# 2

# Human Papillomavirus Type Distribution in Southern China and Taiwan

Chung-Yung Chen[1] and Chin-Hung Wang[2]
[1]*Department of Bioscience Technology, Chung Yuan Christian University, Chung-Li, 320,*
[2]*Genelite Life Science Centre, Taipei, 105,*
*Taiwan*

## 1. Introduction

In 2007, a worldwide analysis was published that assessed the types of HPV infection found in women without cervical disease (1). Of the 291 million women suffered with cervical diseases around the world, it was found that 32% are infected with either HPV16 or HPV18, or both. Data regarding the HPV burden and incidence rates are available on the WHO/ICO Information Centre on HPV and Cervical Cancer Web site (http://www.who.int/hpvcentre). However, HPV prevalence in different regions of Southern China is not mentioned in this website. Hence the diversity of HPV prevalence and distribution in Taiwan, Hong Kong, and various regions of China is the major focus in this chapter.

In Hong Kong, HPV DNA has been detected in 4% of women in 1996 and in 11% in 2002 by utilizing polymerase chain reaction methods on cervical samples, the most common high-risk (HR) HPV types identified being, in decreasing order, HPV 16, 58, 53, 18, 33, 45, and 52. Moreover, HPV 6 and 11, two types responsible for about 90% of genital warts, are among the most frequent HPV types found in Hong Kong population. In Taiwan, the five most common HPV types, also listed in decreasing order of frequency, are: HPV 16, 18, 58, 33, and 52 for women with cervical cancer, and HPV 16, 52, 58, 18, and 51 for women with normal cytology (2, 3). According to literature, there are, to date, fifty cities and provinces including Hong Kong and Taiwan whose predominant HPV types are already known. Table 1 shows the prevalence of HR-HPV in different regions in China such as, Zhejiang Province, Tianjin City, Shanxi Province, Hong Kong (HK), Guangzhou, Shandong Province, Shenzhen, Fujian, Liaoning Province, Beijing, Gansu province, Shanghai, Sichuan province, Guangdong province, Shenyang City, and in Taiwan. HPV type 16 exhibits the highest incidence in majority of these regions except Zhejiang province, Guangzhou, Fujian province, and in Taiwan (3), where HPV 52 has the highest prevalence. However, an investigation by Jin *et al.* (2010) in the Tibet Autonomous Region (TAR) which included both Tibetan and non-Tibetan populations pointed out that the frequency of HPV 33 may be higher than HPV 16 for non-Tibetan people, with the order of frequency of HPV genotypes being 16, 58, 31, 33, and 52 for Tibetan people. Incidentally, HPV 58 is also the second most common HPV type found in Taiwan (2), Chengdu, Liaoning, Beijing, Shenzhen, Shenyang, Shanxi, and Hong Kong (Table 1).

The three major HR-HPV types which can be deduced from Table 1 infect over 50% of patients in every city/region included in the list. In Taiwan (2), the TAR, Liaoning,

Shenzhen, and Shanxi, the order of frequency of HPV type is 16, 58 and 52, while the order that can be found in Shandong, Hong Kong, and Shenyan is 16, 52 and 58. Another combination of frequency order, namely, HPV 52, 16, and 58, has also been discovered in Taiwan (3), Guangzhou, and Zhejiang, whereas the order 16, 58, and 33 is inherent to Beijing, Shanxi, and Shenzhen (4). Both Chengdu and Shenyang (cancer cases) are represented by the order HPV 16, 58, and 18. Only cancer cases in Shanxi consist of the order 16, 58, and 56. To summarize, HPV 16, 52, and 58 are the three major types affecting 87% of the geography that includes these selected areas.

The relationship between geography and HPV types is demonstrated in Figure 1, with A~D corresponding to the distribution of HPV 16, 18, 52, and 58, respectively. Coastal areas in the southeast such as Taiwan and Hong Kong display a higher prevalence than inland cities. HPV prevalence may vary among different regions due to geographical separation, an example of which is Taiwan and Hong Kong. The political separation of Taiwan and Hong Kong most likely caused the HPV types diverse than mainland China. Moreover, the TAR is isolated by mountains from mainland China while Taiwan and Hong Kong are separated by sea. Thus, the lower number of HPV patients in the TAR compared with other regions can

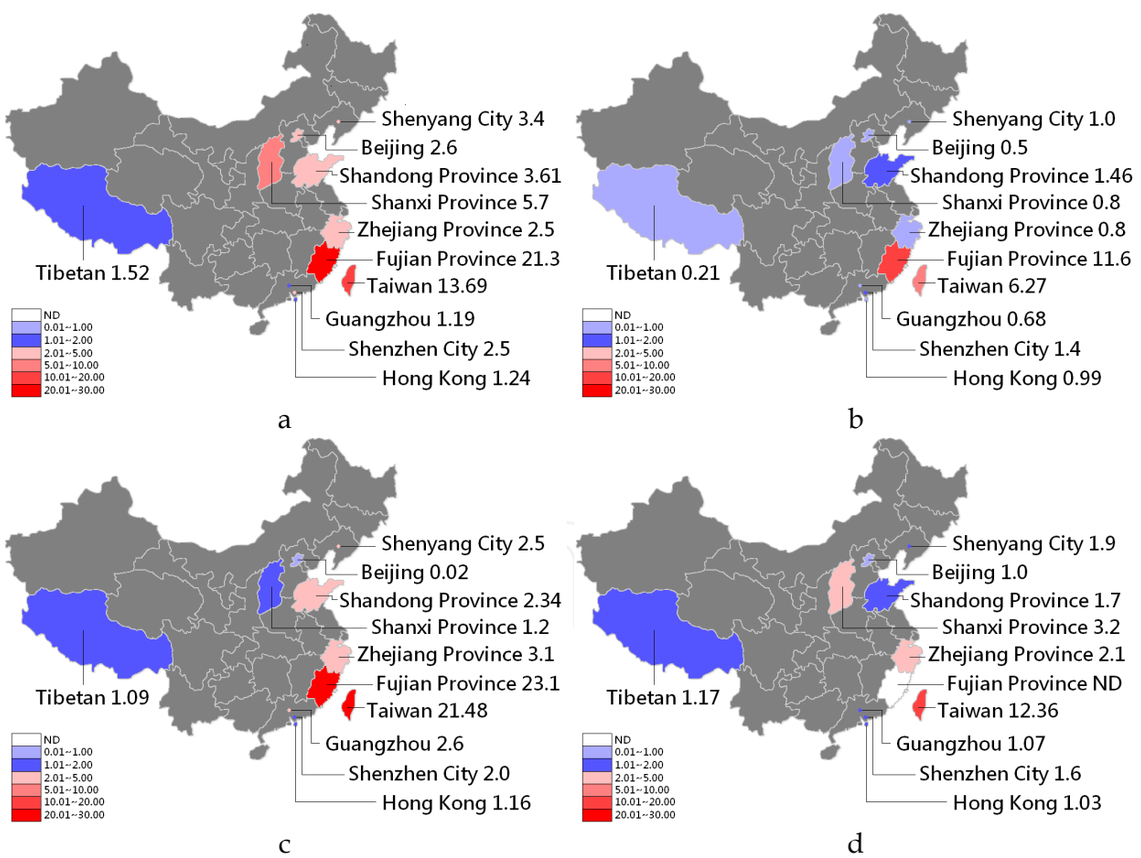



Fig. 1. The prevalence of major HPV types in some of China areas, Hong Kong and Taiwan. Four different HPV types show as (A) HPV16 (B) HPV18 (C) HPV52 (D) HPV58

be attributed to population conservation. In Taiwan, from 52 HPV types screening, HPV type 52 has the highest frequency (21.48% flowing HPV type 16, 58, 56, 39, 51, 18, 68, 31, 33, 59, 45, and 35(3) among HR-HPV types that is distinguish HPV combination compared to other regions. This also demonstrates the effect of geography despite Taiwan and China essentially being of the same ethnicity only partitioned over 60 years to affect two generations of people including marriage. The more independent, younger generation and their sexual culture are two major factors that cause the variations in HPV types distribution.

Since the prevalence of HPV types in each age group can be linked to sexual behavior, it is reasonable to investigate the multiple HPV infection types that can be found in patients (Table 2). In Taiwan, the multiple HPV infection rate is over 19%, only slightly lower than Hong Kong's (22.8%) but distinctly higher compared to others. For instance, most of the cities/regions that belong to mainland China, specifically inland cities like Beijng, Shangdong, Shanxi, Shengyang, Shenzhen, and Zhejiang, possess only 4~5% multiple HPV infection rates. Only Guangdong province has 11.1% between inland and island; however, Guangdong province is closest to Hong Kong and is more well-developed than inland cities. In contrast to Hong Kong and Taiwan, the TAR is isolated from immigration and might have conservative social behaviors, resulting to the lowest fraction of multiple HPV types (1.3%).

| Regions\ HPV types (%) | 16 | 18 | 31 | 33 | 35 | 39 | 45 | 51 | 52 | 56 | 58 | 59 | 68 | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Beijing** | 2.6 | 0.5 | 0.4 | 0.8 | 0.6 | 0.1 | 0.1 | 0.2 | 0.02 | 0.7 | 1.0 | 0.3 | 0.5 | (Zhao et al., 2009) |
| **Chengdu, western China (Cancer)** | 68.1 | 4.9 | ND | 0.7 | ND | ND | 0.7 | ND | 2.8 | ND | 8.3 | ND | ND | (Li et al., 2011) |
| **Fujian province** | 21.3 | 11.6 | ND | 11.2 | ND | ND | ND | ND | 23.1 | ND | ND | ND | ND | (Wu et al., 2010) |
| **Gansu Province (Cancer)** | 80.4 | 3.6 | 1.8 | 1.8 | ND | ND | ND | ND | 3.6 | ND | 3.6 | 3.6 | ND | (Wu et al., 2009) |
| **Guangdong province (Cancer)** | 25.0 | 20.8 | ND | ND | ND | ND | ND | ND | 20.8 | ND | ND | ND | ND | (Lin et al., 2008b) |
| **Guangzhou** | 1.19 | 0.68 | 1.16 | 0.59 | 0.07 | 0.32 | 0.24 | 0.14 | 2.6 | 0.27 | 1.07 | 0.15 | 0.39 | (Liu et al., 2011) |
| **Hong Kong** | 1.24 | 0.99 | 0 | 0.25 | 0 | 0.04 | 0.15 | 0 | 1.16 | 0 | 1.03 | 0.09 | 0.23 | (Liu et al., 2011) |
| **Hong Kong (Cancer)** | 18.3 | 9.1 | ND | ND | ND | ND | ND | 8 | 18.3 | ND | 17.7 | ND | ND | (Chan et al., 2009a) |
| **Hong Kong (Cancer)** | 43.2 | 4.8 | 3.2 | 3.2 | 0.8 | 0.8 | 1.1 | 0.5 | 9.1 | 0 | 5.9 | 0.8 | 0.8 | (Chan et al., 2009b) |
| **Liaoning province (Cancer)** | 19.64 | 1.8 | 3.03 | 4.6 | 1.03 | 1.59 | 0.29 | 0.77 | 6.4 | 0.61 | 8.39 | ND | ND | (Sun et al., 2010) |
| **Taiwan (Cancer)** | 18.4 | 1.7 | 0.3 | 3.6 | 0.6 | 1.5 | 0.6 | 2.9 | 9.4 | 0.6 | 7.6 | 1.5 | 0.6 | (Chen et al., 2006) |

| Regions\ HPV types (%) | 16 | 18 | 31 | 33 | 35 | 39 | 45 | 51 | 52 | 56 | 58 | 59 | 68 | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Taiwan** | 13.4 | 4.6 | 3.2 | 5.8 | 1.6 | 3.7 | 1.8 | 6.0 | 10.4 | 3.7 | 7.6 | 1.2 | 1.4 | (Lin et al., 2008a) |
| **Taiwan** | 13.69 | 6.27 | 3.52 | 3.42 | 0.95 | 8.46 | 2.38 | 8.17 | 21.48 | 9.03 | 12.36 | 2.66 | 4.66 | (Wang et al., 2010) |
| **Tibetan** | 1.52 | 0.21 | 1.17 | 1.17 | 0.04 | 0.21 | 0.17 | 0.21 | 1.09 | 0.21 | 1.17 | 0.08 | 0.5 | (Jin et al., 2010) |
| **Shandong Province** | 3.61 | 1.46 | 0.85 | 1.46 | 0.21 | 0.42 | 0.21 | 0.21 | 2.34 | 1.27 | 1.7 | 0 | 2.76 | (Yuan et al., 2011) |
| **Sichuan province (Cancer)** | 41.6 | 3.2 | 1.1 | ND | ND | ND | 1.1 | ND | 2.1 | 2.6 | 1.1 | ND | ND | (Wu et al., 2008) |
| **Shanxi Province** | 5.7 | 0.8 | 0.5 | 1.2 | ND | 0.6 | 0.6 | 0.6 | 1.2 | 0.8 | 3.2 | 0.3 | 0.2 | (Dai et al., 2006) |
| **Shenyang City** | 3.4 | 1 | 1 | 0.9 | 0.3 | 0.9 | 0.6 | 0.6 | 2.5 | 0.9 | 1.9 | 0.6 | 0.3 | (Li et al., 2006) |
| **Shenzhen City** | 2.5 | 1.4 | 1.5 | 0.3 | 0.4 | 1.5 | 0.7 | 0.6 | 2 | 1 | 1.6 | 0.9 | 0.5 | (Wu et al., 2007) |
| **Shenzhen City (Cancer)** | 29.7 | 18.9 | 5.4 | 9 | 6.3 | ND | 1.8 | ND | 1.8 | 3.6 | 18.9 | 9 | ND | (Shi et al., 2006) |
| **Zhejiang Province** | 2.5 | 0.8 | 0.8 | 0.8 | 0.2 | 0.3 | 0.3 | 0.9 | 3.1 | 0.4 | 2.1 | 0.7 | 1.0 | (Ye et al., 2010) |

Table 1. The HR-HPV types distribution in China, Hong Kong and Taiwan

Numerous investigations focused on HR-HPV due to its higher relationship to cervical cancer and high-grade squamous intraepithelial lesion. To survey high-risk and low-risk HPV, HR-HPV frequently found in women with ASCUS and CIN3/cervical cancer, and might be at least double frequencies than LR-HPV cases (Table 2). The average incidence of HR-HPV in population is over 10%, but an extremely high incidence has been found in CIN3/cervical cancer cases (Taiwan reports, Table 2). However, the LR-HPV prevalence might not be estimated correctly due to less LR-HPV types screening. A survey of 52 HPV types reported in Taiwan suggests that the prevalence of LR-HPV (37 types) and HR-HPV (15 types) is 10% and 5%, respectively (3). Other HPV reports listed less than 37 LR-HPV types and focused only on HR-HPV. The same HPV screening type but few LR-HPV screening types caused underestimation for the incidence of LR-HPV that showed in Table 2. For example, incidences of LR-HPV in Beijing, Hong Kong, the TAR, Shandong, Shanxi, Shenyang, Shenzhen, and Zhejiang are 2.0, 2.4, 2.1, 1.7, 3.8, 6.4, 6.6, and 3.5, respectively, and 5.8, 74.8, 7.1, 11.0, 12.2, 11.7, 12.2, and 10.2 for HR-HPV.

To compare HPV infections in different geographies around the world, the data from IARC and Table1 combined into Appendix 1. For overall HPV infection rate, Kenya has the highest HPV prevalence (38.8%) region and Span has the lowest HPV infection (1.5%). The Asia region including, China, Hong Kong, Japan, Korea, Taiwan and Thailand, are around 10~15% of overall infection rate except Thailand (4.8%). The most of developed countries, such as, Italy, Japan, Span, Sweden, UK, and USA are less HPV prevalence than most of the

developing countries and under-developed countries, such as Argentina, Honduras, Kenya and Nigeria. For East-Asia, like, China, Japan, Hong Kong and Taiwan, HPV type 52 is higher HPV incidence than HPV 16. Other regions, HPV type 16 is the major incidence. HPV type 51 is another typical case for geographic : HPV 51 is higher incidence than HPV 52 in Brazil, Costa Rica, Republic of Korea, Scotland, and USA. In China and Hong Kong, HPV 51 is not significant prevalence in population. For top five prevalence of HR-HPV, HPV 16, 18, 31, 52, 58 are found in most of the countries/regions but different orders. However, the geography separated populations to cause the diverse of HPV infection types can be deduced from Appendix 1.

| Regions\HPV types (%) | Multiple HPV % | LR | HR | References |
|---|---|---|---|---|
| **Beijing** | 2.6 | 2.0 | 5.8 | (Zhao et al., 2009) |
| **Guangdong province (Cancer)** | 11.1 | ND | 7.4 | (Lin et al., 2008) |
| **Hong Kong (Cancer)** | 22.8 | 2.4 | 74.8 | (Chan et al., 2009) |
| **Taiwan** | 4.9 | 4.4 | 52.3 | (Chen et al., 2006) |
| **Taiwan (Cancer)** | 19.9 | 70.4 | 29.6 | (Chao et al., 2008) |
| **Taiwan (Cancer)** | 19.4 | 68.9 | 31.1 | (Lai et al., 2008) |
| **Taiwan** | 4.5 | 10.0 | 5.0 | (Wang et al., 2010) |
| **Tibetan** | 1.32 | 2.14 | 7.05 | (Jin et al., 2010) |
| **Shandong Province** | 4.2 | 1.70 | 11.04 | (Yuan et al., 2011) |
| **Shanxi Province** | 4.5 | 3.8 | 12.2 | (Dai et al., 2006) |
| **Shenyang City** | 5.3 | 6.4 | 11.7 | (Li et al., 2006) |
| **Shenzhen City** | 4.4 | 6.6 | 12.2 | (Wu et al., 2007) |
| **Zhejiang Province** | 3.5 | 2.7 | 10.2 | (Ye et al., 2010) |

Table 2. A list of Multiple HPV infection rate in individual region.

## 2. Age related to HPV genotypes

Based on our previous study of Taiwan cases, the prevalence of LR-HPV is diverse among different age groups. For instance, HPV 84 is found most frequently in the 20–29 age group, HPV 54 in the 30–39 age group, HPV 53 in the 40–49 age group, and HPV 72 in the over-50 age group. When the range of HPV genotypes that could be identified among cases of multiple infections was examined, 38 HPV genotypes were found in the over-50 age group and 40 genotypes in the 40–49 age group. In addition, 41 HPV genotypes were identified in the 30–39 age group, while 42 genotypes were discovered in the 20–29 age group (3). HR-HPV genotypes in Taiwan have the highest peak in the younger population (<20 years old, 28.1%), subsequently decreasing as it moved from the 20-29 age group (26.7%), 30-39 age group (15.5%), and 40-49 (12.1%) age group, to the over-50 age group (10.4%). This pattern, however, is different from those found in other regions (Table 3).

Based on the epidemiological distribution of HPV in Beijing city, the 30-34 age group has the highest HPV frequency, while the 25-29 and 50-54 age groups have the lowest (5). By contrast, according to Guangdong province cervical cancer cases, older women tended to have higher HPV infection rates, as evidenced by the 11.7%, 8.2%, 8.1%, and 3.4% rates representing the 51-60, 41-50, 31-40, and 21-30 age groups, respectively (6). For people in Guangzhou, a high HPV rate (15.1%) is evident in the 20-29 age group and lower HPV rates

(11.7% and 11.8%) can be observed in the 40-49 and over-60 age groups (7). However, there is no significant difference in HPV rates among age groups in Guangzhou. In Hong Kong, the 20-29 age group has the highest peak in both cancer report and population screening; however, the 40-49 age group had less HPV frequency (7, 8) which remains without clear explanation. In other south coast cities, namely, Shanghai and Shenzhen, the 20-29 age group also exhibited the highest HPV infection rate but in Shanghai only; an opposite trend was found in Shenzhen city, where a high infection rate manifested in older people (45-59 age group). Two recent reports related to Shenzhen city have pointed out the discrepancy about HPV prevalence. One demonstrated an increased HPV infection along with elder people and another report mentioned the 25-29 age group is the lowest. However, Shenzhen city has many plants with numerous temporary residents and tertiary sector workers from other counties that might cause residential status being significantly associated with HPV positivity.

| Regions\Age Groups (%) | A | B | C | D | E | F | G | H | References |
|---|---|---|---|---|---|---|---|---|---|
| **Beijing** | 25-29<br>4.9% | 30-34<br>8.2% | 35-39<br>7.1% | 40-44<br>7.5% | 45-49<br>6.4% | 50-54<br>4.9% | | | (Zhao et al., 2009) |
| **Guangdong province (Cancer)** | 21-30<br>3.4% | 31-40<br>8.1% | 41-50<br>8.2% | 51-60<br>11.7% | | | | | (Lin et al., 2008) |
| **Guangzhou** | 20-29<br>15.1% | 30-39<br>14.2% | 40-49<br>11.7% | 50-59<br>14.0% | ≧60<br>11.8% | | | | (Liu et al., 2011) |
| **Hong Kong** | 20-29<br>13.0% | 30-39<br>4.9% | 40-49<br>4.6% | 50-59<br>7.1% | ≧60<br>9.6% | | | | (Liu et al., 2011) |
| **Hong Kong (Cancer)** | <26<br>10.0% | 26-30<br>14.0% | 31-35<br>9.5% | 36-40<br>6.0% | 41-45<br>5.6% | 46-50<br>7.5% | 51-55<br>6.5% | >55<br>3.5% | (Chan et al., 2009) |
| **Taiwan** | <20<br>28.1% | 20-29<br>26.7% | 30-39<br>15.5% | 40-49<br>12.1% | ≧50<br>10.4% | | | | (Wang et al., 2010) |
| **Tibetan** | 19-29<br>9.2% | 30-39<br>9.2% | 40-49<br>9.1% | ≧50<br>9.1% | | | | | (Jin et al., 2010) |
| **Shanxi Province** | 15-24<br>13.3% | 25-34<br>7.5% | 35-44<br>20.5% | 45-54<br>17.0% | 55-59<br>14.3% | | | | (Dai et al., 2006) |
| **Shanghai** | 18-20<br>54.4% | 21-30<br>26.4% | 31-40<br>30% | 41-50<br>32.0% | 51-60<br>31.0% | 61-78<br>31.5% | | | (Zhang et al., 2008) |
| **Shenyang City** | <25<br>2.7% | 25-34<br>11.8% | 35-44<br>12.5% | 45-54<br>13.0% | 55-59<br>6.3% | | | | (Li et al., 2006) |
| **Shenzhen City** | <25<br>14.3% | 25-34<br>16.2% | 35-44<br>15.2% | 45-59<br>24.4% | | | | | (Wu et al., 2007) |
| **Shenzhen City** | 15-24<br>15.5% | 25-29<br>17.7% | 30-34<br>12.6% | 35-39<br>8.8% | 40-44<br>10.2% | 45-49<br>15.3% | 50-59<br>21.0% | | (Wu et al., 2010) |
| **Zhejiang Province** | 20-24<br>14.5% | 25-29<br>9.3% | 30-34<br>8.4% | 35-39<br>10.7% | 40-44<br>10.7% | 45-49<br>9.2% | 50-54<br>14.4% | 55-79<br>8.6% | (Ye et al., 2010) |

Table 3. A list of HPV infection rates among different age groups

Zhejiang province provided more interesting data (9) showing a similar low HPV frequency in each age group (Table 3). Although both the 20-24 and 50-54 age groups have slightly

higher rates, the highest (14.4%) and lowest (8.4%) frequencies indicated a less diverse range of HPV prevalence than in other cities/regions. For the north coast city of Shenyang, HPV infection rate initially increases with respect to age, starting from 2.7% for women <25 years old to 13% for women 45-54 years old, but then drops to 6.3% for the 55-59 age group. This pattern is unique among coastal cities and is compatible with the flat age-curves that have been described in other countries such as India and Africa (10). A flat age-curve indicates that young women are not infected with new HPV types more frequently than older women (11). The number of sexual partners as well as the husband's extramarital sexual relationships are believed to be explanatory of this flat age-curve. For inland cities, the TAR has consisted of HPV prevalence around 9% in every age group. For Shanxi province, the 35-44 age group has the highest peak of infection distribution (20.5%), followed by age groups 45-54 with 17.0%, 55-59 with 14.3%, 15-24 with 13.3%, and 25-34 with 7.5%. Finally, for Guangzhou, Hong Kong, Shenzhen, and Zhejiang, the age distribution of cervical HPV infection shows a bimodal curve in half of the regions, with a first peak at younger women, a lower prevalence plateau at middle-aged women, and a variable rebound at older ages (≧45 years). One explanation for this is sexual behavior, which is considered an important risk factor for HPV infection. On the other hand, HPV incidence associated with unmarried status along with a high peak of HPV infection suggests that younger, single women may have an increased possibility of encountering complicated sexual relationships (11). However, the lower prevalence plateau at middle-aged women may be caused by less sexual frequency and single sex partners for married Chinese women.

## 3. HPV type distribution in invasive cervical cancer and high-grade squamous intraepithelial lesion

Overall HPV prevalence in invasive cervical cancer (ICC) is 87%, ranging from 86% to 94% by region, according to literature. In Jiashan, data for the incidence of invasive cervical cancer (ICC) from 1998 to 2002 has been reported. Incidence rates of cervical cancer ranged from 2.4 per 100,000 women to 4.6 per 100,000 women in Guangzhou (12). Some areas have notably high cervical cancer incidence rates, such as in Yangcheng and Shanxi, where there is an estimated rate of about 81 per 100,000 women between 1998–2002 (12). Incidentally, the incidence rates for cervical cancer in Hong Kong, Singapore, and Taiwan are 9.6, 10.6, and 18.6 per 100,000 women, respectively (13). Between these three regions, the incidence of cervical cancer is highest in Taiwan and is nearly double than Hong Kong's. However, it has declined since 1993 to 2003.

Tay *et al.* (2008) has reported the five most common HPV types in Taiwan to be, in decreasing frequency order: HPV 16, 18, 58, 33, and 52 for women with cervical cancer, and HPV 16, 52, 58, 18, and 51 for women with normal cytology (13). Due to a high HPV prevalence, the Taiwanese National Health Insurance launched a screening program in 1995 for women aged 30 years old and above. This program included quality control monitoring and a training system for medical doctors, public health nurses, cytologists, and medical technicians. By 2001, the screening program has been estimated to reduce cervical cancer incidence by 29% and mortality by 50%, and has been shown to be cost-effective for Taiwanese public health (14). Upon analysis of HPV genotypes present in ICC, HPV 16 was found to be the most common type, rating 52% in Asia and 58% in Europe, while HPV18 was the second most common type which rated from 13% in South/Central America to 22%

| Regions\Abnormal (HPV%) | ASCUS | ICC | HSIL | LSIL | CIN1 | CIN2 | CIN3 | References |
|---|---|---|---|---|---|---|---|---|
| **Beijing** | 56.0 | Unknown | 93.3 | Unknown | Unknown | Unknown | 85.7 | (Zhao et al., 2009) |
| **Chengdu, western China** | Unknown | 80.6 | 61.9 | Unknown | Unknown | Unknown | Unknown | (Li et al., 2011) |
| **Fujian province** | Unknown | 94.3 | Unknown | Unknown | 70.5 | 90.2 | Unknown | (Wu et al., 2010a) |
| **Gansu Province** | Unknown | Unknown | Unknown | Unknown | 70.5 | Unknown | Unknown | (Wu et al., 2009) |
| **Guangdong province** | 12.4 | 1 | Unknown | 2.1 | Unknown | Unknown | Unknown | (Lin et al., 2008) |
| **Guangdong and Jiangxi** | Unknown | 89.9 | Unknown | Unknown | 68.8 | 80.3 | 90.2 | (Wu et al., 2006) |
| **Liaoning province** | 54.6 | 83.1 | Unknown | Unknown | 64.1 | Unknown | Unknown | (Sun et al., 2010) |
| **Taiwan** | 13.4 | Unknown | 89.4 | 84.7 | Unknown | Unknown | Unknown | (Chen et al., 2006) |
| **Taiwan** | 41.2 | 66.7 | 87.5 | Unknown | Unknown | 5.7 | Unknown | (Chao et al., 2008) |
| **Taiwan** | Unknown | Unknown | Unknown | Unknown | 81 | 84 | 90 | (Tsai et al., 2005) |
| **Tibetan** | 7.41 | Unknown | 56.8 | 24.3 | Unknown | Unknown | Unknown | (Jin et al., 2010) |
| **Shandong Province** | Unknown | 81.3 | Unknown | Unknown | 34.8 | 59.8 | 74.5 | (Yuan et al., 2011) |
| **Shanghai** | Unknown | 52.9 | Unknown | Unknown | 34.4 | 31.7 | 47.1 | (Zhang et al., 2008) |
| **Shanxi Province** | Unknown | Unknown | Unknown | Unknown | 46.2 | 68.8 | 92.5 | (Dai et al., 2006) |
| **Shanxi Province** | 7.3 | Unknown | 25.8 | 2.7 | 13.1 | 5.7 | Unknown | (Shi et al., 2009) |
| **Shenzhen City** | Unknown | Unknown | Unknown | Unknown | 16.6 | 11.9 | 68.2 | (Wu et al., 2007) |
| **Shenzhen City** | 47.8 | Unknown | Unknown | Unknown | 77.8 | 100 | 100 | (Wu et al., 2010b) |

Table 4. Incidence of HPV infection related to ICC, HSIL and LSIL in China, Hong Kong and Taiwan

in North America (13). Other HPV types most commonly related to ICC were HPV 31, 33, 35, 45, and 52. However, the prevalence of both HPV 58 and 52 were notably higher in ICC cases in Asia. For example, the prevalence of HPV 58 and 52 was found to be as important as the prevalence of HPV 16 and 18 in early cervical cancer patients as well as patients with advanced cervical cancer in Taiwan (15). As shown in Table 4, the frequency of HPV in HSIL, ICC, and CIN3 samples is higher than in ASCUS, LSIL, CIN1, and CIN2.

In Beijing, 85.7% of CIN3 patients have been diagnosed with HPV infections similar to 93.3% of HSIL patients (Table 4). In ASCUS cases, only 56.0% involve HPV infection (5). In all of these cases, HPV 16 was found to be the most common type (2.6% overall; 39.1% of HPV-positive women), followed by HPV 58 (1.0% overall) and HPV 33 (0.8% overall). For inland regions like Shandong and Shanxi province, CIN3/ICC patients have the highest HPV infection rate. HPV types 16, 52, 58, and 31 are the most prevalent HPV genotypes found in Shandong, whereas HPV 16, 58, 52, 33, and 18 are the predominant genotypes in Shanxi province (16, 17). In the TAR, HPV prevalence in HSIL cases is twice that of LSIL patients (Table 4). The descending order of HPV incidence among Tibetan women is HPV 16, 33, 58, 31, 52, and 68 (18).

For coastal areas like Fujian, Guangdong, Jiangxi, Liaoning, Shanghai, Shenzhen, and Taiwan, a similar prevalence of HPV types in ICC/CIN3 cases is observable (Table1 and Table 4). In Fujian province, HPV 16 (24.5%), HPV 33 (21.6%), and HPV 52 (19.6%) are the major genotypes present in CIN2/3 patients. In addition, HPV 16 (42.7%), HPV 18 (20.8%), and HPV 33 (12.5%) are also frequently found in squamous cell carcinoma (SCC) and adenocarcinoma (ADCA) (19). For Guangdong and Jiangxi, there is a significantly increased risk of elevating the CIN stage with high viral load. Thus, 68.8% of CIN1, 80.3% of CIN2, 90.2%of CIN3 and 90.0% of CIS contain HR-HPV genotypes like HPV 16 (79.6%), HPV 58 (5.92%), HPV 33 (3.29%), HPV 18 (1.97%), HPV 6 (1.97%), HPV 31 (1.31%), HPV 39 (1.31%), and HPV 68 (1.31%) (20). In Liaoning province, the most common HPV genotypes are HPV 16, HPV 58, HPV 52, HPV 33, HPV 53, and HPV 31, occurring in 54.6% of ASCUS patients, 64.1% of CIN, and 83.1% of ICC (21). For the island of Taiwan, the HPV prevalence for ASCUS, LSIL, HSIL, and squamous cell carcinoma are 41.2%, 76.9%, 87.5%, and 66.7%, respectively. The five high-incidence HPV genotypes are HPV 52, 18, 58, 53, and 70 in Taiwanese CIN2 patients (22). For Shanghai city, HPV viral load values in women with CINs and cervical cancer were calculated to be 68.8% in CIN1, 66.7% in CIN2, 76.5% in CIN3, and 94.1% in cervical cancer (23). For Shenzhen city, the incidence of HR-HPV genotypes increased with increasing severity of cervical lesions, such as 50.0% of CIN1, and 74.0% of CIN2 /CIN3. However, the most common types were HPV52, 16, and 18 in CIN samples that are different with population screening which the most common genotypes are HPV 16, 52, 58, 31 and 39 (24).

## 4. HPV vaccination in Southern China, Hong Kong, and Taiwan

Based on statistical calculations to determine the link between HPV and cervical cancer, many strategies for the prevention of cervical cancer have been proposed, including vaccination in younger women and improved HPV screening in older women (25). Two HPV vaccines have been generated from the recombinant L1 protein into non-infectious capsids (virus-like particles, VLPs). Gardasil™ (Merck and Co, USA) already has approval for vaccination against HPV6/11/16/18 in several countries including Singapore and Hong Kong. The bivalent

vaccine, Cervarix™ (GlaxoSmithKline, Belgium), has also been approved in both countries. Both vaccines were developed for HPV16 and HPV18, which cause approximately 70% of all reported cervical cancer cases worldwide (26). Thus, the quadrivalent vaccine can be expected to prevent CIN-2 and CIN-3 (CIN-2,3), cervical cancer, as well as genital warts. However, HPV 18 is less common than HPV 52 and 58 in places like China, Hong Kong, and Taiwan (Table 1) where there is no publicly funded vaccination program. Hence vaccination is voluntary and paid by individuals.

HPV vaccination does not increase the clearance of established infections; therefore, young females are ideally targeted before the development of sexual behavior. Initiation of HPV vaccination in younger cohorts combined with HPV screening in older women is a good strategy for HPV prevention. In China and Taiwan, evaluation of HPV vaccination as primary care HPV and assessment of the threshold cost per vaccinated girl (CVG) became potential feasible strategies in public health. Singapore's policy regarding the management of HPV can be a reference for China and Taiwan. In a cervical cancer awareness survey for Singaporean women aged 30-55 years in 2006, 80% have had at least one Pap smear although 25% did not fully understand the significance behind it (13). Furthermore, 80% were unaware of HPV. In Hong Kong, most women have never heard of HPV or its infection by sexual transmission (27). Thus, participants had no knowledge or means of understanding the link between cervical cancer and HPV infection. However, participants agreed to HPV vaccination for both themselves and their teenage daughters if a health department endorsement was provided. Another study demonstrated that 32% of participants accepted HPV vaccination prior to receiving an educational booklet, and that this number increased to 52% after reading the pamphlet (28). About 48% of women remained undecided or disagreed with vaccination after education; 84% were worried about the side effects of vaccination, and 63% of women augmented fear of earlier sexual activity and unsafe sex. In China, a population-based survey related to knowledge concerning HPV vaccination reported that 15.8% of women between the ages of 15–54 have never heard of HPV, of which 49% bewared that HPV was related to cervical cancer. Around 87% of women agreed to be vaccinated with the prophylactic HPV vaccine and, in addition, 88% of women expressed that they would like to have their daughters vaccinated (29). In rural Shanxi, 67% of surveyed women did not believe that they were at risk of HPV infection and cervical cancer, while 65% of women thought there would be no difference whether or not they were vaccinated. However, 98% of the surveyed women preferred to receive information about the HPV vaccine from doctors, nurses, and hospital staff rather than from family members or friends.

To improve the coverage of vaccination programs, a low vaccine price is one important issue to consider, and 83% of the women hoped that health insurance or the government can cover all or part of vaccine-related costs (30). When asked about the vaccine cost, 42% of women said they are willing to pay USD 2.50 or less and 50% agreed to pay USD 2.50–14.00, while only 8% can afford to pay more than USD 15.00 (31). However, according to investigation conducted by Canfell *et al.* (2011), vaccination combined with once- or twice-in-a-lifetime screening is sufficiently cost-effective with a CVG of USD 52. But the maximum vaccine unit cost per dose is USD 9.00-14.00 that is also implied by maximum CVG of $50–54. Therefore, HPV vaccination is potentially feasible for Chinese women at a reasonable price. However, in order to sustain a wide vaccine coverage, vaccine price would be one of the largest barriers for promotion (31).

In terms of HPV vaccine safety, data from pharmaceutical companies responsible for bivalent and quadrivalent vaccines suggest that some patients could be expected to experience mild, transient vaccine-related side effects upon receiving the HPV vaccine (32, 33). From reports, pain is the most frequently reported adverse effect, with a prevalence ranging from 83% to 93% in tested vaccine group (34). With the exception of pain, no differences in serious vaccine-related events were prominent between vaccine and placebo groups. Data regarding the long-term safety of these vaccines are not yet available. HPV vaccination tests also did not include pregnant women. Although incidence of spontaneous abortion occurred in 10% of the vaccine group, it also occured in 7% of the placebo group, hence there is no significant difference between the two groups (35). Similarly, results from the quadrivalent vaccine Phase III studies indicated no observable differences in relation to the incidence of spontaneous abortions, late fetal death, or congenital abnormal infants between both groups. Even women who became pregnant more than 30 days after vaccine administration did not contribute any statistical difference whatsoever (35).

Currently, available vaccines contain HPV 16 and 18; however, HPV types 52 and 58 are more prevalent in Southeast Asia, especially in Hong Kong and Taiwan. Although, HPV16 and 18 are major genotypes found in CIN3 and cervical cancer patients, HPV types 52 and 58 also have high prevalence rate in cancer cases. For example, HPV types 52 and 58 have 25% and 12.5% infection rate in Taiwan (15), As shown in Table 1, the prevalence of HPV 52 and HPV 58 in Chengdu, Fujian, Gansu, Guangzhou, Hong Kong, Liaoning, Taiwan, Shandong, Shanxi, Shenyang, Shenzhen, and Zhejiang is higher than HPV 18, 6, and 11. This indicates that bivalent and quadrivalent vaccines are only capable of covering a small part of prospective patients infected with HPV. The emerging question then is, *Should women pay for HPV vaccines without understanding their HPV infection types or not*? It is safe to say at the present time that a vaccination program, combined with HPV Pap smear screening, is necessary to avoid useless vaccine treatment. The prevalence of HPV 52 and HPV 58 is nearly equal to the frequency of HPV 16 in China, Hong Kong, and Taiwan whether in cervical cancer-related or population-based surveys (Table 1). Moreover, a 1997–2007 report in Hong Kong showed that aside from 68.0% of all histological groups combined, 62.6% of squamous cell carcinoma and 93.8% of adenocarcinoma and adenosquamous cell carcinoma were covered by HPV 16 and HPV 18. Hence if vaccines included HPV 52 and HPV 58, it could increase the coverage by 15.9% for cervical cancers overall, 18.4% for squamous cell carcinoma, and 4.1% for adenocarcinoma and adenosquamous cell carcinoma (8). To summarize, pharmaceutical companies should make an effort to include more high prevalence HPV types in the next generation of vaccines they develop.

The limitations of vaccine programs must also be recognized, because HPV 16 and 18 account for approximately 70% of all invasive cervical cancers in nine countries (36), excluding Chinese people. Thus, women should be advised that the HPV vaccine does not confer full protection against cervical cancer. To reduce the risk of HPV infection and cervical cancer, safe sexual practices, which include the use of condoms and routine Pap smear testing, are necessary. Another important issue is the HPV genotypes screening. There are over 100 different HPV types, but only 13 HR-HPVs were routine in Pap smear screening. In our previous data, 52 HPV genotypes were adopted to screen 10,543 cases, of which 1,021 involve HR-HPVs and 556 involve non-HR-HPVs. Our investigation supported more HPV genotypes prevalence than other literatures. Majority of existing reports focus on HR-HPV due to a high risk of cervical cancer associated with it. However, other LR-HPV

types may be valuable, especially when indicating the risk in women's sexual behavior which could bring about a high chance of incurring HR-HPV infection in the future. Any HR-HPV/LR-HPV infection is worth to notice the cervical cancer possibility in women even HR-HPV is significant in ICC/CIN3 samples. Although there are little evidences to prove the relationship between LR-HPV and cervical cancer, we would like to point out the importance of LR-HPV screening, which could be useful to get rid of HPV attack, if the cost is reasonable for both HR-HPV and LR-HPV tests.

## 5. Conclusion

HPV 16, 52, and 58 are the most predominant types of HPV in China, Hong Kong, and Taiwan. HPV 18, on the other hand, may have lower prevalence than types 39, 51, and 56 in some regions, such as Taiwan. Single/multiple HPV infection types do not distinguish between different age groups. The incidence of HPV types reflect women's sexual behavior in different ages. However, HPV 16 is clearly the most common type of HPV in the world. Because HPV 16, 52, and 58 are more common than HPV 18 in China, Hong Kong, and Taiwan, the protective effect of an HPV16/18 vaccine against HR-HPV infection in these regions should be a major consideration because both subtypes are not powerful enough to reduce the prevalence of cervical cancer. Geographic variation with regard to distribution of HPV genotypes should also be an important consideration, especially in the tailoring of vaccines in different regions. The prevalence of HPV genotypes may be caused by the complex interplay among different HPV genotypes, safety of sexual practices, and host immunogenetic factors.

## 6. Appendix: The HPV prevalence around the world

| Area | Overall HPV (%) | HPV Genotypes (%) | | | | | | | | | | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 6 | 11 | 16 | 18 | 31 | 33 | 35 | 39 | 45 | 51 | 52 | 56 | 58 | 59 | 68 | 73 | 82 | |
| Argentina | 16.7 | 0.1 | 0.3 | 4.0 | 1.9 | 1.8 | 1.4 | 1.9 | 1.0 | 1.1 | 0.4 | 1.2 | 0.9 | 1.3 | 0.8 | 0.8 | 0.2 | 0.1 | (Matos et al., 2003) |
| Brazil | 13.8 | 0.5 | 0.5 | 2.7 | 0.8 | 1.1 | 0.4 | 0.2 | 0.1 | 0.5 | 0.7 | 0.6 | 0.6 | 2.1 | 0.1 | 0.4 | 0.2 | 0.1 | (Franco et al., 1999) |
| Chile | 11.2 | 0.2 | 0.4 | 2.2 | 0.4 | 0.5 | 0.1 | 0.3 | 0.7 | 0.7 | 0.7 | 0.8 | 1.3 | 1.0 | 0.9 | 0.0 | 0.2 | 0.0 | (Ferreccio et al., 2004) |
| China (Beijing) | 7.9 | ND | ND | 2.6 | 0.5 | 0.4 | 0.8 | 0.6 | 0.1 | 0.1 | 0.2 | 0.0 | 0.7 | 1.0 | 0.3 | 0.5 | 0.1 | ND | (Zhao et al., 2009) |
| China (Guangzho) | 8.9 | ND | ND | 1.2 | 0.7 | 1.2 | 0.6 | 0.1 | 0.3 | 0.2 | 0.1 | 2.6 | 0.3 | 1.1 | 0.2 | 0.4 | ND | ND | (Liu et al., 2011) |
| China (HK) | 5.2 | ND | ND | 1.2 | 1.0 | 0.0 | 0.3 | 0.0 | 0.1 | 0.2 | 0.0 | 1.2 | 0.0 | 1.0 | 0.1 | 0.2 | ND | ND | (Liu et al., 2011) |
| China (Shandong) | 16.5 | ND | ND | 3.6 | 1.5 | 0.9 | 1.5 | 0.2 | 0.4 | 0.2 | 0.2 | 2.3 | 1.3 | 1.7 | 0.0 | 2.8 | ND | ND | (Yuan et al., 2011) |
| China (Shanxi) | 15.9 | ND | ND | 5.7 | 0.8 | 0.5 | 1.2 | ND | 0.6 | 0.6 | 0.6 | 1.2 | 0.8 | 3.2 | 0.3 | 0.2 | ND | 0.2 | (Dai et al., 2006) |
| China (Shenyang) | 14.8 | ND | ND | 3.4 | 1.0 | 1.0 | 0.9 | 0.3 | 0.9 | 0.6 | 0.6 | 2.5 | 0.9 | 1.9 | 0.6 | 0.3 | ND | 0.2 | (Li et al., 2006) |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| China (Shenzhen) | 15.2 | ND | ND | 2.5 | 1.4 | 1.5 | 0.3 | 0.4 | 1.5 | 0.7 | 0.6 | 2.0 | 1.0 | 1.6 | 0.9 | 0.5 | 0.1 | 0.2 | (Wu et al., 2007) |
| China (Zhejiang) | 13.9 | ND | ND | 2.5 | 0.8 | 0.8 | 0.8 | 0.2 | 0.3 | 0.3 | 0.9 | 3.1 | 0.4 | 2.1 | 0.7 | 1.0 | 0.0 | ND | (Ye et al., 2010) |
| China (Tibetan) | 7.8 | ND | ND | 1.5 | 0.2 | 1.2 | 1.2 | 0.0 | 0.2 | 0.2 | 0.2 | 1.1 | 0.2 | 1.2 | 0.1 | 0.5 | ND | ND | (Jin et al., 2010) |
| Costa Rica | 22.4 | 0.4 | 0.2 | 2.2 | 1.1 | 1.1 | 0.5 | 0.2 | 0.4 | 0.5 | 1.5 | 1.1 | 0.5 | 1.3 | 0.3 | 0.2 | 0.3 | 0.3 | (Herrero et al., 2005) |
| Ho Chi Minh. | 10.9 | 0.0 | 0.0 | 3.3 | 1.2 | 0.8 | 1.1 | 0.3 | 0.9 | 0.7 | 0.8 | 1.1 | 1.1 | 1.5 | 0.0 | 0.7 | 0.1 | 0.0 | (Ahn et al., 2003) |
| Honduras | 39.0 | 0.2 | 1.8 | 10.9 | 4.1 | 3.4 | 0.7 | 0.2 | 0.0 | 0.0 | 0.0 | 0.2 | 0.0 | 1.8 | 0.0 | 0.0 | 0.0 | 0.0 | (Ferrera et al., 1999) |
| Italy | 7.8 | 0.1 | 0.2 | 2.7 | 0.1 | 0.3 | 0.1 | 0.1 | 0.3 | 0.6 | 0.1 | 0.3 | 0.4 | 0.4 | 0.1 | 0.2 | 0.0 | 0.0 | (Ronco et al., 2005) |
| Japan | 10.2 | 0.1 | 0.0 | 0.5 | 0.2 | 0.3 | 0.4 | 0.8 | 0.1 | 0.0 | 0.9 | 1.2 | 0.6 | 0.2 | 0.2 | 0.5 | 0.0 | 0.0 | (Asato et al., 2004) |
| Kenya | 38.8 | 0.5 | 0.5 | 3.5 | 2.2 | 3.3 | 1.9 | 2.7 | 1.4 | 1.6 | 1.1 | 6.2 | 1.4 | 2.7 | 0.3 | 1.6 | ND | ND | (De Vuyst et al., 2003) |
| Mexico | 13.5 | 0.5 | 1.0 | 1.8 | 1.1 | 1.5 | 1.0 | 0.3 | 1.0 | 0.6 | 0.8 | 0.8 | 0.3 | 1.0 | 0.2 | 0.3 | 0.1 | 0.3 | (Lazcano-Ponce et al. 2001) |
| Nigeria | 24.8 | 0.4 | 0.4 | 3.0 | 1.7 | 2.6 | 0.6 | 3.0 | 0.4 | 2.1 | 1.1 | 1.5 | 2.1 | 2.5 | 0.6 | 0.2 | 0.5 | 0.4 | (Thomas et al., 2004) |
| Republic of Korea | 15.2 | 0.7 | 0.3 | 1.3 | 1.2 | 0.7 | 0.4 | 0.3 | 0.9 | 0.1 | 1.8 | 1.3 | 1.5 | 0.7 | 0.4 | 0.5 | 0.5 | 0.0 | (Shin et al., 2004) |
| Scotland | 12.7 | ND | ND | 3.4 | 1.4 | 0.7 | 0.5 | 0.3 | 0.4 | 0.9 | 0.9 | 0.8 | 0.6 | 0.7 | 0.7 | 0.2 | 0.8 | 0.1 | (Cuschieri et al., 2004) |
| Senegal | 12.5 | 0.2 | 0.0 | 1.0 | 0.9 | 0.4 | 0.7 | 0.0 | 0.1 | 0.2 | 0.3 | 0.5 | 0.3 | 0.7 | 0.4 | 0.1 | 0.3 | 0.1 | (Xi et al., 2003) |
| South India | 14.0 | 0.2 | 0.0 | 2.8 | 0.8 | 0.8 | 0.8 | 0.8 | 0.6 | 0.3 | 0.4 | 0.7 | 1.1 | 0.2 | 0.7 | 0.0 | 0.2 | 0.2 | (Franceschi et al., 2005) |
| Spain Hanoi, Vietnam | 1.5 | 0.1 | 0.0 | 1.0 | 0.0 | 0.4 | 0.0 | 0.5 | 0.1 | 0.0 | 0.4 | 0.0 | 0.2 | 0.1 | 0.2 | 0.2 | 0.0 | 0.0 | (de Sanjose et al., 2003) |
| Sweden | 6.8 | ND | ND | 2.1 | 0.6 | 1.1 | 0.4 | 0.3 | 0.2 | 0.8. | 0.4 | 0.3 | 0.5 | 0.3 | 0.1 | ND | ND | ND | (Forslund et al., 2002) |
| Taiwan | 15.0 | 0.5 | 0.1 | 1.4 | 0.6 | 0.3 | 0.3 | 0.1 | 0.8 | 0.2 | 0.8 | 2.1 | 0.9 | 1.2 | 0.3 | 0.1 | 0.2 | 1.6 | (Wang et al., 2010) |
| Thailand | 4.8 | 0.0 | 0.0 | 0.7 | 0.3 | 0.3 | 0.5 | 0.2 | 0.3 | 0.1 | 0.2 | 0.3 | 0.2 | 0.4 | 0.1 | 0.2 | 0.0 | 0.0 | (Sukvirach et al., 2003) |
| UK | 3.5 | ND | ND | 1.3 | 0.7 | 0.9 | 0.7 | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | ND | (Cuzick et al., 1995) |
| USA | 15.8 | 0.6 | 0.6 | 2.5 | 0.8 | 0.9 | 0.6 | 0.3 | 0.7 | 0.9 | 1.8 | 0.8 | 0.5 | 0.9 | 0.7 | 0.2 | 0.0 | 0.0 | (Liaw et al., 1999) |

Appendix 1. Data summarized from IARC and this article.

## 7. References

[1] de Sanjose, S., Diaz, M., Castellsague, X., Clifford, G., Bruni, L., Munoz, N. and Bosch, F.X. (2007) Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis*, 7, 453-459.

[2] Chen, C.A., Liu, C.Y., Chou, H.H., Chou, C.Y., Ho, C.M., Twu, N.F., Kan, Y.Y., Chuang, M.H., Chu, T.Y. and Hsieh, C.Y. (2006) The distribution and differential risks of human papillomavirus genotypes in cervical preinvasive lesions: A Taiwan Cooperative Oncologic Group Study. *Int J Gynecol Cancer*, 16, 1801-1808.

[3] Wang, C.H., Garvilles, R.G. and Chen, C.Y. (2010) Characterization of human papillomavirus infection in north Taiwan. *J Med Virol*, 82, 1416-1423.

[4] Shi, J.F., Wu, R.F., Liu, Z.H., Zhou, Q.Z., Li, N., Wu-Lan, N., Li, Q., Wang, Q., Liu, B., Li, R.Z. *et al.* (2006) (Distribution of human papillomavirus types in Shenzhen women). *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*, 28, 832-836.

[5] Zhao, R., Zhang, W.Y., Wu, M.H., Zhang, S.W., Pan, J., Zhu, L., Zhang, Y.P., Li, H., Gu, Y.S. and Liu, X.Z. (2009) Human papillomavirus infection in Beijing, People's Republic of China: a population-based study. *Br J Cancer*, 101, 1635-1640.

[6] Lin, M., Yang, L.Y., Li, L.J., Wu, J.R., Peng, Y.P. and Luo, Z.Y. (2008) Genital human papillomavirus screening by gene chip in Chinese women of Guangdong province. *Aust N Z J Obstet Gynaecol*, 48, 189-194.

[7] Liu, S.S., Chan, K.Y., Leung, R.C., Chan, K.K., Tam, K.F., Luk, M.H., Lo, S.S., Fong, D.Y., Cheung, A.N., Lin, Z.Q. *et al.* (2011) Prevalence and risk factors of Human Papillomavirus (HPV) infection in southern Chinese women - a population-based study. *PLoS ONE*, 6, e19244.

[8] Chan, P.K., Ho, W.C., Yu, M.Y., Pong, W.M., Chan, A.C., Chan, A.K., Cheung, T.H., Wong, M.C., To, K.F. and Ng, H.K. (2009) Distribution of human papillomavirus types in cervical cancers in Hong Kong: current situation and changes over the last decades. *Int J Cancer*, 125, 1671-1677.

[9] Ye, J., Cheng, X., Chen, X., Ye, F., Lu, W. and Xie, X. (2010) Prevalence and risk profile of cervical Human papillomavirus infection in Zhejiang Province, southeast China: a population-based study. *Virol J*, 7, 66.

[10] Li, L.K., Dai, M., Clifford, G.M., Yao, W.Q., Arslan, A., Li, N., Shi, J.F., Snijders, P.J., Meijer, C.J., Qiao, Y.L. *et al.* (2006) Human papillomavirus infection in Shenyang City, People's Republic of China: A population-based study. *Br J Cancer*, 95, 1593-1597.

[11] Vaccarella, S., Franceschi, S., Herrero, R., Munoz, N., Snijders, P.J., Clifford, G.M., Smith, J.S., Lazcano-Ponce, E., Sukvirach, S., Shin, H.R. *et al.* (2006) Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev*, 15, 326-333.

[12] Shi, J.F., Qiao, Y.L., Smith, J.S., Dondog, B., Bao, Y.P., Dai, M., Clifford, G.M. and Franceschi, S. (2008) Epidemiology and prevention of human papillomavirus and cervical cancer in China and Mongolia. *Vaccine*, 26 Suppl 12, M53-59.

[13] Tay, S.K., Ngan, H.Y., Chu, T.Y., Cheung, A.N. and Tay, E.H. (2008) Epidemiology of human papillomavirus infection and cervical cancer and future perspectives in Hong Kong, Singapore and Taiwan. *Vaccine*, 26 Suppl 12, M60-70.

[14] Koong, S.L., Yen, A.M. and Chen, T.H. (2006) Efficacy and cost-effectiveness of nationwide cervical cancer screening in Taiwan. *J Med Screen*, 13 Suppl 1, S44-47.

[15] Ho, C.M., Chien, T.Y., Huang, S.H., Lee, B.H. and Chang, S.F. (2006) Integrated human papillomavirus types 52 and 58 are infrequently found in cervical cancer, and high viral loads predict risk of cervical cancer. *Gynecol Oncol*, 102, 54-60.

[16] Dai, M., Bao, Y.P., Li, N., Clifford, G.M., Vaccarella, S., Snijders, P.J., Huang, R.D., Sun, L.X., Meijer, C.J., Qiao, Y.L. *et al.* (2006) Human papillomavirus infection in Shanxi Province, People's Republic of China: a population-based study. *Br J Cancer*, 95, 96-101.

[17] Yuan, X., Yang, Y., Gu, D., Liu, H., Yang, H. and Wang, M. (2011) Prevalence of human papillomavirus infection among women with and without normal cervical histology in Shandong Province, China. *Arch Gynecol Obstet*, 283, 1385-1389.

[18] Jin, Q., Shen, K., Li, H., Zhou, X.R., Huang, H.F. and Leng, J.H. (2010) Age-specific prevalence of human papillomavirus by grade of cervical cytology in Tibetan women. *Chin Med J (Engl)*, 123, 2004-2011.

[19] Wu, D., Cai, L., Huang, M., Zheng, Y. and Yu, J. (2010) Prevalence of genital human papillomavirus infection and genotypes among women from Fujian province, PR China. *Eur J Obstet Gynecol Reprod Biol*, 151, 86-90.

[20] Wu, Y., Chen, Y., Li, L., Yu, G., Zhang, Y. and He, Y. (2006) Associations of high-risk HPV types and viral load with cervical cancer in China. *J Clin Virol*, 35, 264-269.

[21] Sun, Z.R., Ji, Y.H., Zhou, W.Q., Zhang, S.L., Jiang, W.G. and Ruan, Q. (2010) Characteristics of HPV prevalence among women in Liaoning province, China. *Int J Gynaecol Obstet*, 109, 105-109.

[22] Chao, A., Hsu, K.H., Lai, C.H., Huang, H.J., Hsueh, S., Lin, S.R., Jung, S.M., Chao, F.Y., Huang, S.L., Huang, C.C. *et al.* (2008) Cervical cancer screening program integrating Pap smear and HPV DNA testing: a population-based study. *Int J Cancer*, 122, 2835-2841.

[23] Zhang, W.Y., Xue, Y.Z., Chen, M., Han, L. and Luo, M. (2008) Prevalence of high-risk human papillomavirus infection in different cervical lesion among organized health-examination women in Shanghai, China. *Chin Med J (Engl)*, 121, 1578-1582.

[24] Wu, R.F., Dai, M., Qiao, Y.L., Clifford, G.M., Liu, Z.H., Arslan, A., Li, N., Shi, J.F., Snijders, P.J., Meijer, C.J. *et al.* (2007) Human papillomavirus infection in women in Shenzhen City, People's Republic of China, a population typical of recent Chinese urbanisation. *Int J Cancer*, 121, 1306-1311.

[25] Schiffman, M., Castle, P.E., Jeronimo, J., Rodriguez, A.C. and Wacholder, S. (2007) Human papillomavirus and cervical cancer. *Lancet*, 370, 890-907.

[26] Smith, J.S., Lindsay, L., Hoots, B., Keys, J., Franceschi, S., Winer, R. and Clifford, G.M. (2007) Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer*, 121, 621-632.

[27] Kwan, T.T., Chan, K.K., Yip, A.M., Tam, K.F., Cheung, A.N., Young, P.M., Lee, P.W. and Ngan, H.Y. (2008) Barriers and facilitators to human papillomavirus vaccination among Chinese adolescent girls in Hong Kong: a qualitative-quantitative study. *Sex Transm Infect*, 84, 227-232.

[28] Chan, S.S., Cheung, T.H., Lo, W.K. and Chung, T.K. (2007) Women's attitudes on human papillomavirus vaccination to their daughters. *J Adolesc Health*, 41, 204-207.

[29] Lai, H.C., Lin, W.Y., Lin, Y.W., Chang, C.C., Yu, M.H., Chen, C.C. and Chu, T.Y. (2005) Genetic polymorphisms of FAS and FASL (CD95/CD95L) genes in cervical carcinogenesis: An analysis of haplotype and gene-gene interaction. *Gynecol Oncol*, 99, 113-118.

[30] McIntosh, J., Sturpe, D.A. and Khanna, N. (2008) Human papillomavirus vaccine and cervical cancer prevention: practice and policy implications for pharmacists. *J Am Pharm Assoc (2003)*, 48, e1-13; quiz e14-17.

[31] Canfell, K., Shi, J.F., Lew, J.B., Walker, R., Zhao, F.H., Simonella, L., Chen, J.F., Legood, R., Smith, M.A., Nickson, C. *et al.* (2011) Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies. *Vaccine*, 29, 2487-2494.

[32] Villa, L.L., Costa, R.L., Petta, C.A., Andrade, R.P., Ault, K.A., Giuliano, A.R., Wheeler, C.M., Koutsky, L.A., Malm, C., Lehtinen, M. *et al.* (2005) Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*, 6, 271-278.

[33] Villa, L.L., Costa, R.L., Petta, C.A., Andrade, R.P., Paavonen, J., Iversen, O.E., Olsson, S.E., Hoye, J., Steinwall, M., Riis-Johannessen, G. *et al.* (2006) High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer*, 95, 1459-1466.

[34] Garland, S.M., Hernandez-Avila, M., Wheeler, C.M., Perez, G., Harper, D.M., Leodolter, S., Tang, G.W., Ferris, D.G., Steben, M., Bryan, J. *et al.* (2007) Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*, 356, 1928-1943.

[35] (2007) Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*, 356, 1915-1927.

[36] Munoz, N., Bosch, F.X., de Sanjose, S., Herrero, R., Castellsague, X., Shah, K.V., Snijders, P.J. and Meijer, C.J. (2003) Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*, 348, 518-527.

[37] Matos, E., Loria, D., Amestoy, G.M., Herrera, L., Prince, M.A., Moreno, J., Krunfly, C., van den Brule, A.J., Meijer, C.J., Munoz, N. *et al.* (2003) Prevalence of human papillomavirus infection among women in Concordia, Argentina: a population-based study. *Sex Transm Dis*, 30, 593-599.

[38] Franco, E.L., Villa, L.L., Sobrinho, J.P., Prado, J.M., Rousseau, M.C., Desy, M. and Rohan, T.E. (1999) Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis*, 180, 1415-1423.

[39] Ferreccio, C., Prado, R.B., Luzoro, A.V., Ampuero, S.L., Snijders, P.J., Meijer, C.J., Vaccarella, S.V., Jara, A.T., Puschel, K.I., Robles, S.C. *et al.* (2004) Population-based prevalence and age distribution of human papillomavirus among women in Santiago, Chile. *Cancer Epidemiol Biomarkers Prev*, 13, 2271-2276.

[40] Herrero, R., Castle, P.E., Schiffman, M., Bratti, M.C., Hildesheim, A., Morales, J., Alfaro, M., Sherman, M.E., Wacholder, S., Chen, S. *et al.* (2005) Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. *J Infect Dis*, 191, 1796-1807.

[41] Ahn, W.S., Bae, S.M., Chung, J.E., Lee, H.K., Kim, B.K., Lee, J.M., Namkoong, S.E., Kim, C.K. and Sin, J. (2003) Evaluation of adenoassociated virus 2 and human papilloma virus 16 and 18 infection in cervical cancer biopsies. *Gynecol Oncol*, 89, 105-111.

[42] Ferrera, A., Velema, J.P., Figueroa, M., Bulnes, R., Toro, L.A., Claros, J.M., De Barahona, O. and Melchers, W.J. (1999) Human papillomavirus infection, cervical dysplasia and invasive cervical cancer in Honduras: a case-control study. *Int J Cancer*, 82, 799-803.

[43] Ronco, G., Ghisetti, V., Segnan, N., Snijders, P.J., Gillio-Tos, A., Meijer, C.J., Merletti, F. and Franceschi, S. (2005) Prevalence of human papillomavirus infection in women in Turin, Italy. *Eur J Cancer*, 41, 297-305.

[44] Asato, T., Maehama, T., Nagai, Y., Kanazawa, K., Uezato, H. and Kariya, K. (2004) A large case-control study of cervical cancer risk associated with human papillomavirus infection in Japan, by nucleotide sequencing-based genotyping. *J Infect Dis*, 189, 1829-1832.

[45] De Vuyst, H., Steyaert, S., Van Renterghem, L., Claeys, P., Muchiri, L., Sitati, S., Vansteelandt, S., Quint, W., Kleter, B., Van Marck, E. *et al.* (2003) Distribution of human papillomavirus in a family planning population in nairobi, kenya. *Sex Transm Dis*, 30, 137-142.

[46] Lazcano-Ponce, E., Herrero, R., Munoz, N., Cruz, A., Shah, K.V., Alonso, P., Hernandez, P., Salmeron, J. and Hernandez, M. (2001) Epidemiology of HPV infection among Mexican women with normal cervical cytology. *Int J Cancer*, 91, 412-420.

[47] Thomas, J.O., Herrero, R., Omigbodun, A.A., Ojemakinde, K., Ajayi, I.O., Fawole, A., Oladepo, O., Smith, J.S., Arslan, A., Munoz, N. *et al.* (2004) Prevalence of papillomavirus infection in women in Ibadan, Nigeria: a population-based study. *Br J Cancer*, 90, 638-645.

[48] Shin, H.R., Franceschi, S., Vaccarella, S., Roh, J.W., Ju, Y.H., Oh, J.K., Kong, H.J., Rha, S.H., Jung, S.I., Kim, J.I. *et al.* (2004) Prevalence and determinants of genital infection with papillomavirus, in female and male university students in Busan, South Korea. *J Infect Dis*, 190, 468-476.

[49] Cuschieri, K.S., Cubie, H.A., Whitley, M.W., Seagar, A.L., Arends, M.J., Moore, C., Gilkisson, G. and McGoogan, E. (2004) Multiple high risk HPV infections are common in cervical neoplasia and young women in a cervical screening population. *J Clin Pathol*, 57, 68-72.

[50] Xi, L.F., Toure, P., Critchlow, C.W., Hawes, S.E., Dembele, B., Sow, P.S. and Kiviat, N.B. (2003) Prevalence of specific types of human papillomavirus and cervical squamous intraepithelial lesions in consecutive, previously unscreened, West-African women over 35 years of age. *Int J Cancer*, 103, 803-809.

[51] Franceschi, S., Rajkumar, R., Snijders, P.J., Arslan, A., Mahe, C., Plummer, M., Sankaranarayanan, R., Cherian, J., Meijer, C.J. and Weiderpass, E. (2005) Papillomavirus infection in rural women in southern India. *Br J Cancer*, 92, 601-606.

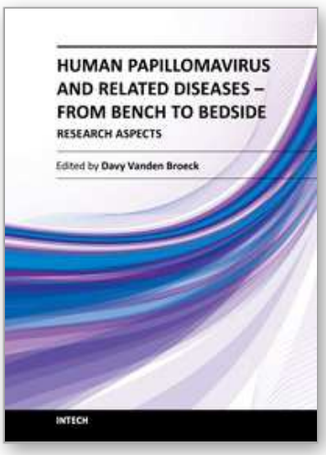
[52] de Sanjose, S., Almirall, R., Lloveras, B., Font, R., Diaz, M., Munoz, N., Catala, I., Meijer, C.J., Snijders, P.J., Herrero, R. *et al.* (2003) Cervical human papillomavirus infection in the female population in Barcelona, Spain. *Sex Transm Dis*, 30, 788-793.

[53] Forslund, O., Antonsson, A., Edlund, K., van den Brule, A.J., Hansson, B.G., Meijer, C.J., Ryd, W., Rylander, E., Strand, A., Wadell, G. *et al.* (2002) Population-based type-specific prevalence of high-risk human papillomavirus infection in middle-aged Swedish women. *J Med Virol*, 66, 535-541.

[54] Sukvirach, S., Smith, J.S., Tunsakul, S., Munoz, N., Kesararat, V., Opasatian, O., Chichareon, S., Kaenploy, V., Ashley, R., Meijer, C.J. *et al.* (2003) Population-based human papillomavirus prevalence in Lampang and Songkla, Thailand. *J Infect Dis*, 187, 1246-1256.

[55] Cuzick, J., Szarewski, A., Terry, G., Ho, L., Hanby, A., Maddox, P., Anderson, M., Kocjan, G., Steele, S.T. and Guillebaud, J. (1995) Human papillomavirus testing in primary cervical screening. *Lancet*, 345, 1533-1536.

[56] Liaw, K.L., Glass, A.G., Manos, M.M., Greer, C.E., Scott, D.R., Sherman, M., Burk, R.D., Kurman, R.J., Wacholder, S., Rush, B.B. *et al.* (1999) Detection of human papillomavirus DNA in cytologically normal women and subsequent cervical squamous intraepithelial lesions. *J Natl Cancer Inst*, 91, 954-960.




**Human Papillomavirus and Related Diseases - From Bench to Bedside - Research aspects**

Edited by Dr. Davy Vanden Broeck

ISBN 978-953-307-855-7
Hard cover, 406 pages
**Publisher** InTech
**Published online** 25, January, 2012
**Published in print edition** January, 2012

Cervical cancer is the second most prevalent cancer among women worldwide, and infection with Human Papilloma Virus (HPV) has been identified as the causal agent for this condition. The natural history of cervical cancer is characterized by slow disease progression, rendering the condition, in essence, preventable and even treatable when diagnosed in early stages. Pap smear and the recently introduced prophylactic vaccines are the most prominent prevention options, but despite the availability of these primary and secondary screening tools, the global burden of disease is unfortunately still very high. This book will focus on epidemiological and fundamental research aspects in the area of HPV, and it will update those working in this fast-progressing field with the latest information.



INTECH
open science | open minds

**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

**InTech China**
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen