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Health Promotion and Chronic Disease Prevention in Canada: Research, Policy and Practice **is the monthly, online scientific journal of the Health Promotion and Chronic Disease Prevention Branch of the Public Health Agency of Canada. The journal publishes articles on disease prevention, health promotion and health equity in the areas of chronic diseases, injuries and life course health. Content includes research from fields such as public/community health, epidemiology, biostatistics, the behavioural and social sciences, and health services or economics.**

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Arsenic exposure and type 2 diabetes: results from the 2007–2009 Canadian Health Measures Survey

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Abstract

Introduction: Inorganic arsenic and its metabolites are considered dangerous to human health. Although several studies have reported associations between low-level arsenic exposure and diabetes mellitus in the United States and Mexico, this association has not been studied in the Canadian population. We evaluated the association between arsenic exposure, as measured by total arsenic concentration in urine, and the prevalence of type 2 diabetes (T2D) in 3151 adult participants in Cycle 1 (2007–2009) of the Canadian Health Measures Survey (CHMS).

Methods: All participants were tested to determine blood glucose and glycated hemoglobin. Urine analysis was also performed to measure total arsenic. In addition, participants answered a detailed questionnaire about their lifestyle and medical history. We assessed the association between urinary arsenic levels and T2D and prediabetes using multivariate logistic regression while adjusting for potential confounders.

Results: Total urinary arsenic concentration was positively associated with the prevalence of T2D and prediabetes: adjusted odds ratios were 1.81 (95% CI: 1.12–2.95) and 2.04 (95% CI: 1.03–4.05), respectively, when comparing the highest (fourth) urinary arsenic concentration quartile with the lowest (first) quartile. Total urinary arsenic was also associated with glycated hemoglobin levels in people with untreated diabetes.

Conclusion: We found significant associations between arsenic exposure and the prevalence of T2D and prediabetes in the Canadian population. Causal inference is limited due to the cross-sectional design of the study and the absence of long-term exposure assessment.

Keywords: *urinary arsenic, Canadian Health Measures Survey, type 2 diabetes, population survey*

Key findings

- Our study included 1520 men and 1631 women aged 20 to 79 years with known urine arsenic measures. Diabetes was defined as a fasting glucose level of 126 mg/dL or a hemoglobin A1c (HbA1c) of 6.5% or higher, or diabetes treatment.
- Total urinary arsenic concentration was positively associated with the prevalence of T2D and prediabetes: adjusted odds ratios were 1.81 (95% CI: 1.12–2.95) and 2.04 (95% CI: 1.03–4.05), respectively, when comparing the highest (fourth) urinary arsenic concentration quartile with the lowest (first) quartile.
- Total urinary arsenic was also associated with glycated hemoglobin levels in people with untreated diabetes.

Introduction

The *Canadian Environmental Protection Act* describes inorganic arsenic and its metabolites as toxic enough to ''constitute a danger in Canada to human life or health.''[1] In fact, arsenic is one of the most toxic elements in the environment, where it is present in both organic and inorganic forms, mostly from natural sources. Canadians are exposed to arsenic mainly through food as well as through drinking water, soil and ambient air. Although the concentration of arsenic in drinking water in most municipalities in Canada is less than the Health Canada guideline of 10 µg/L,[2] there are areas in several provinces—particularly those served by private wells—where concentrations exceed this amount.[2]

Seafood is the largest dietary source of organic arsenic.[3,4] The major organic arsenical in most seafood is arsenobetaine, which is considered harmless.[5] Inorganic arsenic, the most toxic form of the metalloid,[6] is metabolized in the liver and transformed into monomethyl and dimethyl species, which are excreted in urine along with unmetabolized inorganic arsenic.[6,7] The toxicity of arsenic may be altered by selenium.[8]

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Low-level inorganic arsenic exposure increases the risk of pre-malignant skin lesions,[9,10] hypertension[11,12] and neurological dysfunctions.[13] Observational studies in humans and experimental studies in animals have found arsenic to be potentially diabetogenic.[14] This effect of arsenic on type 2 diabetes (T2D), a disease which affects approximately 346 million people worldwide[15,16] and 2.4 million people in Canada,[17] is a major public health issue.[14,18]

Early studies were conducted in populations exposed to high levels of arsenic in drinking water in Taiwan and Bangladesh or were occupational studies of copper smelter and glass workers in the United States and Europe. Measures of exposure vary between these studies, from area-wide exposure estimates based on measurement of arsenic in drinking water to individual-level exposure estimates based on detailed water consumption history, work history or actual biomarkers of exposure. A systematic literature review of epidemiological research of arsenic exposure and T2D showed that most of these studies used ecological methods of exposure assessment and did not adjust for potential confounders.[14] Some of the studies that used urinary arsenic levels as a biomarker of exposure did not find any association between arsenic exposure and diabetes[19,20] while others reported a dose-response relationship.[21–27] Moreover, there are no studies evaluating this association in the Canadian population. Therefore, the main objective of this study was to evaluate the association between arsenic exposure, as measured by total arsenic concentration in urine, and the prevalence of T2D in adults who participated in the first cycle of the Canadian Health Measures Survey (CHMS).

Methods

Study population

We used cross-sectional data from the CHMS, Cycle 1, a complex sampling survey designed to collect data on a representative sample of approximately 5600 Canadians aged 6 to 79 years, which took place from 2007 to 2009. The CHMS covers approximately 96.3% of the Canadian population living in private dwellings in all the provinces and territories, but excludes institutional residents and full-time members of the Canadian Forces as well as those living on reserves and certain remote areas. We excluded participants aged less than 20 years. As a result, data from 3517 participants aged 20 to 79 years were available for this study.

Data collection

Data were collected from March 2007 through February 2009 from 16 sites in the Atlantic provinces (Moncton, New Brunswick), Quebec (Québec, Montréal, Monteregie, South Mauricie), Ontario (Charlington, North York, Don Valley, St. Catharines, Kitchener, Northumberland Country), the Prairies (Edmonton and Red Deer, Alberta), and British Columbia (Vancouver, Williams Lake and Quesnel).[28] The survey consisted of a personal household interview followed by a physical examination and biological sampling at a mobile examination centre within 2 days to 6 weeks of the interview. Overall, the combined response rate was 51.7 % for Cycle 1 of CHMS.[29]

Exclusion criteria

For this study, the following exclusion criteria were added: type 1 diabetes ($n = 19$), pregnancy ($n = 11$) and liver problems ($n = 72$). This last criterion was chosen because individuals with elevated liver enzymes, even within the normal range as defined in clinical practice, are at higher risk of diabetes.[30] We also excluded participants who reported high seafood and shellfish consumption ($\geq$ 104 times a year) or high fish consumption ($\geq$ 156 times a year) ($n = 264$) based on the distribution of the sea food consumption in number of meals a week because those participants were likely to have high seafood-derived arsenic levels.

Our final analyses included data from 3151 participants aged 20 to 79 years.

Urine arsenic assessment

Collection of urine samples

Mid-stream spot urine samples (60 ml) were obtained from participants in the mobile examination centres. Urine samples for arsenic analysis were collected in arsenic-free containers, shipped on dry ice and stored at -20°C.

Analysis of urine samples

Total arsenic was measured at the Laboratoire de toxicologie of the Institut national de santé publique du Québec following a standardized protocol accredited under ISO 17025 and using numerous internal and external quality control programs.[31] Urine samples were diluted with an aqueous nitric acid solution (0.5%) and analyzed for total arsenic by inductively coupled plasma-mass spectrometry (ICP-MS) on an Elan DRC II instrument. Matrix-matched calibration was performed using urine from non-exposed individuals.[32] Urinary concentrations were also corrected for creatinine concentrations, to account for urine dilution, which were determined by the Jaffe method.[33] The limit of detection for total urinary arsenic was 0.524 µg/L. The percentage of study participants with total urinary arsenic levels below the limit of detection was 0.35%.

Type 2 diabetes end points

Prevalent T2D was defined as a fasting serum glucose level of 126 mg/dl or more ($\geq$ 7 mmol/L) or a glycated hemoglobin (HbA1c) of 6.5% or more, as recommended by the World Health Organization (WHO) and the American Diabetes Association (ADA).[34,35] A self-reported physician diagnosis of diabetes or the self-reported use of insulin or oral hypoglycemic medication were also used as alternative criteria. Prevalent prediabetes was defined as a fasting serum glucose of between 100 and 125 mg/dl (5.6–6.9 mmol/L) or HbA1c between 5.7% and 6.4% (as recommended by WHO and ADA).[34,35]

Fasting blood glucose

Fasting blood samples were collected from 1714 study participants in the morning, after they had fasted for at least 10 hours. Venous plasma glucose was determined using the clinical chemistry system, VITROS 5.1 FS Ortho-Clinical Diagnostics.[36]

Glycated hemoglobin level

HbA1c concentrations were measured using clinical chemistry system VITROS 5.1 FS Ortho-Clinical Diagnostics.[37]

Other laboratory parameters

Urinary creatinine was determined using the colorimetric end-point Jaffe method to account for urine dilution in spot urine samples. The absorbance was read at 505 nm on a Hitachi 917 chemistry autoanalyzer (C-530).[38]

Urinary selenium concentrations were measured using ICP-MS in the same analysis as arsenic (described above). The limit of detection was 0.08 µmol/L.

Other variables

Blood pressure was measured electronically with an automated oscillometric device (BpTRU™).[39] We used the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure* definition of hypertension: systolic blood pressure of 140 mmHg or above and diastolic blood pressure of 90 mmHg or above. We also accepted the use of hypertension medications or self-reported medical diagnosis of hypertension as criteria.

Questionnaire

CHMS questionnaire data included self-reported information on sociodemographic variables and an in-depth health questionnaire. The CHMS age groups were 20 to 39, 40 to 59 and 60 to 79 years. Racial background was defined as White and non-White. The level of education was defined as less than secondary, secondary graduation, some postsecondary and postsecondary graduation. Smoking status was divided into three categories: current smoker, former smoker and non-smoker. Alcohol consumption was divided into three categories: current, former and never.

The overall frequency of seafood consumption and of shellfish consumption was categorized into four groups based on the consumption of at least one type of sea fish on the nutrition CHMS survey checklist and of shellfish: less than 12 times per year, 12 to 51 times per year, 52 to 103 times per year and 104 to 155 times per year. The categorization of sea fish and shellfish was based on the distribution of the sea food consumption in terms of number of meals a week, which was then converted into number of meals per year in the study population.

Body mass index (BMI) was calculated by dividing measured weight in kilograms by measured height in metres squared.

Participants were asked if they used municipal treated tap water, private well water, bottled water or other sources of drinking water. We categorized the responses into two: municipal tap water or other.

Statistical analysis

All statistical analyses were performed using the statistical package SAS version 9.3 (SAS Institute Inc., Cary, NC, US), incorporating the CHMS sampling weights. We completed variance estimation (95% confidence intervals [CI]) and significance testing (chi-square) on differences between estimates using the bootstrap weights provided with the data, which account for the complex sampling design.[40] We used descriptive statistics (frequencies, geometric means) to estimate total urinary arsenic concentrations by participant's characteristics. Total urinary arsenic, selenium, fasting plasma glucose and HbA1c were log-transformed for geometric mean analyses. Concentrations below the limit of detection of the analytical method were replaced by a value equal to half of the limit of detection.[42] For each of these laboratory variables, the geometric mean concentrations and 95% CI in participants with prediabetes and diabetes were compared with values in control participants without diabetes or prediabetes, using multivariate regression models. Total urinary arsenic concentration was considered either as a continuous variable or in quartiles.

We used binomial (non-diabetes versus prediabetes or diabetes) and ordinal logistic regression analyses (with the three categories simultaneously) to estimate odds ratios (OR) with their 95% confidence intervals. Our logistic regression models for total urinary arsenic concentrations and diabetes end points were fitted with increasing degrees of adjustment. First, we adjusted for age, sex, educational level, alcohol drinking status, smoking status, BMI, hypertension and for urinary creatinine to account for urine dilution in spot urine samples.[43] Each model was further adjusted for seafood consumption using the categories explained in the questionnaire section.

We analyzed the association between urinary arsenic concentrations and HbA1c in models stratified by diabetes treatment status because HbA1c is an indicator of diabetes control.[44] We used binomial logistic regression models to estimate odds ratios of HbA1c by urinary arsenic concentrations with the same adjustment strategy described in the primary diabetes analysis. We tested the interaction of selenium with arsenic because selenium may be protective against arsenic-induced toxicity.[45]

We also used propensity scores to evaluate the potential selection bias caused by non-respondents by balancing the distribution of covariates on the main risk factor levels.[46] A propensity score–weighted regression model was fitted to compare the outcome of T2D and of prediabetes with urinary arsenic exposure and to study the possible predictors of T2D. A propensity score–weighted regression model was then used to assess the association of urinary arsenic exposure among people with untreated diabetes with biological outcome.

Results

Participant characteristics

Our study included 3151 participants (1520 men and 1631 women). The weighted prevalence of T2D and prediabetes in the study population was 7.1% (95% CI: 6.2%–7.9%) and 26.4% (95% CI: 24.8%–27.9%), respectively. Participants with T2D or prediabetes were significantly older, more frequently non-White, less educated and more likely to have a higher BMI compared with the control participants with neither prediabetes nor T2D (Table 1). The general characteristics of participants

TABLE 1
Diabetes status based on characteristics of study participants, CHMS, Cycle 1, 2007–2009

Characteristics	Diabetes status of participants, % (95% CI)[a]		
	Neither diabetes nor prediabetes n = 2054	Prediabetes[b] n = 831	Type 2 diabetes[c] n = 225
Age, years			
20–39	42.0 (39.8–42.8)	18.7 (17.6–19.8)	8.9 (8.4–10.1)
40–59	35.5 (34.5–36.4)	38.8 (38.1–39.5)	27.6 (26.8–28.7)
60–79	22.5 (21.9–23.6)	42.5 (41.9–43.8)	63.5 (62.0–64.8)
Sex			
Female	46.9 (45.2–47.8)	48.4 (47.9–49.7)	55.1 (54.2–56.5)
Male	53.1 (51.4–54.3)	51.6 (49.2–52.8)	44.9 (44.0–45.8)
Education			
≤ High school	10.7 (10.2–11.8)	18.5 (18.2–18.9)	24.4 (23.9–24.8)
Some post-secondary	25.4 (24.9–25.1)	24.3 (23.1–24.8)	25.3 (24.2–26.2)
≥ University	63.9 (63.7–64.6)	57.2 (56.4–58.1)	50.3 (50.2–51.3)
Ethnicity			
White	88.0 (79.2–88.7)	85.9 (84.8–86.8)	82.7 (81.3–83.1)
Non-White	12.0 (11.2–12.8)	14.1 (13.2–15.4)	17.3 (16.2–17.8)
Smoking status			
Current	21.6 (20.1–21.8)	21.2 (20.9–21.7)	15.5 (14.9–16.1)
Former	29.3 (28.7–30.0)	35.6 (35.2–36.3)	38.7 (38.2–39.4)
Never	49.1 (48.5–49.8)	43.2 (42.6–43.8)	45.8 (45.3–46.2)
Alcohol consumption			
Current	88.2 (87.5–88.9)	79.7 (78.8–80.3)	70.6 (69.2–79.9)
Former	7.4 (6.9–7.8)	14.8 (14.2–16.1)	20.6 (19.9–21.4)
Never	4.4 (4.0–4.8)	5.5 (4.9–5.8)	8.8 (8.1–9.2)
BMI, kg/m^2			
<25	42.1 (41.6–42.7)	26.5 (25.7–27.2)	15.3 (14.4–15.9)
25–29	32.7 (31.8–33.0)	31.5 (31.1–32.4)	26.6 (26.2–27.4)
≥30	25.2 (24.3–25.8)	42.0 (41.2–42.9)	58.1 (57.7–60.2)
Water source			
Municipal tap water	87.2 (86.5–87.8)	85.9 (85.2–86.3)	83.3 (82.9–84.3)
Other	12.8 (12.3–13.6)	14.1 (13.5–14.9)	6.7 (6.2–7.1)

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin.

[a] Missing data, n = 41.

[b] Fasting serum glucose = 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c = 5.7%–6.4%.

[c] Fasting serum glucose ≥ 126 mg/dL (≥ 7 mmol/L) or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

with prediabetes were between those of participants with diabetes and of controls (Table 1). The source of water was the same for all the three groups.

The geometric mean of total urinary arsenic concentrations tended to be higher in female, older and non-White participants and in current alcohol drinkers and former smokers, but the differences were not statistically significant (Table 2).

Arsenic and type 2 diabetes

Geometric means of total urinary arsenic concentrations were greater in participants with diabetes (12.9 µg/L; 95% CI: 9.4–17.7 µg/L) and prediabetes (12.5 µg/L; 95% CI: 10.1–15.4 µg/L) than in controls (11.5 µg/L; 95% CI: 9.4–14.1 µg/L). After correction for urinary creatinine, we observed the same difference for participants with prediabetes and diabetes compared to controls (Table 3). Urinary selenium levels did not differ significantly between the three groups.

Table 4 shows the results for the models derived from the binomial logistic regression analysis of participants with T2D and prediabetes according to urinary arsenic quartiles. Participants in the highest quartile of total urinary arsenic showed a nearly 2-fold higher risk of T2D compared with those in the lowest quartile, after adjustment for sociodemographic characteristics (age and gender), diabetes risk factors, urinary creatinine and seafood consumption (OR = 1.8; 95% CI: 1.1–3.0). Similarly, participants with prediabetes showed a similar association after adjustment for potential confounders (OR = 2.1; 95% CI: 1.0–4.1).

Ordinal logistic regression for T2D, prediabetes and controls together resulted in total urinary arsenic concentrations and diabetes status similar to the previous models for diabetes or prediabetes only. Moreover, there was a general trend of increasing ORs with total urinary arsenic increase and a statistically significant dose response (Table 5).

Finally, total urinary arsenic was not associated with HbA1c among people with treated diabetes (Table 6), but was strongly associated with HbA1c among untreated participants after adjustment for potential confounders.

Selenium did not interact with any arsenic effect in this study (data not shown).

After using the propensity score–inverse probability weight, the results were found to be similar to those found from the initial regression models (data not shown). A regression model conducted to assess the association of urinary arsenic exposure in people with untreated diabetes with biological outcome resulted in similar association (data not shown).

Discussion

We found a positive association between total urinary arsenic concentrations and the prevalence of T2D and prediabetes,

TABLE 2
Levels of urinary arsenic based on participants' characteristics in CHMS, Cycle 1, 2007–2009

Population characteristics	N (%)	Geometric means of urinary arsenic, µg/L (95% CI)	
		Urinary arsenic not corrected for creatinine, µg/L	Urinary arsenic corrected for creatinine, µg/ creatinine
Age, years			
20–39	1059 (33.6)	11.4 (10.0–13.1)	12.8 (9.4–17.4)
40–59	1126 (35.7)	12.0 (10.0–14.3)	15.4 (12.3–19.2)
60–79	966 (30.7)	11.4 (9.3–14.0)	16.0 (11.8–21.6)
Sex			
Female	1520 (48.2)	10.2 (7.6–13.7)	16.4 (12.5–21.5)
Male	1631 (51.8)	13.2 (10.0–17.5)	12.8 (9.6–17.0)
Education			
≤High school	429 (13.6)	11.2 (9.2–13.7)	13.7 (10.6–17.7)
Some post-secondary	780 (24.8)	10.6 (8.4–13.2)	13.5 (10.7–16.9)
≥University	1942 (61.6)	14.1 (10.2–19.7)	17.1 (12.8–22.8)
Ethnicity			
White	2708 (85.9)	11.2 (9.5–13.2)	13.7 (11.1–16.9)
Non-White	443 (14.1)	14.0 (9.6–20.5)	18.4 (12.0–28.3)
Smoking status			
Current	655 (20.8)	10.5 (8.3–13.2)	12.0 (8.1–17.8)
Former	990 (31.4)	12.6 (10.0–15.9)	15.5 (12.0–20.0)
Never	1506 (47.8)	11.7 (10.0–13.6)	15.0 (12.5–18.1)
Alcohol consumption			
Current	2663 (84.5)	11.9 (9.9–14.4)	14.5 (11.5–18.3)
Former	334 (10.6)	9.7 (5.7–16.6)	13.9 (10.9–17.7)
Never	154 (4.9)	11.3 (8.2–15.6)	16.3 (11.3–23.5)
BMI, kg/m^2			
<25	1157 (36.7)	11.7 (10.3–13.3)	16.0 (12.7–20.1)
25–29	989 (31.4)	12.1 (9.9–14.7)	14.1 (11.6–17.0)
≥30	1005 (31.9)	11.2 (9.1–13.8)	13.0 (9.8–17.4)
Water source			
Municipal tap water	2702 (86.0)	12.0 (10.1–14.2)	14.9 (12.0–18.6)
Other	449 (14.0)	10.0 (5.9–16.9)	12.2 (6.8–21.9)

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin.

after adjustment for several potential confounders and for seafood consumption, in a representative sample of Canadian adults who participated in the 2007–2009 CHMS. The association between arsenic and HbA1c was significant only in participants with untreated diabetes.

These results are similar to those of several previous studies of lower levels of exposure as well as those with better measures of outcome and exposure.[14,26] The latter estimated exposure to inorganic arsenic and its metabolites[21,22,24] or measured inorganic arsenic as total arsenic with adjustment of results for markers of seafood intake.[23,26] Our findings are also in line with results from a cross-sectional study using data from the National Health Nutrition and Examination Survey (NHANES), suggesting an increased risk for diabetes with urinary arsenic concentrations after adjustment for arsenic contribution from seafood.[23] After adjusting for diabetes risk factors and markers of seafood intake, Navas-Acien et al.[23] found the OR for T2D to be 2.6 (95% CI: 1.1–6.0) when comparing participants in the 80th versus the 20th percentile of total urinary arsenic concentration (7.4 µg/L vs 1.6 µg/L). The researchers also reported a positive association between arsenic concentrations and HbA1c after adjusting for biomarkers of seafood intake (urinary arsenobetaine and mercury), although the association was not statistically significant.[23]

Rhee et al.[26] analyzed data from the Korean KNHANES cross-sectional study (2008–2009) and found that the ORs for diabetes mellitus in all participants were 1.56 (95% CI: 1.03–2.36) within the highest urinary arsenic quartile after adjusting for serum mercury level as an indicator of seafood intake.

The literature on experimental studies on arsenic and diabetes in animals is considered inconclusive, but this has been explained as being due to methodological problems in those studies.[14] In vitro or mechanistic studies suggest several pathways by which arsenic could influence pancreatic β-cell function and insulin sensitivity, including oxidative stress and effects on glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and calcium signalling.[47–50]

Urinary arsenic is generally considered the most reliable indicator of recent exposure to arsenic and is used as the main biomarker of exposure.[51] Arsenic tends not to accumulate in the body but is readily excreted via the kidneys.[52] Urinary profiles of inorganic arsenic metabolites have been used in some epidemiological studies to estimate exposure to inorganic arsenic,[14,53] but such data were not available in CHMS Cycle 1.

By excluding participants who reported high seafood and shellfish consumption and adjusting our models for seafood consumption for other categories of sea fish and seafood consumption, we indirectly controlled the contribution of the low toxicity organic arsenicals of marine origin to total urinary arsenic in order to isolate the influence of inorganic arsenic concentrations. Longnecker,[54] in a commentary entitled ''On confounded fishy results regarding arsenic and diabetes,'' recognized the merit of the measure of total urinary arsenic adjusted for markers of seafood intake as an indicator of inorganic arsenic exposure in a population with low exposure.[23] However, this was challenged by Steinmaus et al.[20] who found no

TABLE 3
Laboratory variables for CHMS participants with prediabetes[a] or diabetes[b] and controls, CHMS cycle 1, 2007–2009

Laboratory analyses	Geometric means (95% CI)		
	Controls (N = 2054)	Prediabetes[a] (N = 831)	Diabetes[b] (N = 225)
Urinary arsenic, μg/L[c]	11.5 (9.4–14.1)	12.5 (10.1–15.4)	12.9 (9.4–17.7)
Urinary arsenic, μg/g creatinine[d,e]	12.3 (9.8–15.4)	15.5 (10.9–22.0)	14.6 (10.5–20.4)
Selenium, μg/L[f]	46.9 (45.1–48.7)	45.8 (43.2–47.9)	49.9 (44.3–54.7)
Fasting glucose, mg/dl[g]	4.7 (4.3–5.2)	5.3 (4.7–5.9)	6.5 (4.2–10.0)
HbA1c, %[h]	5.3 (4.9–5.7)	5.8 (5.3–6.3)	6.9 (4.8–9.8)

Abbreviations: CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin.

[a] Fasting serum glucose = 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c 5.7%–6.4%.

[b] Fasting serum glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

[c] Urinary arsenic not corrected for urinary creatinine.

[d] Urinary arsenic corrected for urinary creatinine.

[e] Missing data for urinary arsenic corrected for urinary creatinine, n = 39.

[f] Missing data for selenium, n = 76.

[g] Missing data for fasting glucose, n = 1437.

[h] Missing data for HbA1c, n = 106.

association between risk of diabetes and inorganic arsenic exposure based on inorganic and methylated metabolites.

Because drinking water is an important source of arsenic exposure, we assessed the study participants' sources of drinking water and found no association between this and diabetes status. This might be due to our crude classification of exposure or the low level of arsenic in Canadian drinking water. The toxicity of arsenic species can be reduced by selenium through the formation of an arsenic–selenium complex;[45] however, we found no interaction between selenium and arsenic.

Strengths and limitations

One of the strengths of our study is that it was population based and conducted on a large sample of adults assessed as having diabetes or prediabetes based on objective criteria proposed by the ADA and WHO.[34,35] In addition, the HbA1c test

TABLE 4
Binomial logistic regression analysis of participants with prediabetes[a] and type 2 diabetes[b] with controls based on urinary arsenic concentration quartiles, CHMS, Cycle 1, 2007–2009

Urinary arsenic (μg/L)[c]	Number of participants[d]			Crude OR (95% CI)		Adjusted OR (Model 1)[e] (95% CI)		Adjusted OR (Model 2)[f] (95% CI)	
	Controls (n = 2054)	With prediabetes[a] (n = 831)	With diabetes[b] (n = 225)	Prediabetes[a]	Diabetes[b]	Prediabetes[a]	Diabetes[b]	Prediabetes[a]	Diabetes[b]
< 5.71	554	171	46	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
5.71–11.20	520	197	54	1.14 (0.86–1.52)	1.44 (1.08–1.92)	1.38 (0.87–2.21)	1.06 (0.60–1.87)	1.37 (0.88–2.17)	1.20 (0.70–2.05)
11.21–22.98	530	192	64	1.28 (0.92–1.62)	1.65 (1.07–2.54)	1.46 (0.92–2.32)	1.31 (0.63–2.74)	1.46 (0.92–2.35)	1.55 (0.83–2.90)
≥ 22.99	450	271	61	1.48 (1.18– 2.50)	1.92 (1.11–3.33)	2.04 (1.03–4.05)	1.54 (0.74–3.18)	2.14 (1.02–4.07)	1.81 (1.12–2.95)
p for trend				.015	.019	.042	.246	.043	.017

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

[a] Fasting serum glucose 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c 5.7%–6.4%.

[b] Fasting serum glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

[c] Urinary arsenic not corrected for urinary creatinine.

[d] Data missing for n = 41 participants.

[e] Model 1 adjusted for urinary creatinine, age, sex, alcohol status, smoking status, educational status, BMI and hypertension.

[f] Model 2 adjusted as for Model 1 plus seafood consumption.

TABLE 5
Multivariable ordinal logistic regression analysis comparing participants with prediabetes[a] and diabetes[b] based on urinary arsenic concentrations quartiles, CHMS, Cycle 1, 2007–2009

Urinary arsenic, μg/L[c]	Number of participants[d]			OR (95% CI)		
	Controls (n = 2054)	With prediabetes[a] (n = 831)	With diabetes[b] (n = 225)	Crude OR	Adjusted OR (Model 1)[e]	Adjusted OR (Model 2)[f]
< 5.71	554	171	46	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)
5.71–11.20	520	197	54	1.20 (0.98–1.47)	1.35 (0.95–1.79)	1.35 (0.97–1.82)
11.21–22.98	530	192	64	1.20 (0.88–1.64)	1.39 (1.01–2.00)	1.41 (1.02–2.04)
≥ 22.99	450	271	61	1.56 (1.00–2.44)	1.85 (1.11–3.13)	1.89 (1.12–3.13)
p for trend				.049	.019	.016

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

[a] Fasting glucose 100–125 mg/dl (5.6–6.9 mmol/L) or HbA1c 5.7%–6.4%.

[b] Fasting glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% or self-reported medication use or self-reported health care professional diagnosis.

[c] Urinary arsenic not corrected for urinary creatinine.

[d] Data missing for n = 41 participants.

[e] Model 1 adjusted for urinary creatinine, age, sex, alcohol status, smoking status, educational status, BMI and hypertension.

[f] Model 2 adjusted as for Model 1 plus for seafood consumption.

was used not only to assess diabetes (when other criteria were not available) but also to evaluate the adequacy of glycemic management. We also considered criteria for prediabetes and used rigorous laboratory procedures with a low limit of detection of assay for urinary arsenic. Moreover, we considered relevant potential confounders (diabetes risk factors and indicators of seafood intake) in our analysis and adjusted for urinary creatinine levels to account for urine dilution.[55]

Our study was cross-sectional and so did not allow us to establish a temporal association between urinary arsenic and type 2 diabetes. Urinary arsenic has a half-life of approximately 3 days, making it a biomarker of short-term exposure only. This makes it difficult to ascertain historical exposures that may be more relevant to the pathogenesis of T2D.[56] Moreover, the exposure assessment in our study was based on urinary arsenic concentration measured in a single spot urine specimen and so reflected exposure at only one point in time. As discussed previously, we did not quantify arsenic species in urine and so could not test based on inorganic or methylated organic arsenic levels. Instead, we adjusted total arsenic concentration for seafood consumption, the main source of organic arsenic, as previously recommend.[23,52] However, seafood consumption was measured using a food frequency questionnaire, and so the information is subject to recall error. Misclassification

TABLE 6
Odds ratio of glycated hemoglobin[a] by urinary arsenic concentrations among participants with treated and untreated diabetes in CHMS, Cycle 1, 2007–2009

Urinary arsenic, (μg/L)[b]	Number of participants, N		OR (95% CI)					
			Crude OR		Adjusted OR (Model 1)[c]		Adjusted OR (Model 2)[d]	
	Treated diabetes[e] (n = 129)	Untreated diabetes[f] (n = 96)	Treated diabetes	Untreated diabetes	Treated diabetes	Untreated diabetes	Treated diabetes	Untreated diabetes
< 5.71	30	22	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)
5.71–11.20	34	26	0.78 (0.41–1.49)	1.22 (0.99–1.48)	0.65 (0.39–1.08)	1.61 (1.47–2.23)	0.66 (0.44–1.04)	1.62 (1.19–2.22)
11.21–22.98	36	27	0.94 (0.58–1.51)	1.21 (0.89–1.65)	0.85 (0.46–1.59)	1.72 (1.13–2.57)	0.80 (0.48–1.34)	1.74 (1.18–2.59)
≥ 22.99	29	21	1.11 (0.59–2.04)	1.74 (1.06–2.89)	0.87 (0.52–1.46)	2.84 (1.62–4.98)	0.85 (0.55–1.32)	2.89 (1.65–5.08)
p for trend			.7444	.005	.6122	.001	.7538	.001

Abbreviations: BMI, body mass index; CHMS, Canadian Health Measures Survey; CI, confidence interval; HbA1c, glycated hemoglobin; OR, odds ratio.

[a] 3 levels of HbA1c: < 5.7%, 5.7%–6.4% and ≥ 6.5%.

[b] Urinary arsenic not corrected for urinary creatinine.

[c] Adjusted for urinary creatinine, age, sex, alcohol intake, smoking, educational status, BMI and hypertension.

[d] Adjusted as for Model 1 plus seafood consumption.

[e] All participants with diabetes who reported use of insulin or oral hypoglycemic medication.

[f] All participants with diabetes who reported no use of insulin or oral hypoglycemic medication.

bias could also occur from inaccuracies in diagnosing T2D; since medical records were not reviewed, errors in self-reported diagnoses or use of insulin or oral hypoglycemic medication may have occurred. However, this issue did not seem to significantly affect the validity of the primary findings because the positive relationship between urinary arsenic exposure and T2D remained after a sensitivity analysis of only biological criteria (HbA1c or fasted blood glucose) in untreated patients. There was also an important non-response rate among eligible participants, which might lead to selection bias. However, our analysis using the propensity score seems to demonstrate that this issue might, at worst, be minor. Nevertheless, we recognize that residual confounding cannot be entirely excluded.

Conclusion

We examined the association between total urinary arsenic concentrations and diabetes status in an adult Canadian population with relatively low to moderate exposure to arsenic via drinking water. Using several accepted approaches to reduce potential misclassification of exposure to organic arsenic, our analysis found an association between total urinary arsenic exposures and T2D in this population study. However, because of the limitations of the cross-sectional design and the absence of long-term assessment of arsenic exposure, we recommend further prospective studies with improved assessment of arsenic exposure. Analysis of recent data from CHMS Cycle 2 with speciated arsenic data in urine might also be useful.

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References

1. Environment Canada; Health Canada. Arsenic and its compounds. Canadian Environmental Protection Act. Introduction [Internet]. Ottawa (ON): Health Canada; [modified 2007 Apr 19; accessed 2013 Mar 26]. Available from: http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl1-lsp1/arsenic_comp/index-eng.php.

2. Health Canada. Guidelines for Canadian drinking water quality: guideline technical document: arsenic [Internet]. Ottawa (ON): Health Canada; 2006 [cited 2014 Mar 26]. Available from: http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/arsenic/index-eng.php.

3. Borak J, Hosgood HD. Seafood arsenic: implications for human risk assessment. Regul Toxicol Pharmacol. 2007;47(2):204-12.

4. Munoz E, Palmero S. Analysis and speciation of arsenic by stripping potentiometry: a review. Talanta. 2005;65(3):613-20.

5. Vahter M, Concha G. Role of metabolism in arsenic toxicity. Pharmacol Toxicol. 2001;89 (1):1-5.

6. Subcommittee on Arsenic in Drinking Water; Committee on Toxicology; Board on Environmental Studies and Toxicology; Commission on Life Sciences; National Research Council. Arsenic in drinking water. Washington (DC): National Academy Press; 1999.

7. Tam GK, Charbonneau SM, Bryce F, Pomroy C, Sandi E. Metabolism of inorganic arsenic (74As) in humans following oral ingestion. Toxicol Appl Pharmacol. 1979;50(2):319-22.

8. Berry JP, Galle P. Selenium-arsenic interaction in renal cells: role of lysosomes electron microprobe study. J Submicrsc Cytol Pathol. 1994;26(2):203-10.

9. Chen Y, Parvez F, Gamble M, Islam T, Ahmed A, Argos M, et al. Arsenic exposure at low-to-moderate levels and skin lesions, arsenic metabolism, neurological functions, and biomarkers for respiratory and cardiovascular diseases: review of recent findings from the Health Effects of Arsenic Longitudinal Study (HEALS) in Bangladesh. Toxicol Appl Pharmacol. 2009;239(2):184-92.

10. Saha KC. Diagnosis of arsenicosis. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2003;38(1):255-72.

11. Jones MR, Tellez-Plaza M, Sharrett AR, Guallar E, Navas-Acien A. Urine arsenic and hypertension in US adults: the 2003–2008 National Health and Nutrition Examination Survey. Epidemiology. 2011;22(2):153-61.

12. Kwok RK, Mendola P, Liu ZY, Savitz DA, Heiss G, Ling HL, et al. Drinking water arsenic exposure and blood pressure in healthy women of reproductive age in Inner Mongolia, China. Toxicol Appl Pharmacol. 2007;222(3):337-43.

13. Mukherjee SC, Rahman MM, Chowdhury UK, et al. Neuropathy in arsenic toxicity from groundwater arsenic contamination in West Bengal, India. J Environ Sci Health A Tox Hazard Subst Environ Eng. 2003;38 (1):165-83.

14. Maull EA, Ahsan H, Edwards J, et al. Evaluation of the association between arsenic and diabetes: a National Toxicology Program workshop review. Environ Health Perspect. 2012;120(12):1658-70.

15. Lopez AD, Mathers CD, Ezzati M, Jamison DT. Measuring the global burden of disease and risk factors, 1990–2001. In: Lopez AD, Mathers CD, Ezzati M, Jamison DT, editors. Global burden of disease and risk factors. Washington (DC): World Bank; 2006.

16. Kapur A, Harries AD. The double burden of diabetes and tuberculosis - public health implications. Diabetes Res Clin Pract. 2013;101(1):10-9.

17. Pelletier C, Dai S, Roberts KC, Bienek A, Onysko J. Pelletier L. Diabetes in Canada: facts and figures from a public health perspective [Internet]. Chronic Dis Inj Can. 2012 [accessed 2014 Mar 26]; 33(1):53-4. Available from: http://origin.phac-aspc.gc.ca/publicat/cdic-mcbc/33-1/assets/pdf/CDIC_MCC_Vol33_1-dic-eng.pdf.

18. Abernathy CO, Thomas DJ, Calderon RL. Health effects and risk assessment of arsenic. J Nutr. 2003;133(5 Suppl 1):1536S-8S.

19. Chen Y, Ahsan H, Slavkovich V, et al. No association between arsenic exposure from drinking water and diabetes mellitus: a cross-sectional study in Bangladesh. Environ Health Perspect. 2010;118(9): 1299-305.

20. Steinmaus C, Yuan Y, Liaw J, Smith AH. Low-level population exposure to inorganic arsenic in the United States and diabetes mellitus: a reanalysis. Epidemiology. 2009;20(6):807-15.

21. Gribble MO, Howard BV, Umans JG, et al. Arsenic exposure, diabetes prevalence, and diabetes control in the Strong Heart Study. Am J Epidemiol. 2012;176(10):865-74.

22. Del Razo LM, García-Vargas GG, Valenzuela OL, et al. Exposure to arsenic in drinking water is associated with increased prevalence of diabetes: a cross-sectional study in the Zimapan and Lagunera regions in Mexico. Environ Health. 2011;10:73.

23. Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, Guallar E. Rejoinder: Arsenic exposure and prevalence of type 2 diabetes: updated findings from the National Health Nutrition and Examination Survey, 2003–2006. Epidemiology. 2009;20(6):816-20.

24. Coronado-Gonzalez JA, Del Razo LM, García-Vargas G, Sanmiguel-Salazar F, Escobedo-de la Peña J. Inorganic arsenic exposure and type 2 diabetes mellitus in Mexico. Environ Res. 2007;104(3):383-9.

25. Wang SL, Chang FH, Liou SH, Wang HJ, Li WF, Hsieh DP. Inorganic arsenic exposure and its relation to metabolic syndrome in an industrial area of Taiwan. Environ Int. 2007;33(6):805-11.

26. Rhee SY, Hwang YC, Woo JT, Chin SO, Chon S, Kim YS. Arsenic exposure and prevalence of diabetes mellitus in Korean adults. J Korean Med Sci. 2013;28(6):861-8.

27. Kim NH, Mason CC, Nelson RG, et al. Arsenic exposure and incidence of type 2 diabetes in Southwestern American Indians. Am J Epidemiol. 2013;177(9):962-9.

28. Giroux S. Canadian Health Measures Survey: sampling strategy overview. Health Rep. 2007;18 Suppl:31-6.

29. Tremblay M, Wolfson M, Connor Gorber S. Canadian Health Measures Survey: rationale, background and overview. Health Rep. 2007;18 Suppl:7–20.

30. Schneider AL, Lazo M, Ndumele CE, et al. Liver enzymes, race, gender and diabetes risk: the Atherosclerosis Risk in Communities (ARIC) Study. Diabet Med. 2013;30(8):926-33.

31. Valcarcel M. Lucena R. Synergistic relationships between analytical chemistry and written standards. Anal Chim Acta. 2010;788:1-7.

32. Institut national de santé publique du Québec. Analytical method for the determination of metals in urine by inductively coupled plasma mass spectrometry (ICP-MS), DRC II (M-571), version condensée et pour certains éléments de sélection. Québec (QC): Laboratoire de toxicologie; 2009 Apr 17.

33. Jaffe M. Hoppe-Seyler's Z. Physiol Chem. 1886;10:391-400.

34. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013;36(Suppl 1):S67-74.

35. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care. 2009;32(7):1327-34.

36. Ortho-Clinical Diagnostics, no de publication MP2-8_FR (version 4.0), Plaques GLU VITROS Chemistry Products.

37. Ortho-Clinical Diagnostics, no de publication J23413_FR (version 2.0), Réactifs VITROS Chemistry Products A1C.

38. Institut national de santé publique du Québec. Analytical method for the determination of urine creatinine on Hitachi 917 (C-530), condensed version. Québec (QC): Laboratoire de toxicologie; 2009.

39. Campbell NR, Joffres MR, McKay DW. Hypertension surveillance in Canada: minimum standards for assessing blood pressure in surveys. Can J Public Health. 2005;96(3):217-20.

40. Rao JN, Wu CF, Yue K. Some recent work on resampling methods for complex surveys. Survey Methodology (Statistics Canada, Catalogue 12-001). 1992;18(2):225-34.

41. Canadian Health Measures Survey (CHMS). Data user guide: cycle 1 [Internet]. Ottawa (ON): Statistics Canada; April2011 [modified 2014 Apr 4; accessed 0014 Jul 10]. Available from: http://www23.statcan.gc.ca/imdb-bmdi/pub/document/5071_D2_T1_V1-eng.htm.

42. Cole SR, Chu H, Nie L, Schisterman EF. Estimating the odds ratio when exposure has a limit of detection. Int J Epidemiol. 2009;38(6):1674-80.

43. Vahter M, Bjorkman L, Goessler W. Concentrations of biomarkers in spot urine samples need adjustment for variation in dilution–Comment on: ''Distribution of urinary selenium and arsenic among pregnant women exposed to arsenic in drinking water'' [Environ Res. 2006;100(1): 115–122]. Environ Res. 2007;104(2):312–3; discussion 314.

44. Koenig RJ, Peterson CM, Jones RL, Saudek C, Lehrman M, Cerami A. Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus. N Engl J Med. 1976;295(8):417-20.

45. Alp O, Zhang Y, Merino EJ, Caruso JA. Selenium effects on arsenic cytotoxicity and protein phosphorylation in human kidney cells using chip-based nanoLC-MS/MS. Metallomics. 2011;3(5):482-90.

46. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399-424.

47. Diaz-Villasenor A, Burns AL, Salazar AM, et al. Arsenite reduces insulin secretion in rat pancreatic b-cells by decreasing the calcium-dependent calpain-10 proteolysis of SNAP-25. Toxicol Appl Pharmacol. 2008;231(3):291-9.

48. Druwe IL, Vaillancourt RR. Influence of arsenate and arsenite on signal transduction pathways: an update. Arch Toxicol. 2010;84(8):585-96.

49. Tseng CH. The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol Appl Pharmacol. 2004;197(2):67-83.

50. Fu J, Woods CG, Yehuda-Shnaidman E, et al. Low-level arsenic impairs glucose-stimulated insulin secretion in pancreatic beta-cells: involvement of cellular adaptive response to oxidative stress. Environ Health Perspect. 2010;118:864-70.

51. Calderon RL, Hudgens E, Le XC, Schreinemachers D, Thomas DJ. Excretion of arsenic in urine as a function of exposure to arsenic in drinking water. Environ Health Perspect. 1999;107(8):663-7.

52. Vahter M, Lind B. Concentrations of arsenic in urine of the general population in Sweden. Sci Total Environ. 1986;54:1-12.

53. Valenzuela OL, Borja-Aburto VH, Garcia-Vargas GG, et al. Urinary trivalent methylated arsenic species in a population chronically exposed to inorganic arsenic. Environ Health Perspect. 2005;113(3):250-4.

54. Longnecker MP. On confounded fishy results regarding arsenic and diabetes. Epidemiology. 2009;20(6):821-3.

55. Basu A, Mitra S, Chung J, et al. Creatinine, diet, micronutrients, and arsenic methylation in West Bengal, India. Environ Health Perspect. 2011;119(9):1308-13.

56. Chen YC, Amarasiriwardena CJ, Hsueh YM, Christiani DC. Stability of arsenic species and insoluble arsenic in human urine. Cancer Epidemiol Biomarkers Prev. 2002; 11(11):1427-33.

Status Report

The Cancer in Young People in Canada surveillance system

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Introduction

Although childhood cancer remains the leading cause of disease-related deaths among children younger than 14 years of age, it is relatively rare.[1,2] Each year, an average of 910 children are diagnosed with cancer in Canada, and 139 children die of the disease.[3] Cancers in children differ biologically from those usually found in adults.[4,5] The majority of cancers in adults are carcinomas of the epithelial tissues that line organs such as the breast, lung, colon and prostate. In children, carcinomas are rare and childhood tumours are more likely to be embryonic or hematopoietic in origin.[5] Leukemias, lymphomas and central nervous system cancers represent the largest diagnostic groups.[5] Compared to cancers in adults, cancers in children have shorter latency periods and are generally more aggressive, invasive and advanced at diagnosis.[5]

Despite the high ranking of cancer as a cause of death in children, survival rates have improved substantially over the last two decades so that more children survive cancer than ever before.[6] However, over 60% of childhood cancer survivors face long-term physical and mental side-effects from the disease and its treatment, and nearly 30% have severe or life-threatening late effects.[7] Survivors of childhood cancer have an 11-fold increased risk of death, an increased risk of second cancers up to 30 years after treatment and a wide variety of chronic physical, psychosocial and cognitive problems.[8] The recognition of the unique nature of cancers in this age group and extensive long-term late effects has led many countries to establish specialized pediatric cancer surveillance and follow-up systems.[8,9–11,13]

In 2009, the Public Health Agency of Canada (PHAC) launched a pan-Canadian specialized childhood cancer surveillance system that actively follows children aged up to 14 years treated at one of the 17 pediatric oncology centres across the country (Table 1). The Cancer in Young People in Canada (CYP-C) program is a renewal of the federal government's Canadian Childhood Cancer Surveillance and Control program (CCCSCP). Established under the Brighter Futures Initiative in 1992, the program includes comprehensive data on a child's cancer diagnosis, treatments, outcomes and health care utilization.[12,13]

In this article, we describe the strengths and successes of CYP-C by highlighting rigour in data collection and quality control methodology as well as recent achievements and future directions.

Highlights

- The Cancer in Young People in Canada (CYP-C) program is a population-based surveillance system that was launched in 2009 to contribute to cancer control in all children aged 14 years or less in Canada.
- The CYP-C remains a critical component of reducing the burden of childhood cancer in Canada.
- The program is one of the most in-depth pediatric oncology surveillance systems in the world and allows for the development of an enabling framework for investigating important questions relevant to pediatric cancer control.

Program objectives and data collection

CYP-C was designed to fill in gaps in knowledge about cancer control. The national program is one of the few pediatric cancer surveillance systems in the world that cover nearly all their target populations.[13] The objectives of the program are to (1) provide national and regional population-based childhood cancer data on incidence, mortality, survival and time trends; (2) describe patterns of incidence and survival of childhood cancer by diagnosis, stage, risk category and extent of disease; (3) assess short- and medium-term outcomes such as relapses, toxicities and complications related to treatment; (4) provide data on the timing, location and utilization of health care for evaluation and planning; and (5) function as a resource for generating hypotheses and research into pediatric cancer (see Table 2).

All children aged 0 to 14 years who are diagnosed with a new malignancy that is listed in the *International Classification of Childhood Cancer, 3rd Edition* (ICCC-3)[4] in 2001 or later and who are residents of Canada for at least one month prior to their diagnosis are included in CYP-C. Langerhans cell and other histiocytosis are also included in CYP-C because of the histopathology of these conditions, even though they are not classified as malignant according to the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3), on which the ICCC-3 is based.[4] Information is collected on each eligible

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TABLE 1
Pediatric oncology centres participating in the Cancer in Young People in Canada surveillance system

Centre	Location
B.C. Children's Hospital	Vancouver, British Columbia
Alberta Children's Hospital	Calgary, Alberta
Stollery Children's Hospital	Edmonton, Alberta
Saskatoon Cancer Centre	Saskatoon, Saskatchewan
Allan Blair Cancer Centre	Regina, Saskatchewan
CancerCare Manitoba	Winnipeg, Manitoba
Children's Hospital	London, Ontario[a]
McMaster Children's Hospital	Hamilton, Ontario[a]
The Hospital for Sick Children	Toronto, Ontario[a]
Kingston General Hospital	Kingston, Ontario[a]
Children's Hospital of Eastern Ontario	Ottawa, Ontario[a]
Centre Hospitalier Universitaire Sainte-Justine	Montréal, Quebec
The Montreal Children's Hospital	Montréal, Quebec
Centre Hospitalier Universitaire de Sherbrooke	Sherbrooke, Quebec
Centre Hospitalier Universitaire de Quebec	Québec, Quebec
Izaak Walton Killam Health Centre	Halifax, Nova Scotia
Janeway Children's Health and Rehabilitation Centre	St. John's, Newfoundland

[a] Centres where data are submitted through the Pediatric Oncology Group of Ontario.

case from diagnosis to 5 years post-diagnosis. In Ontario, the Pediatric Oncology Group of Ontario (POGO) collects similar data on childhood cancer cases treated in one of the five pediatric centres in the province.[14] Information is then shared with CYP-C through a data-sharing agreement. In all other jurisdictions, data are abstracted from patient charts and entered into an electronic data entry and management tool called E-CYP. Data are transmitted on a regular schedule over a secure connection to a national database maintained by PHAC. Direct identifiers such as names and health card numbers are not sent to the national database.

Research ethics approval has been given by participating hospitals and Health Canada to allow for data collection without individual consent for sites where direct data collection occurs.[15]

Current status

CYP-C has registered over 5850 cases and contains over 2900 cases with 5 full years of data diagnosed between January 1, 2001, and December 31, 2006 (Table 3). CYP-C data will be available for research once data from Ontario has been integrated into the surveillance system, which is expected to occur in the spring of 2015. This integration will be followed by the publication of a descriptive data report highlighting national childhood cancer statistics on incidence, mortality, treatment, and outcomes by age, sex, diagnosis, and geography. CYP-C data have already been used for local surveillance purposes and include a peer-reviewed publication on morbidity and survival in First Nations children with cancer in Manitoba.[16]

Data quality

CYP-C aims to achieve complete and accurate case registration. Close collaboration between all clinical research associates and pediatric oncologists–hematologists at the participating centres and PHAC enable accurate and timely entry of case details. Built-in edit and logic checks ensure accuracy and validity, and include ranges and numeric entries for dates and the requirement for appropriate metrics for drug dosage fields. Data abstractors participate in an annual in-person training session to review case definitions and data entry procedures. They meet monthly by teleconference to discuss new challenges relating to data abstraction through a community of practice. During each data upload cycle, the database administrator conducts data quality control and validation procedures designed to identify missing information, logic and data consistency errors and duplicate entries. Reports summarizing results are submitted to the data abstractors for resolution. Periodic re-abstraction audits are also performed to further ensure the accuracy of the data. Ten centres across the country have been audited

TABLE 2
Data collected by the Cancer in Young People in Canada surveillance system

Demographics	Diagnostics	Time to treatment	Treatment	Other
Sex	Date of diagnosis	First health care professional contacted	Treatment plan and start date	Previous organ transplant
Date of birth	ICD-O-3 morphology and topography codes, ICCC-3 codes	Dates first seen by oncologist, surgeon, and/or specialist	Reason for early termination	Complications
Age at diagnosis	Stage at diagnosis		Chemotherapy and dose	Hospitalizations
Province	Risk/Grade		Surgery details (cancer-related and secondary)	Relapse
Postal code	Chromosomal testing		Radiation (intent, type, site)	Vital status
Ethnicity	Metastases and site of metastases		Hematopoietic stem cell transplantation	Height and weight

Abbreviations: ICCC-3, *International Classification of Childhood Cancer, 3rd edition*; ICD-O-3, *International Classification of Diseases for Oncology, 3rd edition.*

TABLE 3
New cases of childhood cancer reported in the Cancer in Young People in Canada surveillance system, by cancer type, 0–14 years, 2001–2006, Canada (excluding Ontario)

Cancer Type	Cases	
	Number, N	Percent, %[a]
Leukemias, myeloproliferative diseases and myelodysplastic diseases	978	34.3
Lymphomas and reticuloendothelial neoplasms	310	10.9
CNS and miscellaneous intracranial and intraspinal neoplasms[b]	669	23.4
Neuroblastoma and other peripheral nervous cell tumours	226	7.9
Retinoblastoma	42	1.5
Renal tumours	148	5.2
Hepatic tumours	44	1.5
Malignant bone tumours	130	4.6
Soft tissue and other extraosseous sarcomas	157	5.5
Germ cell tumours, trophoblastic tumours, and neoplasms of gonads[b]	80	2.8
Other malignant epithelial neoplasms and malignant melanomas	63	2.2
Other and unspecified malignant neoplasms	8	0.3
Langerhans Cell histiocytosis (LCH) and other histiocytosis	61	
All cancers, and LCH	2916	

Source: The Cancer in Young People in Canada (CYP-C) program. Diagnostic groups were based on the *International Classification of Childhood Cancer, 3rd edition*.

Abbreviations: CNS, central nervous system; CYP-C, Cancer in Young People in Canada; ICCC-3, *International Classification of Childhood Cancer, 3rd edition*; LCH, Langerhans cell histiocytosis.

[a] For the calculation of relative frequencies, only malignancies coded to the ICCC-3 were included.

[b] Includes tumours with non-malignant behaviour.

and results show that key data items are abstracted correctly, with few transcription errors or omissions. Complex data items that require interpretation at the point of entry (for example, stage at diagnosis) appear to be most accurate in centres where data abstractors have access to oncologists and other experts.

The completeness of ascertainment is an integral component of the program and CYP-C is routinely compared to the Canadian Cancer Registry, the most complete source of data on new cancer cases in Canada.[17] A recent comparison showed that CYP-C includes approximately 90% of all children aged up to 14 years who have been diagnosed with cancer in Canada, with some regional variations in case ascertainment (Table 4). Investigations are underway for a study on the feasibility of linking the CYP-C data to provincial and/or national cancer and vital registries for data validation that will include the identification of missing cases, duplicates and death clearance.

TABLE 4
Ratios of the number of new cases of childhood cancer in the Cancer in Young People in Canada surveillance system and the Canadian Cancer Registry, by province and region, 0–14 years, 2001–2006, Canada (excluding Ontario)

Province/Region	CYP-C/CCR Ratios
Alberta	0.92
British Columbia	0.93
Manitoba	1.00
New Brunswick	0.95
Newfoundland and Labrador	0.96
Nova Scotia	1.05
Prince Edward Island	1.14
Quebec	0.83
Saskatchewan	0.96
North[a]	0.90
Canada	0.90

Source: Ratios were derived from data in the CYP-C program and the CCR. Numbers used to derive ratios exclude Langerhans cell histiocytosis, benign brain tumours and non-melanoma skin carcinomas.

Abbreviations: CCR, Canadian Cancer Registry; CYP-C, Cancer in Young People in Canada.

[a] North refers to the Northwest Territories, Nunavut, and Yukon.

Future prospects

CYP-C provides a population-based sampling frame for cancer control in the pediatric population through the systematic collection of data on risk factors, incidence, mortality and the cancer care continuum for each child diagnosed with a malignancy in Canada. The enhanced components of CYP-C allow for the examination of a wide array of issues that impact access, quality and equity in care, and ultimately, long-term health outcomes. It also forms a crucial basis for understanding the etiology and epidemiology of childhood cancers and helps to identify childhood cancer survivors most at risk of adverse health outcomes such as toxicities, relapses or second malignancies. The CYP-C program remains one of the most in-depth pediatric oncology surveillance systems in the world and will continue to expand until it approaches real-time data collection.[18]

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Contact: For current information on the CYP-C program, please contact cypc-ccjc@phac-aspc.gc.ca or visit the program website at www.c17.ca/index.php?cID=70.

References

1. Mitra D, Shaw AK, Hutchings K. Trends in incidence of childhood cancer in Canada, 1992-2006. Chronic Dis Inj Can. 2012; 32(3):131-9.

2. Statistics Canada. CANSIM database: Table 102-0522: Deaths, by cause, Chapter II: Neoplasms (C00 to D48), age group and sex, Canada [Internet]. Ottawa (ON): Statistics Canada; [modified: 2014 Jan 28; cited: 2014 Sep 21]. Available from: http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=1020522

3. Canadian cancer statistics 2014. Toronto (ON): Canadian Cancer Society/National Cancer Institute of Canada; 2014.

4. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International Classification of Childhood Cancer, third edition. Cancer. 2005;103(7):1457-67.

5. Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology, 6th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2010.

6. Ellison LF, Pogany L, Mery LS. Childhood and adolescent cancer survival: a period analysis of data from the Canadian Cancer Registry. Eur J Cancer. 2007;43(13): 1967-75.

7. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355(15):1572-82.

8. Eiser C, Absolom K, Greenfield D, et al. Follow-up care for young adult survivors of cancer: lessons from pediatrics. J Cancer Surviv. 2007;1(1):75-86.

9. Michel G, von der Weid NX, Zwahlen M, et al. The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001-2005. Swiss Med Wkly. 2007;137 (35-36):502-9.

10. Stiller CA, Allen MB, Eatock EM. Childhood cancer in Britain: the National Registry of Childhood Tumours and incidence rates 1978–1987. Eur J Cancer. 1995;31A: 2028-34.

11. Grabow D, Spix C, Blettner M. Strategy for long-term surveillance at the German Childhood Cancer Registry - an update. Klin Padiatr. 2011;223(3):159-64.

12. Barr RD, Greenberg ML, Shaw AK, Mery L. The Canadian Childhood Cancer Surveillance and Control Program (CCCSCP): a status report. Pediatr Blood Cancer. 2008 Feb. 50(2 Suppl):518-9.

13. Parker L. Childhood cancer registration: meeting the challenge. Pediatr Blood Cancer. 2014;61(12):2147-8.

14. Bleyer WA, Tejeda H, Murphy SB, et al. National cancer clinical trials: children have equal access; adolescents do not. J Adolesc Health. 1997;21:366-73.

15. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement: Ethical conduct for research involving humans [Internet]. Ottawa (ON): Interagency Secretariat on Research Ethics; 2010 Dec [cited 2015 Feb 16]. Available from: http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf

16. Stammers DM, Israels SJ, Lambert PJ, Cuvelier GD. Cancer incidence, morbidity, and survival in Canadian First Nation children: a Manitoba population-based study from the Cancer in Young People in Canada (CYP-C) registry. Pediatr Blood Cancer. 2014; 61(12): 2164-9. doi: 61(12)10.1002/pbc.25005.

17. Statistics Canada. Canadian Cancer Registry (CCR) [Internet]. Ottawa (ON): Statistics Canada; [2008; modified: 2012 Oct 3; cited: 2015 Feb 16]. Available from: www.statcan.gc.ca/cgi-bin/imdb/p2SV.pl?Function=getSurvey&SDDS=3207&lang=en&db=imdb&adm=8&dis=2.

18. Mitra D, Carswell K, Hutchings K, Shaw AK. Opportunities for improving pediatric cancer surveillance in Canada. Proceedings of the 2011 Health Data Users Conference; 2011 September 22-23; Ottawa (ON): Statistics Canada; c2011.

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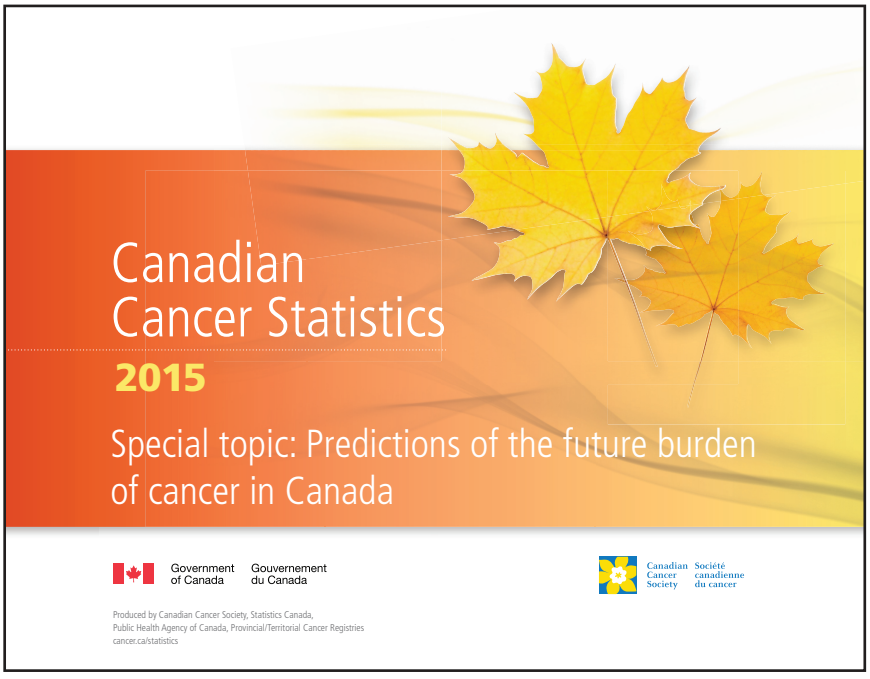

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Austin SE, Ford JD, Berrang-Ford L, Araos M, **Parker S**, **Fleury MD**. Public health adaptation to climate change in Canadian jurisdictions. Int J Environ Res Public Health. 2015;12(1):623-651.

Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2015. Canadian Cancer Society. Toronto (ON): Canadian Cancer Society; 2015.

Desai S, **Smith T**, Thorley BR, Grenier D, Dickson N, Altpeter E, et al. Performance of acute flaccid paralysis surveillance compared with World Health Organization standards. J Paediatr Child Health. 2015;51(2):209-214.