Maternal and Fetal Exposure to Four Carcinogenic Environmental Metals[1]

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Objective To examine maternal and fetal exposure levels to four carcinogenic metals, arsenic (As), cadmium (Cd), nickel (Ni), and beryllium (Be), and to investigate their environmental influences. **Methods** Metal concentrations in maternal and umbilical cord blood were measured by inductively coupled plasma–mass spectrometry (ICP-MS). Environmental factors that might play a role in exposure were analyzed using Mann–Whitney nonparametric *U*-tests and multiple linear regression. **Results** The concentrations of As, Cd, and Ni in umbilical cord blood (5.41, 0.87, and 139.54 μg/L) were significantly lower than those in maternal blood (6.91, 1.93, and 165.93 μg/L). There were significant positive correlations between the maternal and cord concentrations of each carcinogen. Our results showed that: (i) exposures to potentially harmful occupational factors during pregnancy were associated with high levels of maternal As, Cd, and Ni; (ii) living close to major transportation routes (<500 m) or exposure to second-hand smoke during pregnancy increased the maternal Cd levels and (iii) living close to industrial chimneys induced high maternal Ni levels. Multiple linear regression analysis showed that these environmental factors remained significant in models of the influences of these four carcinogens. **Conclusion** Both mothers and fetuses had been exposed to As, Cd, Ni, and Be. The increased levels of these carcinogens in pregnant women were associated with some detrimental environmental factors, such as occupational exposure, contact with second-hand smoke and living close to major transportation routes or industrial chimneys.

Key words: Carcinogenic metals; Exposure *in utero*; Maternal blood; Cord blood; Environment

INTRODUCTION

Cancer comprises a number of diseases, which threaten human health and life span severely. Cancer was recognized about 3 000 years ago[1], but has not been controlled effectively until now. In the USA, cancer mortality rates have declined slowly but steadily after a peak in 1990, whereas the overall incidence rates have been climbing since cancer record keeping begun in 1930[1]. In China, the morbidity and mortality of cancer have been rising in the past three decades.

Cancer is now widely accepted to arise from interactions between genetic and environmental factors[2]. Over the past three decades, there has been considerable research on the contributions of environmental and occupational exposures to the public health burden of cancer[3-5]. About two-thirds of human cancers are caused by environmental factors[4]. Moreover, the causes of cancers—or of susceptibility to cancer—might be a result of cumulative exposure over time rather than exposure at or near the time of tumor detection[6]. In particular, exposure to environmental compounds *in utero* has highlighted the etiology of cancer[7]. Herbst *et al.*[8] first reported the clear association between fetal exposure to diethylstilbestrol (DES) and clear-cell adenocarcinomas of the vagina that developed later in young women. From then on, significant epidemiological data[9-10] have revealed the associations between maternal occupational exposure to some chemicals (such as solvents, paints, and thinners) and increased incidence of childhood cancers in offspring, such as brain tumors and leukemia. These lines of evidence suggested the possibility of human transplacental transport of carcinogenic chemicals. However the correlation between exposure and effect might have been

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estimated at the wrong time: in adults who developed cancer[6]. If prenatal or early life-stage exposure is critical to disease susceptibility, why do we not measure environmental chemicals in the population as early as possible[6]?

Many environmental pollutants have now been proven to be human carcinogens[11], of which carcinogenic metals are important[13]. Arsenic (As), cadmium (Cd), nickel (Ni), and beryllium (Be) are all accepted as definite human carcinogens and have proved to be associated with an excess risk of developing tumors, including lung, dermal, and nasal cancers[12]. Recent reports[13-15] have revealed that As and Ni are potential transplacental carcinogens in rodent experiments. However, few studies have focused on the exposure of maternal and/or fetal organisms to these carcinogenic metals.

Dalian is an important commercial and industrial city in China. It has a famous metal smeltery and the biggest shipbuilding yard in the whole country. The cancer mortality of Dalian residents in the past decades has been higher than the average and is on an ascending trend. From 1996 to 2004, the mortality rate increased by 18.6% (Fig. 1). Therefore, we conducted a cross-sectional study to test exposures to As, Cd, Ni, and Be in mothers and neonates and to evaluate the environmental risk factors that might contribute to any increased levels of four carcinogenic metals. We hope to provide a new perspective for health care during pregnancy and new evidence for potential human exposure to carcinogenic metals *in utero*.

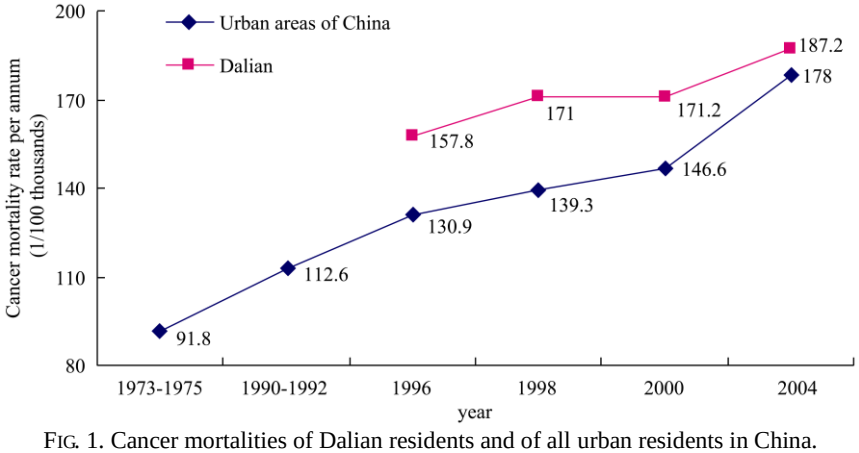

FIG. 1. Cancer mortalities of Dalian residents and of all urban residents in China.

METHODS

Study Population

This study was conducted at the Department of Obstetrics and Gynecology of No. 210 Hospital of the Chinese People's Liberation Army (PLA) in Dalian from October 2006 to March 2007. Mother-infant pairs were recruited immediately after hospitalization and birth. Exclusion criteria were as follows: 1) multiple pregnancy; 2) any maternal history of illness involving the major organs before or during pregnancy; 3) very premature births (delivery at < 32 completed weeks or birth weight < 1 500 g) or 4) delivery of an infant with a notifiable birth defect. The final cohort included 125 mother-infant pairs.

All mothers were interviewed after admission and asked to fill out a lifestyle and social environment questionnaire that included demographic information, history of any abnormal gravidity and parturition, working history, tobacco use, alcohol and water consumption, source of drinking water, environment factors around their residence and exposure to harmful occupational factors. The habitat-related environmental factors investigated in our study included the distance between the mother's living place and major transportation routes, the distance between their residence and any industrial chimneys and recent decoration of their house. A distance of <500 meters between any two locations was defined as 'close'. The potentially harmful occupational factors included any exposure to industrial dust, solder, decorating materials, chemical reagents, gasoline or gas. After delivery, anthropometric indices were recorded for each infant. Informed consent was obtained from all the women. The study was approved by the Human Subjects Review Committee of Dalian Medical University and the Ethics Committee of the No. 210 Hospital of the PLA. General characteristics of the women and infants are presented in Table 1.

Blood Sampling

Whole blood samples were collected from the mothers when they were admitted for delivery to the

maternity ward of the hospital, and umbilical cord vein blood samples were collected immediately after clamping and before delivery of the placenta. Blood samples were stored immediately in 7mL EDTA-treated vacutainers at -80 ℃ until they were transported on dry ice to Shanghai Key Laboratory of Children's Environmental Health for elemental analysis.

TABLE 1

Demographic Characteristics of the Study Population (125 Mother-infant Pairs)

Maternal Characteristic	Value
Age (Years; $\bar{x} \pm S$)	28.67 ± 4.02
Height (cm; $\bar{x} \pm S$)	162.18 ± 5.20
Weight at Delivery (Kg; $\bar{x} \pm S$)	74.66 ± 8.98
Education [*n* (%)]	
≤Junior High School	44 (35.2)
High School	34 (27.2)
≥College	47 (37.6)
Parity of Child Times; [n (%)]	
1	104 (83.2)
2	17 (13.6)
3+	4 (3.2)
Gestational Age at Birth [Weeks; *n*(%)]	
< 37	4 (3.2)
37-41	119 (95.2)
42+	2 (1.6)
Infant Characteristic	
Weight at Birth (Kg; $\bar{x} \pm S$)	3.48 ± 0.52
Length at Birth (cm; $\bar{x} \pm S$)	52.52 ± 2.85
Sex [*n* (%)]	
Male	54 (43.2)
Female	71 (56.8)

Sample Analysis

Whole blood samples (200 μL) were digested in 400 μL nitric acid (69%). After digestion, samples were diluted with double distilled (dd) H_2O up to 4.5 mL and then analyzed for As, Cd, Ni, and Be concentrations by inductively coupled plasma–mass spectrometry (ICP-MS) using an Agilent 7500CE system (Agilent Technologies, Santa Clara, CA, USA). Routine checks of accuracy and precision were accomplished using standard reference materials from the Kaulson Laboratories (CORTOX, HMB59311; West Caldwell, NJ, USA). In addition, 10% of the samples were assayed in duplicate. The detection limits of As, Cd, Ni, and Be were 0.1, 0.08, 1.3, and 0.019 μg/L, respectively.

Statistical Methods

Data were analyzed using SPSS software (version 11.5, SPSS Inc, Chicago, IL, USA). Undetected samples were assigned a value of one half the detection limit[16]. Because of the skewed distribution of raw data and the need to log-transform values of the blood As, Cd, Ni, and Be levels, nonparametric statistical methods were used primarily to analyze the data. The distributions of the four metal concentrations in maternal and cord blood were described by arithmetic means and standard deviations, by lower, median and upper quartiles, and by detection rate. The Mann-Whitney nonparametric *U*-test was applied to compare the concentration of each metal in maternal with that in cord blood, as well as to compare the maternal blood levels (in μg/L) of the four carcinogenic metals between the populations, grouped by environmental influencing factors or histories of maternal abnormal gravidity and parturition. Spearman correlation analysis was used to explore the association between quantitative variables.

To investigate the effects of multiple factors on maternal exposures to the four carcinogenic metals, we made a further analysis of the data. Because subjects with concentrations below the detection limits had obviously suffered negligible exposure, these data were removed. Consequently, the remaining data on maternal As, Cd, Ni, and Be concentrations were log-normally transformed. We defined these data elements (the log-transformed values of maternal As, Cd, Ni, and Be concentrations exceeding detection limits) as dependent variables in stepwise multiple linear regression analysis. The possible influencing factors, including maternal age, height, weight at delivery, parity, history of spontaneous abortion, history of stillbirth, gestational age at birth, exposure to harmful occupational factors, living close to a major transportation route or to an industrial chimney, exposure to second-hand smoke during pregnancy and recent family home decoration were treated as independent variables. Significance was set at $P<0.05$.

RESULTS

Table 1 shows the demographic characteristics of our study population. Among the 125 mothers, 104 (83.2%) delivered for the first time, while others had delivered at least once before. Among the 125 infants, 4 (3.2%) were delivered at < 37 completed weeks but at≥32 completed weeks; the others were delivered at full term.

Table 2 lists the distributions of As, Cd, Ni, and Be in maternal and umbilical cord blood. The absolute detection rates of all metals were high, with all above 50%. Especially, for As and Ni the detection rates in maternal and cord blood both exceeded 90%. The concentrations of As, Cd, and Ni

TABLE 2

Distributions of As, Cd, Ni, and Be in Maternal and Cord Blood

Metal Carcinogens	Specimen	% Detected	Concentration (μg/L)					Z	P_1	r	P_2
			Mean	SD	Lower Quartile	Median	Upper Quartile				
As	Maternal	98.40	6.91	5.32	3.39	5.30	8.55	–3.11	0.00	0.85	0.00
	Cord	97.60	5.41	4.81	2.50	3.71	6.41				
Cd	Maternal	76.00	1.93	2.24	0.24	1.15	2.62	–4.50	0.00	0.83	0.00
	Cord	55.20	0.87	1.21	0.04	0.63	1.40				
Ni	Maternal	94.40	165.93	202.45	34.49	62.65	212.55	–2.77	0.01	0.58	0.00
	Cord	94.40	139.54	259.48	25.67	38.67	171.45				
Be	Maternal	55.20	0.03	0.03	0.01	0.01	0.04	–0.81	0.42	0.72	0.00
	Cord	55.20	0.03	0.04	0.01	0.01	0.04				

Note. P_1 Mann-Whitney *U*-test (between maternal and cord blood concentrations), P_2 Spearman correlation analysis (between maternal and cord blood concentrations).

in cord blood (medians, 5.41, 0.87, and 139.54 μg/L) were significantly lower than those in maternal blood (medians, 6.91, 1.93, and 165.93 μg/L) (P<0.05). For Be, the concentration in cord blood was almost as high as that in maternal blood (not significant, NS). There were significant positive correlations between maternal and cord concentrations of each carcinogen.

Table 3 shows correlations among the concentrations of As, Cd, Ni, and Be in maternal or cord blood. In maternal blood, there were significant positive correlations between As and Cd, Ni and Be, but significant negative correlations between Cd and Be, and between Cd and Ni (P<0.05). In cord blood, there was a significant positive correlation between Ni and Be and significant negative correlations between Cd and Be, and Cd and Ni (P<0.05).

Table 4 shows the effect of some influencing factors on maternal concentrations of the four carcinogenic metals. There was a significant difference in maternal As level between mothers exposed to harmful occupational factors during pregnancy and unexposed mothers; the former showed a significantly higher median As level than the latter (13.96 μg/L *vs*. 5.18 μg/L, P<0.01). There was no significant change in maternal As level in mothers grouped by other environmental factors or some abnormal gravidity/parturition factors. The mothers exposed to harmful occupational factors during pregnancy also had significantly higher Cd levels than did unexposed mothers (2.49 μg/L *vs*. 1.06 μg/L, P<0.05). Furthermore, mothers living close to major transportation routes had significantly higher Cd levels than those living far away (2.79 μg/L *vs*. 1.06 μg/L, P<0.05). Also, mothers who had been exposed to second-hand smoke during pregnancy had significantly higher Cd levels than did unexposed mothers (1.97 μg/L *vs*. 0.85 μg/L, P<0.05). In addition, higher maternal Cd levels were found in mothers with a history of spontaneous abortion (4.13 μg/L *vs*. 1.06 μg/L, P<0.01). There were significantly increased Ni levels in mothers exposed to harmful occupational factors during pregnancy compared with unexposed mothers (357.69 μg/L *vs*. 62.65 μg/L, P<0.05). Also, mothers living close to an industrial chimney had significantly higher Ni levels than those who lived far away (451.40 μg/L *vs*. 59.17 μg/L, P<0.05). As for maternal Be levels, mothers whose age at delivery age was ⩾35 years had significantly higher levels than did younger mothers (0.05 μg/L *vs*. 0.01 μg/L, P<0.05). Additionally, higher maternal Be levels were found in mothers with a history of stillbirth (0.05 μg/L *vs*. 0.01 μg/L, P<0.05). Other environmental factors and abnormal gravidity/parturition factors had no significant positive associations with maternal Be level: on the contrary, it tended to decrease in such women.

TABLE 3

Correlations among Concentrations of the Four Carcinogenic Metals in Maternal and Cord Blood

Maternal Blood							Cord Blood						
	Be		Ni		Cd			Be		Ni		Cd	
	r	P	r	P	r	P		r	P	r	P	r	P
As	–0.11	0.27	0.04	0.69	0.21	0.02	As	0.03	0.76	0.04	0.70	–0.01	0.92
Cd	–0.46	0.00	–0.32	0.00			Cd	–0.58	0.00	–0.59	0.00		
Ni	0.30	0.00					Ni	0.39	0.00				

Note. P Spearman correlation analysis (among concentrations of As, Cd, Ni, and Be in maternal or cord blood).

TABLE 4

Comparing the Maternal Blood Levels (μg/L) of the Four Carcinogens between the Population Grouped by Environmental Influencing Factors and Histories of Maternal Abnormal Gravidity and Parturition

Parameter	*n*	As			Cd			Ni			Be		
		Median	Interquartile Range	*P*	Median	Interquartile Range	*P*	Median	Interquartile Range	*P*	Median	Interquartile Range	*P*
Maternal Age; yrs													
< 35	112	5.30	5.02	0.90	1.14	2.37	0.56	71.15	178.25	0.34	0.01	0.03	0.02
⩾35	13	5.18	10.33		1.65	2.96		65.03	465.43		0.05	0.10	
History of Spontaneous Abortion													
No	115	5.30	5.03	0.53	1.06	2 .29	0.00	69.44	182.55	0.65	0.02	0.03	0.65
Yes	10	6.25	6.95		4.13	2.46		64.17	178.13		0.01	0.06	
History of Stillbirth													
No	120	5.14	4.78	0.69	1.15	2.40	0.92	59.17	165.93	0.43	0.01	0.03	0.04
Yes	5	5.79	5.27		1.09	3.72		95.04	274.33		0.05	0.10	
Exposure to Harmful Occupational Factors													
No	111	5.18	4.43	0.00	1.06	2.38	0.03	62.65	162.07	0.02	0.02	0.03	0.02
Yes	14	13.96	11.84		2.49	2.82		357.69	507.37		0.01	0.00	
Residential House close to Major Transportation Route													
No	101	5.30	5.12	0.95	1.06	2.27	0.01	71.15	177.37	0.12	0.02	0.03	0.21
Yes	24	5.59	6.61		2.79	4.35		38.96	350.95		0.01	0.03	
Second-hand Smoke during Pregnancy													
No	75	5.34	5.24	0.59	0.85	2.45	0.04	67.73	173.42	0.54	0.02	0.03	0.02
Yes	50	4.74	5.13		1.97	3.66		73.57	369.73		0.01	0.02	
Residential House close to Industrial Chimney													
No	116	5.30	3.38-8.49	0.62	1.07	0.19-2.52	0.33	59.17	34.43-196.50	0.01	0.02	0.01-0.04	0.41
Yes	9	4.76	2.90-12.39		1.73	1.18-3.08		451.40	200.10-486.40		0.01	0.01-0.03	

Note. P Mann-Whitney *U*-test (between population grouped by different influencing factors).

Table 5 shows the final multiple linear regression model predicting the interactions of some environmental factors or demographic independent variables with As, Cd, Ni, and Be levels detected in maternal blood. Exposure to harmful occupational factors showed a positive association with log-transformed values of maternal As concentration. Two independent variables, exposure to second-hand smoke during pregnancy and a history of spontaneous abortion, were positively associated with log-transformed values of maternal Cd. Living close to an industrial chimney was positively associated with log-transformed values of maternal Ni. High maternal age at labor was positively associated with maternal log-transformed values of Be.

DISCUSSION

We have measured As, Cd, Ni, and Be concentrations in maternal and fetal blood samples and have indicated some environmental influences. In fact, a few studies[16-18] examined the levels of As and Cd in maternal and cord blood. The metabolism of As during early human development and the association of As exposure during pregnancy in women with fetal loss and infant death have also been analyzed[18-20].

However, there are few studies investigating multiple metals in terms of fetal exposure to carcinogens *in utero*. Therefore, we hope that our study might trigger a new research field.

It is well known that developing organisms are especially vulnerable to exposure to some toxicants[7,21], especially carcinogens, as they undergo rapid cell proliferation and extensive differentiation. Waalkes *et al*. reported that, in a series of mouse experiments, a short period of maternal exposure to As in the drinking water resulted in multi-tissue carcinogenesis in the adult offspring[22]. Diwan *et al*. showed in F344/NCr rats that Ni (II) was a potent transplacental initiator of epithelial tumors in the fetal rat kidney and a complete transplacental carcinogen for the pituitary[15]. Thus, these carcinogenic metals could be important transplacental carcinogens.

In addition, As, Cd, Ni, and Be have been demonstrated to have genotoxic effects to different degrees *in vitro* and *in vivo*[23-31]. The induction of cancers by genotoxic carcinogens is often considered to be linear even at low doses in dose-response analysis and thus do not exhibit a lower threshold[32]. In another words, no dose level can be a ‘zero’ risk. Regardless of the dose of genotoxic carcinogens, if an embryo is exposed to them *in utero* there is a risk

TABLE 5

Multiple Linear Regression Analysis of Influencing Factors Associated with Log-transformed Values of Detected Maternal Blood As, Cd, Ni, and Be Levels (> Detection Limit)

Dependent Variable	Variable	B	SE	β	*t*	*P*
lgAs (*n*=123)						
	Exposure to Harmful Occupational Factors (no. *vs*. yes)	0.41	0.15	0.31	2.70	0.01
lgCd (*n*=95)						
	Second-hand Smoke During Pregnancy (no. *vs*. yes)	0.23	0.11	0.26	2.16	0.04
	History of Spontaneous Abortion (no. *vs*. yes)	0.37	0.18	0.25	2.07	0.04
lgNi (*n*=118)						
	Residential House close to industrial Chimney (no. *vs*. yes)	0.77	0.27	0.35	2.91	0.01
lgBe (*n*=69)						
	Maternal age (< 35 vs. ⩾35ys)	0.36	0.14	0.44	2.51	0.02

Note. B Unstandardized coefficients. SE B's standard error. β Standardized Coefficients. *t* test of significance. *P* two-tail error probability.

for postnatal cancers to be induced. Moreover, some carcinogenic metals including As, Cd, and Ni, also show efficient cocarcinogenesis. This indicates that even if each of these carcinogens is at a low concentration, the risk of developing cancers could be enhanced by such syncarcinogenic effects. Therefore, more attention should be paid to the potentially transplacental carcinogenesis induced by the coexposure of these carcinogenic and genotoxic metals. In our study, most mothers and infants were faced with such coexposure.

Comparing the four carcinogenic metal concentrations in maternal blood with those in cord blood suggests that the placental barrier differed between metals in its effectiveness. The placenta prevented part of the maternal As, Cd, and Ni from entering the fetal body. However, it did not offer effective protection against Be. Positive relationships in the four carcinogen concentrations between maternal and cord blood revealed a risk that the exposure of the fetus to these environmental carcinogens would be increased proportionately to the maternal concentrations. Therefore, the first step in prenatal care should be to avoid or reduce maternal exposure to these carcinogenic metals.

We also explored the effects of influencing factors, especially the environmental ones, on these carcinogen levels in maternal blood. Increased maternal concentrations were associated with exposure to harmful occupational factors. Also, the latter entered the regression model as the only influencing factor. This indicates that occupational environmental factors may be the most important source of exposure to these carcinogenic metals in pregnant women. Thus, cigarette smoking is a major source of Cd exposure[33] and the blood level of Cd in smokers is generally 3-4 times higher than that in nonsmokers[34]. In our investigation, all participants were nonsmokers, while 40% (50/125) of them were exposed to second-hand smoke. According to the analysis of variance, the blood level of Cd in mothers exposed to second-hand smoke was double that of the mothers who were not. This was in accordance with the literature. Our results indicate that second-hand smoke is a risk factor for increasing the blood level of Cd in pregnant women. It has been reported that suspended particulate matter resulting from traffic pollution contains some toxic metals, such as Pb and Cd[35]. Our results showed that increased maternal Cd concentration was also associated with living close to a major transportation route. This indicates that the exposure of pregnant women to transport pollution could also contribute to the maternal Cd burden. We also found an association between increased maternal Ni levels and living close to an industrial chimney. This indicates that industrial pollution is an important source of maternal exposure to Ni.

Our results showed that a history of spontaneous abortion was associated with high maternal Cd levels, being accordance with reports that Cd has a wide range of detrimental effects on mammalian reproduction[36-38]. Animal experiments showed that clearance of inhaled Be was multiphasic and half was cleared in about 2 weeks; the remainder was removed slowly[32]. In our study, Be concentrations in women ⩾35 years old were higher than those aged <35 years, indicating potential accumulation of Be in the body. In addition, a history of stillbirth was associated with high maternal Be levels: consistent with the report by Sharma *et al*.[39]. They observed that a single administration of beryllium nitrate in rats during gestation caused reductions in fetal and placental

weights, in the numbers of implantation sites and corpora lutea, as well as causing postimplantation loss, stunted growth and an increase in the number of fetal resorptions. Our findings of increased maternal Cd and Be level associated with some histories of abnormal gravidity and parturition indicated that these factors could help us to focus on certain at-risk populations.

In conclusion, our results have revealed that these mothers and their fetuses had indeed been exposed to all four carcinogens and that the exposure levels in fetuses were proportional to the maternal concentrations. Moreover, some environmental pollution factors were associated with increased levels of these carcinogens in pregnant women. Therefore, it is imperative to investigate the causal relationships between prenatal exposure of fetus to these carcinogenic metals and any postnatal development of cancer. Meanwhile, to avoid or prevent such postnatal development of cancer, we should also prioritize prenatal care by decreasing the exposure of pregnant women to these carcinogens as much as possible.

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