ONCOGENIC HIGH-RISK HUMAN PAPILLOMAVIRUS DETECTION AND EVALUATION OF RISK FACTORS IN THE CERVICAL INTRAEPITHELIAL NEOPLASIA I

Detecção do papilomavírus humano de alto risco oncogênico e avaliação dos seus fatores de risco nas neoplasias intraepiteliais cervicais grau I

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ABSTRACT

Introduction: The cervical intraepithelial neoplasia grade I (CIN I) shows an important percentual of spontaneous regression (80%) and there is no universal consensus if these lesions should be treated or only monitored. Lesions at risk for progression are precisely those associated with high-risk HPV. Knowing which CIN I are related to these viruses may be one of the determining factors for the decision to treat or not. **Objective:** To determine the prevalence of high-risk HPV in women with CIN I and to evaluate if there is an association between the presence of the virus and some risk factors. **Methods**: Cross-sectional descriptive study. We evaluated 55 women with histological diagnosis of CIN I. All of them were previously submitted to HPV-DNA testing. **Results:** 25 out of 55 (45.5%) women analyzed were positive for high-risk HPV. The virus infection was related with higher level of education, smoking and history of sexually transmitted diseases. Other risk factors like age, number of sexual partners, age at first sexual intercourse, use of hormonal contraceptives, and immunosuppression condition did not show a relation to the high-risk HPV infection. **Conclusions:** The prevalence of high-risk HPV in women with histological diagnosis of CIN I was 45.5%. HPV-DNA detection was associated with smoking, history of sexually transmitted diseases, and higher level of education. **Keywords:** Papillomaviridae; DNA probes, HPV; cervical intraepithelial neoplasia.

RESUMO

Introdução: As neoplasias intraepiteliais cervicais grau I (NIC I) apresentam um percentual importante de regressão espontânea (cerca de 80%) e não há um consenso universal se essas lesões devam ser tratadas ou apenas acompanhadas. As lesões que apresentam risco de progressão são justamente aquelas associadas aos HPV de alto risco oncogênico. O conhecimento de quais lesões estão relacionadas a esses vírus pode ser um dos fatores determinantes para a decisão de se tratar ou não tais lesões. Objetivo: Determinar a prevalência do papilomavírus humano (HPV) de alto risco oncogênico em mulheres com resultado histológico de NIC I e verificar a existência da associação entre a presença do vírus e alguns fatores de risco. Métodos: Trata-se de um estudo transversal, de caráter descritivo, onde foram avaliadas 55 mulheres com diagnóstico histopatológico de NIC I. Todas foram submetidas ao teste de DNA-HPV previamente. Resultados: Das 55 mulheres analisadas, 25 (45,5%) apresentaram HPV de alto risco positivo. A infecção pelo vírus foi associada às mulheres com mais anos de estudo, tabagismo e à história de alguna doença sexualmente transmissível. Outros fatores de risco, como a idade, o número de parceiros sexuais, a faixa etária em que ocorreu a coitarca, o uso de anticoncepcionais hormonais e o estado de imunossupressão, não mostraram relação com a infecção pelo HPV. Conclusão: A prevalência do HPV de alto risco oncogênico nas mulheres com diagnóstico histológico de NIC I foi de 45,5%. A detecção do vírus foi associada ao tabagismo, à história de doença sexualmente transmissível e a um grau maior de escolaridade. Palavras-chave: Papillomaviridae; sondas de DNA de HPV; neoplasia intraepitelial cervical.

INTRODUCTION

Cervical cancer is the second most common malignancy in the female population wordlwide (about 471,000 new cases per year). About 80% of them occur in developing countries, where in some regions, it becomes the most frequent one. In Brazil, the cervical

cancer is the third most common malignancy among women, being preceded only by breast cancer and colorectal cancer, and the fourth cause of death by cancer among women. The estimate of cervical cancer for 2016 is 16,340 new cases and a mean of 5,000 deaths/year⁽¹⁾.

The invasive cervical cancer is preceded by premalignant or precursory lesions, represented by cellular atypia of the cervical epithelium⁽²⁾. As for the etiology, it is currently well established that the human papillomavirus (HPV) is the cause of cervical cancer and their precursory lesions, the high-grade cervical intraepithelial neoplasias (CIN II and III)⁽³⁻⁵⁾. There are over 45 different genotypes of these viruses infecting the anogenital area, both among men and women, which associate to benign lesions and invasive cancers, though most cases are caused by HPV 16 and 18^(6,7).

The HPV infection is common, especially among young women, and their prevalence is related, mainly, to sexual behavior^(8,9). The infection alone is not enough to cause cervical cancer. Other factors associated to the host (genetic and immunologic) or environmental (smoking, high-dosage oral contraceptive, diet low in

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vitamins and oligoelements, sexual activity, pregnancies, among others) also contribute to the progression of HPV lesion inducing carcinoma⁽¹⁰⁾. A compulsory phase in the development of this cancers is the integration of the viral DNA to the DNA of host cells, leading to an uncontrolled cell division and the onset of tumor⁽¹¹⁾. This integration happens almost exclusively with the oncogenic high-risk (HR) virus^(2,12-15). It is the persistence of the infection by these specific HPV types, especially the 16 and the 18, the factor responsible for the development, maintenance and progression of a CIN for the invasive cancer^(10,12,13,16).

As the cervical carcinoma is preceded by preinvasive lesions, the best prevention is the diagnosis and treatment of these lesions. There is no doubt that all the cases of high-grade lesions (mainly CIN III) should be treated, since they have great chances of evolving into the invasive form⁽¹³⁾. However, the low-grade lesion (CIN I) presented an important percentage of spontaneous regression (about 80%)^(17,18) and there is no universal consensus if these lesions should be treated or just monitored⁽¹³⁾. The lesions that represent the risk of progressions are precisely those associated to oncogenic HR-HPV^(13,19). The knowledge of which lesions are related to this virus may be one of the determining factors for the decision of treating or not such lesions.

OBJECTIVE

In order to evaluate the prevalence of the oncogenic HR-HPV in the CIN I and to relate this finding to other possible cofactors associated with the progression of these lesions. It is expected that this study may contribute to establish strategies for a more suited therapeutic planning, avoiding, thus, the treatment of unnecessary cases (overtreatment) or the absence of treatment of the cases of risk for progression into cancer (undertreatment).

METHODS

It is a prospective, observational, descriptive, and cross-sectional study carried out at the Genital Oncology Clinic of the University Hospital of the Universidade Federal de Santa Catarina (HU/UFSC), evaluating 55 women who had histopathological results for CIN I and who performed the DNA test for oncogenic HR-HPV by the hybrid capture method II (Digene & Co.).

The age of those women were stratified into \leq 30 years or >30 years of age, because the presence of oncogenic HR-HPV persisting among women aged over 30 years represents a risk factor for the development of cervical carcinoma, according to various studies ^(9,16,18).

The educational level was stratified into elementary school and high school/college degree in a same group, since there was only one case with college degree and, for statistical reasons, these two variables were combined. There was no discrimination in relation to the level being complete or incomplete.

The number of sexual partners women had in their lives was subdivided into <3 or \geq 3 partners. Several studies have showed that the higher the number of sexual partners, the higher is the prevalence of oncogenic HR-HPV^(16,18).

Other variables considered to be risk factors for infection by HPV were analyzed such as parity, age at the first sexual intercourse, and current and previous history of sexually transmitted diseases (STDs)^(9,18,20).

When we analyzed the variable smoking, women who smoke or who have smoked in the past were considered smokers. Similarly, women who use or who have used hormonal contraception were considered users of this method.

Regarding their immunosuppression status, only the presence or absence of HIV infection was considered, since there were no other cases of immunosuppression among these women.

The results of the oncotic colpocytology were based on the Cytological Classification of Bethesda 2001⁽²¹⁾.

The result of the colposcopic evaluation was divided into atypical transformation zone (ATZ) with smaller and greater cervical alterations, depending on the images observed⁽²²⁾.

The anatomopathologic results of the biopsy of cervix were classified into CIN I and alterations consistent with HPV.

The data necessary to conduct this study were obtained by means of the information registered in the medical charts of patients who underwent some kind of follow-up or treatment of cervical intraepithelial lesions in the Genital Oncology Clinic of the HU/UFSC. The data collection was based on a semistructured research protocol.

The colposcopy and the cervical biopsy were carried out in the Ginecology Service and the histopathological tests at the Pathological Anatomy Service of the HU/UFSC. The test to detect oncogenic HR-HPV DNA was performed at the *Laboratório DNAnálise*, in Florianópolis, Santa Catarina. The types of HPV tested were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 68, corresponding to 99% of the HR-HPV. The test was considered positive when the rate of relative light units (RLU) of the test on two positive controls equals 1 pg/ml of DNA-HPV or more. According to recent studies, this cut-off value is what represents greater sensitivity and specificity to the test⁽²³⁻²⁷⁾.

The analysis of the data was carried out by the Epi Info 6.0 software. In order to verify the possible associations between the presence of HR-HPV and the variables, the chi-square (χ^2) test was used. The result was considered significant if the probability of error was <5% (p<0.05). When the p-value did not show significance, it was presented as p=NS.

This study was approved by the Human Being Research Ethics Committee of the UFSC.

RESULTS

The HR-HPV was detected in 25 (45.5%) women with CIN I.

The age of the women varied from 14 to 45 years of age. By correlating age and the presence of HR-DNA-HPV, we observed that there was no significant difference between them. However, on analyzing women with positive HR-HPV, a higher prevalence (60%) of the virus among the youngest ones (\leq 30 years) was observed.

As for the level of education, there was a prevalence twice as high (68.4%) among women with more years of study (high school to college degree) than among those with lower schooling (33.3%), achieving statistical significance, with p=0.012 (**Table 1**).

The sexual behavior was assessed as the beginning of sexual activity and the number of partners. Regarding the first sexual intercourse, the prevalence of the virus was 1.7 times higher among women who began their sexual activities after 18 years of age; however, the statistical value was not significant. With regard to the number of sexual partners, despite not being statistically significant, a greater prevalence of DNA-HPV was observed among the women with three or more partners (58.8%) than among women with less than three (39.5%).

Contrary to what was expected, we found greater HR-HPV detection among women who had two pregnancies or less (50%). This infection was present in 36.8% of the women with more than two pregnancies. However, this difference was not significant.

In relation to the habit of smoking, there was a statistically significant difference between smoking women, who had double the prevalence of HR-HPV (63.6%) in relation to nonsmokers (33.3%) (p=0.027) (**Table 2**).

There was no difference regarding the use of oral contraception (OC) and the presence of HR-HPV. More than half of the positive cases (51.4%) were among women using OC.

Of the 55 women, only 8 had the history of STDs (syphilis, anogenital HPV, Chlamydia and Ureaplasma). Of those, seven of them had oncogenic HR-HPV (87.5%), observing a significant difference with p=0.0097 (**Table 3**).

When evaluating the presence of immunosuppression, there was no statistical difference, despite the two cases of HIV infection being positive for HR-HPV (100%). The negative HIV women were positive for HR-HPV in 43.4%.

In relation to the previous colpocytologic test of women diagnosed with CIN I, only 16 (29.1%) had agreeable diagnosis. We also observed the subdiagnosis in 58.2% of them and overdiagnosis (high grade lesion) in 12.7%. As the distribution of the cases was small for each result, these data were not subjected to statistical calculation (**Table 4**).

We observed great correlation between the colposcopic result of ATZ with minor changes and the histologic result of CIN I (87.3%). There was no statistical difference between women with minor alterations (43.8%) or major alterations in the colposcopy (57.1%) (**Table 5**).

 Table 1 – Prevalence of the oncogenic high-risk human papillomavirus according to the education level.

	Oncogenic high-risk HPV		Total
Education	Positive	Negative	Total
	n (%)	n (%)	n (%)
Elementary	12 (33.3)	24 (66.7)	36 (65.5)
High School/ College	13 (68.4)	6 (31.6)	19 (34.5)
Total	25 (45.5)	30 (54.5)	55 (100.0)

Source: Serviço de Arquivo Médico HU/UFSC. HPV: human papillomavirus; χ^2 =6.18; p<0.05.

 Table 2 – Prevalence of the oncogenic high-risk human papillomavirus according to the habit of smoking.

	Oncogenic high-risk HPV		Total
Smoking	Positive	Negative	Total
	n (%)	n (%)	n (%)
Yes	14 (63.6)	8 (36.4)	22 (40.0)
No	11 (33.3)	22 (66.7)	33 (60.0)
Total	25 (45.5)	30 (54.5)	55 (100.0)

Source: Serviço de Arquivo Médico HU/UFSC.

HPV: human papillomavirus; χ^2 =4.89; p<0.05.

DISCUSSION

The relation between the HPV and cervical cancer is already well established^(3,4,6,8). However, there is a considerable variation in the literature about the frequency of detection for DNA-HPV among women with precancerous lesions (CIN). This may be explained by the differences of the evaluated populations and by the kinds of studies, which have varying designs, in addition to the difference on sensitivity and specificity of the tests used⁽⁹⁾. Thus, a great variability in the prevalence of HR-HPV in CIN I is observed, varying from 41⁽²⁵⁾ to 86%^(2,9,12,28-30). Borges *et al.*⁽²⁹⁾ observed the oncogenic virus in all ten CIN I cases studied. In our study, we found a prevalence of 45.5%, similar to what was found by Santos *et al.*⁽²⁵⁾ (41%). Another study carried out in our city showed a very similar prevalence of 47%⁽³⁰⁾. Quite different from most studies, Cavalcanti *et al.*⁽¹⁵⁾ found a lower rate, with 16.9% of prevalence for this type of virus.

Table 3 – Prevalence of the oncogenic high-risk humanpapillomavirus according to previous or current history of sexuallytransmitted diseases.

	Oncogenic h	Oncogenic high-risk HPV	
STDs	Positive	Negative	Total
	n (%)	n (%)	n (%)
No	18 (38.3)	29 (61.7)	47 (85.5)
Yes	7 (87.5)	1 (12.5)	8 (14.5)
Total	25 (45.5)	30 (54.5)	55 (100.0)

Source: Serviço de Arquivo Médico HU/UFSC.

STDs: sexually transmitted diseases; χ^2 =6.68; p<0.05.

Table 4 – Prevalence of the oncogenic high-risk human papillomavirus according to the result of the previous pap smear.

	Oncogenic high-risk HPV		Total
PAP	Positive	Negative	TOtal
	n (%)	n (%)	n (%)
Negative	3 (17.6)	14 (82.4)	17 (30.9)
Inflammatory	7 (53.8)	6 (46.2)	13 (23.6)
ASCUS	2 (100.0)	_	2 (3.7)
LSIL	9 (56.3)	7 (43.7)	16 (29.1)
HSIL	4 (57.1)	3 (42.9)	7 (12.7)
Total	25 (45.5)	30 (54.5)	55 (100.0)

Source: Serviço de Arquivo Médico HU/UFSC.

PAP: pap smear; ASCUS: atypical squamous cells of undetermined significance; LSIL: Low grade squamous intraepithelial lesion; HSIL: High grade squamous intraepithelial lesion

Table 5 – Prevalence of the oncogenic high-risk human papillomavirus according to the colposcopic findings.

	Oncogenic high-risk HPV		Total
Colposcopy	Positive	Negative	TOtal
	n (%)	n (%)	n (%)
Minor alterations	21 (43.8)	27 (56.2)	48 (87.3)
Major alterations	4 (57.1)	3 (42.9)	7 (12.7)
Total	25 (45.5)	30 (54.5)	55 (100.0)

Source: Serviço de Arquivo Médico HU/UFSC.

 χ^2 =0.44; nonsignificant p-value.

Several studies showed that the CIN I is more prevalent among young women^(3,9,12). The same occurs with the infection by HR-HPV. Many studies found this greater prevalence among women with less than 30 years of age^(3,13-15,20,31). However, with aging, despite there is a decline of this prevalence, infection by HPV becomes more persistent^(9,13,14,32,33). In our study, we observed 50% positive results for the HR-HPV for younger women (\leq 30 years) and 40% for those aged over 30 years. Cohort studies indicate that most infections by oncogenic HPV are transitory and that its lower prevalence in older age may be due to an acquired immunity to the virus through previous exposures and their elimination⁽³⁴⁾. Dalstain et al.⁽¹³⁾ suggest that this greater prevalence of HR-HPV among young women is due mainly to new acquisitions of the virus through sexual relations or reactivations of preexisting infections. Also, since some women with negative HPV have altered cytology, they defend the hypothesis that floating infections, false-negatives or low concentrations of the virus, which were not detected is supported. Woodman et al.⁽²⁰⁾ also confirm these hypothesis and add that it is not possible to distinguish these alternatives.

Our study was a cross-sectional observation, in which a single sample was used to characterize the women with HR-HPV; this can mean only transitory infections or reactivation of latent infections. Also, there might have been false-negatives due to an inappropriate sample or due to low levels of the virus, which were undetectable by hybrid capture.

Many sociodemographic and behavioral factors are classically described as risk factors for cervical cancer. Most authors show significance when comparing data related to education, demonstrating that the risk of cervical lesions is increased among women with lower schooling^(12,35,36). Leal *et al.*⁽³⁵⁾ suggest that this relation may be explained by the lack of knowledge about the Pap smear and its benefits, in addition to other risk factors associated to low socioeconomic levels. However, Adam *et al.*⁽⁹⁾ did not find an association between the level of education and HPV infection. However, we observed that women with higher schooling had greater prevalence of HR-HPV, which was statistically significant (68.4 *versus* 33.3%). However, this finding may not be considered isolated, because there might be an association with other risk factors, which were not surveyed.

According to Hernández-Hernández *et al.*⁽¹²⁾, the early onset of sexual activity is associated to infections by HPV and precursor lesions of cervical cancer. Brito *et al.*⁽³⁷⁾ add that the early onset of sexual activity may increase the sensitivity of the cervix to the effects of a sexually transmitted agent. In our cases, there was no statistical difference when comparing the first sexual intercourse with higher or lower age than 18 years.

The relation between the number of sexual partners and the risk of infection by HPV for the development of precursor lesions of cervical cancer is considered an important risk factor by many authors^(12,34,35,37,38). Ho *et al.*⁽³⁴⁾ demonstrated that women who had four or more partners, in a period of 6 months, presented a risk almost four times higher of acquiring HR-HPV when compared to women with three partners or less. Leal *et al.*⁽³⁵⁾ observed greater alterations of the cervical epithelium among women with eight or more sexual partners, with a prevalence of 1.6 times higher when compared to women with only one partner. Our study showed a higher rate

of HR-HPV among women who had three or more partners in life; however, this relation was not statistically significant.

Great part of the literature also shows a strong association between the multiple pregnancies and the risk of infections by HR-HPV, as well as risk of invasive cervical cancer^(9,10,12,39). Adam *et al.*⁽⁹⁾ demonstrated that three or more pregnancies were considered an independent risk factor for HPV infection. Hernández-Hernández *et al.*⁽¹²⁾ also found similar results, demonstrating that the number of pregnancies (three or more previous pregnancies) was the most important cofactor for infection by HPV and the development of a CIN. However, Beby-Defaux *et al.*⁽¹⁴⁾ found a significant decrease in the prevalence of HR-HPV among women with more pregnancies. Although not statistically significant, these data were also observed in our sample, in which women with two pregnancies or less had a higher rate of viral infection (50 *versus* 36.8%), perhaps due to age.

As expected, we observed a significantly higher prevalence of HR-HPV (almost double) between female smokers and former smokers. Smoking is one of the most important risk factors for cervical cancer^(5,9,14,35,40). Moore *et al.*⁽⁴⁰⁾ suggest that the components of cigarettes, when secreted through the cervical mucus, cause a local immunosuppressive effect and/or a carcinogenic effect directly on the uterine cervix. Beby-Defaux *et al.*⁽¹⁴⁾ showed an important association between smoking and the HPV infection, once that female smokers had a prevalence of HPV four times as high as nonsmokers. However, some authors do not demonstrate relevance of smoking as a risk factor for the disease^(12,15). In contrast, Ho *et al.*⁽³⁴⁾ considered it as a protection factor against persistent infections.

The relation between the use of OC and cervical cancer is not a consensus. Most authors consider that the hormonal factor plays a role of cofactor for both the infection by HPV and the progressions of lesions related to the virus^(3,14). More recent researches demonstrate that the risk for these lesions increase significantly among users of OC for more than 5 years^(39,41). However, some authors described that there was no correlation between the use of OC with infection by HPV and their manifestations^(12,15). In the present study, the prevalence of HR-HPV also showed no association with the use of OC, despite a higher rate of the virus (51.4%) being present among its users. Although the HPV has estrogen receptors, it is likely that the relation of OC with this infection and cervical lesions is associated with hormonal concentration.

SDTs have been described as a great risk factor for cervical lesions caused by HPV⁽³⁵⁾. Cavalcanti *et al.*⁽¹⁵⁾ when prospectively studying Brazilian women, reported an important contribution of STDs in the progressions of these lesions, suggesting they could act out as cofactors in the activation of the mechanisms of cellular transformation or in the decreased local immunity of the genital tract. Also, when analyzing the different diseases, they found that *Chlamydia trachomatis* and *Neisseria gonorrhoeae* showed greater association. In our study, a greater prevalence of the HR-HPV was observed among women with a history of STDs, with an important statistical value (p=0.0097). Beby-Defaux *et al.*⁽¹⁴⁾, however, did not find a significant relation between HR-HPV and STDs.

Women with immunodeficiency, such as the HIV infection, have increased rates of HPV infection and are more likely to develop high-grade cervical lesions, once that there is a greater tendency to persistently keep the DNA of the HPV^(15,42-44). Branca *et al.*⁽⁴²⁾ suggest that the increased risk for high-grade lesions among women with HIV is due to the different risk factors that these women are exposed to, the direct effects of HIV or to the molecular interactions between the HIV and the HPV. In our casuistic, we found just two patients infected by HIV, considering both of them had infections by oncogenic HR-HPV.

The favorable evolution of the low-grade lesions depends on proper handling. Thus, it is important that the investigative methods are reliable, in order to diagnose them at an early stage. However, the citopathologic test is not a perfect screening method. Agorastos et al.⁽⁴⁵⁾ mention some of the problems involved, such as limitations on the population coverage, technical limitations in relation to the sample, and laboratory error in the test and in the interpretation. They also add that many false-positive cytologic tests lead to frequent and unnecessary invasive procedures. On the other hand, the false-negative could cause serious problems to women. In our study, we observed a high rate of false-negatives (CIN I with cytology without atypia) comprising 54.5% of the case. In the colposcopy, however, there were no false-negatives, once that most findings corresponded to the ATZ of minor lesions. This way, it is important to emphasize that the cytologic screening is only one part of the approach to cervical cancer, considering there should be conducted, at least, one good speculum examination associated to the use of acetic acid and Lugol solution, or ideally, a colposcopy.

The ideal handling of the CIN I lesions is still not a consensus, once that great part of them regresses without treatment. Another part, however, may persist or even progress^(17,18,46,47). Most of these studies show that 80% of these lesions will spontaneously regress within 1 year and just 20% of them will persist. Therefore, it is important to

identify which are the persistent lesions, once that they are the higher-risk ones for progression to a high-grade lesion^(13,16). Thus, the use of techniques for the detection of DNA-HPV has been proposed by various authors^(31,48,49), once that this test has showed increased sensitivity when detecting high-grade lesions with high negative predictive value^(2,23,24). So, it is argued that those exam would have an important role in the populations with low prevalence of HPV and low risk of cervical cancer, and it may be associated to the cytopathological exam, or even being performed alone^(26,45).

Sherman *et al.*⁽⁵⁰⁾ demonstrated that when the result of the combined test (cytology and DNA-HPV) is negative, the interval of the cytopathologic tests among these women could be longer. Whereas, if the combined test is positive, this would identify a small group that would need more appropriate further examinations, such as the colposcopy. In face of this evidence, it would be useful to use the DNA-HPV test in screening. With a longer interval between the HPV tests (5 years, for example), we would have a reduction in costs. The use of HPV test could result in improvement of the detection of cervical lesions, with consequent reduction of the incidence of mortality by cervical cancer. **Figure 1** presents a proposed screening of cervical cancer using HPV test, which could be applied in Brazil and could even use a self-collection method.

CONCLUSION

The prevalence of oncogenic HR-HPV among women with histologically confirmed CIN I was of 45.5%, those being the cases with risk for progression and which should be conducted more cautiously. The detection of the virus was associated to smoking, the history of STDs and a higher schooling level.



Figure 1 – Strategy of prevention of cervical cancer in Brazil, based on primary screening with DNA test for HR-HPV and secondary screening by means of cytology.

Conflict of interests

The authors reported no conflict of interests.

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