Review Article

Risk Factors and Genetic Markers of Human Papillomavirus-induced Cervical Carcinogenesis: A Focus on Chinese Populations in Southeast Asia and Southern China

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Abstract

Cervical cancer is a disease that is caused by persistent human papillomavirus (HPV) infection. The fate of this sexually transmitted infection is determined by long-term host-viral and host-environmental interactions. Given that the majority population of Han Chinese have a similarity in genetic makeup, and cultural and social systems, it is not surprising to see a common spectrum of type- or variant-specific HPV prevalence and risk for cervical cancer in Taiwan, Hong Kong and Singapore. These populations also share similar behavioral and environmental exposure risks, as well as genetic susceptibility to cervical cancer. In this post-genomic era, when the code, control and function of the human genome are being quickly unveiled, new genetic and epigenetic biomarkers for cervical cancer are emerging systemically and in an overwhelming way. This review covers the conventional epidemiological risks of HPV infection and the development of cervical cancer, as well as the emerging new molecular biomarkers, in a focused population of Chinese subjects in Southeast Asia and Southern China. (Tzu Chi Med J 2008;20(2):91–100)

Article Info

Article history:
Received: September 11, 2007
Revised: October 23, 2007
Accepted: November 16, 2007

Keywords:
Cervical cancer
Chinese population
Genetic marker
Human papillomavirus

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1. Ancestors and origin of Chinese populations in Taiwan and Southeast Asia

The Han people, sharing the same culture and language, are by far the largest ethnic group in the world. Aside from the more than one billion people living in mainland China, over 30 million Han Chinese live in Taiwan, Hong Kong and Singapore, representing 98%, 95% and 77% of their populations, respectively. Most of them are immigrants from the southeast coast of China. Starting from the 5th century, after the fall of...
the Han Dynasty, there were three waves of large-scale migration of people from Northern China to Southern China, and to the southeast coast, including Hong Kong (Fig. 1). The massive movements resulted in the demographic expansion of Han people and their culture. Over one millennium, gene flow between the Han population and the native populations, most of them originating from Southeast Asia (1), shaped the genetic profile of the population in Hong Kong, and those who had immigrated to Taiwan, Singapore and other countries in Southeast Asia over the past 400 years. Observations of haplotypes in mitochondria DNA and Y chromosomes are in line with these historical accounts (2).

Although sharing common ancestry, populations in Taiwan, Hong Kong and Singapore differ to some extent from that in China, mainly because of gene flow from the native populations, such as the aborigines in Taiwan, and Thais, Malays and Indians in Singapore. A recent large-scale immigration of Han Chinese from all over mainland China to Taiwan around 1949 also contributed significantly to the population constituents in Taiwan. Moreover, early colonization by the English, Spanish and Dutch from the 17th to 19th centuries, and the fast globalization of these three areas has also added characteristics to these Chinese immigrants.

The cultural and genetic makeup of Chinese immigrants in Taiwan, Hong Kong and Singapore very much determine the risk of cervical cancer development, by affecting behavior and environmental exposure relating to carcinogenesis, as well as genetic susceptibility to carcinogenesis. Known determinants of cervical carcinogenesis, including infection and persistence of human papillomavirus (HPV), sexual behavior, pregnancy and type of birth, exposure to smoking and infectious agents, and genetic and epigenetic changes of genes in Chinese immigrants, will be the focus of this review.

2. HPV coevolves with its human host

Infection by HPV, the first necessary etiological factor found in human cancers, has been found to cause a high risk of cervical cancer development. HPV coevolved with its human host long before the origin of Homo sapiens some 500 million years ago. In association with the migration of early human ancestors, the variants defined by small-scale DNA sequence variations of the locus control region (LCR) of specific HPV are unique to each ethnic group. For instance, specific haplotypes of HPV 16 and 18 were identified in the Chinese population living in Singapore (3–5). Sequence analysis of HPV 31 and 52 also showed colocalization of HPV variants, collected from Taiwan and Hong Kong, in the evolutionary tree (6). A common pattern of HPV type and variant distribution, and genetic traits related to HPV infection and carcinogenesis are, therefore, expected in these three regions. Within this Chinese immigrant pattern of HPV distribution is the more prevalent HPV 52 and HPV 58 infections (7), and the sharing of Asian variants of HPV 16 and 18 (3,4), which have different biological and clinical significance in cervical carcinogenesis.

A showcase of the ethnic-specific distribution of HPV in Chinese populations is shown in Fig. 2: the distribution of HPV genotypes in the general population in Taiwan differs greatly from that in Shenyang (a major city in Northern China) and less so from that in Shenzhen (a major city in Southern China). Of note is the difference in the prevalence of HPV 16, which is very dominant in north China (8,9), less dominant in south China (10), and is similar to HPV 52 and 58 in Taiwan (11). A similar ethnic-specific distribution of HPV types was also noted in cervical cancer from different areas. As shown in Fig. 3 (12–15), HPV 16 was found in 80% of cervical cancers in China (12) but was found in only 50% of cervical cancers in Taiwan and south China (13), and other Asian countries (14,16). In areas with Chinese immigrants, such as Taiwan (17,18) and Hong Kong (19), and in Southern China (20,21), HPV 58 is the second or the third most common HPV type found in cervical cancer but the same HPV is relatively rare.

Fig. 1 — Migration of the Han population. Starting in the 5th century, the Han population from Northern China migrated to Southern China and all the way to the southeast coast, including Hong Kong (dotted arrows). Immigration of Han Chinese from Southeast China to Taiwan and Singapore occurred from the 17th century (solid arrows).
in other parts of the world (14) and most probably in Northern China, although evidence of the latter is lacking so far.

3. **HPV is the major risk factor for cervical carcinogenesis worldwide and in Chinese immigrants: HPV type-, variant- and load-dependent risk**

 Worldwide studies have disclosed extremely high risks of cervical cancer in women infected with different types of HPV, with odds ratios ranging from 62 to 282 (22). On the other hand, HPV transformation of cervical epithelium is of low efficiency and typically takes more than a decade to become invasive cancer. From worldwide epidemiology studies conducted by the International Agency for Research on Cancer (IARC), the World Health Organization (WHO) has disclosed other independent risk factors for cervical cancer, such as cigarette smoking (23), long-term use of oral contraceptives (24), high parity (25) and sexually transmitted infections (i.e., *Chlamydia trachomatis* and Herpes simplex virus-2) (26, 27), after adjustment for HPV infection. Most of these international studies, however, did not include the Chinese population.

Table 1 (7, 18, 28–31) shows the oncogenic risk of HPV infections in different grades of cervical neoplasia in Chinese subjects living in Taiwan and Hong Kong. Depending on the nature and stringency of selection of cases and controls, the odds ratio of finding squamous intraepithelial lesions of high-grade (HSIL) or above is 29–1280 times higher in high-risk HPV (HR-HPV)-infected women than non-infected women (7, 28). HPV type-specific risk for HSIL or above lesions was higher in women infected with HPV 16 than those infected with HPV 58 and HPV 52 (29). An earlier study in Taiwan also showed that HPV 52 and 58 had a much smaller risk for HSIL than HPV 16 (18). Not only is it less risky but HPV 58-related cervical cancers also had a favorable survival compared to those with HPV 16 and HPV 18 (17). In comparison to HPV 16, 18, 31 and 33, the E6 and E7 genes of HPV 52 had a much...
more limited in vitro transformation capability (32). It rarely integrates into host genome in cervical cancer (33). In analysis of the distributional proportion of different HPV types in the spectrum of cervical neoplasia, HPV 52 was found to be highly prevalent in pre-cancerous infections but much less in invasive cervical cancer (34), indicating a less oncogenic nature than other high risk types of HPV.

In addition to HPV genotypes, a study in Hong Kong showed that DNA sequence variations at the E7 gene of HPV 58 conferred different risks for cervical cancer. For instance, the E7 632C>T (T20I) and E7 760G>A (G63S) variants were associated with the severity of cervical neoplasia. HPV 58 variants carrying these two substitutions had a 6.9-fold higher risk for cervical cancer than variants without these substitutions (35).

With regard to HPV infection load, the amount of HR-HPV infection as measured by Hybrid Capture 2 (Digene, Silver Spring, MD, USA), a higher viral load conferred higher risk for HSIL or above lesions (30,31). Looking in more detail, the significance of HPV infection load in different severities of cervical neoplasia is HPV type-dependent. Two studies in Taiwan (33,36) showed that the viral load of HPV 16, HPV 18 and HPV 52 correlated significantly with disease severity. However, infection loads of HPV 58, HPV 31 and HPV 33 do not correlate to clinical severity. The wide variation in HPV infection loads among different HPV types and among different severities of squamous intraepithelial lesions makes the viral load test unrealistic for differentiating different severities of cervical neoplasia.

4. Other environmental and behavioral risk factors for cervical carcinogenesis in Chinese immigrants

Table 2 (8,28,30,37–41) summarizes the environmental and behavioral risk factors for cervical carcinogenesis in populations in Hong Kong, Taiwan and Singapore. Risk or protective factors of HPV infection included number of sex partners, a partner’s promiscuous sexual affairs, active and passive smoking, barrier contraception, vitamin supplement and previous Pap screening, and these did not differ from those found in other populations. Of particular note was the role of frequent vaginal douching, which is a risk factor for prevalent HPV infection (37) as well as persistent low-grade squamous intraepithelial lesions. There were reports showing that frequent vaginal douching may increase a woman’s susceptibility to sexually transmitted agents (42). Vaginal douching may eliminate the normal vaginal microflora (43) and protective cervical mucus, and increase the risk of persistence or acquisition of HPV by altering the vaginal milieu.

Also shown in Table 2 (8,28,30,37–41) are environmental and behavioral factors related to risk of cervical cancer or cervical intraepithelial neoplasia (CIN), and these are similar to those found in studies worldwide. Universal risk factors, such as high-risk sexual behavior of a woman and her partner, parity and Chlamydia infection, were found in studies in Hong Kong, Taiwan and Singapore (30,38,39,41,44). Of interest is the lack of cigarette smoking in the list of

Table 1 — HPV as the oncogenic risk of cervical neoplasia in Taiwan and Hong Kong

<table>
<thead>
<tr>
<th>Source</th>
<th>Cases and controls (n)</th>
<th>Risk target</th>
<th>Risk factors</th>
<th>OR (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>40 CIN 1, 9 CIN 2, 56 CIN 3, 3 ICC, 261 controls</td>
<td>HSIL+</td>
<td>HPV+</td>
<td>122 (39–389)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR-HPV</td>
<td>1280 (189–8830)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MR-HPV</td>
<td>99 (24–411)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LR-HPV</td>
<td>4.8 (0.5–48)</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>51 LSIL, 99 HSIL+, 420 normal controls</td>
<td>LSIL HSIL+</td>
<td>HPV 52/58</td>
<td>12 (4–38)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 16</td>
<td>42 (17–105)</td>
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<td></td>
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<td></td>
<td>HPV 52/58</td>
<td>29 (6–139)</td>
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<td></td>
<td></td>
<td></td>
<td>HPV 16</td>
<td>326 (90–1186)</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>471 LSIL, 460 HSIL/ICC, 148 ACUS-N controls</td>
<td>HSIL+</td>
<td>HPV 16</td>
<td>8.67 (3.46–21.70)</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 52</td>
<td>3.04 (1.42–6.47)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 58</td>
<td>5.22 (2.07–15.19)</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>10 LSIL, 20 HSIL, 80 controls</td>
<td>HSIL</td>
<td>HR-HPV high viral load</td>
<td>6.6 (2.6–17.0)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.0 (3.0–108.5)</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>19 LSIL, 32 HSIL or above, 22 normal</td>
<td>Lesion size and HSIL+</td>
<td>High viral load</td>
<td>Large lesion: 5.5 (1.1–24.9)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HSIL+ 55.0 (4.2–294.5)</td>
<td></td>
</tr>
<tr>
<td>Hong Kong</td>
<td>2080 population for Pap Smear</td>
<td>SIL</td>
<td>Any HPV</td>
<td>19.51 (10.08–37.76)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR-HPV</td>
<td>28.91 (14.37–58.14)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LR-HPV</td>
<td>1.52 (0.20–11.67)</td>
<td></td>
</tr>
</tbody>
</table>

CIN = cervical intraepithelial neoplasia; ICC = invasive cervical cancer; HSIL/LSIL = high/low grade squamous intraepithelial lesion; ACUS-N = colposcopy-negative ASCUS.
Table 2 — Risk factors of HPV infection and cervical carcinogenesis in Chinese populations

<table>
<thead>
<tr>
<th>Source</th>
<th>Cases and controls (n)</th>
<th>Target</th>
<th>Risk factors</th>
<th>OR (95% CI)</th>
<th>Protective factors</th>
<th>OR (95% CI)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td>2080 women, 7.3% HPV positive</td>
<td>HPV Prevalence</td>
<td>Number of sex partners</td>
<td>4.85 (2.30–10.23)</td>
<td>Old age (&gt; 55 vs. &lt; 35)</td>
<td>0.13 (0.05–0.40)</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking</td>
<td>5.07 (2.06–12.44)</td>
<td>Barrier contraception</td>
<td>0.46 (0.74–0.29)</td>
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<tr>
<td></td>
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<td></td>
<td>Smoker in family</td>
<td>1.57 (1.10–2.25)</td>
<td>Previous Pap smear</td>
<td>0.71 (0.44–0.91)</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>1264 women with abnormal Pap Smear</td>
<td>HPV Prevalence</td>
<td>Number of sex partners</td>
<td>2.44 (1.44–4.15)</td>
<td>Vitamin supplement</td>
<td>0.71 (0.55–0.92)</td>
<td>37</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Frequent vaginal douching</td>
<td>1.44 (1.01–2.04)</td>
<td>Regular Pap smear</td>
<td>0.45 (0.24–0.84)</td>
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<td></td>
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<td></td>
<td>Sexual promiscuity of partners</td>
<td>2.01 (1.46–2.76)</td>
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</tr>
<tr>
<td>Taiwan</td>
<td>114 (42 incident and 72 prevalent) ICC, 519 matched controls</td>
<td>ICC</td>
<td>HPV 16 seropositivity</td>
<td>6.33 (3.45–11.62)</td>
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<td>40</td>
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<td></td>
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<td></td>
<td>C. trachomatis</td>
<td>2.94 (1.17–7.42)</td>
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</tr>
<tr>
<td>Taiwan</td>
<td>10 LSIL, 20 HSIL, 80 controls</td>
<td>HSIL</td>
<td>Early sex exposure</td>
<td>5.0 (1.6–15.2)</td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR-HPV infection</td>
<td>6.6 (2.6–17.0)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>High HPV viral load</td>
<td>18.0 (3.0–108.5)</td>
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<tr>
<td>Taiwan</td>
<td>535 biopsy-proved ICC and 175,825 normal cytology</td>
<td>ICC</td>
<td>Age</td>
<td>p &lt; 0.00001</td>
<td>Use of condom</td>
<td>0.38 (0.16–0.95)</td>
<td>39</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Years of marriage</td>
<td>p &lt; 0.001</td>
<td>Regular Pap smear</td>
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<td></td>
<td>Contraception</td>
<td>p &lt; 0.0001</td>
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<td></td>
<td></td>
<td>No. of full term delivery</td>
<td>p &lt; 0.00001</td>
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<td></td>
<td></td>
<td></td>
<td>Lower education</td>
<td>p &lt; 0.00001</td>
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<tr>
<td>Taiwan</td>
<td>288 CIN, 576 controls</td>
<td>CIN</td>
<td>Cytology sign of HPV infection</td>
<td>5.02 (2.54–8.01)</td>
<td>Use of condom</td>
<td>0.38 (0.16–0.95)</td>
<td>39</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Prostitute of husband</td>
<td>2.56 (1.68–3.82)</td>
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<td></td>
<td>4 or more vaginal delivery</td>
<td>2.01 (1.50–3.84)</td>
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<td></td>
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<td>2 or more induced abortion</td>
<td>1.96 (1.45–3.77)</td>
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<td></td>
<td>Multiple sex partner (&gt; 1)</td>
<td>1.87 (1.32–2.64)</td>
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<tr>
<td>Singapore</td>
<td>75 ICC, 62 CIN or stage Ia Ca and 1:1 controls</td>
<td>ICC</td>
<td>Parity (0 vs. 2)</td>
<td>25.5 (3.0–25)</td>
<td>Education</td>
<td>0.24 (0.08–0.74)</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Number of sex partners</td>
<td>3.47 (1.43–8.40)</td>
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</tr>
</tbody>
</table>

CIN = cervical intraepithelial neoplasia; ICC = invasive cervical cancer; HSIL/LSIL = high/low grade squamous intraepithelial lesion.
risk factors in these studies. The female smoking popu-
lation in Chinese societies is typically low [38]. A re-
cent nationwide survey of 4,160,844 Taiwanese adults
revealed a female smoking rate of 4.5% compared to
42.8% in males.

5. Genetic predispositions for cervical
carcinogenesis

Large-scale epidemiological evidence of a genetic
predisposition for cervical cancer has been docu-
mented [45]. DNA polymorphisms of different cancer-
related genes may confer different risks for cervical
cancer. Table 3 [46–53] summarizes studies of risk
for cervical neoplasia and polymorphisms, mainly in
women in Taiwan and Hong Kong. The discovered
polymorphic gene alleles include apoptosis-related
genes FAS -670A/G 44, FASL -844C/CC and their as-
sociations [47], the short tandem repeat polymor-
phism of immune cytokine gene IFNG [48], tissue
remodeling gene MMP1 -160G/GG [49], and phase I
and II metabolizing enzymes CYP1A1 G allele and
GSTM1-null [50]. Different human leukocyte antigen
(HLA) gene polymorphisms and risk of HPV-related
cervical cancer were reported in women in Hong
Kong. Among them were HLA-A*0207/0215N or A*2402,
which is protective for HPV 16 cervical cancer, HLA-
A*1104, which is a risk for all cervical cancer [51],
HLA-DQ-B1*06, which is a risk for HPV 58 CIN3 and
cervical cancer [52], HLA-DRB1*12, which is protec-
tive for CIN and cervical cancer, and HLA-DRB1*03,
which is a risk for HPV 18 CIN and cervical cancer [53].
Interestingly, HLA-DQB1*03, previously found to be a
risk allele for cervical cancer in European women, was
found to be protective in the Hong Kong study [52].

6. New biomarkers in development:
chromosomal loss, methylation-
silenced genes and protein markers

In additional to environmental and constitutional fac-
tors, genetic alterations affecting the growth, apopto-
sis, differentiation and genome stability of cells, and
the angiogenesis and remodeling of tissue, are usually
crucial steps in cancer development. They, therefore,
serve as significant diagnostic and prognostic markers
for cancer. They include loss of heterozygosity (LOH) or
allelic loss, gene mutations and methylation-induced
gene silencing.

With the dominant oncogenic effect of HPV, which
controls cell cycle by its oncoproteins, mutations of
tumor suppressor genes commonly found in other
cancers were lacking in cervical cancer. Studies in
Taiwan, Hong Kong and Singapore on P53 [54–56],
FHIT [57], RII [58], TSG101 [59], CYCD1, CDK4 [60]
and PTEN [61] showed absence of loss of function
mutations. However, larger-scale chromosomal alter-
ations, such as LOH and methylation-mediated gene
silencing, were frequently found in different grades
of cervical carcinogenesis. Table 4 [57,62–77] sum-
marizes these genetic and epigenetic changes in cer-
vical cancers in the three areas. Allelic losses at 3p14,
3p22-24 and 3p25 were repeatedly noted in studies
in Taiwan [57,58,62,63] and Hong Kong [64–66].
Allelic losses at other chromosomal loci, such as
5p15-5p13 [62], 1p31, 1p36.3 and 1q25 [67,68],
were also noted in studies in Taiwan and Hong Kong.
While the crucial genes responsible for cancer devel-
opment have yet to be identified in these chromo-
somal loci, detection of LOH and other microsatellite
alterations in exfoliate cervical epithelial cells may
help in the early diagnosis of cervical cancer [63].

<table>
<thead>
<tr>
<th>Source</th>
<th>Gene polymorphisms</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>Fas-670A/A</td>
<td>Risk for HSIL and ICC.</td>
<td>46</td>
</tr>
<tr>
<td>Taiwan</td>
<td>IFNG (CA)12 or (CA)14</td>
<td>Risk for HSIL in accordance with severity of CIN and ICC.</td>
<td>48</td>
</tr>
<tr>
<td>Taiwan</td>
<td>IFNG (CA)13 or -(CA)18</td>
<td>Protect for HSIL and ICC in accordance with severity.</td>
<td>49</td>
</tr>
<tr>
<td>Taiwan</td>
<td>MMP1 -1607G</td>
<td>Associated with lymph node metastasis of ICC.</td>
<td>47</td>
</tr>
<tr>
<td>Taiwan</td>
<td>MMP1 -1607G</td>
<td>Associated with advance stage of ICC.</td>
<td>49</td>
</tr>
<tr>
<td>Taiwan</td>
<td>FAS -670A/G</td>
<td>FAS -670A confers risk for HSIL and ICC.</td>
<td>50</td>
</tr>
<tr>
<td>Taiwan</td>
<td>FAS -1377G/A -670A/G haplotype</td>
<td>FAS -1377A/-670A haplotype and FAS -670AA/FASL -844C/T confers a higher risk.</td>
<td>51</td>
</tr>
<tr>
<td>Taiwan</td>
<td>CYP1A1-A/G or G/G</td>
<td>Protect for ICC.</td>
<td>52</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>GSTM1-null</td>
<td>Protect for ICC. (In contrast to studies on European) risk for HPV 58 SIL and ICC.</td>
<td>53</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>HLA-DRB1*12</td>
<td>Protect SIL and ICC. (The protective effect of HLA-DRB1*13 that had been reported from other populations was not observed.) Risk for HPV-18 SIL and ICC.</td>
<td>54</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>HLA-DRB1*03</td>
<td>Protect for ICC.</td>
<td>55</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>HLA-DQB1*03</td>
<td>Protect for ICC.</td>
<td>56</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>HLA-A<em>2027/0215N or A</em>2402</td>
<td>Protect ICC and HPV16 ICC.</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>HLA-A*1104</td>
<td>Protect for ICC.</td>
<td>58</td>
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</table>
DNA hypermethylation, with subsequent epigenetic silencing of tumor suppressor genes, is one of the hallmarks of cancer and accounts for the second hit of the two-hit hypothesis of carcinogenesis (78,79). The epigenetic silencing of tumor suppressor genes is commonly seen in cervical cancer worldwide (80,81), as well as in Hong Kong, Taiwan and Singapore (Table 4). Among the methylated genes were P16 at 9p21 (69), BLU and RASSF1A at 3p21.3 (70,71), PTEN at 10q23 (72), P73 at 1p36 (73), DAPK at 9q34, MGMT at 10q26 (74) and DLC1 at 8p22 (75). As noted, some of these methylation markers showed dramatic differences among normal, precancerous and invasive carcinoma of the uterine cervix, and can be detected in cervical scraping samples, which potentially allows self-sampling, and feature a promising diagnostic biomarker compatible with and even more specific than the HPV test.

A number of protein biomarkers, typically defined by specific antibodies, have been investigated in cervical cancer. Among them is p16/INK4A (p16), which shows promising sensitivity and specificity in the diagnosis of cervical high-grade dysplasia and invasive cancer. p16 is a tumor suppressor protein, also known as a cyclin-dependent kinase (CDK) inhibitor, which decelerates the cell cycle by inactivating CDKs. p16 protein was found to be overexpressed in cervical preneoplastic and neoplastic lesions in which HR-HPV existed (82,83). Several studies in Taiwan (84–86) and elsewhere have demonstrated that p16 immunocytochemistry can be applied successfully to conventional Pap smears and tissue sections, and helps to clarify ambiguous cytological and pathological interpretations such as atypical squamous cells of unknown significance (ASCUS), atypical glands of unknown significance (AGUS) and squamous intraepithelial lesions (84–86). Aside from p16, other protein markers, including cell proliferation markers such as hTERT and Ki-67, were also found to be associated with HSIL and invasive cervical cancer (87–90). However, these markers also appeared in proliferative and reactive cells, and thus limited their specificity and future applications.

### Table 4 — Chromosome allelic losses and methylation of tumor suppressor genes in cervical neoplasia in Taiwan, Hong Kong and Singapore

<table>
<thead>
<tr>
<th>Source</th>
<th>Chromosome loci</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taiwan</td>
<td>5p15.1-15.3</td>
<td>Genomic deletion on 3p and 5p correlated with genetic or epigenetic p53 inactivation pathways, including p53 mutation, genetic deletion of p53 and cervical infection with HPV.</td>
<td>62</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>3p14, 3p25, 9 loci at 3p</td>
<td>LOH was found in 10/12 ICC at 3p25 and 10/11 cases at 3p14. The incidence of LOH at 3p13 was the highest among 9 markers examined. Frequent LOH was found at 3p26 (41%), 3p25 (31%), 3p25.1 (24%), 3p21 (29%), 3p1 (24%), and 3p13 (25%) in CIN.</td>
<td>64–66</td>
</tr>
<tr>
<td>Taiwan</td>
<td>3p14, 3p22-24, 3p25</td>
<td>37% ICC showed LOH at 3p14 and 43% showed LOH at 3p22-24. LOH at one of the three sites was observed in 23%, 27% and 31% of LSILs, HSILs, and ICC.</td>
<td>57,62,63,76</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>1p31, 1p36.3, 1q25</td>
<td>LOH at 1p31, 1p36.3 and 1q25 exceeded 30%. 12 other loci exhibited frequencies of LOH of 20–30%.</td>
<td>67,68</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>Gene</th>
<th>Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td>RASSF1A at 3p21</td>
<td>8/12 hypermethylated primary cancers showed concomitant LOH at 3p21.</td>
<td>70</td>
</tr>
<tr>
<td>Taiwan</td>
<td>BLU &amp; RASSF1A at 3p21.3</td>
<td>BLU was methylated in 76.9% of ICC, 57.4% of HSIL, 20.0% of LSIL and 12.5% of normal tissues (p &lt; 0.001). RASSF1A was methylated in 15% of ICC, 17.5% of HSIL, but not in LSIL or normal. The methylation of RASSF1A was inversely related to HPV infection in patients with HSIL/SCC (p = 0.005).</td>
<td>71</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>PTEN at 10q23</td>
<td>PTEN was methylated in 40% HSIL and 58% ICC.</td>
<td>72</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>P73 at 1p36</td>
<td>P73 was methylated in 39% ICC, conferring resistance to radiotherapy.</td>
<td>73</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>DAPK at 9q34, p16 at 9p21, and MGMT at 10q26</td>
<td>Methylation rate of DAPK, P16 and MGMT in ICC were 60%, 28.2% and 18.8%, respectively.</td>
<td>74</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>p16/INK4A at 9p21</td>
<td>p16/INK4A was methylated in 31% of ICC.</td>
<td>69</td>
</tr>
<tr>
<td>Singapore</td>
<td>DLC1 at 8p22</td>
<td>DLC1 was methylated and silenced in 7/8 CxCa.</td>
<td>75</td>
</tr>
<tr>
<td>Singapore</td>
<td>HPV 16 LCR</td>
<td>HPV 16 LCR was methylated in 52% of subclinical HPV, 21.7% of precursor lesions and 6.1% of ICC.</td>
<td>77</td>
</tr>
</tbody>
</table>
7. Perspectives

In this post-genomic era when the code, control and function of the human genome is being quickly unveiled, characteristic genotypic and phenotypic changes in human cancers are being discovered at an ever increasing pace. With the aid of various genome-wide technologies, genetic and epigenetic markers for cancers are emerging systematically and in an overwhelming way. With the massive candidate markers being discovered, each has to be verified and tested clinically in line with the risk, diagnosis and prognosis of cancer. In a disease that is caused by persistent viral infection, and whose fate is determined by long-term host-viral and host-environmental interactions, it is not surprising to see a common spectrum of type- or variant-specific HPV prevalence, with similar behavioral and environmental risk factors for cervical cancer in people in Taiwan, Hong Kong and Singapore, who share a great similarity in genetic background, culture and social systems. With the emergence of more and more candidate tumor markers, and the rate-limiting nature of translational research, further investigation into this fascinating disease will demand systematic work among these and other regions in a collaborative, as well as competitive, way.

References


