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Positivity and prevalence of human papillomavirus among a large population of women in southeastern China

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Abstract

Objective: To formulate strategies for prevention of cervical cancer, we investigated the prevalence of human papillomavirus (HPV) infection and the age-specific distribution among female participants in southeastern China.

Methods: From January 2016 to July 2018, 36,871 women from Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University were enrolled in this prospective study. HPV genotypes were detected using Luminex technology.

Results: HPV infection was observed in 18.34% of the participants, and 79.98% were infected with high-risk HPVs. The five most prevalent genotypes were HPV52 (18.18%), HPV16 (16.06%), HPV58 (11.37%), HPV53 (8.82%), and HPV39 (6.42%). The 9-valent HPV vaccine efficiently reduced the HPV infection rate by more than 10%, which is twofold the rate of other vaccines. Most HPV infections were observed in women age 40 to 49 years, and those age 30 to 59 years accounted for 79.62% of positive patients.

Conclusion: Our findings regarding HPV genotypes and the age-specific distribution of HPV infection in the study area will contribute to the development of cervical cancer screening programs and vaccine strategies.

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Introduction

Human papillomavirus (HPV) is a spherical DNA virus, with a genome 7900 base pairs in length, that infects the skin or epithelial mucosa tissue.[1] It is now widely accepted that HPV infection is highly correlated with cervical cancers and other genital diseases.[2] In addition, a recent study has suggested that HPV infection causes at least 25% of head and neck cancers, of which up to 60% are oropharyngeal cancers.[3]

Cervical cancer is the fourth most common cancer in women, leading to 570,000 new cases and 311,000 deaths annually at global level.[4,5] Notably, the prevalence of cervical cancer is high in developing countries. Whereas most cases are detected at later stages, the outcomes of cervical cancer are poor.[6]The prevalence of cervical cancer among women in China is estimated to be 8.7 to 11.3/100,000 annually and nearly half of these women die of cervical cancer.[7–9] Most patients with cervical cancer have been infected with HPV.[10] Women under the age of 25 years have the highest prevalence of HPV infection, and most are infected shortly after initiating sexual activity.[11] The distribution of HPV infection and genotypes vary by country or region,.[12,13] Guangdong, one of the most important provinces in southeastern China, is among those regions with high HPV infection rates (20.02%), which are above the global average.[7]

Because cervical cytology testing for HPV is subjective and comparatively insensitive, molecular testing for HPV detection is recommended in some instances.[10] About 200 HPV subtypes have been identified and classified as high-risk (HR) or low-risk (LR), based on oncogenic risk. A total of 13 HR HPVs have been defined, of which12 (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) are known to be carcinogenic to humans and one (HPV68) is probably carcinogenic to humans.[14] These 13 HPV genotypes cause more than 96% of cervical cancers.[15] In addition, another 11 HPVs (HPV26, 30, 34, 53, 66, 69, 70, 73, 82, and 97) are classified as having a high risk as they are possibly carcinogenic to humans.[16] Low-risk genotypes, including HPV6, 11, 40, 42, 43, 44, 55, 61, 81, and 83, typically result in benign conditions.[17] The progression from HPV infection to cervical cancer usually takes several years, and women with persistent HPV infection are more likely to develop cervical cancer.[18]

It has been proven that HPV vaccines can prevent persistent infection and cervical disease.[19] Currently, three licensed HPV vaccines are available on the market, including bivalent (HPV16/18, Cervarix), quadrivalent (HPV6/11/16/18, Gardasil), and nonavalent (HPV6/11/16/18/31/33/45/52/58, Gardasil) vaccines.[20] Detection and genotyping of HPV can provide guidance in the development of HPV vaccines. However, cultural factors, such as relatively conservative women and underdeveloped economies, result in less likelihood of women undergoing HPV screening or vaccination in some areas.

In the present study, we analyzed and genotyped HPV infections among women attending the gynecological or reproductive

center of Meizhou People's Hospital. The aim of this study was to assess the HPV prevalence and genotype distribution among women in this region of China and to provide epidemiological evidence for the clinical application of HPV vaccines.

Patients and methods

Study participants

We enrolled women who attended the gynecological or reproductive center of Meizhou People's Hospital (Huangtang Hospital), Meizhou Hospital Affiliated to Sun Yat-sen University from 1 January 2016 to 7 July 2018. Eligible participants met the following two criteria: (i) age >15 years; (ii) provided sufficient DNA for HPV screening. This study was approved by the Ethics Committee of Meizhou People's Hospital (reference No.: MPH-HEC 2015-A-19). Informed consent was obtained from all participants.

Sample collection

Cervical specimens were collected by gynecologists using plastic cervical brushes. Briefly, a cervical brush was inserted into the cervix and rotated five full turns in a clockwise direction. The head of the brush was then placed in a tube containing transport medium (Tellgen Life Science Co., Shanghai, China) and stored at 4°C.

DNA extraction

DNA was isolated from cervical specimens using a DNA extraction kit (Tellgen Life Science Co.), following the manufacturer's protocol. Briefly, samples were divided into four groups, according to turbidity: (i) clear, (ii) mildly turbid, (iii) moderately turbid, and (iv) very turbid. Samples were mixed for 2 minutes and then transferred in various volumes to 1.5-mL containers, based on sample quality: 800 μL, 500 μL, 300 μL, and 100 μL for the categories i, ii, iii and iv, respectively. Another volume of transport medium was added to each sample to make a final volume of 1 mL, and the solution was mixed and centrifuged at 12,000 rpm for 3 minutes. The supernatant was removed and the pellet suspended in 200 μL of extraction reagent. The suspension was then placed in a metal bath for 15 minutes at 100°C and subsequently centrifuged at 12,000 rpm for 5 minutes. The supernatant was collected and stored until testing.

HPV genotyping

HPV DNA genotyping was performed using a Tellgenplex® HPV27 genotyping assay (Tellgen Life Science Co.), following the manufacturer's protocol. This method can detect 27 HPV genotypes, including 17 HR genotypes (HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 82) and 10 LR genotypes (HPV6, 11, 40, 42, 43, 44, 55, 61, 81, 83). Briefly, each color-coded bead was coated with a predesigned HPV type-specific probe. The HPV DNA sample was amplified using biotin-labeled consensus PCR primers. The products were hybridized to beads bearing type-specific probes, then incubated with phycoerythrin (PE)-conjugated streptavidin (SA-PE). The signal were measured using a Luminex 200 system (Luminex Corporation, Austin, Texas, USA).[21] A signal over 100 copies was judged as positive.

Data analysis

We calculated the percentage of women in each age group, per year. We determined the incidence of specific HPV and corresponding 95% confidence intervals (CIs). The statistical analysis was performed using IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA). Pearson's χ^2 or Fisher's exact test were used, as

appropriate. $P < 0.05$ was considered to indicate statistical significance.

Results

Prevalence of HPV infection

A total of 38,851 women who received HPV DNA testing were included in our study. We excluded 1980 women: 12 who were age <16 years and 1968 with missing age data. Finally, 36,871 participants were analyzed in this study. The median age of participants was 44 years (16–89 years). During the study period, 6,761 (18.34%) women tested positive for HPV infection. Of these, 5,408 (14.67%), 1,353 (3.67%), and 760 (2.06%) had HR infection, LR infection, or both HR and LR infection, respectively (Table 1).

Genotype distribution of HPV infection

We detected 27 HPV subtypes in this study. HPV52 was the predominant genotype, with a positivity rate of 18.18%; this was followed by HPV16, 58, 53, 39, 18, 81, 51, 61, and 44, with respective positivity rates of 16.06%, 11.37%, 8.82%, 6.42%, 5.81%, 5.80%, 5.50%, 4.90%, and 4.82% (Table 2). Most infections involved HR HPVs; LR HPV infections comprised HPV81, 61, and 44. The proportion of women infected with multiple HPVs was about the same as that of women infected with a single HPV. HPV52, 16, and 58 were the most frequently observed HPV subtypes in multiple infections.

The annual HPV type-specific positivity from 2016 to 2018 is shown in Table 3. Most HPV HR and LR infections tended to stabilize during the study period. Infection with HPV53 decreased and then increased over the study period whereas infection with HPV68 increased over the study period. Among participants, we also analyzed the protective capacity of the HPV vaccines available on the market. The 9-valent HPV vaccine was capable of reducing HPV prevalence by about 10% each year, which is twice the rate of the other two vaccines (Table 3).

Age-specific prevalence of HPV infection

Next, we analyzed the age-specific prevalence of HPV infection in our study. As shown in Table 4, most HPV infections occurred among women in the age group 30 to 59 years, accounting for nearly 80% of HPV infections. Furthermore, positive rates of HPV subtypes varied by age. As illustrated in Figure 1, the age-specific prevalence of total HPV infections appeared as a U-shaped curve. Positive rates of HPV combined infections (4v HPV, 9v HPV, HR HPV) peaked among participants age 15 to 19 years, stabilized among participants age 20 to 59 years, then increased again among participants older than age 60 years. Combined HPV16/18 infections increased with age.

Discussion

In the present study, we investigated the prevalence of HPV infection in

Table 1. Prevalence of human papillomavirus infection (HPV) among women in southeastern China.

	Single	Multiple	Total
Negative	–	–	30110 (81.66%)
Positive	5201 (14.11%)	1560 (4.23%)	6761 (18.34%)
HR	3951 (10.72%)	1457 (3.95%)	5408 (14.67%)
LR	1250 (3.39%)	103 (0.28%)	1353 (3.67%)

HR: high-risk; LR: low-risk.

Table 2. Genotypes of human papillomavirus (HPV) infection among women in southeastern China.

HPV type	Single	Multiple	Total
High risk			
16	776 (11.48%)	310 (4.59%)	1086 (16.06%)
18	241 (3.56%)	152 (2.25%)	393 (5.81%)
26	9 (0.13%)	7 (0.10%)	16 (0.24%)
31	80 (1.18%)	57 (0.84%)	137 (2.03%)
33	155 (2.29%)	123 (1.82%)	278 (4.11%)
35	69 (1.02%)	64 (0.95%)	133 (1.97%)
39	243 (3.59%)	191 (2.83%)	434 (6.42%)
45	52 (0.77%)	41 (0.61%)	93 (1.38%)
51	210 (3.11%)	162 (2.40%)	372 (5.50%)
52	807 (11.94%)	422 (6.24%)	1229 (18.18%)
53	324 (4.79%)	272 (4.02%)	596 (8.82%)
56	164 (2.43%)	162 (2.40%)	326 (4.82%)
58	478 (7.07%)	291 (4.30%)	769 (11.37%)
59	117 (1.73%)	143 (2.12%)	260 (3.85%)
66	91 (1.35%)	117 (1.73%)	208 (3.08%)
68	76 (0.67%)	59 (0.87%)	135 (2.00%)
82	59 (0.87%)	50 (0.74%)	109 (1.61%)
Low risk			
6	142 (2.10%)	113 (1.67%)	255 (3.77%)
11	84 (1.24%)	84 (1.24%)	168 (2.48%)
40	34 (0.50%)	43 (0.64%)	77 (1.14%)
42	83 (1.23%)	82 (1.21%)	165 (2.44%)
43	161 (2.38%)	140 (2.07%)	301 (4.45%)
44	194 (2.87%)	137 (2.03%)	331 (4.90%)
61	188 (2.78%)	155 (2.29%)	343 (5.07%)
81	220 (3.25%)	172 (2.54%)	392 (5.80%)
83	35 (0.52%)	51 (0.75%)	86 (1.27%)

southeastern China during 2016 to 2018. To our knowledge, few studies have investigated the genotypes (27 subtypes) of HPV infection among women in southeastern China.

Persistent HPV infection is a risk factor for cervical cancer; the most common carcinogenic subtypes are HPV16 and HPV18.[22,23] In China, cervical cancer is the second leading cause of cancer-related deaths among women age 15 to 44 years.[24] We found that over 90% of HPV infections occurred in participants between age 20 and 59 years, which emphasizes the need for protection against HPV infection among women in this age group. In developed countries where cervical cancer screening systems have been established, the prevalence of cervical cancer and related mortality have shown a substantial declining trend.[25,26] Cervical cancer screening using HPV molecular detection is widely recognized for its high sensitivity and specificity.[27,28]

In addition to HPV screening, it has been proven that HPV vaccination can fundamentally block HPV transmission. At the end of 2014, the World Health Organization issued a position paper on HPV vaccines, recommending that girls

Table 3. Positivity of human papillomavirus (HPV) infection among women in southeastern China from 2016 to 2018.

	2016 (N = 13632)		2017 (N = 15286)		2018 (N = 7953)		
HPV type	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	*P*
High risk							
16	424	3.11 (2.82–3.40)	419	2.74 (2.48–3.00)	243	3.06 (2.94–3.18)	0.145
18	136	1.00 (0.83–1.16)	179	1.17 (1.00–1.34)	78	0.98 (0.91–1.05)	0.253
26	4	0.03 (0.00–0.06)	6	0.04 (0.01–0.07)	6	0.08 (0.06–0.09)	0.136
31	53	0.39 (0.28–0.49)	56	0.37 (0.27–0.46)	28	0.35 (0.31–0.39)	0.904
33	101	0.82 (0.68–0.97)	110	0.72 (0.59–0.85)	67	0.84 (0.78–0.91)	0.576
35	64	0.47 (0.35–0.58)	46	0.30 (0.21–0.39)	23	0.29 (0.25–0.33)	<0.05
39	186	1.36 (1.17–1.56)	169	1.11 (0.94–1.27)	79	0.99 (0.92–1.06)	<0.05
45	34	0.25 (0.17–0.33)	43	0.28 (0.20–0.37)	16	0.20 (0.11–0.30)	0.511
51	124	0.98 (0.82–1.14)	180	1.18 (1.01–1.35)	68	0.86 (0.79–0.92)	<0.05
52	431	3.16 (2.87–3.46)	530	3.47 (3.18–3.76)	268	3.37 (3.24–3.50)	0.345
53	224	1.64 (1.43–1.86)	219	1.43 (1.24–1.62)	153	1.92 (1.83–2.02)	<0.05
56	135	0.99 (0.82–1.16)	124	0.81 (0.67–0.95)	67	0.84 (0.78–0.91)	0.242
58	279	2.05 (1.81–2.28)	315	2.06 (1.84–2.29)	175	2.20 (2.10–2.30)	0.719
59	93	0.68 (0.54–0.82)	109	0.71 (0.58–0.85)	58	0.73 (0.67–0.79)	0.913
66	82	0.60 (0.47–0.73)	80	0.52 (0.41–0.64)	46	0.58 (0.53–0.63)	0.663
68	44	0.32 (0.23–0.42)	49	0.32 (0.23–0.41)	42	0.53 (0.48–0.58)	<0.05
82	48	0.35 (0.25–0.45)	42	0.27 (0.19–0.36)	19	0.24 (0.20–0.27)	0.277
HR HPV	2052	15.05 (14.45–15.65)	2204	14.42 (13.86–14.98)	1152	14.49 (14.24–14.73)	0.274
Low risk							
6	99	0.73 (0.58–0.87)	105	0.69 (0.56–0.82)	53	0.67 (0.61–0.72)	0.861
11	66	0.48 (0.37–0.60)	75	0.49 (0.38–0.60)	28	0.35 (0.31–0.39)	0.284
40	25	0.18 (0.11–0.26)	39	0.26 (0.18–0.34)	13	0.16 (0.14–0.19)	0.249
42	57	0.42 (0.31–0.53)	63	0.41 (0.31–0.51)	45	0.57 (0.51–0.62)	0.203
43	102	0.75 (0.60–0.89)	120	0.79 (0.65–0.92)	53	1.28 (1.04–1.52)	0.608
44	135	1.18 (1.00–1.36)	126	0.82 (0.68–0.97)	70	0.88 (0.82–0.95)	0.322
61	112	0.82 (0.67–0.97)	140	0.92 (0.76–1.07)	91	1.46 (1.20–1.71)	0.057
81	146	1.07 (0.90–1.24)	167	1.09 (0.93–1.26)	79	0.99 (0.92–1.06)	0.778
83	30	0.22 (0.14–0.30)	36	0.24 (0.16–0.31)	8	0.10 (0.08–0.12)	0.076
LR HPV	513	3.76 (3.44–4.08)	549	3.59 (3.30–3.89)	291	3.66 (3.53–3.79)	0.739
Any HPV	2565	18.82 (18.16–19.47)	2753	18.01 (17.40–18.62)	1443	18.14 (17.88–18.41)	0.185
Valent							
16/18	547	4.01 (3.68–4.34)	581	3.80 (3.50–4.10)	318	4.00 (3.86–4.13)	0.602
4v HPV	698	5.12 (4.75–5.49)	735	4.81 (4.47–5.15)	395	4.97 (4.82–5.12)	0.475
9v HPV	1472	10.80 (10.28–11.32)	1605	10.50 (10.01–10.99)	845	10.62 (10.41–10.84)	0.713

4v HPV: 4-valent HPV vaccine (HPV6, 11, 16, and 18); 9v HPV: 9-valent HPV vaccine (HPV6, 11, 16, 18, 31, 33, 45, 52, and 58); HR HPV: high-risk HPV (HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, and 82); LR HPV: low-risk HPV (HPV6, 11, 40, 42, 43, 44, 55, 61, 81, and 83); Any HPV: any of the 27 HPV types listed above; CI, confidence interval.

age 9 to 13 years should receive HPV vaccination to prevent cervical cancer.[20] Three HPV vaccines are currently administered to protect against HPV infection, including a bivalent (HPV16/18), tetravalent (HPV6/11/16/18), and nonavalent vaccine (HPV6/11/16/18/31/33/45/52/58).[29–31] Clinical trials have confirmed that the bivalent and tetravalent vaccines can prevent 90% to 98% of cervical

Table 4. Age-specific distribution of human papillomavirus (HPV) among women in southeastern China.

Age (years)	2016 (N = 13632)		2017 (N = 15286)		2018 (N = 7953)		HPV positive (N = 6761)	
	n	%	n	%	n	%	n	% (95% CI)
16–19	153	1.12	81	0.50	29	0.37	51	0.75 (0.55–0.96)
20–29	1484	10.89	1719	10.55	769	9.66	738	10.92 (10.17–11.66)
30–39	3051	22.38	3552	21.80	1768	22.23	1567	23.18 (22.17–24.18)
40–49	5194	38.10	5553	34.07	2749	34.56	2461	36.40 (35.25–37.55)
50–59	2687	19.71	3019	18.53	1810	22.76	1355	20.04 (19.09–21.00)
60–69	809	5.93	1069	6.56	615	7.73	435	6.43 (5.85–7.02)
70–79	223	1.64	239	1.47	162	2.04	126	1.86 (1.54–2.19)
80–89	31	0.23	53	0.32	51	0.64	28	0.41 (0.26–0.57)

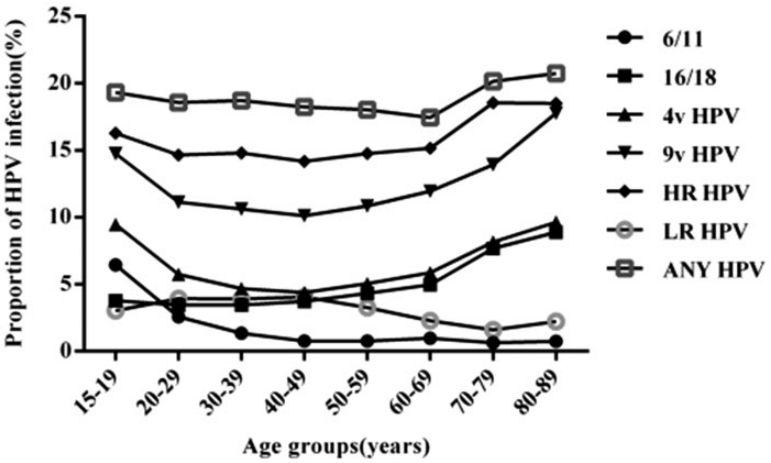

Figure 1. Age-specific prevalence of human papillomavirus (HPV) infection among women in southeastern China, by age group.
4v HPV: 4-valent HPV vaccine (HPV6, 11, 16, and 18); 9v HPV: 9-valent HPV vaccine (HPV6, 11, 16, 18, 31, 33, 45, 52, and 58); HR HPV: high-risk HPV (HPV16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, and 82); LR HPV: low-risk HPV (HPV6, 11, 40, 42, 43, 44, 55, 61, 81, and 83). Any HPV: any of the 27 HPV types listed above.

intraepithelial neoplasias.[32] In the present study, our data showed that the 9-valent vaccine reduced HPV prevalence by 10%, including infection with 13 HR HPV subtypes. These results are consistent with those of previous studies.[33]

In this study, we found that the overall infection rate of HPV was 18.34% among participants in this area of southeastern China who received HPV screening. HPV prevalence varies widely across different regions and populations. Previous studies have indicated that in Guangdong Province, the total HPV positivity has reached 20.16%.[34] The data vary greatly in other areas of China, for example, 12.9% in Yunnan Province, 14.0% in Xinjiang Province, 17.7% in Nanjing city, 22.5% in Jiangsu and Jiangxi provinces, 22.8% in Taizhou city, and 26.2% in Chongqing city.[35–40] The HPV prevalence in Meizhou City has remained stable, as

the present findings were similar to those from our previous study.[33]

It has been suggested that several factors are conducive to HPV infection, including genetic susceptibility, sexual behavior (earlier age of sexual activity, many sexual partners), long-term use of contraceptives, and lifestyle.[41,42] Furthermore, of the 27 HPV genotypes screened in this study, HPV52, 16, 58, and 53 were the four most common subtypes among women in this area, accounting for up to 54.43% of HPV infections. In addition, the prevalence of HPV52 and HPV53 among the women in this study was significantly higher than in our previous study ($P<0.001$, data not shown).[33] This suggests that vaccines against infection with HPV16, 18, 58, and 52 would be valuable for people in southeastern China, and vaccines against HPV53 should be investigated in future.

A previous meta-analysis reported that globally, HPV infection rates are higher among younger and older women. Previous studies have shown that in cities of China such as Kunming and Hong Kong, the HPV prevalence presents a similar pattern.[43,44] In the present study, we observed a similar pattern, with peak prevalence among participants age 15 to 19 and 80 to 89 years. The precise relationship between HPV infection and age is unclear. It is likely that women in these age groups have lower hormone levels and weaker immune function. Additionally, a large number of younger women fail to use protection during sexual activity, which makes them susceptible to HPV infection.[10] It is strongly recommended that young women in southeastern China receive HPV vaccination to prevent cervical cancer. Our data revealed the age-specific prevalence of HPV infection, with most HPV infections occurring among women between age 40 and 49 years. These results might be owing to the largest number of study participants falling into this age group, leading to findings showing that women in this age group were most seriously affected by HPV infection.

The following limitations of our study should be noted: i) data of abnormal cervical histology for enrolled women was lacking; thus, we unable to analyze the relationship between HPV infection and cervical lesions; ii) samples were collected from a single center; the present findings should be validated in multiple centers.

Conclusion

Our study confirmed that the HPV prevalence in southeastern China was 18.34%. The most prevalent HR HPV subtypes among women in this study were HPV52, 16, 58, 53, and 39. Over 90% of HPV infections occurred in women age 20 to 59 years among our participants. The 9-valent HPV vaccine effectively reduced HPV infections by more than 10%, which is twice the rate of other vaccines. Our findings provide useful information for HPV screening and vaccine strategies in southeastern China.

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Authors' contributions

SL conceived and designed the experiments. XG contributed to the data collection and drafting of the manuscript. RW, JL, and ZZ helped to collect clinical data and conducted the clinical procedures and research. SL and XG analyzed the data. SL and XG wrote the paper.

Availability of data and materials

The datasets generated during the current study are not yet publicly available owing to privacy concerns and ongoing additional research.

Data can be made available for peer review on reasonable request by contacting the corresponding author.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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