Int J Clin Exp Med 2015;8(9):16007-16014
www.ijcem.com /ISSN:1940-5901/IJCEM0012905

Original Article

Epidemiology and genotype distribution of high risk human papillomavirus in population of hospital opportunistic screening

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Received July 14, 2015; Accepted September 1, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: This study aimed to determine the prevalence of high-risk human papillomavirus (HR-HPV) in population of hospital opportunistic screening and to identify the correlation of prevalent genotypes and cervical cytological abnormalities. A cross-sectional study was employed between July 2013 and July 2014 in the Chaoyang hospital, in Beijing. Cervical samples were collected for the Type-specific HPV and the cervical cytological analyses in the population of hospital opportunistic screening. Total of 8975 samples from female patients aged 17-86 years were tested. Of these, 10.4% were infected by HR-HPV, the highest prevalence of HR-HPV in the youngest group and decreasing with aging (X^2=19.68, P=0.02). Of these, 78.73% were single infections and 21.27% were multiple infections. Age-specific prevalence of multiple HPV exhibited a "U" shaped curve (X^2=19.98, P=0.018). The most prevalent genotype is HPV 52, then descending order of frequency were HPV-58, 16, 39, 51, 56, 59, 18, 31, 33, 35, 68 and 45. 15.9% had an abnormal cytology in HR-HPV positive women, vs 4.13% in HR-HPV negative women. The prevalence of HR-HPV were 9.2%, 26.8%, 32%, 35.3% and 36.4% in normal cell, ASCUS, LSIL, ASC-H and HSIL, respectively (X^2=234.67, P=0.000). Women with HPV 52, 16, 18, 58, 39, 51, 59, 56, 33, 31 infections related to the abnormal cytology, while the HPV68, 45, 35 didn't. The prevalent characteristic in population of the hospital opportunistic screening is similar to the population of cervical screen, But the most five prevalent genotype in rank are different .Women with HR-HPV infections were more likely to have the cervical abnormal cytology.

Keywords: High risk human papillomavirus, epidemiology, cervical cytology, population of hospital opportunistic screening

Introduction

Cervical cancer continues to be a global concern. It is estimated that each year approximately 493,000 new cases are diagnosed and 274,000 women die from cervical cancer worldwide [1]. The American Cancer Society estimates that 12,340 new cases of invasive cervical cancer will be diagnosed, and 4030 women will die of cervical cancer in 2013 in the United States [2]. According to World Health Organization statistical data, about 75,000 of the annual new cervical cancer cases were estimated to be in the People's Republic of China, where cervical cancer was responsible for 33,000 deaths in 2008 [3]. The link between HR-HPV and cervical cancer has been well established; of the more than 100 types of HPV identified, 14 oncogenic subtypes are associated with the majority of cases of cervical cancer, which were considered HR-HPV ,which including genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 [2].

A global meta-analysis showed that the prevalence of HPV in 157,879 women with normal cytology was 10.4%. The prevalence estimates by region were 22.1% in Africa, 20.4% in Central America and Mexico, 11.3% in Northern America, 8.1% in Europe, and 8.0% in Asia. Of all HR-HPV genotypes, HPV 16 has been regarded as the most prevalent genotypes [3]. Ding et

Table 1. The distribution and proportion of the 8975 cases and the prevalence of HR-HPV according to age

Age	Numbers and proportion		Prevalence of HR-HPV	
	No	%	No	%
≤24	398	4.43	58	14.6
25-29	1596	17.78	184	11.5
30-34	2022	22.53	218	10.8
35-39	1097	12.22	115	10.5
40-44	1012	11.28	98	9.7
45-49	766	8.53	63	8.2
50-54	935	10.42	97	10.4
55-59	623	6.94	56	9.0
60-64	304	3.39	27	8.9
≥65	222	2.47	15	6.8
Total	8975	100	931	10.4
X^2			19.68	
P			0.02	

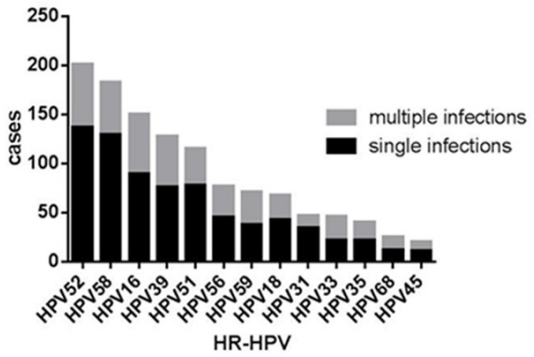

Figure 1. The prevalent characteristic of HR-HRV genotype in the 931 positive cases.

al [4] reported the 24.0% and 73.4% of the prevalence of infection by HR-HPV genotypes in the cervicitis group and the cervical lesion group, respectively, among the 1,082 patients of colposcopic clinic in Beijing. Few studies had examined the epidemiology of HR-HPV in the population of the hospital opportunistic screening in China. An accurate assessment of the regional distribution of HR-HPV genotypes in the population of hospital opportunistic screening is extremely important for both prevention of cervical cancer and for public hygiene management.

The present study aims to evaluate the prevalence of HR-HPV infection in population of hospital opportunistic screening in Beijing and to identify the correlation of prevalent genotypes and cervical cytological abnormalities.

Materials and methods

Study population

The study group consisted of a consecutive sample of all women who proceeded to the Outpatient Gynecological Clinic of Chaoyang Hospital in Beijing from July 2013 to July 2014 and were tested for Type-specific HR-HPV analyses and cytological testing as cervical cancer screening, excluding these women: pregnant women, history of hysterectomy, any gynecological malignancy. The study was approved by the ethic committee of Chaoyang Hospital affiliated to Capital Medical University, Beijing, China.

Sample preparation

Two cervical samples were obtained via cytobrush from each woman: One sample was resuspended in 20 mL of liquid-based cytology medium (ThinPrep, Cytyc Corporation, MA), and the other one were resuspended in 2.5 mL of special liquid for detecting the Type-specific HR-HPV.

Type-specific HR-HPV analyses

Type-specific HR-HPV analyses were made by diagnostic kit (Shanghai ZJ Bio-tech Co., LTD). Real-Time Ploymerase Chain Reaction (PCR) test was employed. The 13 HR-HPV genotypes were detected, including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.

Cytological diagnosis criteria

Cervical exfoliative cell slides were prepared using a liquid-based cytology method, the ThinPrep system (Cytyc Corporation). Cytological classifications were made in according to the Bethesda 2001 criteria by pathologists of Chaoyang hospital. A diagnosis was assigned to each case as having negative for intraepithelial lesion or malignancy (NILM) or having an abnormality cytology such as atypical squamous cells of undetermined significance (ASCUS), Atypical Squamous cells-Cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous

Table 2. Distribution of high-risk HPV, in single or multiple infections, according to age

Age classes	Single infections (n, %)	Multiple infections (n, %)	Total
≤24	39 (67.2%)	19 (32.8%)	58
25-29	135 (73.4%)	49 (26.6%)	184
30-34	175 (80.3%)	43 (19.7%)	218
35-39	100 (87.0%)	15 (13.0%)	115
40-44	80 (81.6%)	18 (18.4%)	98
45-49	53 (84.1%)	10 (15.9%)	63
50-54	73 (75.3%)	24 (24.7%)	97
55-59	49 (87.5%)	7 (12.5%)	56
60-64	19 (70.4%)	8 (29.6%)	27
≥65	10 (66.7%)	5 (33.3%)	15
Total	733 (78.7%)	198 (21.3%)	931
χ^2=13.58, *P*=0.009			

intraepithelial lesion (HSIL) and invasive cervical cancer (ICC), atypical glandular cells (AGC) and adenocarcinoma.

Statistical analysis

All statistical analyses were performed using SPSS 22.0 statistical package for Windows. Chi-square test was used to evaluate the significance of differences among various groups. Frequencies and odds ratios (ORs) point estimates and 95% confidence intervals (95% CI) were measured by the correlation degree between two classification variables. Statistical significance was accepted if the *p* value was less than 0.05.

Results

The study group consisted of a consecutive sample of 8975 women between 17 and 86 years old from the Outpatient Gynecological Clinic of Chaoyang Hospital in Beijing from July 2013 to July 2014, excluding these women: pregnant women (1716 cases), history of hysterectomy (167 cases), any gynecological malignancy (6 cases), 8975 women were eligible for analyses. The size of age classes among the women enrolled in the study is reported in **Table 1**.

The prevalence of HR-HPV infection according to age in population of hospital opportunistic screening

A total of 8975 cervical samples were analyzed. HR-HPV was detected in 931 samples and the overall prevalence was 10.4% (931/8975). The prevalence of HR-HPV according to age is in **Table 1**. The prevalence of HR-HPV was highest in younger women, then decreasing with aging. There are significant different in the age classes about the prevalence of HR-HPV (χ^2=19.68, P=0.02).

The prevalence of HR-HPV genotypes

The most prevalent genotype is HPV 52, which was detected in 201 (21.58%) out of the 931 HR-HPV positive samples. The second genotype was HPV 58, which was detected in 183 (19.66%). Genotypes 16 was the third one, which was 16.11% (150/931). Genotypes 18 was the 6th one of 7.30% (68/931) (**Figure 1**). And the type-specific prevalence of HR-HPV in the overall population of hospital opportunistic screening in **Table 3**, the highest prevalence is 2.24% in the HPV-52, regardless of the status of single-type or multiple-type infection.

Multiple HR-HPV infection

Of these HR-HPV positive, 733 (78.7%) were single infection, and 198 (21.3%) were multiple infections. Among women with multiple infections, 166 women were infected with two HR-HPV types, 26 women infected three HR-HPV types, 5 cases with four HR-HPV types, and 1 case with five HR-HPV types. The proportion of the multiple high-risk HPV infections were higher in these women who were younger than 30 years and older than 50 years (**Table 2**), the highest in the oldest group, these differences were statistically significant (χ^2=19.98, P= 0.018). The proportion of the multiple HR-HPV in the 13 types were significant different (χ^2=23.18, P=0.026) (**Figure 2**), the lower prevalent genotypes have the higher proportion of the multiple HR-HPV, The proportion of the multiple HR-HPV in HPV 68 was 52.6%, HPV 45 45%, HPV 33 52.2%, and HPV 35 45%, while the HPV 52 31.8%, HPV 58 29.5%, but the HPV 16 has not only higher prevalent, but also the higher proportion of the multiple HR-HPV infection.

The association between the HPV infection and the cervical cytological results

The Pap test result was available in 8975 women: 8495 (94.7%) were negative, 480 (5.3%) had abnormal cytological diagnosis, of

Table 3. The prevalence of HPV types in the screening population by cytological findings

Types	Total	Normal cytology	Abnormal cytology			N OR (95% CI)	
			ASCUS	LSIL	ASCH/HSIL*		
	N (%)	N (%)	N (%)	N (%)	N (%)		
HR-HPV infection							
HR-HPV(+)	931 (10.4)	783 (9.2)	49 (26.77)	63 (31.98)	36 (36.73)	148	4.39 (3.6-5.4)
HR-HPV(-)	8044 (89.63)	7712 (90.78)	134 (73.22)	134 (68.02)	62 (63.27)	332	
HR-HPV infection, single or multiple							
Single	733 (78.8)	622 (79.3)	39 (79.6)	46 (69.8)	26 (72.3)	111	
Multiple	198 (21.2)	161 (20.7)	10 (20.4)	17 (30.2)	10 (27.7)	37	0.7 (0.7-1.1)
HPV16	150 (1.67)	126 (1.48)	3 (1.64)	12 (6.09)	9 (9.18)	24	4.4 (2.8-6.9)
HPV18	68 (0.76)	56 (0.66)	6 (3.28)	2 (1.02)	3 (3.06)	11	5.00 (2.6-9.4)
HPV31	47 (0.52)	36 (0.42)	6 (3.28)	2 (1.02)	3 (3.06)	11	7.1 (3.6-14.1)
HPV33	45 (0.50)	40 (0.47)	0 (0)	3 (1.52)	3 (3.06)	5	2.9 (1.1-7.4)
HPV35	40 (0.45)	36 (0.42)	0 (0)	4 (2.03)	0 (0)	4	2.7 (0.94-7.51)
HPV39	128 (1.43)	109 (1.29)	8 (4.37)	5 (2.54)	6 (6.12)	19	4.1 (2.5-6.7)
HPV45	20 (0.22)	18 (0.21)	1 (0.55)	0 (0)	1 (1.02)	2	2.6 (0.6-11.2)
HPV51	115 (1.28)	93 (1.09)	4 (2.19)	10 (5.08)	8 (8.16)	22	5.8 (3.6-9.3)
HPV52	201 (2.24)	170 (2.00)	8 (4.37)	16 (8.12)	7 (7.14)	31	4.2 (2.8-6.3)
HPV56	77 (0.86)	56 (0.66)	11 (6.01)	9 (4.57)	1 (1.02)	21	8.7 (5.2-14.6)
HPV58	183 (2.04)	156 (1.84)	11 (6.01)	10 (5.08)	6 (6.12)	27	4.0 (2.6-6.1)
HPV59	71 (0.79)	58 (0.68)	3 (1.64)	7 (3.55)	3 (3.06)	13	5.2 (2.8-9.6)
HPV68	25 (0.28)	22 (0.26)	1 (0.55)	2 (1.02)	0 (0)	3	3.2 (0.9-10.6)

*Including 2 cases of atypical glandular cell and 2 cases of the squamous cancer and1 case of adenocarcinoma.

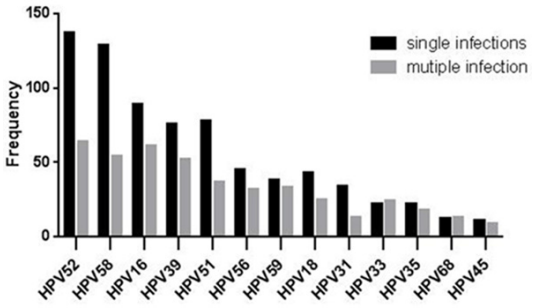

Figure 2. The proportion of the multiple HR-HPV infections in various HR-HPV genotypes.

the 480, 183 had a cytological diagnosis of ASCUS, 197 of LSIL, 32 of ASC-H, and 63 of HSIL, and 2 of the squamous cancer, 2 cases of AGC and 1 case of adenocarcinoma. There were no significant difference about the frequency of abnormal cytology in various age group (χ^2=9.52, *P*=0.39).

Among HR-HPV positive women, 15.90% (148/931) had an abnormal cytology, vs. 4.13% (332/8044) in HR-HPV negative women, 30.83% (148/480) of abnormal cytology women had also an HR-HPV infection, while the 69.17% (332/480) of abnormal cytology had HR-HPV negative. The prevalence of HR-HPV was 9.2%, 26.8%, 32%, 35.3% and 36.4% in normal cell, ASCUS, LSIL, ASC-H and HSIL respectively (**Table 3**). There are significant difference in HR-HPV prevalence according to the results of Pap test (χ^2=234.67, *P*=0.000).

Women with HR-HPV infections were more likely to have abnormal cytology (OR=4.39, 95% CI 3.57-5.40), for the HSIL and ASCH, OR 5.54 (95% CI 3.66-8.39), LSIL group OR 4.63 (95% CI 3.40-6.30), ASCUS OR 3.60 (95% CI 2.58-5.04). As expected, HR-HPV positivity was greater in higher grade cytological abnormalities.

Of the 931 HR-HPV positive women, 733 (78.7%) were single infection, and 198 (21.3%) were multiple infections. The multiple infection association with the cytology results in **Table 3**. The multiple infection didn't increase the abnormal cytology (χ^2=3.96, P=0.27).

The most common HR-HPV genotypes were HPV 52, 58, 16, 39, 51, 56, 59 and 18 in the population of screening. HPV 52, HPV 16, 18,

58, 39, 51, 59, 56, 33, 31 infection were more likely to have the abnormal cytology, while the HPV 68, 45, 35 have not increase the risk of abnormal cytology, the OR and their 95% CI for each genotype HPV in **Table 3**.

Discussion

The prevalence of HR-HPV

We presented a large study of HR-HPV prevalence in population of opportunistic hospital screening in different ages in Beijing, from which interesting conclusions was drawn. The results indicated higher prevalence of HR-HPV in young women (17-29 years) and HR-HPV infection decreasing with aging. In an attempt to compare the current study results with other countries' epidemiological data, we presented an age-related prevalence curve of HR-HPV infection. This curve showed that the highest prevalence at the ≤24 age group, then a steady decrease of HR-HPV prevalence across increasing age, until the age group of ≥50 years. Younger women are more prone to develop an HR-HPV infection as they are less likely to have developed immunity to HR-HPV given their recent exposure to the virus, this is consistent with worldwide data. The prevalence has a mild increasing in the age group of 50-59, as they are premenopause, which may make them anxiety, sleeplessness, and so on, all of these discomfort may affect the immunity.

The study population have the overall 10.4% prevalence of HR-HPV infections, it is higher than 7.2% (5585/77069), which was reported in screening populations in the Southern China [5], but it is lower than that described in mid-south China (20.0%) [6] and southern China (13.7%) in the cervical cancer screening populations [7] and it is similar to the result from ZheJiang Province in the cervical screening population (10.2%) [8]. These different prevalence of the HR-HPV in various studies and the current study may be the different populations and different areas.

For the population of opportunistic-hospital screening, the overall 10.4% of prevalence of HR-HPV is lower than that described in other area of the world , such as, the prevalence of HR-HPV infection was 29.9% from women seeking gynecological care in Southern Brazi [9], 14.2% and 13.7% in with and without cervical lesions, respectively in women attending regular gynecological visit in Croatian [10], 27.4% in the population of gynecological outpatient clinic in Green [11], 24.0% and 73.4%, in cervicitis group and the cervical lesion group, respectively in China [4]. However, it was higher than that found in Green, a cross-sectional study carried out in 5379 women showed the overall 5.8% (295/5107) of the HR-HPV infection [12] and it was similar to in other parts of world, such as Eastern Brazilian Amazon (10.5%) [13]. The differential prevalence of HR-HPV in the population of opportunistic-hospital screening in various area of the world may be related to the different socio-economic and cultural factors.

Prevalence trend

It is important to identify which are the most common genotypes in the positive HR-HPV, and which types associated with the cervical abnormal cytology. Knowledge of the distribution of HR-HPV genotypes in women will make it possible to evaluate the potential efficacy of the next generation of HPV prophylactic vaccines.

The current study show that the most prevalent genotypes in descending order of frequency were subtypes 52, 58, 16, 39, 51, 56, 59, 18, 31, 33, 35, 68 and 45 in the population of opportunistic-hospital screening in Beijing, which is similar to the other's results in population of opportunistic-hospital screening or cervical screening populations in China, for example, Ding reported that the most common HPV genotypes were HPV 52, 16, 58, and 18 in the patient of colposcopy clinic in Beijing [4]. The five most common HPV types were HPV 16, 52, 58, 18 and HPV 6 in the southern China [5], the date from the Zhejiang shows that the HPV-52 was the most prevalent type, followed by HPV-16, 58, 68 and 81 in a cervical screen population [8]. The most common HR-HPV genotype was HPV-16, followed by -52, -58, -18, -6 and -39 in the mid-south in China [6] and so on.

Most dates from areas of China about the specific-types of HR-HPV distribution are similar, the most prevalent three types HPV 16, 58, 52, while the rank varied by various studies, most dates showing the HPV 16 detected first and HPV 52, 58 ranking second or third [14, 15]. It was inconsistency with the current study, which shows HPV-52, rather than HPV-16, was the most commonly identified type, HPV16 ranked

the third, HPV-58, another common type, ranked the second. The most prevalent of HR-HPV genotypes from China were similar to the results in the other areas of Asia [16], for example, the most prevalent HR-HPV genotypes in descending order of frequency were HPV 51, 16, 52, 58 and 66 [17].

But besides the Asia, the distribution of HR-HPV were differential from other area of the world, for example, the date from the Green show that the most common HR-HPV types were HPV-16, 31, 35, 53, 18 [12]. The date from Italy showing the commonest types were HPV-52, 53, 16 and HPV-6 [18], the most three frequent genotype were HPV-16, 18, and 33 in Southern Brazil [9] and so on. The difference of the distribution of HR-HPV in various region of the world may be due to the geographical and biological interplay between HPV types and host immunogenic factors [19].

Most studies show that the HPV 18 is one of the most commonly identified type [20], but in current study, HPV 18 not the commonly type, ranking the eighth, 68 cases of the 931 HR-HPV positive women were detected the HPV18 (7.30%), 0.76% the prevalence. When analysis the association between the HR-HPV infection and the cervical lesions, we found that HPV 18 was more likely to have the abnormal cytology (OR 4.98, 95% CI 2.64-9.38), although the lower prevalent. So, we should raise concern to the HPV 18 infecting the genital tract.

The proportion of multiple HR-HPV infections were 198/931 (21.3%) in the population of opportunistic-hospital screening in Beijing. Multiple HR-HPV positivity was more common in younger women and older women. It is may be that the younger women are less likely to have developed immunity to resist the HPV infection, the women older than 50 years old are premenopause or menopouse, who may be inclined to anxiety, sleeplessness, and so on, which may influence the immunity. The study presented that the proportion of the multiple HR-HPV in the 13 types were significant differental, the lower prevalent genotypes have the higher proportion of the multiple HR-HPV. The proportion of the multiple HR-HPV in HPV-68 was 52.6%, HPV 33 52.2%, HPV 45 45%, and HPV35 45%, while the HPV 52 31.8%, HPV 58 29.5%, but the HPV 16 has not only higher prevalent, but also the higher proportion of the multiple HR-HPV infection. The most proportion of multiple HR-HPV infection (HPV 68, 45, 35) not increase the cervical abnormal cytology.

HR-HPV infection is the principal etiological factor for cervical cancer. In the present study, the prevalence of HR-HPV were 9.2%, 26.8%, 32%, 35.3% and 36.4% in normal cell, ASCUS, LSIL, ASC-H and HSIL, respectively. The prevalence increase with the cervical lesions progression. This is in agreement with other's studies [21]. The low rate of HR-HPV infection in women with overall cytological abnormalities, including ASCUS, is an unexpected finding as there is no clear explanation to it; one can argue about the possibility of inadequate way in cervical sample collection or low sensitivity of HR-HPV test; these questions need further investigation.

This studies results demonstrate that HR-HPV infection increased odds ratio of having abnormal cervical cytology, with the highest OR found in the HSIL and ASC-H cytology groups when compared to normal cytology. Women with HR-HPV infections have the OR 5.54 (95% CI 3.66-8.39) for HSIL and ASCH, OR 4.63 (95% CI 3.40-6.30) for LSIL, OR 3.60 (95% CI 2.58-5.04) for ASCUS. As expected, HR-HPV positivity was greater OR in higher grade cytology abnormalities.

About 1/3 of the women with a positive Pap test (including ASCUS) were also infected by HR-HPV. This finding emphasizes the need of a follow up in women who are HR-HPV infection. However, HR-HPV test is not sufficient in surveillance for cervical cancer: as a matter of fact that the test were negative in about two-third (69.3%) of the 480 women with squamous intraepithelial lesions of low or high grade and therefore HPV surveillance would have missed about two-third of the negative HR-HPV women with an abnormal Pap test result requiring a cytological follow up.

When we analysis the association between the type-specific HPV infection and the cervical abnormal cytology, it was found that HPV 16, 52, 58, 39, 18, 51, 56, 59 and 31 infecting will increase the risk of abnormal cytology, all of these HPV had a significantly OR, higher than 4.0, and HPV 33 had a significantly, but lower OR (2.9), while the HPV 35, 45, 68 infection show do not increase the risk of cervical cytology. The most five prevalent HR-HPV (HPV 52,

58, 16, 39 and 51) infection not only have higher prevalent, but also increase the risk of cervical abnormal cytology. The lower prevalence HR-HPV (HPV 35, 45, 68) infection do not associate with the cervical abnormal cytology.

In conclusion, the current study showed a 10.4% prevalence of HR-HPV in the population of opportunistic-hospital screening in Beijing, the most prevalent HR-HPV were similar to other population in the china, but the rank varied. This finding might influence vaccine impact in our country. Further prospective investigations are needed to determine which types HR-HPV were more possible to develop continuous infections and the association with the abnormal cervical cytology and cervical cancer.

Acknowledgements

This research was funded by the Natural Science Foundation of Beijing, China. Grant # 7122069.

Disclosure of conflict of interest

None.

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