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Original Article

Exposure to environmental polycyclic aromatic hydrocarbons may be a cause of breast cancer

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Abstract: The present study is to investigate the relationship between environmental polycyclic aromatic hydrocarbons (PAHs) exposure and breast cancer occurrence. Case-control study was performed in the present study. The patient group included 129 patients with breast cancer, while the control group included 129 healthy female subjects. Liquid chromatography - mass spectrometry was used to measure the levels of PAH hydroxyl metabolites in urine. Enzyme-linked immunosorbent assay was employed to determine the levels of aromatic hydrocarbon receptor (AhR) and metabolic enzymes in peripheral blood. The level of 1-hydroxypyrene in urine samples from patient group was significantly higher than that from control group. Breast cancer patients had higher concentrations of AhR, GST and NQO1 in peripheral blood than healthy subjects. AhR had higher correlation with GST or NQO1 in patient group than in control group. The levels of AhR and GST were significantly different among different grades of ER, with the expression of GST being the highest in ER (++). Environmental PAHs may be a chemical factor that leads to human breast cancer. Reducing contact and intake of PAHs may be of help in lowering the incidence of breast cancer. Abnormal elevation of AhR, GST, and NQO1 protein concentrations in peripheral blood may be important for the early diagnosis of breast cancer.

Keywords: Breast cancer, polycyclic aromatic hydrocarbon, aromatic hydrocarbon receptor

Introduction

Breast cancer is one of the malignant tumors that women are most susceptible to [1]. The incidence of breast cancer is increasing year by year around the world, especially in young female population [1]. The morbidity of breast cancer in China has exceeded the world average level [2], while that in Xinjiang Autonomous Region has become the second highest among all malignant tumors that can affect women [3]. The occurrence of breast cancer is the result of interactions among multiple factors, including age, heredity, breast diseases, abnormal menstruation, the age of menarche, body mass index, drinking habits, body exercises, viral infections, fertility circumstances, mental status, and occupations [4]. However, it is unknown whether breast cancer is related to environmental pollutants. A study shows that polycyclic aromatic hydrocarbons (PAHs) have carcinogenic, teratogenic, mutagenic and immunotoxic activities for mammals, and exposure to environmental PAHs has become an indicator for the potential risk of cancers [5]. PAHs in the surrounding environment or food can be taken by human bodies via respiratory tract, skin and digestive tract [6]. The hydroxyl metabolites of PAHs are usually used as biomarkers for the evaluation of PAH exposure levels [7]. After entering into the cells, PAHs can bind and activate aromatic hydrocarbon receptor (AhR), which further promotes the translation and transcription of multiple genes, including cytochrome P450 (CYP450) family 1 member A1 (CYP1A1) and CYP1A2, as well as PAH metabolism-related enzymes such as glutathione S transferase (GST), NAD(P)H:quinone oxidoreductase 1 (NQO1), and aldehyde dehydrogenase (ALDH) [8]. Another study shows that diox-

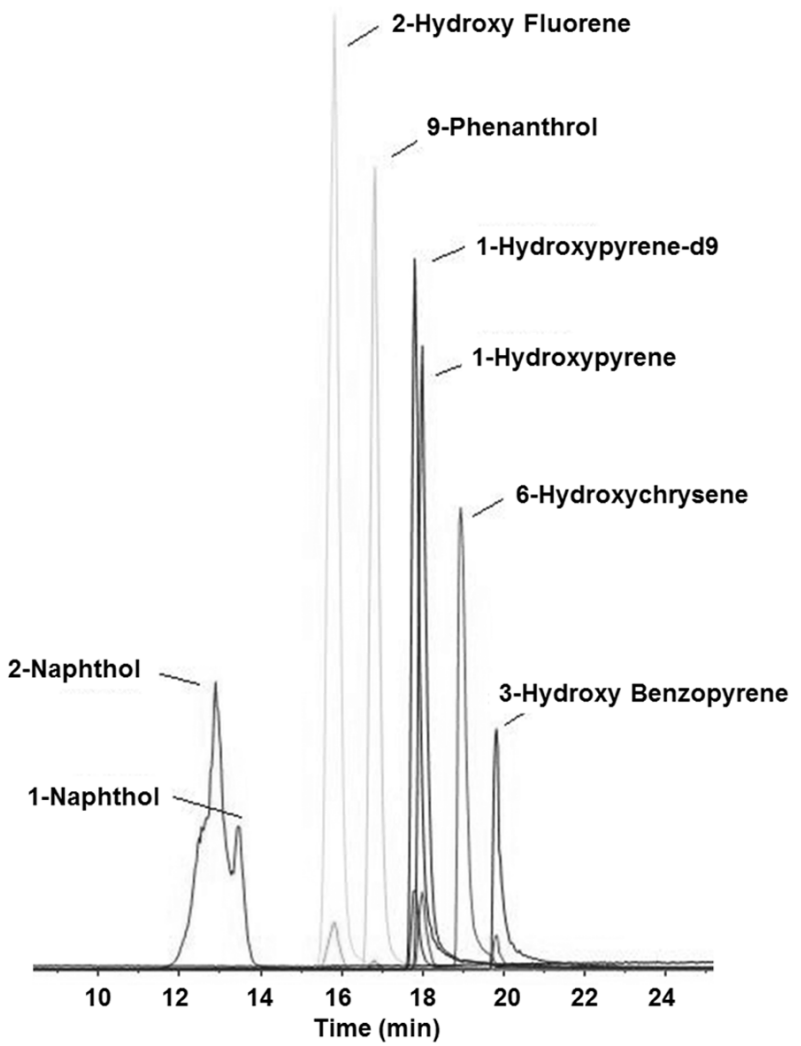

Figure 1. Total ion chromatogram of seven types of polycyclic aromatic hydrocarbon metabolites and inner marks.

in, an environmental endocrine disrupt chemical, activates AhR in human bodies, which subsequently induces the transcription of human epiregulin, and promotes the growth of tumor cells [9]. In the present study, we investigate the relationship between PAH exposure and breast cancer.

Materials and methods

Patients

A total of 129 patients with primary breast cancer hospitalized in the Affiliated Tumor Hospital of Xinjiang Medical University between May 2011 and July 2012 were included in the present study (ages of patients, 19-80 years; average, 48.9 ± 10.8 years). All patients had definitive pathological diagnosis, and no history of other tumors or gynecological diseases. In addition, 129 healthy female subjects were included as controls (ages of controls, 19-80 years; average, 47.2 ± 10.1 years). Peripheral blood and urine samples were collected from all patients and control subjects, and immediately aliquoted for storage at -20°C. Pathological data of breast cancer patients were collected, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her-2). All procedures were approved by the Ethics Committee of Xinjiang Medical University. Written informed consents were obtained from all patients or their families.

Liquid chromatography - mass spectrometry (LC-MS)

Urine samples (5.0 ml) were mixed thoroughly with 50 μL glucuronidase/arylsulfatase (Merck, Kenilworth, NJ, USA), followed by incubation at 37°C in dark overnight. Then, 100 μL 1-hydroxy naphthalene-d9 internal standard solution (100 μg/L; Sigma-Aldrich, St. Louis, MO, USA) was added before vortexing for 1 min at 1000 rpm. Subsequently, the samples were centrifuged at 10,000 rpm for 3 min, followed by collection of supernatants for further use. The supernatants (5 mL) were purified by C18 SPE columns (3 ml/60 mg; SUPELCO, Sigma-Aldrich, St. Louis, MO, USA) that were preactivated by methanol (5 ml; Tedia, San Diego, CA, USA) and water (5 ml). Then, the C18 columns were washed with 5 ml purified water, and dried by N_2. After that, 0.05% ammoniated acetonitrile was used for elution, and elute was collected for rotary evaporation at 30°C. The residues were dissolved in methanol to reach a total volume of 1 ml, followed by filtration

Table 1. Levels of PAHs in urine samples from patient and control groups

OH-PAHs (ng/g Cr)	Patient group (n = 129)	Control group (n = 129)	Z	P
1-hydroxypyrene	0.57 (0.39)	0.13 (0.91)	-1.07	0.007*
9-hydroxyl phenanthrene	3.12 (2.03)	1.25 (2.59)	-1.79	0.072
2-hydroxyfluorene	0.63 (2.65)	0.14 (0.22)	-1.56	0.117
2-hydroxy naphthalene	2.87 (6.10)	2.82 (5.6)	-1.75	0.442
1-hydroxy naphthalene	3.28 (6.07)	1.11 (3.3)	-2.61	0.055
6-hydroxy chrysene	0.11 (0.03)	0.11 (0.01)	-0.84	0.182
3-hydroxy benzopyrene	0.14 (0.01)	0.14(0.01)	-1.35	0.913

Note: OH-PAH, phenolic polycyclic aromatic hydrocarbons. *P < 0.05 between patient group and control group.

through 0.20 μm holes. Liquid chromatography of 20 μL samples was performed using ZORBAX SB-C18 columns (150 mm × 2.1 mm, 3.5 μm; Agilent Technologies, Santa Clara, CA, USA) on 1100 liquid chromatography system (Agilent Technologies, Santa Clara, CA, USA) at room temperature, with the mobile phase being methanol and water at a flow rate of 250 $\mu L \cdot min^{-1}$. Mass spectrometry was performed on ABI4000 Q TRAP (Thermo Fisher Scientific, Waltham, MA, USA) using the following conditions: ion source, electrospray ionization; ion source atomization temperature, 550°C; curtain gas, 30; atomizing gas (GS1), 40 psi; heating auxiliary gas (GS2), 45 psi; collision gas (CAD), 6.00; spray voltage (IS), -4500 V; atomization temperature, 550°C; detection method, negative ion mass spectrometry multiple reaction monitoring (MRM).

Enzyme-linked immunosorbent assay (ELSA)

The levels of GST, NQO1, ALDH, CYP450, and AhR in peripheral blood were measured using ELISA kits (Beijing Biomed, Beijing, China). The procedures were carried out according to the manufacturer's manuals. Coating antibodies were human GST monoclonal antibody, human NQO1 monoclonal antibody, human ALDH monoclonal antibody, human CYP450 monoclonal antibody, and human AhR monoclonal antibody (Beijing Biomed, Beijing, China). The detection antibody was horseradish-peroxidase (Beijing Biomed, Beijing, China). All antibodies were diluted at a ratio of 1:5 before use. Absorbance at 450 nm was measured using a microplate reader (Bio-Rad, Hercules, CA, USA) within 10 min after stopping the reactions.

Statistical analysis

All questionnaire data were input using EpiData software (http://www.epidata.dk/), and analyzed using Logistic stepwise regression. Rank sum test was used to analyze measurement data. Correlation was analyzed using Spearman function correlation analysis. For bilateral tests, $\alpha = 0.05$. Difference with $P < 0.05$ was considered statistically significant.

Results

Patients with breast cancer have higher degrees of exposure to pyrene type PAHs than healthy subjects

To measure the levels of PAH hydroxyl metabolites in urine, LC-MS was performed. Within the linearity range of 0.1-10 μg/L, 1-hydroxypyrene, 2-hydroxyfluorene, 1-hydroxy naphthalene, 2-hydroxy naphthalene, 9-hydroxyl phenanthrene, 3-hydroxy benzopyrene, and 6-hydroxy chrysene showed good linearity ($r \geq 0.999$), and their detection limits were 0.20, 0.20, 0.15, 0.15, 0.15, 0.20, and 0.15 μg/L, respectively (**Figure 1**). LC-MS data showed that the level of 1-hydroxypyrene in urine samples from patient group was significantly higher than that from control group ($P < 0.05$) (**Table 1**). The result suggests that the patients with breast cancer have higher degrees of exposure to pyrene type PAHs than healthy subjects.

The levels of PAH hydroxyl metabolites in urine from breast cancer patients are not significantly related to immunohistochemical indicators ER, PR, and Her-2

To investigate the relationship between the levels of PAH hydroxyl metabolites in urine and pathological indicators, we evaluated ER, PR, and Her-2 indicators. The data showed that the levels of phenolic polycyclic aromatic hydrocarbons (OH-PAHs) in ER, PR or Her-2 negative groups were not significantly different from those in ER, PR or Her-2 positive groups, respectively ($P > 0.05$). In addition, the levels of OH-PAHs in all-negative group were not significantly different from those in not-all-negative group ($P > 0.05$). Furthermore, the levels of

Table 2. Relationship between the levels of PAH metabolites in urine and pathological indicators

		N	1-hydroxypyrene		9-hydroxyl phenanthrene		2-hydroxy-fluorene		2-hydroxy naphthalene		1-hydroxy naphthalene		6-hydroxy chrysene		3-hydroxy benzopyrene	
			Z	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*	*Z*	*P*
ER	-	44	-0.321	0.748	-0.553	0.581	-1.754	0.079	-0.423	0.672	-1.158	0.247	-1.553	0.681	-1.345	0.069
	+	85														
PR	-	67	-0.568	0.570	-0.914	0.360	-1.912	0.056	-0.630	0.528	-0.670	0.503	-0.921	0.973	-0.563	0.783
	+	62														
Her-2	-	32	-0.149	0.882	-0.438	0.661	-0.724	0.469	-0.053	0.957	-0.510	0.610	-0.124	0.765	-0.245	0.287
	+	97														
ER, PR, HER-2	All "-"	8	-0.351	0.742	-0.537	0.607	0.230	0.246	-1.365	0.172	-0.833	0.405	-0384	0.456	0.276	0.725
	Not all "-"	121														
ER	0	44	1.009	0.799	2.462	0.482	4.360	0.225	0.859	0.835	2.546	0.467	0.462	0.724	1.230	0.865
	1	16														
	2	42														
	3	27														
PR	0	67	3.937	0.268	1.563	0.668	5.165	0.160	1.264	0.738	0.822	0.844	0.246	0.978	0.156	0.963
	1	10														
	2	28														
	3	24														
HER-2	0	32	0.361	0.948	0.246	0.970	1.482	0.686	1.136	0.768	1.078	0.782	0.482	0.685	0.136	0.372
	1	44														
	2	24														
	3	29														

Table 3. Correlation analysis between AhR and OH-PAHs

	1-Hydroxypyrene	2-Hydroxyfluorene	9-Hydroxyl phenanthrene	1-hydroxy naphthalene	2-hydroxy naphthalene	3-hydroxy benzopyrene	6-hydroxy chrysene
R	0.309	0.057	0.003	-0.028	0.045	-0.104	0.053
P	0.001	0.367	0.957	0.657	0.478	0.598	0.405

OH-PAHs in different grades of ER, PR or Her-2 were not significantly different from each other (P > 0.05) (**Table 2**). These results indicate that the levels of PAH hydroxyl metabolites in urine are not significantly related to immunohistochemical indicators ER, PR, and Her-2.

The level of 1-hydroxypyrene is correlated with AhR

To examine the relationship between the levels of OH-PAHs and AhR, correlation analysis was performed. The data showed that the correlation between different OH-PAHs and AhR was varied. Of note, only 1-hydroxypyrene and AhR has an R value of 0.309 (P < 0.05) (**Table 3**). The result suggests that the level of 1-hydroxypyrene is correlated with AhR.

Breast cancer patients have higher concentrations of AhR, GST and NQO1 in peripheral blood than healthy subjects

To measure the levels of AhR, ALDH, NQO1, CYP450 and GST in peripheral blood, ELISA was performed. The levels of ALDH and CYP450 in patient group were not significantly different from those in control group (P > 0.05), but the levels of AhR, GST and NQO1 in patient group were significantly higher than those in control group (P < 0.05) (**Table 4**). These results indicate that breast cancer patients have higher concentrations of AhR, GST and NQO1 than healthy subjects.

High level of AhR in breast cancer patients is correlated with the high levels of GST and NQO1

To study the relationship between AhR and GST or NQO1, we performed correlation analysis. The data showed that AhR had higher correlation with GST or NQO1 in patient group (R = 0.665, P < 0.01; R = 0.704, P < 0.01) than in control group (R = 0.503, P < 0.01; R = 0.533, P < 0.01) (**Table 5**). The result suggests that the high level of AhR in breast cancer patients is positively correlated with the high levels of GST and NQO1.

Table 4. The levels of aromatic hydrocarbon receptor and metabolic enzymes in peripheral blood [M(Q)]

Concentrations (ng/mL)	Patient group (n = 129)	Control group (n = 129)	Z	P
AhR	4.53 (3.79)	3.33 (2.05)	2.110	0.036*
ALDH	3.85 (4.15)	3.35 (3.39)	0.582	0.544
NQO1	3.14 (3.39)	2.65 (2.89)	1.443	0.042*
CYP450	4.05 (5.29)	2.84 (3.91)	1.656	0.94
GST	6.12 (6.44)	4.08 (4.78)	3.343	0.001*

Note: AhR, aromatic hydrocarbon receptor; ALDH, aldehyde dehydrogenase; NQO1, NAD(P)H:quinone oxidoreductase I; CYP450, cytochrome P450; GST, glutathione S-transferase. The levels of these indicators were measured using ELISA. *$P < 0.05$ between patient group and control group.

Table 5. Correlation between AhR and GST or NQO1 expression in control and patient groups

	Control group		Patient group	
	GST	NQO1	GST	NQO1
No. of cases (N)	129	129	129	129
Correlation coefficient (R)	0.503	0.533	0.665	0.704
P	0.00*	0.00*	0.00*	0.00*

Note: *$P < 0.01$ compared with AhR.

Levels of AhR and GST in breast cancer patients are correlated with ER grades

To investigate the relationship between pathological indicators and the levels of AhR, ALDH, NQO1, CYP450 and GST, pathological indicators ER, PR or Her-2 were evaluated. The data showed that the levels of AhR, ALDH, NQO1, CYP450 and GST proteins in ER, PR or Her-2 negative groups were not significantly different from those in ER, PR or Her-2 positive groups, respectively ($P > 0.05$). In addition, the levels of AhR and GST were significantly different among different grades of ER ($P < 0.05$), with the expression of GST being the highest in ER (++) (**Table 6**). These results indicate that the levels of AhR and GST in breast cancer patients are correlated with ER grades.

Discussion

The content of 1-hydroxypyrene is usually used as an indicator to evaluate exposure degree of human bodies to environmental pyrene type PAHs. In the present study, the average concentration of 1-hydroxypyrene in urine samples from healthy subjects was 0.13 μmol/mol Cr, while that from breast cancer patients was 0.57 μmol/mol Cr, being higher than those of normal polulations reported in other countries (0.04 μmol/mol Cr in USA [10], 0.04 μmol/mol Cr in Germany [11], 0.03 μmol/mol Cr in Korea [12], 0.08 μmol/mol Cr in Thailand [13], and 0.02-0.04 μmol/mol Cr in New Zealand [14]). This result suggests that exposure to pyrenes may be a risk factor for the occurrence of breast cancer. However, the levels of PAH hydroxyl metabolites in urine are not significantly related to immunohistochemistry indicators ER, PR, and Her-2. This may be due to the ways by which PAHs affect human bodies.

In the present study, the activities of 1-hydroxypyrene in urine and AhR in blood samples from patient group are significantly higher than those from control group, indicating that breast cancer patients and healthy subjects have distinct metabolism of PAHs, and the expression of AhR can indirectly reflect the risk of exposure to environmental PAHs for breast cancer. Correlation analysis shows that AhR is strongly correlated with GST and NQO1, and the expression of GST and NQO1 was enhanced in breast cancer patients, indicating that increased AhR activity may further promote the expression of metabolic enzymes GST and NQO1. Among all known GST types, GST-π is the most closely related with malignant tumors. A report shows that the levels of GST-π in gastric cancer, ovarian cancer, urethral cancer, colorectal cancer, endometrial cancer, prostate cancer, and glioblastoma were significantly higher than control group [15]. It is reported that NQO1 expression in lung cancer, colon cancer and breast cancer tissues was significantly higher than that in normal tissues [16]. In addition, NQO1 can induce the transition of procarcinogens to final carcinogens, or degrade some carcinogens such as quinone [17]. In the present study, we consider using increased AhR activity and enhanced concentrations of GST and NQO1 in peripheral blood as indicators for the early occurrence of breast cancer.

Breast cancer is considered as a kind of hormone-dependent tumor. Estrogen can change the conformation of ER by direct binding, interact with estrogen response elements, and acti-

Table 6. Correlation of aromatic hydrocarbon receptor and metabolic enzymes with pathological indicators

	Immunohistochemical index classification	ER			PR			HER-2		
		N	M(Q)	P	N	M(Q)	P	N	M(Q)	P
ALDH	-	44	2.73 (2.81)	0.194	67	3.16 (3.78)	0.097	32	2.65 (3.32)	0.322
	+	16	1.95 (0.96)		10	2.69 (4.69)		44	3.15 (3.81)	
	++	42	4.43 (4.04)		28	2.66 (457)		24	3.25 (5.72)	
	+++	27	2.15 (3.69)		24	2.23 (3.99)		30	2.09 (3.98)	
AhR	-	44	3.98 (4.57)	0.04*	67	3.79 (4.69)	0.824	32	2.89 (4.23)	0.128
	+	16	4.17 (5.40)		10	2.86 (5.31)		44	4.46 (4.96)	
	++	42	4.02 (4.52)		28	2.78 (4.71)		24	2.43 (5.49)	
	+++	27	3.91 (3.78)		24	2.82 (5.24)		30	2.86 (4.12)	
CYP450	-	44	3.00 (3.86)	0.183	67	3.56 (5.41)	0.054	32	5.12 (5.44)	0.816
	+	16	2.22 (0.91)		10	2.86 (4.35)		44	2.60 (4.67)	
	++	42	3.87 (5.87)		28	2.46 (3.46)		24	2.50 (4.15)	
	+++	27	2.07 (4.44)		24	2.44 (6.42)		30	2.86 (3.22)	
NQO1	-	44	5.01 (3.70)	0.25	67	4.89 (4.09)	0.281	32	3.85 (3.05)	0.489
	+	16	3.11 (0.66)		10	4.00 (2.20)		44	4.48 (4.76)	
	++	42	5.42 (4.38)		28	3.40 (3.49)		24	3.88 (4.35)	
	+++	27	3.72 (3.69)		24	3.44 (4.71)		30	3.44 (3.37)	
GST	-	44	6.72 (8.08)	0.08*	67	6.26 (7.87)	0.695	32	5.35 (6.48)	0.274
	+	16	5.25 (4.54)		10	7.84 (10.37)		44	6.26 (8.30)	
	++	42	8.06 (10.14)		28	4.92 (4.96)		24	3.70 (5.26)	
	+++	27	6.42 (6.94)		24	3.71 (8.13)		30	5.66 (6.95)	

Note: *$P < 0.05$ among different grades.

vate transcription together with multi-protein complex formed by transcriptional factors and auxiliary activators. This is the E2-ER-ERE pathway that plays important roles in carcinogenic process. The inhibition of E2-ER-ERE pathway may be induced by inhibitory interactions of AhR-ER, the mechanism of which may be the degradation of ER induced by AhR ligand [18]. It is shown that AhR promotes the growth and inhibits the apoptosis of breast cancer cells, possibly via immune regulation, Wnt signaling pathway and the activation of nuclear factor kappa B [17]. In addition, activated AhR can also induce proteasome-dependent degradation of ER, which on one hand inhibits hormone-dependent tumors (e.g. breast cancer, endometrial cancer, and prostate cancer), and on the other hand promotes the formation of hormone-independent tumors (e.g. adenocarcinoma and squamous cell carcinoma) [19]. In the present study, the expression of AhR in ER (++) group is the highest, suggesting that ER may play an important role in the endocrine therapy of breast cancer.

Chemotherapy is an important measure for the treatment of breast cancer. However, the effectiveness of chemotherapy may be compromised by the expression of multidrug resistance proteins. GST-π has relatively high positive expression among all multidrug resistance proteins in breast cancer. GST-π can suppress the effect of peroxides produced during the action of anti-tumor drugs, or inhibit the effect of alkylating agents that induce DNA cross-linking in cancer cells [20]. Another study shows that expression of ER and PR is negatively correlated with the positive expression rate of GST-π [21], suggesting that endocrine hormone receptors in breast cancer may inhibit the expression of GST-π. Therefore, the level of GST-π expression in breast cancer cells is of importance for choosing chemotherapy regimens [22]. The relationship of GST with the positive expression of ER may affect the medication during endocrine therapy. In the present study, the expression of GST in ER (++) group is higher than that in ER (-) group, suggesting that the level of GST protein may affect the selec-

tion clinical treatment plans for patients with positive ER expression.

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Disclosure of conflict of interest

None.

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