**MEMORANDUM**

**PROJECT:** SWISSRE CERVICAL CANCER

**FROM**: Nicole Young

**DATE**: October 4th 2020

**RE**: HPV and Cervical cancer core cause model

**HPV epidemiology and associated disease**

* Human papillomavirus (HPV) is a highly prevalent infection in humans.
* There are 170 known genotypes, 40 of which infect genital mucosa and are highly transmissible through sexual intercourse
* The international agency for research on cancer (IARC) has classified HPV genotypes into categories of carcinogenic risk
* 12 high risk genotypes (hrHPV) are defined as the IARC ‘carcinogenic group’ (table 1)
* Persistent infection with carcinogenic genotypes (hrHPV) is now assumed to be the *cause of all cases of cervical cancer*1.

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| **Table 1. IARC classification of carcinogenicity of HPV genotypes** |
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* Over 80% of men and women will come into contact with genital HPV at least once in their lifetime but only a small proportion of these infections will persist to cause cervical intra epithelial neoplasia (CIN)
* CIN can progress from grade 1 (CIN1) to CIN grade 3 or above (CIN3+) and eventually to cancer.
* In high-income countries, CIN2+, identified during screening, is thought to represent a risk of progression to cancer and warrants treatment.
* Persistence is generally defined as detectable HPV genotype specific infection lasting ≥ 6 months2
  + Definition of persistence varies across studies. Most studies defined persistence as HPV +ve at two or more time points, while others used three or more +ve visits.
* Clearance is currently defined as the loss of detection of a previous HPV genotype-specific infection2.
  + **Median** length of genital infection with any HPV genotype is **9.8 months**3
  + **90% of infections** are cleared within **2 years**4**,**5
  + **hrHPV** types on average, persist for longer durations than low-risk types3,6, and are less likely to be cleared6.
    - HPV 16 is the most common genotype present in HPV associated cancers across anatomical sites (over 70% of invasive cervical cancers are attributable to genotypes HPV 16 and 18, which persist and progress to lesions quicker than other high-risk types.
  + One year hrHPV persistence strongly predicts which infection will continue to persist and progress to CIN2/32
* Cervical cancer is third most common cancer worldwide
  + It takes 15 to 20 years for cervical cancer to develop in women with normal immune systems.
  + It can take only 5 to 10 years in women with weakened immune systems, such as those with untreated HIV infection.

**Prevalence, incidence and clearance of HPV**

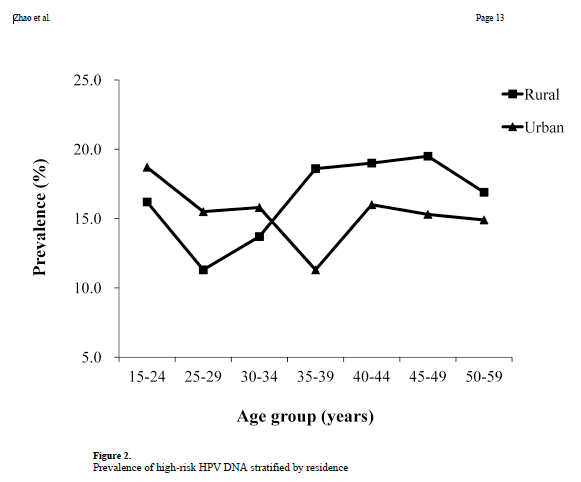
* The worldwide prevalence of cervical HPV DNA in women with normal cytology, adjusted for age, region, study and HPV assay characteristics is estimated to be **10.4%** (95%CI10.2-10.7)7
* A global review of prevalence data indicates that the detection of HPV DNA peaks in women less than 25 years old, then declines, with a small increase again in women over 50 years of age7,8,9. (prevalence highest in 20-25)
* Age-specific hrHPV have demonstrated substantial variability across geographical regions.

**CHINA**

* We will use prevalence and clearance to get internally consistent measure for incidence
* Swissre population is **urban** so we want to use **urban age-specific rates**

**Prevalence**

* For prevalence, there are two papers that report pooled analysis of hrHPV prevalence rates:
  + Zhao 2012
    - – pooled analysis of 17 population based studies with a total screened pop of 29,579 with hrHPV DNA results were included for analysis.
    - Stratified by urban (11.6%) and rural (88.4%); sexual debut at 23.7, sd 3.1 vs 20.8, sd 2.2 respectively
    - More lifetime sexual partners reported by rural women than urban women
    - hrHPV detected by Hybrid Capture 2 test for 13 carcinogenic strains including 16,18,31,33,35,39,45,51,52,56,58,59,68)
    - crude hrHPV prevalence in urban = 15.2%, rural = 18%



* + Li 2019
    - Includes 198 studies
    - Age-specific rates are not stratified into urban vs rural
    - **Age-specific rates stratified into those with no symptoms undergoing routine health check-ups and those with symptoms or suspected HPV infection in outpatient clinics. Table 2 shows prevalence from health check-ups**
    - Overall hrHPV infection rates urban = 14.1% (95% CI, 12.1%-16.2%), rural = 15.7% (95% CI,
    - 12.0%-19.4%).
    - Overall hrHPV includes 17 subtypes 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, and 82) and
    - Age-specific prevalence of 16 and 18 reported as well

**Clearance rate**

* Kang et a (2014)10 investigated age trends of hrHPV in a prospective cohort of 7397 women living in **rural** Shanxi, Henan, and Jiangxi provinces.
* 7397 were tested at baseline (women with cytological confirmed CIN2+ at baseline were excluded)
  + Of the 2147 screen +ve women, 1859 (86.6%) returned for follow-up at 1-year
  + Of the 5250 screen –ve women, 1014 (sampling fraction = 19.3%) were randomly selected for 1-year follow-up, of whom 932 (91.9%) returned.
* 3 HPV tests were used to screen for HPV infection
  + careHPV – detects all 12 carcinogenic genotypes + 66 and 68 in table 1
    - Two types of careHPV rapid tests were used: 1) *care*HPV for a pool of 13 carcinogenic and 1 possible carcinogenic genotype and 2) *care*HPV 16/18/45 for genotype 16, 18, 45
  + Onco E6 – tests for HPV causing onco-proteins made by HPV infections
  + Hybrid capture 2 – all 12 carcinogenic genotypes + 68 in table 1
* The results reported in this study are based on *careHPV* tests. If the three tests were discordant, they would consider someone negative if careHPV is negative (see note in table 3 of Kang). I’m not sure why, and they do not report how many women had discordant test results. Maybe the second author has some affiliation with the producers of careHPV? Just something to keep in mind. We could report –incidence rate as detected by careHPV or something.

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| **Table 2. Prevalence, incidence and clearance rates of hrHPV** | | | | | | | |
|  | **Zhao 2012**11 | **Li 2019**12 | | | **Kang 2014**10 | | |
| **Age** | **Prevalence** (N=29,579) (*urban*)  Note: read off fig 2 | **Prevalence** hrHPV from health check-ups (n=65,750) (*urban and rural*)  Note: read off table 2 | **Prevalence of HPV 16**  from health check-ups (n=65,750)  (*urban and rural*)  Note: read off table 2 | **Prevalence of HPV 18**  from health check-ups (n=65,750)  (*urban and rural*)  Note: read off table 2 | **Prev**  **-alence**  (N=7397)  at baseline (*rural*) | **Incidence** adjusted for sampling fraction at 1-year  f-up  (*rural*) | **Clearance** adjusted for sampling fraction at  1-year f-up10  (*rural*)  Note: read off table 3 |
| **0-15** | 0.001π |  |  |  |  |  |  |
| **15-20** | 18.7% | 14.3% (10.9-17.7) | 2.6% (1.5-3.8) | - | 0 | - | 80%¶ |
| **20-25** | *16.2%*11 | *-* |
| 25-29 | 15.5% | 13.1% (10.3-16.0) | 2.3% (1.1-3.6) | 0.7% (0.5-1) | 13.2%† | 7.8% | 78.8% (26/33) |
| 30-34 | 15.7% | 10.9% | 4.4% | 52.6% (30/57) |
| 35-39 | 11.3% | 11.5% | 7.2% | 54.6% (71/130) |
| 40-44 | 16.0% | 12.1% | 7.8% | 64.6% (106/164) |
| 45-49 | 15.4% | 12.5% (10.5-14.4) | 2.2% (1.2-3.2) | 2.1% (1.2-3.1) | 12.1% | 4.6% | 56.1% (87/155) |
| 50-54 | 14.9% | 13.9% | 5.6% | 42.0% (47/112) |
| 55-59 | 19.3%\* | 4.9% | 38.1% (51/134) |
| 60-65 | 10.5%∆ | 14.6% | 7.0% | 27.7% (13/47) |
| 65+ | - |  |  |  | - | - | - |
| **Overall** | **15.2%** |  |  |  | **13.1%** | **6.2%** | **51.8% (431/832)** |
| **Incidence** = ((1/sampling fraction) \* (Number of baseline screen negatives who tested careHPV-positive at follow-up) + (Number of baseline screen positives with careHPV-negative who tested careHPV-positive at follow-up)) / ((Number of baseline screen negatives) + (Number of baseline screen positives with careHPV-negative who were followed up)).  **Clearance** = (Number of cleared) / (Number of baseline careHPV-positive who were followed up).  † this study lacked the “first peak” in younger women. It has been well acknowledged that cumulative risks of 40-50% of HPV acquisition happened within 2 to 3 years of sexual debut13,14,15 . Since the average age at first sexual intercourse of our study participants **was 21.2 years**, the theoretical peak of HPV prevalence should appear in women aged 23-24 years. In addition, Chinese women were less likely to report their premarital and extramarital sexual histories. In that case, we hypothesize that the actually age of sexual initiation may be even younger. However, we only enrolled women aged over 25 years, therefore we have no chance to see the “first peak” as observed in other studies.  \*other studies in China also observed second peak of HPV prevalence in older women, although the peak age varied between studies.  π used a low prevalence for this age group to make curve more realistic; ¶imputed based on assumption from trend  ∆based on lower bound value from Li for age group | | | | | | | |

**DISCUSSION**

My thinking is that we use Zhao for prevalence input data to dismod notebook because

1. It shows the trend that is reported in other studies 7,8,9
2. It is stratified into urban and rural populations. Urban populations have lower infection prevalence than urban although not by too much.
3. It is stratified by more age-bands which gives us more granularity to show the U-shaped trend.
4. We have clearance data for the age bands
5. Li does not have the finer age bands.
6. Li is not stratified into urban/rural populations.
7. Li’s CIs include those from Zhao –*mostly*
8. We could look through the list of Li papers and see if there are reports for areas that more closely matches swiss re’s populations
9. We don’t have prevalence for HPV in elderly
10. I used the lower bound from Li for age 60 to 65 because otherwise the prevalence increases at age increases
11. I used a prevalence of 0.001 (or anything small, so that the curve looks more realistic.

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| **Without** prevalence in 0-15 and 60-65 | With prevalence of 0.001 in 0-15 and 10.5% in age 60-65 |
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1. We are not seeing the peak in prevalence as described in the literature among the older women age groups.
2. The prevalence seems too high in age group 20-25

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