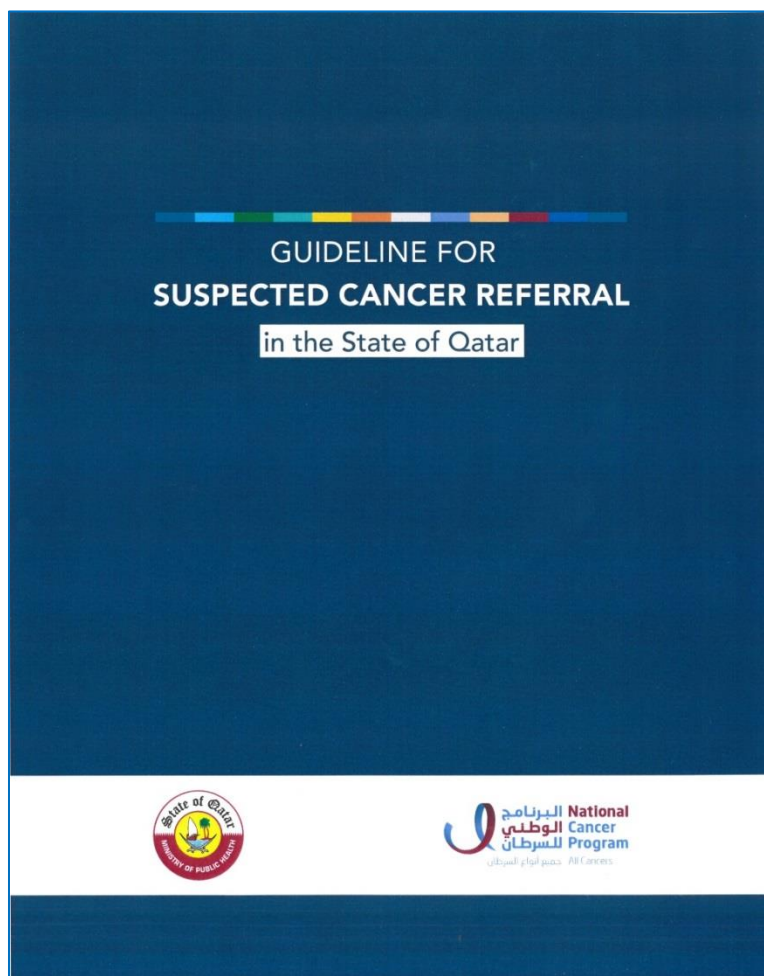
| Program Schedule | |
|-------------------------|---|
| 7:30 - 8:30 | Registration and refreshments |
| 8:30 - 9:00 | Opening remarks and introduction |
| 9:00 - 9:50 | Birth of a Century at Cornell Medical College, New York Nikolaos Chantziantoniou, BSc, ART(CSMLS), CFIAC Cytopathology, Supervisor, Sidra Medical and Research Center, Doha, Qatar |
| 10:00 - 10:50 | A New Cancer Diagnosis - Development of the Pap test (Morphology-based) R. Marshall Austin, MD, PhD Cytopathology, Director, University of Pittsburgh Medical Center, Pittsburgh, USA |
| 11:00 - 11:20 | Break and refreshments |
| 11:20 - 12:10 | Development of Screening Programs for Cervical Cancer - Concept of Precursor Disease Adrian Charles, MD Anatomic Pathology, Division Chief, Sidra Medical and Research Center, Doha, Qatar |
| 12:15 - 1:15 | Lunch |
| 1:15 - 2:05 | Impact of the Pap Test and Screening Programs Hanan Farghaly, MD Cytopathology, Head, Hamad Medical Corporation, Doha, Qatar |
| 2:15 - 3:05 | Pathobiology of Cervical Cancer - Update R. Marshall Austin, MD, PhD Cytopathology, Director, University of Pittsburgh Medical Center, Pittsburgh, USA |
| 3:15 - 3:30 | Break and refreshments |
| 3:30 - 4:20 | The Pap Test in the New Century (Molecular based) Jeremie Arash Rafii Tabrizi, MD, PhD Associate Professor of Genetic Medicine in Obstetrics/Gynecology, Weill Cornell Medical College Qatar |
| 4:30 - 5:30 | Open Discussion (Distinguished Panelists: Dr. M. E. Boon, Dr. R. M. Austin, Dr. Douglas M. Black, Dr. Afaf Al Ansari) |
| 5:30 - 5:45 | Closing remarks - followed by refreshments |



Appendix F: *National Cancer Program, Guidelines For Cervical Cancer Screening In The State Of Qatar* report (2016) published by the Qatar Ministry of Public Health.



Appendix G: National Cancer Program, Guideline For Suspected Cancer Referral In The State Of Qatar report (2016) published by the Qatar Ministry of Public Health. [https://www.moph.gov.qa/health-strategies/Documents/MOPH_%20Suspected%20Cancer%20Referral%20Guideline%20for%20the%20State%20of%20Qatar_V1_2016.pdf]



Appendix H: Cervical cancer health literacy campaign: “Be Well”, produced by the Qatar Cancer Society (2017). [<http://www.qatarisbooming.com/article/qcs-urges-women-go-cervical-cancer-screening>]



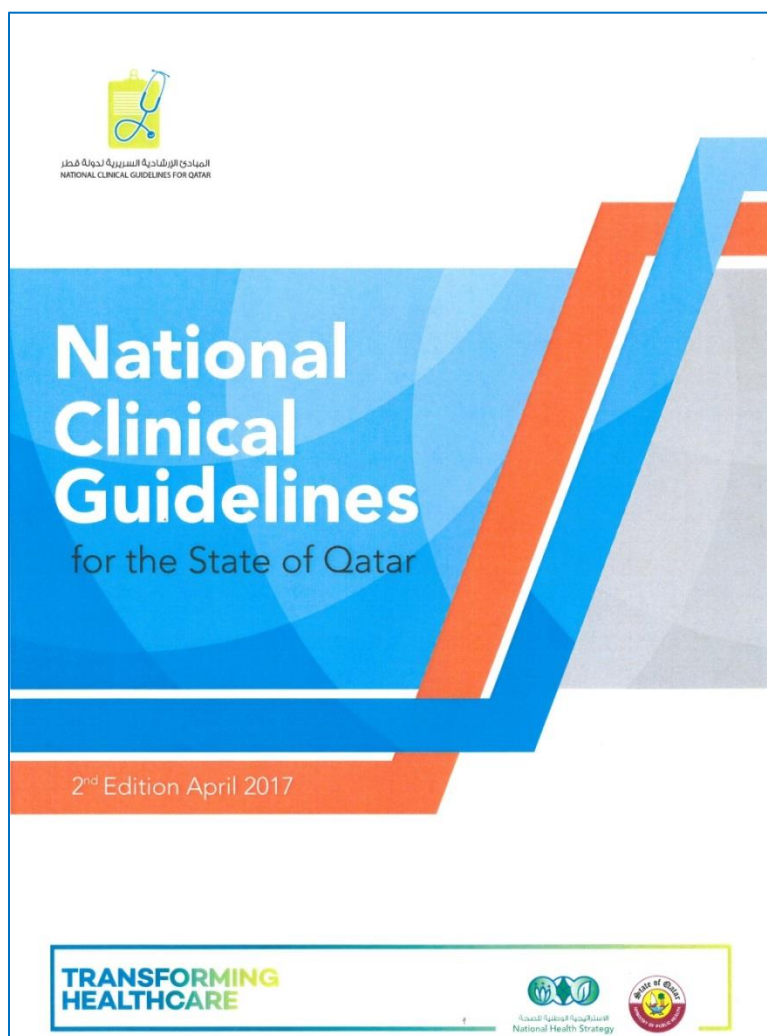
Appendix I: The *National Health Strategy 2018-2022; Our Health Our Future* (2018), published by the Qatar Ministry of Public Health.

[<https://www.moph.gov.qa/HSF/Documents/short%20report%20eng%2020.03.2018.pdf>]

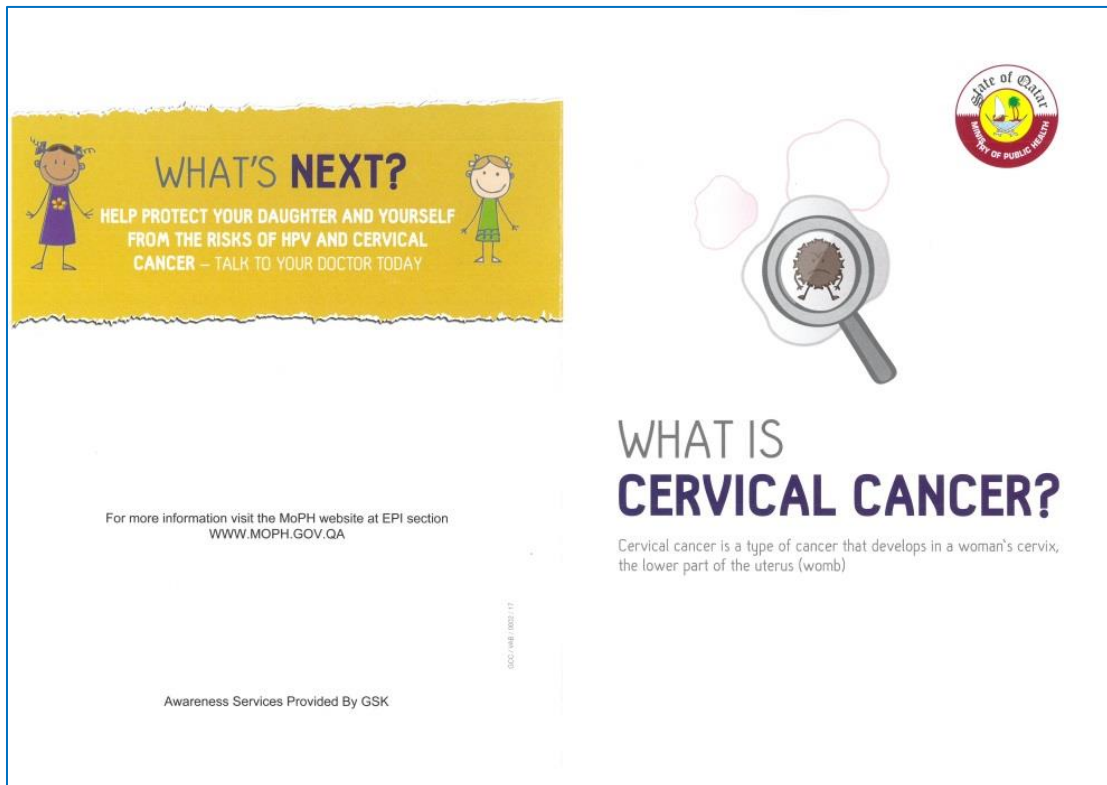


Appendix J: The *National Clinical Guidelines For The State Of Qatar* (2nd Edition, 2017), published by the Qatar Ministry of Public Health.


[<https://www.moph.gov.qa/health-strategies/Documents/April%202017%20clinical%20guideline%20en.pdf>]




Appendix K(a): Infographic, *What Is Cervical Cancer*; a 2-page fold-out brochure produced by the Ministry of Public Health, State of Qatar (Front and Back covers). [www.moph.gov.qa]



Appendix K(b): Infographic, *What Is Cervical Cancer*; a 2-page fold-out brochure produced by the Ministry of Public Health, State of Qatar (Pages 2 and 3). [www.moph.gov.qa]



Cervical cancer is the **fourth-most common cancer** in women worldwide, with an estimated **530,000 new cases** and **270,000 associated deaths** per year.




On average a woman dies every two minutes from cervical cancer in the world


ARE THERE ANY SYMPTOMS OF HPV INFECTIONS AND CERVICAL CANCER?

There are **no specific symptoms of HPV infections** before cancer occurs. The **symptoms of cervical cancer only appear late** when the cancer is advanced.


Symptoms* may include:




Irregular bleeding between periods or after sex




Back, leg or pelvic pain



Fatigue and weight loss or loss of appetite




Vaginal discomfort or smelly discharge



A single swollen leg

*These symptoms are not linked to cervical cancer. Please consult your doctor if you have one or more of the above symptoms.


WHAT CAUSES CERVICAL CANCER?



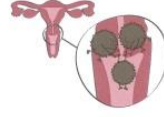
Almost all cervical cancer is caused by **HUMAN PAPILLOMA VIRUS (HPV)** infections.

WHAT IS HPV?

Human papilloma virus (HPV) is the name of a group of viruses that are **very common**. HPV can be transmitted through sexual contact.




HPV IS VERY COMMON. Most sexually active women and men will be infected with HPV at some point in their lives.




Most HPV infections will resolve naturally, but some infections can lead to abnormal cells in the cervix. **IF THE ABNORMAL CELLS ARE NOT REMOVED OR RESOLVED NATURALLY THEY CAN LEAD TO CERVICAL CANCER.**


HOW CAN YOU PROTECT AGAINST HPV AND CERVICAL CANCER?



Cervical cancer can be prevented through **REGULAR SCREENING**. Screening is most commonly done via a technique that is called the **PAP SMEAR**.



Screening can help to **DETECT ABNORMAL CELLS CAUSED BY HPV AT AN EARLY STAGE**. Once detected these cells require careful follow up or may need **TO BE REMOVED THROUGH A SMALL OPERATION.**

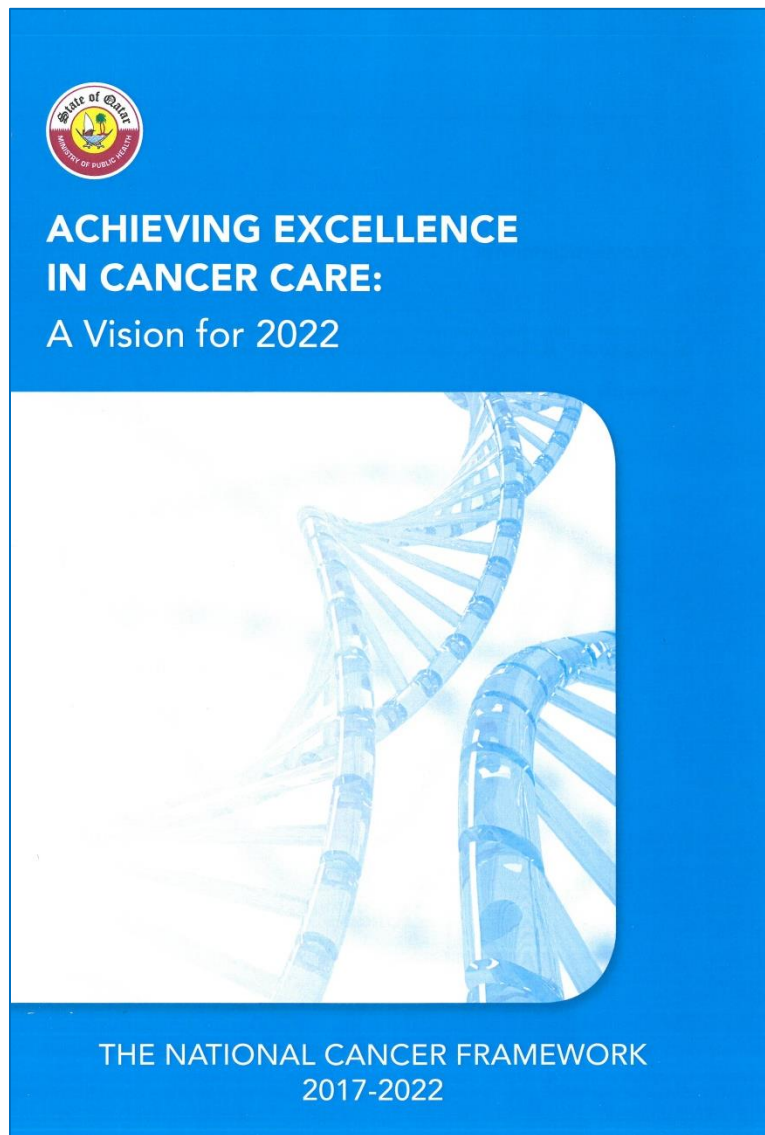


VACCINATION can help to protect against a large proportion of cancer-causing HPV infections in the first place and therefore **STRONGLY REDUCE THE RISK OF CERVICAL CANCER.**

THE WORLD HEALTH ORGANIZATION RECOMMENDS A COMBINATION OF **VACCINATION AND SCREENING TO PREVENT CERVICAL CANCER.**

Appendix L: The National Cancer Framework – Achieving Excellence In Cancer Care: A Vision for 2022, published by the Qatar Ministry of Public Health.

[<https://www.moph.gov.qa/publications/Documents/Health%20Publications/National%20Cancer%20Framework%20English.pdf>]



**Appendix M: Abstract/ePoster, International Academy of Cytology Congress,
Sydney, Australia, May 5-9, 2019**

Topic Area: GYNAECOLOGY

Title: Assessing proportion and age of women deemed at increased-risk for developing cervical cancer due to never having a Pap test: Targeted health literacy supported through a needs-assessment survey at Sidra Medicine, State of Qatar

Authors: Nikolaos Chantziantoniou¹, Ghada AlNajar¹, Denise Howard¹, Mohammed ElAnbari¹, Colin A. Clelland¹, Amber D. Donnelly², Adrian K. Charles¹

Affiliations: Sidra Medicine¹, University of Nebraska Medical Center²

Objective: The State of Qatar experiences a mean cervical cancer (CxCa) burden of 15 cases annually. Given opportunistic Pap testing predominantly secondary to suspicious symptomatology, the majority of women presenting with CxCa harbor advanced-stage disease at diagnosis. The crude incidence rate for CxCa in Qatar is 3.2/100,000; with a bimodal pattern of prevalence based on 2 dominant age-groups: 40-44, and 60-64 years. As Sidra Medicine is a new, premier Women's and Children's hospital in Doha, Qatar, the Cytopathology service sought to assess proportion and age of women deemed at increased-risk for developing CxCa due to never having a Pap test as revealed through a needs-assessment survey. The effort aimed to guide targeted health literacy initiatives. Salient findings from 117 female respondents are discussed.

Methods: A 31-question needs-assessment survey was distributed to volunteering participants, anonymously. Questions were designed to capture demographic data (eg. gender, age-group), also data regarding health literacy of CxCa (eg. Pap testing, preceding timeframe of testing) among other aspects of cervical cancer management.

Results: From 203 surveys, 117 were from women (57.6%). The dominant female age groups were 30-39 years (48/117: 41%) and 20-29 years (33/117: 28.2%) respectively. Of all 117 women, 57 (48.7%) reported never having a Pap test, compared to 52 (44.4%) that had, mainly within 1-3 preceding years.

Conclusions: Preliminary data arising from the needs-assessment survey revealed a dominant population of women (41%) aged 30-39 years that never had a Pap test. These women are deemed at increased-risk for developing CxCa relative to women that have had a Pap test. Based on epidemiological data characteristic of Qatar, these women may represent a clinically high-risk group harboring asymptomatic but developing cervical neoplasia likely to present when this cohort reaches 40-44 years of age. Health literacy initiatives ought to target this specific age-group of women.

Nikolaos Chantziantoniou (nchantziantoniou@sidra.org)

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Nikolaos Chantziantoniou

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