Human papillomavirus genotype distribution in cervical intraepithelial neoplasia 2/3 and invasive cervical cancer among Hakka women in southern China

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Research article

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Abstract

Background: To investigate HPV genotype distribution in cervical intraepithelial neoplasia 2/3 (CIN2/3) and invasive cervical cancer (ICC) among Hakka women in southern China. **Methods:** Results of HPV genotypes from women with histological diagnosis of CIN2/3 and ICC were collected from January, 2017 to December, 2018. HPV genotypes were analyzed by flow cytometry method. Association of HPV infection and lesions severity was estimated using prevalence ratio (PR). **Results:** Overall, 1,408 Hakka women with histological diagnosis of CIN2/3 and ICC were enrolled in this study. HPV infection prevalence was 92.92% in CIN2, 95.77% in CIN3 and 95.88% in ICC. Most frequent genotypes for CIN2 were HPV52 (31.42%), HPV16 (22.12%) and HPV58 (22.12%); for CIN3 were HPV16 (41.90%), HPV52 (20.77%) and HPV58 (18.31%); and for ICC were HPV16 (49.67%), HPV18 (11.25%) and HPV52 (9.80%). PR of HPV16 and HPV33 were significantly higher in CIN3 compared with CIN2 (PR = 2.372, 95%CI = 1.598-3.524; PR = 2.577, 95%CI = 1.250-5.310; respectively). HPV16 and HPV18 prevalence were significantly increasing in SCC compared with CIN3 (PR = 2.517, 95%CI = 1.095-5.786; PR = 2.473, 95%CI = 1.840-3.324; respectively). Most HPV infections were found in women aged 40 – 49 years in CIN2/3 and women aged 50 - 59 years in ICC. **Conclusions:** This is the first study of genotypes and age specific distribution of HPV infection among Hakka women with CIN2/3 and ICC in southern China. Our results provide available information for HPV vaccine development in China.

Background

Cervical cancer is known as the second most common cancers in women around the world, and most cervical cancer occur in developing countries [1]. Incidence of cervical cancer in China is contributed to be about 14% of the world, and therefore it becomes an crucial public health problem in China [2, 3].

Molecular epidemiological evidence suggests that high risk human papillomavirus (HPV) genotypes are the principal cause of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC)[4, 5]. More than 200 HPV genotypes have been recognized [6], and nearly 40 are associated with genital tract infections [7]. At least 15 genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 56, 58, 59, 68, 73 and 82) are considered as high risk HPV genotypes [7]. A meta-analysis analyzed HPV genotypes results among 115,789 women around the world, the most prevalent genotypes are HPV16 and HPV18 [8]. In a large study contained 51,345 cases in China showed that HPV52, HPV16 and HPV58 were top three most prevalent genotypes, while HPV18 was only the sixth most prevalent genotype [9]. China is a large country with unbalanced social and economic conditions from region to region, and hence HPV infections are varying [10]. Guangdong, as the most populous and economically developed province in China, the prevalence of high risk HPV infection is as high as 21.07% [11].

Meizhou is located in the northeastern of Guangdong Province and most people in this area were Hakka. The physical characteristics of Hakka in Meizhou are differ from the populations of northern and southern China[12]. HPV infection of Hakka people in Meizhou was observed up to 19.81% in our

previous study [13]. There are no data available for Hakka area of southern China in relation to the HPV type-specific distribution in women with CIN2/3 and ICC.

HPV vaccine is an important measure to prevent persistent infection and cervical disease[14]. Three virus-like particle vaccines including HPV16/18 (Cervarix), HPV6/11/16/18 (Gardasil) and HPV6/11/16/18/31/33/45/52/58 (Gardasil) were designed based on studies from Western countries [15]. Whether the application of these vaccines in China can achieve the expected preventive effect has not been proven. Therefore, the knowledge of the prevalence of HPV genotypes in CIN2/3 and ICC patients can provide useful information for development of HPV vaccines for Chinese women. The objective of recent study is to estimate HPV type-specific distribution among Hakka women with CIN2/3 and ICC in southern China.

Methods

Study population

From January, 2017 to December, 2018, our study enrolled a total of 1,907 participants with histological diagnosis of CIN 2/3 or ICC by tissue biopsy or cervical conization. All of participants were recruited in Meizhou People's Hospital (Huangtang Hospital), Meizhou Academy of Medical Sciences, Meizhou Hospital Affiliated to Sun Yat-sen University. Subjects were eligible in study meeting the including criteria: (i) age 15 years or older; (ii) provided HPV genotyping results in prior 6 months; (iii) no history of HPV vaccination. Histopathological diagnosis was performed according to the classification of World Health Organization (WHO), using hematoxylin-eosin stained sections by skilled pathologists. When diagnoses of tissue biopsy were inconsistent with cervical conization, the severe histological diagnosis was recognized as final diagnosis. This study was approved by the Human Ethics Committees of Meizhou People's Hospital, Guangdong Province, China. Informed consent was obtained from each participant. If study participants were children (under 16 years of age), informed consents to participate were collected from the parents.

Sample collection

Before histological diagnosis, cervical specimens were collected through plastic cervical brush (Tellgen Life Science Co., Shanghai, China) by a gynecologist. The brush was inserted into cervix and rotated five full turns clockwise to get enough exfoliated cells. The tip of brush was then stored in transport medium tube (Tellgen Life Science Co., Shanghai, China).

DNA extraction

DNA was extracted from cervical exfoliated cells using a DNA extraction kit (Tellgen Life Science Co., Shanghai, China) according to the manufacturer's instructions. Briefly, samples were classified into two grades on the basis of the appearance: (i) clarified and (ii) turbid. Vibrated samples for 2 minutes, transferred 800ul and 400ul volumes of samples corresponding to i and ii into 1.5 ml vessels. Added

samples transport medium to 900ul, mixed well, centrifuged at 12,000 rpm for 3 minutes. Then, removed supernatant, suspended sediment with 200ul nucleic acid releasing agent and taken a metal bath for 15 minutes under 100 °C. Centrifuged at 12,000 rpm for 5 minutes and supernatant was ready for genotyping.

HPV genotyping

HPV DNA genotyping was detected using Tellgenplex® HPV27 genotyping assay (Tellgen Life Science Co., Shanghai, China) according to the manufacturer's instructions. Briefly, each color-coded bead was coated with predesigned HPV type-specific probes that simultaneously identified 27 HPV genotypes, including 17 high-risk genotypes (HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 82) and 10 low-risk genotypes (HPV6, 11, 40, 42, 43, 44, 55, 61, 81, 83). HPV DNA was amplified with 5'-biotinylated consensus PCR primers. PCR products were hybridized to beads with type-specific probes, then incubated with phycoerythrin (PE)-conjugated streptavidin (SA-PE) and final results were analyzed on a Luminex 200 system (Luminex Corporation, Texas)[16]. Quality controls were strictly performed throughout the experiments by applying positive and negative controls for PCR reaction.

Data analysis

Total accounts and proportion of women in different HPV infections were presented. A log binomial model was performed to estimate the prevalence rate (PR) of high risk HPV with 95% confidence intervals (CI) between different histological grades. The PR was adjusted with the age of patient at the time of histological diagnosis. Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences, Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

Participants and overall HPV infection prevalence

As illustrated in Fig.1, our study enrolled a total of 1,907 women with histological diagnosis of CIN2/3 or ICC between January, 2017 and December, 2018. Among these women, 499 were excluded in the analyses as they didn't meet the including criterions. Final, 1,408 participants were included in this study for analyses. The average age at diagnosis and age range in different histological grades were as follows: CIN2, 44 years (17 - 74 years); CIN3, 48 years (20 - 83 years); ICC, 54 years (21 - 89 years).

In total, HPV DNA was identified in 210 of 226 CIN2 samples (92.92%), in 272 of 284 CIN3 samples (95.77%) and in 861 of 898 ICC samples (95.88%). High risk HPV infection was detected in CIN2, CIN3 and ICC with a high detection rate over 90% (Table 1), and single high risk HPV infection among these histological grades were the most common infection, ranged from 61.50% - 74.65%. However, the multiple high risk HPV infection were detected in 29.20% of CIN2 samples, 18.66% in CIN3 samples and 8.46% in ICC samples, presented decreasing prevalence with severity of lesions. The participants only infected with low risk HPV genotypes were rarely detected in all histological grades.

HPV genotype distribution

Table 2 and Fig.2 performed accounts and prevalence of high and low risk HPV genotypes and ten most prevalent HPV genotypes in CIN2/3. Type-specific distribution of high risk HPV infection was significantly different between CIN2 and CIN3. HPV52 (31.42%), HPV16 (22.12%) and HPV58 (22.12%) were most commonly detected in CIN2, however, HPV16 (41.90%), HPV52 (20.77%) and HPV58 (18.31%) were predominately detected in CIN3.

As shown in Table 3, Fig.3 and Fig.4, the genotypes distribution in ICC were observed similarly to CIN2/3 lesions, HPV16 (49.67%) was the most frequent genotype, followed by HPV18 (11.25%) and HPV52 (9.80%). Among these ICC participants, the prevalence of HPV infection in SCC (97.86%) was higher than in ADC (90.57%). HPV16 was most prevalent genotype in SCC (60.24%), followed by HPV52 (8.10%) and HPV58 (8.10%), while HPV18 (22.95%), HPV16 (21.34%) and HPV52 (14.34%) were the top three frequent genotypes in ADC.

HPV prevalence ratio

To assess the risk of CIN progression ascribe to specific high risk HPV, the prevalence ratio (PR) of specific genotype was calculated by contrasting the frequency with CIN2 and CIN3. As presented in Table 2, HPV16 and HPV33 prevalence were positively correlated with progression from CIN2 to CIN3 (PR = 2.372, 95%CI = 1.598-3.524; PR = 2.577, 95%CI = 1.250-5.310; respectively). In contrast, HPV51, HPV52 and HPV66 prevalence were significantly decreased in CIN3 compared with CIN2 (PR = 0.232, 95%CI = 0.097-0.554; PR = 0.610, 95%CI = 0.406-0.917; PR = 0.321, 95%CI = 0.110-0.936; respectively).

As demonstrated in Table 3, high risk genotype prevalence between CIN3 and SCC was estimated. HPV16 and HPV18 prevalence were significantly increasing in SCC compared with CIN3 (PR = 2.517, 95%CI = 1.095-5.786; PR = 2.473, 95%CI = 1.840-3.324; respectively). Conversely, negative association of HPV33, HPV52 and HPV58 were found in SCC compared with CIN3 (PR = 0.490, 95%CI = 0.291-0.826; PR = 0.539, 95%CI = 0.364-0.797; PR = 0.235, 95%CI = 0.146-0.379; respectively).

HPV infection in different ages

The age-specific distribution of HPV infection among Hakka women in southern China was shown in Fig.5. The top three age group of highest prevalence were women with age of 40 - 49, age of 30 - 39 and age of 50 - 59 in CIN2; women in age of 40 - 49, age of 50 - 59 and age of 30 - 39 in CIN3. Additionally, positive rates of participants with diagnosis of ICC/SCC/ADC were highest in women aged 50 - 59 years, followed by women aged 40 - 49 and women aged 60 - 69.

Discussion

Epidemiological studies have demonstrated that HPV infection rate of general population in China ranged from 16.72% to 31.94%, and genotypes distribution of HPV infection varied by different regions [9, 11]. However, studies investigated the prevalence of HPV infection and genotypes distribution of HPV

infection in Chinese women with CIN2/3 and ICC were lacking. Azuma et al. reported that 96.3% of CIN2, 98.8% of CIN3 and 97.8% of ICC among Japanese women were HPV positive [17]. One small samples size study has reported that 41/46 cases of CIN2, all 31 cases of CIN3 and 12 cases of ICC among Chinese women were high risk HPV infection [18]. As we known, our study is the first large-scale research on HPV infection rate and genotype distribution of Hakka women with CIN 2/3 and ICC in southern China, showing that 92.92% cases of CIN2, 95.77% cases of CIN3 and 95.88% cases of ICC were HPV positive.

Similar to previous studies [19, 20], our current study also found that single HPV genotype infection was more frequent than multiple infection. A study reported that multiple HPV genotypes infection has increased risk for cervical intraepithelial neoplasia / cervical cancer [21], while other studies have not found any increased risk for multiple HPV genotypes infection [7, 22]. It remains further studies to elucidate whether multiple HPV genotypes infection is links to progression of cervical intraepithelial neoplasia / cervical cancer.

The HPV genotypes distribution in CIN2/3 in current study presented that the top three most common HPV genotypes were HPV52 (31.42%), HPV16 (22.12%) and HPV58 (22.12%) in CIN2, HPV16 (41.90%), HPV52 (20.77%) and HPV58 (18.31%) in CIN3. Compared with the genotypes distribution in previous study reported by Miura et al. [23], genotypes distribution in SCC and ADC in this study was similar, in which top three most common HPV genotypes were HPV16 (60.24%), HPV52 (8.10%) and HPV58 (8.10%) in SCC, and HPV18 (22.95%), HPV16 (21.34%) and HPV52 (14.34%) in ADC. HPV type-specific distribution has been investigated to be various from different regions in China [9, 24, 25], HPV16, HPV52, HPV58 and HPV18 have been reported to be most frequent genotypes in Chinese Hakka women [13, 26]. Hence, the results in current study indicate the important role of HPV16, HPV18, HPV52 and HPV58 in causing CIN2/3 and ICC in Chinese Hakka women.

A recent prospective research reported the risk of diseases progression related to HPV infection among Japanese women with low-grade squamous intraepithelial lesion [27], shown seven HPV genotypes including HPV16, HPV18, HPV31, HPV35, HPV52 and HPV58 presented a high risk of progression to CIN3. Similar to this study, we observed PR of HPV16 and HPV33 were significantly higher in CIN3 compared with CIN2, indicating a higher likelihood of progression from CIN2 to CIN3 than with other genotypes. Also, PR of HPV16 and HPV18 in SCC were significantly higher than that of other high risk genotypes in CIN3, supporting the important role of sustained HPV16 infection in increasing carcinogenicity. Reversely, low PR of HPV51, HPV52 and HPV53 were found in CIN3 compared with CIN2, suggesting a lower potential for progression to CIN3 than with HPV16 and HPV33 infection. Consistent with previous report [17], in our study PR of HPV33, HPV52 and HPV58 in SCC were significantly lower than in CIN3, which indicates progression to SCC is less likely than with HPV16 and HPV18 infection.

HPV DNA test as a primary method should be offer for women age 25 to 65 years to screen cervical cancer was recommended by the US Food and Drug Administration (FDA). Current study showed top age group of highest prevalence in CIN2/CIN3 was women with age of 40 - 49 and the highest prevalence in ICC/SCC/ADC was observed in women aged 50 - 59 years. These findings indicated that hormones level

and immune function of women in these ages may be lower, so they can hardly resist HPV infection. However, our study presented 4.62% cases were negative for HPV DNA result before histological diagnosis of CIN2/3 and ICC. It remains the limitation of HPV DNA testing as a major for cervical cancer screen.

Currently, no study is available on the type-specific distribution of HPV in precancerous lesions / cervical cancerous among Hakka women in southern China. The present study found HPV16, HPV18, HPV52 and HPV58 were the main genotypes in CIN2/3 and ICC and women aged 40 - 49 suffered severely HPV infection. It would be instructive to estimate the potential protection of current HPV vaccines and future modified vaccines achieve in this area.

Conclusion

Our study presented prevalence and genotyping distribution of HPV infection among Hakka women in southern China, our findings will provide important information for the development and application of HPV vaccines and cervical screening in Chinese Hakka women in southern China.

Abbreviations

HPV: Human papillomavirus; CIN2: cervical intraepithelial neoplasia 2; CIN3: cervical intraepithelial neoplasia 3; ICC: invasive cervical cancer; SCC: squamous cell carcinoma; ADC: adenocarcinoma; PR: prevalence rate; 95%CI: 95% confidence intervals; hr: high-risk; lr: low-risk; PE: phycoerythrin; SA-PE: streptavidin phycoerythrin-conjugated streptavidin;

Declarations

Ethics approval and consent to participate

This study was approved by the Human Ethics Committees of Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University, Guangdong Province, China. All patients provided written informed consent to participate. If study participants were children (under 16 years of age), informed consents to participates were collected from the parents.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during the current study are not publicly available yet, due to privacy concerns and ongoing additional research. Data can be made available for peer review on reasonable request through contacting the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Author's Contributions

Sudong Liu conceived and designed the experiments; Xiaodong Gu contributed to the data collection and the manuscript draft. Ruiqiang Weng and Jing Liu helped to collect clinical data, conducted the clinical performances and researches; Xiaodong Gu analyzed the data and wrote the paper.

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References

1. Forman D, Martel CD, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, Vignat J, Ferlay J, Bray F, Plummer M: Global Burden of Human Papillomavirus and Related Diseases. *Vaccine* 2012, 30(Suppl 5):F12-F23.
2. Freddie B, Jian-Song R, Eric M, Jacques F: Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *International Journal of Cancer Journal International Du Cancer* 2013, 132(5):1133-1145.
3. Shi JF, Qiao YL, Smith JS, Dondog B, Bao YP, Dai M, Clifford GM, Franceschi S: Epidemiology and prevention of human papillomavirus and cervical cancer in China and Mongolia. *Vaccine* 2008, 26(1):M53-M59.
4. Mu?Oz N, ., Bosch FX, Sanjosé S, De, Tafur L, ., Izarzugaza I, ., Gili M, ., Viladiu P, ., Navarro C, ., Martos C, ., Ascunce N, . The causal link between human papillomavirus and invasive cervical cancer: a population-based case-control study in Colombia and Spain. *International Journal of Cancer* 2010, 122(5):743-749.
5. Koutsky LA: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007, 356(19):1915-1927.
6. Hausen HZ: Papillomaviruses in Human Cancers. *Molecular Carcinogenesis* 2010, 111(6):581-587.

- 7.Nubia MO, F Xavier B, Silvia DS, Rolando H, Xavier C, Shah KV, Snijders PJF, Meijer CJLM: Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med* 2003.
- 8.Peng G, Rebecca HJ, Ni L, Laia B, Silvia DS, Silvia F, Clifford GM: Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *International Journal of Cancer* 2012, 131(10):2349-2359.
- 9.Zeng Z, Yang H, Li Z, He X, Griffith CC, Chen X, Guo X, Zheng B, Wu S, Zhao C: Prevalence and Genotype Distribution of HPV Infection in China: Analysis of 51,345 HPV Genotyping Results from China's Largest CAP Certified Laboratory. *Journal of Cancer* 2016, 7(9):1037-1043.
- 10.Zhang R, Velicer C, Chen W, Liaw KL, Wu EQ, Liu B, Cui JF, Belinson JL, Zhang X, Shen GH: Human papillomavirus genotype distribution in cervical intraepithelial neoplasia grades 1 or worse among 4215 Chinese women in a population-based study. *Cancer Epidemiology* 2013, 37(6):939-945.
- 11.Wang R, Guo XL, Wisman GB, Schuurin E, Wang WF, Zeng ZY, Zhu H, Wu SW: Nationwide prevalence of human papillomavirus infection and viral genotype distribution in 37 cities in China. *Bmc Infectious Diseases* 2015, 15(1):257.
- 12.Zheng LB, Li YL, Lu SH, Bao JP, Yang W, Zhang XR, Hong X, Rong WG: Physical characteristics of Chinese Hakka. *Science China-life Sciences* 2013, 56(6):541-551.
- 13.Zhao P, Liu S, Zhong Z, Hou J, Lin L, Weng R, Su L, Lei N, Hou T, Yang H: Prevalence and genotype distribution of human papillomavirus infection among women in northeastern Guangdong Province of China. *Bmc Infectious Diseases* 2018, 18(1):204.
- 14.Giuliano AR, Kreimer AR, Silvia DS: The beginning of the end: vaccine prevention of HPV-driven cancers. *Journal of the National Cancer Institute* 2015, 107(6):djv128.
- 15.Burchell AN, Winer RL, Sanjosé SD, Franco EL: Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. *Vaccine* 2006, 24(1):S52-S61.
- 16.Wei W, Shi Q, Guo F, Zhang BY, Chen C, Zhang NS, Dong XP: The distribution of human papillomavirus in tissues from patients with head and neck squamous cell carcinoma. *Oncology Reports* 2012, 28(5):1750-1756.
- 17.Yukari A, Rika KM, Fumihiko T, Asami U, Kazunari K, Hajime T, Kazunori N, Kei K, Tohru M, Takashi I: Human papillomavirus genotype distribution in cervical intraepithelial neoplasia grade 2/3 and invasive cervical cancer in Japanese women. *Japanese Journal of Clinical Oncology* 2014, 44(10):910-917.
- 18.Zhao F, Nan LI, Junfei MA: Study of the association between human papillomavirus infection and cervical cancer in Xiangyuan county, Shanxi province. *Chinese Journal of Epidemiology* 2001, 22(5):375-378.

- 19.Linqian W, Baiping W, Junjun L, Liyu C: Prevalence of human papillomavirus and its genotype among 1336 invasive cervical cancer patients in Hunan province, central south China. *Journal of Medical Virology* 2015, 87(3):516-521.
- 20.Elizabeth Louise D, Rachel Isaksson V, Bliss RL, Downs LS: Multiple-type human papillomavirus (HPV) infections: a cross-sectional analysis of the prevalence of specific types in 309,000 women referred for HPV testing at the time of cervical cytology. *International Journal of Gynecological Cancer* 2013, 23(7):1295-1302.
- 21.Fife KH, Cramer HM, Schroeder JM, Brown DR: Detection of multiple human papillomavirus types in the lower genital tract correlates with cervical dysplasia. *Journal of Medical Virology* 2001, 64(4):550–559.
- 22.Hee Jung A, Nam Hoon C, Young LS, In Ho K, Chan L, Seung Jo K, Sook MM, Se Hyun K, Jeongmi Kim J: Correlation of cervical carcinoma and precancerous lesions with human papillomavirus (HPV) genotypes detected with the HPV DNA chip microarray method. *Cancer* 2010, 97(7):1672-1680.
- 23.Shiho M, Koji M, Akinori O, Toyomi S, Hajime T, Toshiharu Y, Yuji T, Hiroyuki Y: Do we need a different strategy for HPV screening and vaccination in East Asia? *International Journal of Cancer* 2010, 119(11):2713-2715.
- 24.Xiurong D, Zhizhong L, Jianrong S, Donghui Y, Wei S, Zhaoying Z: Human papillomavirus type-specific prevalence in women referred for colposcopic examination in Beijing. *Journal of Medical Virology* 2015, 86(11):1937-1943.
- 25.Jun CH, Lee AH, Linda C, Binns CW, Daniel X: A review of dietary prevention of human papillomavirus-related infection of the cervix and cervical intraepithelial neoplasia. *Nutrition & Cancer-an International Journal* 2013, 65(3):317-328.
- 26.Zeng XX, Yan LX, Huang XX, He CH, Liu WG, Yuan WQ, Qiu YP, Liu ZX: Prevalence and genotype distribution of human papillomavirus among Hakka women in China. *Ann Transl Med* 2016, 4(15):276.
- 27.Koji M, Akinori O, Reiko F, Hiroo M, Toshiharu Y, Naoyoshi T, Akira M, Takuma F, Yasuo H, Tsuyoshi I: Predicting the progression of cervical precursor lesions by human papillomavirus genotyping: a prospective cohort study. *International Journal of Cancer* 2011, 128(12):2898-2910.

Tables

Table 1 Prevalence of HPV infection in study participants among Hakka women in Southern China

HPV infection	CIN 2	CIN 3	ICC	SCC	ADC
single hr HPV	139 (61.50%)	212 (74.65%)	654 (72.83%)	507 (77.52%)	147 (60.25%)
multiple hr HPV	66 (29.20%)	53 (18.66%)	76 (8.46%)	55 (8.41%)	21 (8.61%)
lr HPV only	2 (0.88%)	0	18 (2.00%)	8 (1.22%)	10 (4.10%)
mix lr & hr HPV	3 (1.33%)	7 (2.46%)	113 (12.58%)	70 (10.70%)	43 (17.62%)
positive	210 (92.92%)	272 (95.77%)	861 (95.88%)	640 (97.86%)	221 (90.57%)
negative	16 (7.08%)	12 (4.23%)	37 (4.12%)	14 (2.14%)	23 (9.43%)
Total	226	284	898	654	244

hr, high risk; lr, low risk.

Table 2 Human papillomavirus (HPV) genotype distribution in CIN2/3 among Hakka women in Southern China

HPV type	CIN2 (n=226)	%	CIN3 (n=284)	%	PR(CIN3 vs. CIN2)(95%CI)	P
16	50	22.12	119	41.90	2.373(1.598-3.524)	< 0.001
18	11	4.87	7	2.46	0.483(0.182-1.283)	0.144
26	2	0.88	3	1.06	0.730(0.110-4.826)	0.744
31	8	3.54	11	3.87	1.181(0.460-3.036)	0.729
33	10	4.42	28	9.86	2.577(1.250-5.310)	0.01
35	1	0.44	6	2.11	1.587(0.386-6.531)	0.522
39	12	5.31	11	3.87	0.621(0.265-1.456)	0.273
45	0	0.00	2	0.70	0.924(0.817-1.046)	0.212
51	24	10.62	7	2.46	0.232(0.097-0.554)	< 0.001
52	71	31.42	59	20.77	0.610(0.406-0.917)	0.017
53	7	3.10	10	3.52	1.030(0.381-2.788)	0.953
56	12	5.31	6	2.11	0.384(0.140-1.054)	0.063
58	50	22.12	52	18.31	0.729(0.469-1.132)	0.159
59	12	5.31	5	1.76	0.377(0.128-1.105)	0.075
66	12	5.31	5	1.76	0.321(0.110-0.936)	0.037
68	4	1.77	4	1.41	0.859(0.208-3.558)	0.834
82	2	0.88	3	1.06	1.252(0.202-7.767)	0.81
6	0	0.00	1	0.35		
11	1	0.44	2	0.70		
40	0	0.00	0	0.00		
42	0	0.00	0	0.00		
43	0	0.00	2	0.70		
44	2	0.88	1	0.35		
55	0	0.00	1	0.35		
61	1	0.44	0	0.00		
81	2	0.88	0	0.00		
83	1	0.44	0	0.00		

CIN2, cervical intraepithelial neoplasia 2; CIN3, cervical intraepithelial neoplasia 3; PR, prevalence ratio; CI, confidence interval.

Table 3 Human papillomavirus (HPV) genotype distribution in ICC among Hakka women in Southern China

HPV type	ICC (n=898)	%	SCC (n=654)	%	ADC (n=244)	%	PR(SCC vs. CIN3) (95%CI)	P
16	446	49.67	394	60.24	52	21.31	2.517(1.095-5.786)	0.03
18	101	11.25	45	6.88	56	22.95	2.473(1.840-3.324)	< 0.001
26	1	0.11	1	0.15	0	0.00	2.220(0.948-5.198)	0.066
31	28	3.12	24	3.67	4	1.64	1.275(0.613-2.651)	0.515
33	52	5.79	40	6.12	12	4.92	0.490(0.291-0.826)	0.007
35	18	2.00	9	1.38	9	3.69	0.540(0.180-1.621)	0.272
39	22	2.45	12	1.83	10	4.10	0.488(0.208-1.149)	0.101
45	18	2.00	7	1.07	11	4.51	0.689(0.115-4.126)	0.683
51	30	3.34	19	2.91	11	4.51	1.580(0.644-3.875)	0.318
52	88	9.80	53	8.10	35	14.34	0.539(0.364-0.797)	0.002
53	31	3.45	20	3.06	11	4.51	0.411(0.165-1.029)	0.057
56	14	1.56	9	1.38	5	2.05	0.621(0.212-1.817)	0.384
58	80	8.91	53	8.10	27	11.07	0.235(0.146-0.379)	< 0.001
59	21	2.34	20	3.06	1	0.41	2.523(0.941-6.766)	0.066
66	6	0.67	5	0.76	1	0.41	0.268(0.066-1.093)	0.066
68	12	1.34	7	1.07	5	2.05	0.755(0.208-2.740)	0.669
82	5	0.56	3	0.46	2	0.82	0.755(0.146-3.897)	0.737
6	13	1.45	11	1.68	2	0.82		
11	6	0.67	6	0.92	0	0.00		

40	2	0.22	0	0.00	2	0.82
42	15	1.67	10	1.53	5	2.05
43	29	3.23	14	2.14	15	6.15
44	17	1.89	7	1.07	10	4.10
55	20	2.23	9	1.38	11	4.51
61	25	2.78	14	2.14	11	4.51
81	26	2.90	16	2.45	10	4.10
83	3	0.33	3	0.46	0	0.00

ICC: invasive cervical cancer; SCC, squamous cell carcinoma; ADC, adenocarcinoma; CIN3, cervical intraepithelial neoplasia 3; PR, prevalence ratio; CI, confidence interval.

Figures

Figure 1

Flow chart of study participants

Figure 2

Type-specific prevalence of 10 most prevalent HPV genotypes in cervical intraepithelial neoplasia (CIN2) and cervical intraepithelial neoplasia (CIN3) among Hakka women in Southern China, prevalence (%) with single infections and overall type specific were shown at the bar.

Figure 3

Type-specific prevalence of 10 most prevalent HPV genotypes in invasive cervical cancer (ICC) among Hakka women in Southern China, prevalence (%) with single infections and overall type specific were shown at the bar.

Figure 4

Type-specific prevalence of 10 most prevalent HPV genotypes in squamous cell carcinoma (SCC) and adenocarcinoma (ADC) among Hakka women in Southern China, prevalence (%) with single infections and overall type specific were shown at the bar.

Figure 5

Age-specific prevalence of HPV infection in CIN2/3 and ICC (SCC and ADC) among Hakka women in Southern China; CIN2: cervical intraepithelial neoplasia; CIN3: cervical intraepithelial neoplasia; ICC: invasive cervical cancer; SCC: squamous cell carcinoma; ADC: adenocarcinoma.