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Morphological difference in adult thyroid papillary carcinoma between Japan and Ukraine

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Abstract. Geographic differences have been reported to affect the morphological and molecular features of papillary thyroid carcinomas (PTCs). The area around Chernobyl is well-known to be iodine-deficient in contrast to Japan, an iodine-rich country. We reviewed histological differences in adult PTC between Ukraine and Japan. In total, 112 PTCs from age- and sex-matched adults (Ukraine 56, Japan 56) were evaluated histologically for several factors including tumor size, capsulation, tumor components (papillary, follicular, solid, trabecular), lymph node metastasis, extrathyroid invasion, lymphocytic infiltration, oxyphilic metaplasia, and MIB-1 index. We demonstrated that tumors were smaller (1.56 *vs*. 2.13 cm, $p<0.05$) and more solid and that lymph node metastasis was less frequent (14.3% *vs*. 48.2%, $p<0.001$) in Ukrainian cases. PTC subtype distribution was significantly different between the two groups. Solid variant (8.9% *vs*. 1.8%) and mixed subtypes with solid components were more frequent in Ukrainian patients. In contrast, classical papillary carcinomas were more frequent in Japanese cases (10.7% *vs*. 50.0%, $p<0.001$). Marked oxyphilic metaplasia was more common in Ukrainian cases (33.9 % *vs*. 8.9 %, $p<0.001$). MIB-1 index was significantly higher in Ukrainian cases (2.9% *vs*. 1.8%, $p<0.001$). However, the frequencies of tumor capsule formation and background lymphoid follicle formation around the tumor were similar between groups. Morphological differences in adult PTCs were similar to those in pediatric PTCs as reported previously, suggesting that morphogenesis of PTC is influenced by environmental factors, especially dietary iodine, as well as genetic factors.

Key words: Thyroid cancer, Chernobyl, Japan, Iodine, Adult

GEOGRAPHICAL differences on morphological and molecular features of papillary thyroid carcinomas (PTCs) have been reported [1-5]. Pediatric papillary carcinomas around Chernobyl showed more solid morphology than those in Japan [1, 2]. The prevalence of ret/PTC rearrangement, one of the responsible gene abnormalities, varies among different countries. The reported overall prevalence of ret/PTC rearrangements in PTC varies from 3% to as high as 85%, depending on detection methods and the geographical location of patients [4, 5]. These diversities in morphology and genetic alteration may be related to the radiation sensitivity of thyroid follicle cells. Iodine environment could be one of the possible factors that contribute to these differences [6]. The area around Chernobyl is well-known as an iodine-deficient area in stark contrast to Japan, an iodine-rich country [6-11]. Urinary content of Ukrainians is about one-tenth (10%) of that of Japanese.

Nuclear power station accidents occurred in Chernobyl and Fukushima. There is a great concern on the influence of radiation exposure to the residents around the accident in Fukushima. It is important to understand the basic features of unexposed thyroid cancer as a consideration for radiation-induced carcinogenesis. However, there has not been a report on the morphological differences of adult PTCs between

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Japanese and residents around Chernobyl. The purpose of this study is to clarify the histological differences of adult PTCs in Ukraine and Japan.

Material and Methods

In total, 112 adult PTCs (Ukraine 56, Japan 56), age- and sex-matched, were evaluated histologically. Two groups were selected from Japanese and Ukrainian adult cases of PTC. Fifty-six Japanese cases, aged 35 to 60 years old, were diagnosed and treated at National Nagasaki Medical Center between 2001 and 2011. Fifty-six Ukrainian cases, age- and sex-matched to Japanese cases, were diagnosed and treated at Kiev Endocrine Institute between 2001 and 2011. All the cases had no history of radiation treatment or no residential history of radioactive contaminated area. Appropriate informed consent was obtained for all tissues studied, and the study was approved by the relevant institutional review boards (No.26047).

Histopathological examination included establishment and reconfirmation of the diagnosis, classification according to the World Health Organization (WHO) guidelines [12], and staging according to the TNM system of the 7th UICC [13]. For exclusion of poorly differentiated carcinoma (PDC), the criteria of PDC proposed in Turin and the WHO classification were used [12, 14]. To provide a quantitative assessment of the morphological features, tumor sections from each case were studied by two pathologists (M.I., T.B.) each of whom scored a series of features using an agreed protocol. Each of the architectural patterns present in the tumor (papillary, follicular, solid/trabecular) was scored as occupancy rate (%) for each tumor. Then all the cases were classified into subtypes: classical (papillary dominant, CL) type, follicular variant (FV), solid variant (SV), and mixed variant (Fig. 1) [15, 16]. Mixed variant consisted of solid follicular variant (SF), solid papillary variant (SP), papillary follicular variant (PF), and papillary follicular solid variant (PFS). The diagnostic criteria for the solid variant was tumors having solid/trabecular growth pattern in ≥80% of the primary tumor, nuclear features of papillary carcinoma, and absence of tumor necrosis. The diagnostic criteria for the classical type was tumors having papillary growth pattern in ≥80% of the primary tumor. The diagnostic criteria for the follicular variant was according to the WHO classification. The diagnostic criteria for the mixed variant was defined as tumors having more than two growth patterns with >20% of each pattern. Peritumour fibrosis was scored on a three-point scale (none, partial, complete). The degree of lymphocytic infiltration in the background was scored on a three-point scale (none, focal, severe),

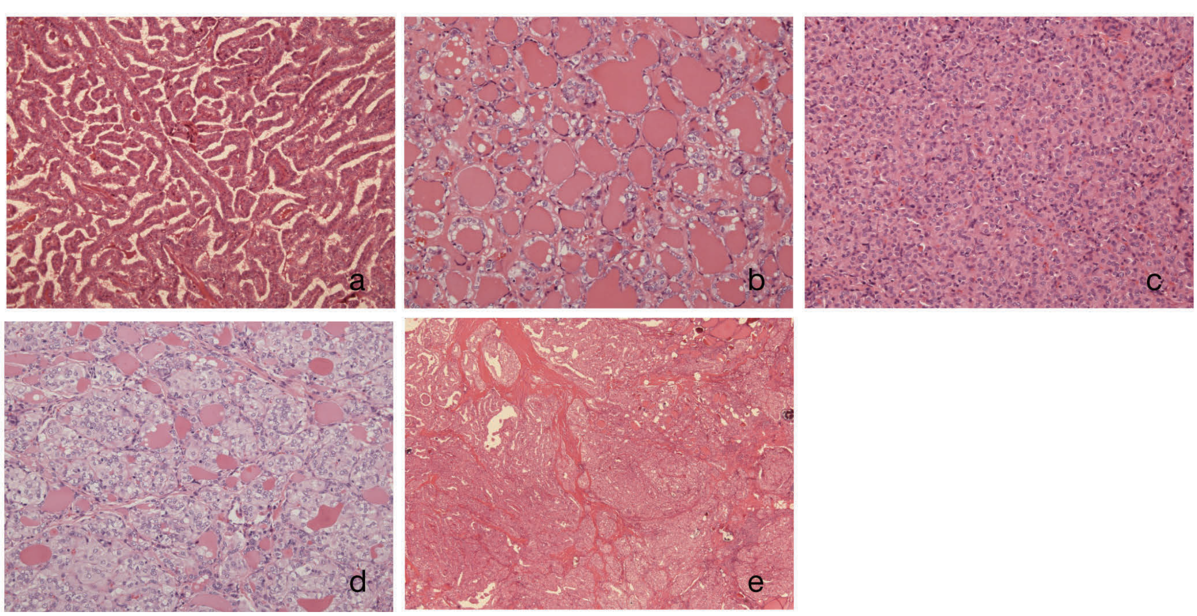

Fig. 1 Morphology of subtypes of papillary carcinoma
Subtypes were classified as followed; classical type (a), follicular variant (b), solid variant (c), and mixed variant. In mixed variant type, solid-follicular type (d), and solid-papillary type (e) are shown (H&E).

and oxyphilic change of tumor cytoplasm was scored on a four-point scale (none, focal, severe, complete). The presence or absence of extrathyroid invasion was recorded. The proliferative activity of tumors was investigated by immunohistochemistry using Ki-67 antibody (clone MIB-1; DAKO, Glostrup, Denmark). MIB-1 index was evaluated with the image-analyzing software (CountσCell, Ki-67 antigen Semi Auto Counter, Seiko Tec LTD, Fukuoka, Japan) by counting all positive PTC cells in the areas where the number of immunoreactive nuclei was the highest (hotspot) and calculating the proportion of positive nuclei. For each case, the scoring was based on 1,500-2,000 cell counts.

Statistical analysis

This was performed using the SAS (Statistical Analysis Software, release 9.2) package. The Student *t* test with double-sided confidence limits, chi-square method, Fisher's exact probability test, and Cochran-Armitage test were used as appropriate. Two values were considered significantly different when the probability of *p* was equal to or less than 0.05. The statistical analyses were carried out by H.K.

Results

Summary of cases and variable clinicopathological factors are shown in Table 1. The mean age was 49.0 years old for Japanese and 47.8 years old for Ukrainian. Both groups included 48 females and 8 males. The overall female-to-male ratio among both groups was 6:1. The mean tumor size of Ukrainian cases was significantly smaller than that of the Japanese patients (1.60 cm *vs.* 2.13 cm, p=0.03, respectively). Extrathyroid invasion was more frequently observed in Japanese cases (37.5% *vs.* 14.3%, p<0.01, Fisher's exact test). Lymph node metastasis was more frequent in Japanese cases (48.2% *vs.* 14.3%, p=0.0001, Fisher's exact test). The pT staging was significantly greater in Japanese cases (p=0.0044, Cochran-Armitage test). Distribution of subtypes was significantly different between the two groups (p<0.0001, chi-square method) as shown in Fig. 2. Classical papillary carcinomas were found more frequently in the Japanese cases than Ukrainian ones (50.0 *vs.* 10.7%, respectively). The incidence of solid variant was significantly higher in Ukraine than in Japan (8.9% *vs.* 1.8%, respectively). Solid-follicular and solid-papillary types in mixed variants were higher in the Ukrainian cases as well. Cases with the solid/trabecular growth pattern occupying more than 10% of the whole tumor were higher in Ukraine than in Japan (67.9 *vs.* 26.8%, p<0.001, respectively) as well. Distribution of tumor components (papillary, follicular, solid/trabecular) was significantly different between the two groups. Japanese cases had more papillary structures (48.0% *vs.* 25.8%, p<0.005). In contrast, the Ukrainian cases had more solid/trabecular component (32.4% *vs.* 8.1%, p <0.0001). There was no difference in follicular structure. Although the Japanese cases tended to form a tumor capsule (complete or incomplete) less frequently (25% *vs.* 39.2.%, *NS*), however, this difference was not statistically significant. There

Table 1 Summary of cases and variable clinicopathological factors

	Japanese	Ukrainian	*p* value
Number	56	56	
Age	49.0 ± 7.6	47.8 ± 6.7	0.3576
Sex ratio (Male:Female)	1:6	1:6	
Tumor size (cm)	2.13 ± 1.57	1.60 ± 1.30	0.0326
Extrathyroid invasion (%)	37.5	14.3	0.0089
Lymph node metastasis (%)	48.2	14.3	<0.0001
Tumor stage (%)			<0.005
pT1a	17.9	35.7	
pT1b	26.8	30.1	
pT2	10.7	14.3	
pT3	42.9	19.6	
pT4	1.8	0	
Subtypes (%)			<0.0001
Classical	50.0	10.7	
Follicular variant	28.6	17.9	
Solid variant	1.8	8.9	
Mixed variant	28.6	62.5	
Solid-follicular	5.4	30.4	
Solid-papillary	1.8	12.5	
Papillary-follicular	21.4	14.3	
Papillary-follicular-solid	0	5.4	
Component (%)			
Papillary	48.0 ± 39.1	25.8 ± 34.2	<0.005
Follicular	43.8 ± 37.4	31.8 ± 32.2	0.5124
Solid/trabecular	8.1 ± 15.7	32.4± 32.6	<0.0001
Capsule (%)	25.0	39.2	0.596
Background lymphocytic infiltration (%)			0.217
None	41.1	41.1	
Focal	46.4	28.6	
Severe	12.5	30.4	
Oxyphilic change (%)			<0.001
None	51.8	41.1	
Focal	39.3	42.9	
Severe	5.3	10.7	
Complete	3.6	23.2	
MIB-1 index (%)	1.8 ± 1.7	2.9 ± 2.7	<0.0001

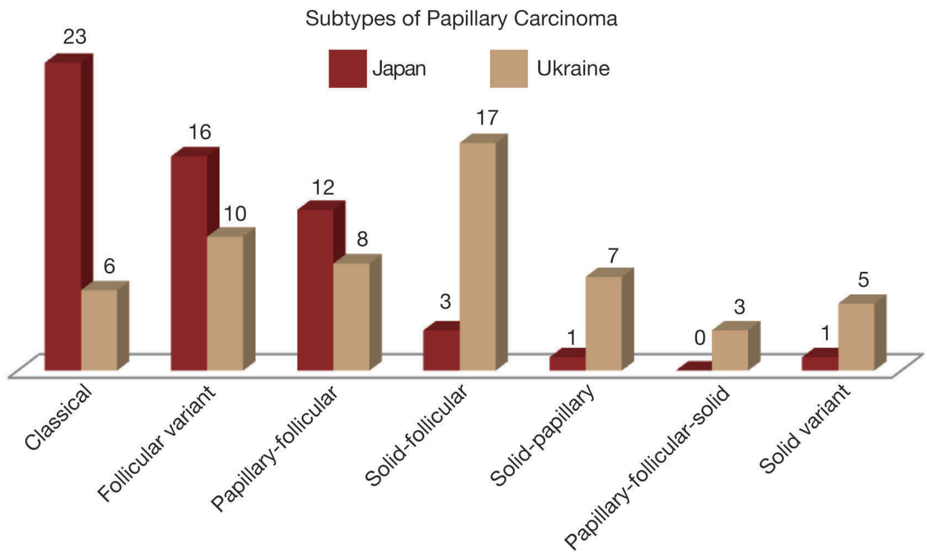

Fig. 2 Distribution of subtypes
Classical papillary carcinomas were found more frequently in the cases in Japan. The incidence of a solid variant was higher in Ukraine. Cases with the solid growth pattern in mixed variant were significantly higher in Ukraine than in Japan. Values indicate the number of cases.

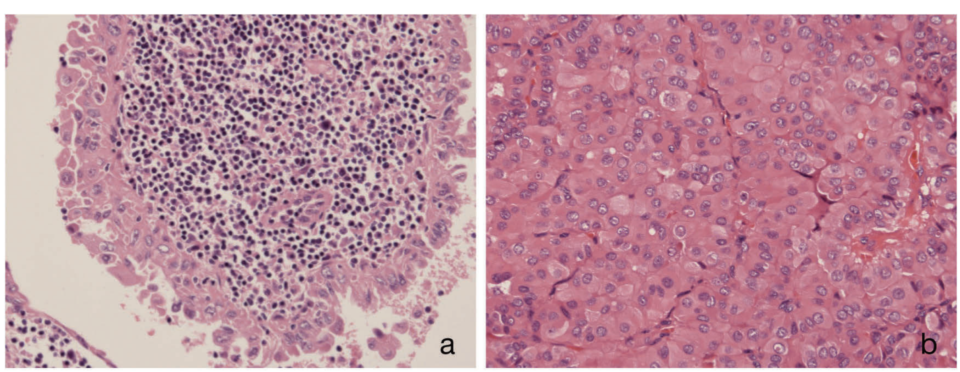

Fig. 3 Oxyphilic metaplasia of Ukrainian cases
Complete oxyphilic change was more frequently observed in Ukrainian cases. Some cases showed Warthin-like appearance (a), and most cases included a solid component (b) (H&E).

was no difference in background lymphocytic infiltration (p=0.217). However, severe lymphocytic infiltration (chronic thyroiditis) was more prevalent in the Ukrainian cases (30.4%) than in the Japanese ones (12.5%). Marked oxyphilic metaplasia (severe and complete) of tumor cytoplasm was more frequently observed in the Ukrainian cases compared with Japanese ones (33.9% *vs*. 8.9 %, p<0.001, respectively). Complete oxyphilic metaplasia (oncocytic tumor) was observed in 23.2% of Ukrainian cases (Fig. 3) and 3.6% of Japanese cases. A solid component was commonly observed in oncocytic tumors from Ukrainian patients (13 cases). They consisted of 2 SV, 4 SF, 4 SP, one PFS, one PF, and one CL. Warthin-like lesion was observed in three cases (one CL and 2 SP). In the background thyroid of Ukrainian oncocytic tumors, chronic thyroiditis and mild lymphocytic thyroiditis were present in seven and five cases, respectively. Only one case lacked background lymphocytic infiltration. MIB-1 index of Ukrainian cases was significantly higher than that of Japanese cases (2.9% *vs.* 1.8%, p<0.001, respectively).

Discussion

The evidence presented in this report shows clearly that there is significant differences in adult PTC morphology between cases in Japan and Ukraine. These results were very similar to pediatric PTCs of the two regions [1]. Similar to pediatric cases, the solid pattern was frequently observed, especially in the Chernobyl cases [1, 2]. Excluding the pediatric cases, the papillary pattern was highly prevalent in Japanese cases [1]. Our results suggest that geographical differences are as important as the age factor when considering PTC morphology, tumorigenesis, and the related prognosis.

A higher prevalence of the solid variant was observed among papillary carcinoma from children exposed to radiation after the Chernobyl nuclear accident, in which up to 34% of all tumors had a predominantly or exclusively solid growth pattern [15]. Tumors with this phenotype in unexposed children occurred predominantly in very young cases, suggesting a link to short latency [1]. In this study, the cases were adults without radiation-exposed history. Then it is not likely that short latency and radiation exposure contributed to the solid morphology of adult PTCs. At present, the geographical factor would be more relevant to solid morphology. Among several possible factors such as dietary, genetic, and environmental factors, iodine deficiency is most likely linked to solid morphology in Ukrainian adult cases.

Relations between iodine environment and morphology of thyroid cancers have been well-documented in many reports. The level of dietary iodine intake is thought to influence the growth pattern of differentiated follicular tumor of thyroid [1]. The incidence of follicular carcinoma in areas of iodine deficiency is higher than in areas of an iodine-rich diet [17, 18]. In contrast, PTC is the most frequent type of thyroid cancer in iodine-sufficient regions [17, 18]. In a population with dietary iodine deficiency, iodine supplementation increased the relative incidence of papillary carcinoma [18, 19]. Interestingly, in animal models, iodine supplementation causes experimental thyroid cancers to change from follicular to papillary morphology, indicating that one of the roles of iodine in thyroid carcinogenesis is modulating tumor morphology, rather than cancer initiation [20]. Despite these well-documented relationships, the role of iodine in thyroid carcinogenesis is still unclear.

Dietary iodine status is important in thyroid cancer susceptibility after radioactive fallout exposure [1, 6, 11]. Our previous study also showed the possibility of iodine influence to morphology of childhood thyroid cancers in Chernobyl, England and Wales, and Japan [1]. Chernobyl cases showed less differentiated morphology, Japanese cases showed papillary dominant morphology, and England and Wales showed variants between the other two countries. The results showed that less differentiated features (solid/trabecular) were closely associated with less dietary iodine levels. The dietary habits of Japanese people include abundant iodine-rich food. In contrast, Ukraine is an iodine-deficient country regardless of iodine supplementation, while England and Wales people have an intermediate intake.

The solid variant of PTCs has been described in several papers. In 1992 in the 3rd series of AFIP [21], Rosai proposed that, "The term solid/trabecular variant should be used when all or nearly all of a tumor not belonging to any of the other variants has a solid and/or trabecular appearance." However, a quantitative description has not been provided; the definition of solid variant still varies among pathologists and institutions. The prerequisite occupancy rate of the solid component in the tumor was variable from 50% to 70% in reported studies [22, 23]. We defined it as covering over 80% of the PTC. Accordingly, the occupancy ratio of the papillary or follicular component to the solid component in the mixed variant (SF, SP, and PFS) was different in this study. Nikiforov *et al.* examined American cases (the Mayo Clinic) and found that this phenotype was observed in 3% of 756 adult PTCs, with solid variant defined as over 70% predominancy [22]. Carcangiu *et al.* reported 12.8% of 241 Italian adult PTCs with this variant, which was defined as over 50% predominancy [23]. We compared our results with these reports. According to Carcangu's definition (more than 50%), the solid variant was observed in 28.6% of our Ukrainian cases and 3.6% of Japanese ones. Using Nikiforov's criteria (>70%), this variant was found in 12.5% of our Ukrainian patients and 1.8% of Japanese ones. Despite these differences in actual values, we clearly demonstrated that there was a higher incidence of solid variant in cases from Ukraine than those from the others. Italian and American cases showed intermediate frequencies of this variant as compared to those from Ukraine and Japan (Table 2). Thus, Japanese and Ukrainian cases may represent extreme poles in incidence of the solid variant of PTC. Our results suggest that geographical differences are

Table 2 Prevalence of solid variant of PTC in different areas by two different criteria

	more than 50% of solid area	more than 70% of solid area
Ukraine*	28.6%	12.5%
Italy [23]	12.8%	ND
USA[22]	ND	3.0%
Japan*	3.6%	1.8%

%: solid variant/PTC, *: data of this study

as important as the age factor when considering PTC morphology.

Differentiation of PDC from the solid variant of PTC requires special attention, since both tumors contain a solid component. Furthermore, different diagnostic criteria for PDC have been proposed, resulting in wide discrepancies and confusion among pathologists and clinicians. PDC was first described by Sakamoto *et al.* [24] in 1983. Carcangiu *et al.* suggested that insular carcinoma is a type of PDC in 1984 [25]. Thus, the WHO classification (2004) [12] and Turin proposal [14] of 2007 recommended that its definition include the presence of necrosis and/or mitosis as well as solid/trabecular/insular component. Nikiforov *et al.* suggested that the solid variant of PTC should be distinguished from PDC because its prognosis was not as poor as PDC [22]. In Japan, PDC is defined by the general rules for the description of thyroid cancer, as edited by The Japanese Society of Thyroid Surgery (JSTS). In the most recent edition [26], differentiated papillary or follicular carcinomas showing trabecular, solid, or insular growth patterns even in small areas of a resected surgical specimen should be classified as a PDC. Ito *et al.* suggested that PDC defined by JSTS should be a subtype of PTC rather than as an independent entity from the point of view of its prevalence and prognosis [27]. When the criteria of JSTS were applied to Ukrainian cases, approximately 70% of papillary carcinomas were classified as PDC.

In this study, the Ukrainian cases showed a significantly higher incidence of oncocytic tumors. The oncocytic (oxyphilic) variant of papillary carcinoma represents an unusual neoplasm whose clinicopathological features have not been thoroughly characterized. This variant commonly shows the formation of papillary structures, but admixture with other features can also be present [28]. Warthin-like tumors, which show an admixture of oncocytic papillary features and abundant chronic inflammation [29], and other combinations such as solid and papillary or follicular features were observed in the Ukrainian cases. Another common finding was association with Hashimoto's or lymphocytic thyroiditis in the surrounding thyroid tissue. Further, elevated antibodies to thyroid peroxidase was reported in the Ukrainian cohort study [30], but the relation of dietary iodine intake to spontaneous Hashimoto's thyroiditis is unclear [31].

The average tumor size was significantly smaller in the Ukrainian patients than in the Japanese cases, while the proliferative activity was significantly higher in the Ukrainian cases. This suggests that the Ukrainian cases were detected earlier than the Japanese cases. Intensive screening for younger people has been carried out in Ukraine after the Chernobyl accident, leading to earlier detection of lesions. This may stem from a difference in attitude and consciousness with regard to radiation risk in the aftermath of the Chernobyl accident. More PTCs are diagnosed among populations with wider access to healthcare in recent reports [32-34]. Markers for higher levels of health care access, both sociodemographic and age-based, are associated with higher PTC incidence rates.

The purpose of this study was to understand the morphological difference of PTC of geographically different areas especially from the point of view of iodine intake. Assessment of the clinical outcome (prognosis, mortality rate) is not a purpose of this study because the number of subjects was not large enough and follow up was not long enough. Based on these results, further examination is necessary to assess the clinical outcome and to perform molecular analysis.

In conclusion, this study revealed that Ukrainian adult PTCs showed more solid nature than Japanese cases. This difference was also observed in pediatric cases as reported previously, suggesting that morphogenesis of PTC is influenced by iodine intake as well as hereditary factors. Taking into account of histological diversities is as important as the comparison of molecular analytic data and radiation sensitivity.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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