# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Contents</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>III</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>V</td>
</tr>
<tr>
<td>LIST OF APPENDICES</td>
<td>VI</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>VII</td>
</tr>
</tbody>
</table>

## CHAPTER 1: INTRODUCTION

1.1 General introduction 1
1.2 Pathogenesis of Human papillomavirus infection 2
1.3 Pathophysiology of cervical cancer 3
1.4 Histology of the cervix uteri 5
1.5 Colposcopy of cervix uteri 7
1.6 The limitations of cervical cytology 8
1.7 The role of HPV DNA in cervical screening 8
1.8 Clinical considerations and recommendations 9
1.8.1 Management of Human papillomavirus infection 10
1.8.2 Management of cervical cancer 11
1.8.3 Vaccines 12
1.9 Social relevance of the study 12
1.10 Aim of the study 12
1.11 Objectives of the study 13

## CHAPTER 2: REVIEW OF LITERATURE

2.1 Introduction to Human papillomavirus and cervical cancer 14
2.2.1 History of Human papillomavirus infection 16
2.2.2 History of cervical cancer 17
2.3 Morphology and molecular structure of Human papillomavirus 18
2.3.1 Life cycle of Human papillomavirus 20
2.3.2 Immune response to the host 21
2.3.3 Human papillomavirus types 22
2.3.4 Early and late proteins in Human papillomavirus infection 22
2.3.5 Mucosal and cutaneous Human papillomavirus infections 24
2.3.6 Classification of cervical cancer 26
2.3.7 Presentation, clinical features and staging of cervical cancers 27
2.3.8 Pathology of cervical cancer 29
2.4 Associated Human papillomavirus cancers 30
2.5 Respiratory papillomatosis 30
2.6 HPV infection in immunocompromised patients 31
2.7 Oral infection 31
2.8 Risk factors associated with the Human papillomavirus infection 31
2.9 Trends in Human papillomavirus types distribution 35
2.9.1 Global trends in Human papillomavirus infection and cervical cancer 36
2.9.2 Trends in India 40
2.10 Diagnosis of Human papillomavirus infection 42
2.11 Clinical utility of molecular Human papillomavirus diagnosis 46
2.12 Prevention of Human papillomavirus infection 47
2.13 Prevention of cervical cancer 47
2.14 Barriers to cervical cancer control programs 48
2.15 Limitations of current literature and areas for future study 49
2.16 Rationale of exploratory research of Human papillomavirus and cervical cancer in Mangalore 50

CHAPTER 3: MATERIALS AND METHODS

3.1 Study setting 51
3.2 Ethical clearance 51
3.3 Study population 51
3.4 Sample size 51
3.5 Inclusion criteria 51
3.6. Exclusion criteria
3.7. Work plan of the study
3.8. Collection of specimen
3.8.1. Patient preparation for Pap smear and cytobrush sample collection
3.8.2. Cytobrush collection and storage
3.8.3. Pathological analysis of tissue biopsies and Pap smears (for cytobrush samples)
3.8.4. Pap smear preparation
3.8.4.1. Papanicolaou (Pap) staining for cytology
3.8.4.2. Interpretation of results
3.8.5. Hematoxylin and Eosin (H and E) staining for tissue biopsies
3.8.5.1. Interpretation of results
3.9. Molecular analysis
3.9.1. Preparation of samples prior to DNA extraction
3.9.2. HPV DNA extraction
3.9.2.1. DNA extraction from tissue biopsy samples
3.9.2.2. DNA extraction from cytobrush samples
3.9.3. Polymerase chain reaction
3.9.4. Gel electrophoresis and interpretation of results under UV transilluminator
3.9.5. DNA sequencing
3.10. Qualitative analysis
3.10.1. Questionnaire based assessment of the knowledge regarding Human papillomavirus infection and cervical cancer
3.10.2. Questionnaire based assessment of the risk factors associated with the HPV Infection
3.11. Statistical analysis

CHAPTER 4: RESULTS

4.1. Clinical specimens
4.2. Socio demographic details of the study participants
4.3. Distribution of study participants and HPV DNA positive participants in different age group
4.4. Histopathological findings of biopsy samples 72
4.5. Pathology of the cytobrush samples by Pap smear 73
4.6. Occurrence of HPV DNA in women suspected with HPV infection 73
4.7. HPV typing and detection of E6/E7 oncoproteins by polymerase chain reaction 76
4.7.1. Distribution of the Human papillomavirus types and E6/E7 oncogenes among the various pathologies of the tissue biopsies 77
4.7.2. Distribution of the Human papillomavirus types and E6/E7 oncogenes among the various pathologies of the cytobrush samples 77
4.8. Comparison of pathological findings with Molecular findings 78
4.9. DNA sequencing and interpretation of results using BioEdit software 78
4.10. Assessment of risk factors associated with the Human papillomavirus infection 80
4.11. Assessment of awareness and knowledge about cervical cancer and HPV/HPV vaccine among study participants 82

CHAPTER 5: DISCUSSION

5.1. Demographic distribution 87
5.2. Human papillomavirus type distribution among women with cervical abnormalities 87
5.3. Detection of E6/E7 oncogenes of HPV 16/18 from HPV DNA positive samples 90
5.4. Comparison of cytology/histopathology results with the PCR results 91
5.5. DNA sequencing of HPV 16/18 and HPV 16/18 E6/E7 oncoproteins 92
5.6. Predisposing risk factors for the acquisition of HPV infection 92
5.7. Knowledge and awareness regarding HPV infection and cervical cancer 94

CHAPTER 6: SUMMARY AND CONCLUSIONS

6.1. Summary of work done 97
6.2. Summary of study findings 97
6.3. Conclusion and Limitations of the study 98
6.4. Future scope 99

REFERENCES 100

APPENDICES 133