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Determinants of selenoneine concentration in red blood cells of Inuit from Nunavik (Northern Québec, Canada)

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ABSTRACT

Selenium (Se) is a trace mineral essential to human health, and is especially abundant in marine foods consumed by Inuit populations in Nunavik (northern Quebec, Canada), leading to exceptionally high whole blood Se levels. While most epidemiological studies to date examine plasma or whole blood Se, little is known about the health implications of specific Se biomarkers (e.g. selenoproteins and small Se compounds). Selenoneine, a novel Se compound, is found in high concentrations in marine foods (and particularly beluga *mattaaq*) and the red blood cells (RBCs) of populations that consume them. We report here RBC selenoneine concentrations in a population of Inuit adults (n = 885) who participated in the *Qanuippitaa*? 2004 survey. Simple associations between RBC selenoneine and other Se and mercury (Hg) biomarkers were assessed using Spearman correlations and linear regressions. Wilcoxon ranksum tests were used to examine differences in biomarkers and characteristics between tertiles of RBC selenoneine concentration. A multiple linear regression analysis was used to determine factors (sociodemographic, lifestyle, and dietary) associated with RBC selenoneine concentrations. Selenoneine comprised a large proportion of whole blood Se and RBC Se in this population. Age and sex-adjusted geometric mean RBC selenoneine concentration was 118 μg/L (range: 1–3226 μg/L) and was much higher ($p = 0.001$) among women (150.3 μg/L) than men (87.6 μg/L) across all regions of Nunavik after controlling for age, region, and diet. RBC selenoneine was highly correlated with RBC Se ($r_s = 0.96$, $p < 0.001$) and whole blood Se ($r_s = 0.89$, $p < 0.001$), but only weakly correlated with plasma Se ($r_s = 0.13$, $p < 0.001$). Overall, increasing age (standardized $\beta = 0.24$), higher body-mass index (BMI; $\beta = 0.08$), female sex ($\beta = 0.10$), living in a Hudson Strait community (compared to Hudson Bay and Ungava Bay; $\beta = 0.38$), and consuming beluga *mattaaq* (g/day; $\beta = 0.19$) were positively associated with RBC selenoneine. Meanwhile, consumption of market meats (g/day; $\beta = -0.07$) was negatively associated with RBC selenoneine. RBC selenoneine is an important biomarker of Se dietary intake from local marine foods in Inuit populations. Further studies are needed to examine the health effects of selenoneine intake and the underlying mechanisms for sex differences among Inuit populations.

1. Introduction

Selenium (Se) is a trace element essential to human health (Brown and Arthur, 2001). Se is acquired through the diet and is present in high concentrations in Arctic marine foods such as beluga *mattaaq* (skin with underlying layer of fat), walrus meat, marine mammal offals, and fish eggs (Laird et al., 2013; Lemire et al., 2015). Such foods represent important components of the traditional diet among Inuit in North America and Greenland (AMAP, 2015). Consequently, Inuit populations exhibit one of the highest intakes of Se and one of the highest mean

Abbreviations: FFQ, food frequency questionnaire; GPx-3, glutathione peroxidase 3; Hg, mercury; HPLC, high performance liquid chromatography; ICP-MS, inductively coupled plasma mass spectrometry; INSPQ, Institut national de santé publique du Quebec; IOM, Institute of Medicine; LOD, level of detection; MeHg, methylmercury; OCTN1, carnitine/organic cation transporter; RBC, red blood cell; Se, selenium; SeAlb, selenoalbumin; SeCys, selenocysteine; SelP, selenoprotein P; SeMet, selenomethionine; WHO, World Health Organization

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whole blood concentrations of Se in the world (Achouba et al., 2016; Nielsen et al., 2012).

Se is primarily incorporated into selenoproteins in the form of selenocysteine (SeCys). Upwards of 25 selenoproteins have been identified that play various roles in metabolic pathways, antioxidant defense systems, and neurological and immune functions (Labunskyy et al., 2014; Hatfield et al., 2014). A total of three Se-containing proteins have been identified in human plasma; namely, glutathione peroxidase 3 (GPx-3), selenoprotein P (SelP), and selenoalbumin (SeAlb) (Rayman, 2012). GPx-3 plays a role in detoxification of hydrogen peroxide and fatty acid hydroperoxides (Imai and Nakagawa, 2003). SelP is responsible for Se transport from the liver to peripheral tissues and exhibits antioxidant functions, thus protecting astrocyte and neuronal cells (Steinbrenner and Sies, 2013). Meanwhile, SeAlb has no known biological function, although it may act as a Se storage protein (Suzuki and Ogra, 2002; Rayman, 2008).

Inuit populations also experience high methylmercury (MeHg) exposure due to its bioaccumulation and biomagnification in large marine mammals and predatory fish species (AMAP, 2015). Exposure to MeHg has been linked to cardiovascular and neurological developmental deficits in Inuit populations (Ayotte et al., 2011; Boucher et al., 2010; Boucher et al., 2012; Boucher et al., 2016; Jacobson et al., 2015; Nielsen et al., 2012; Saint-Amour et al., 2006; Valera et al., 2009). Several laboratory and animal studies suggest that Se may be involved in the demethylation and detoxification of MeHg (Cuvin-Aralar and Furness, 1991; Khan and Wang, 2009; Palmisano et al., 1995) and that Hg-Se complexes, which are found in marine mammal, seabird livers, as well as in the human brain, may be the final product of MeHg biotransformation by Se-compounds (Ikemoto et al., 2004; Korbas et al., 2010; Lailson-Brito et al., 2012). Indeed, a growing number of epidemiological studies among the Inuit and other fish-eating populations suggest that high Se intake may mitigate or modify cardiometabolic and neurotoxic MeHg effects (Ayotte et al., 2011; Boucher et al., 2010; Fillion et al., 2013; Hu et al., 2017; Lemire et al., 2010).

Meanwhile, evidence from Inuit and other populations suggests that high Se status may also convey certain health risks, including selenosis (Se toxicity), poorer visual acuity among children (Saint-Amour et al., 2006), type 2 diabetes (Vinceti et al., 2018), hypercholesteremia (Stranges et al., 2010), and hypertension (Rayman and Stranges, 2013). Additionally, randomized trials have found that Se supplementation (particularly among Se-replete populations) may be associated with increased risk of type 2 diabetes (Stranges et al., 2007), high-grade prostate cancer (Kristal et al., 2014), and all-cause mortality (Rayman et al., 2018). However, evidence on the health impacts of Se intake and high Se status is far from consistent (Rayman, 2012). Variability in findings may be due to differences in the source of Se and the use of toenail, plasma, or whole blood Se concentration to assess Se status, markers that may not reflect the kinetics and metabolic pathways of various forms of dietary Se (Rayman et al., 2008). Further, co-exposure to other nutrients (e.g. n-3 fatty acids) and environmental contaminants (e.g. MeHg) may confound associations between Se status and health outcomes (Laird et al., 2013). There is therefore a need to identify and study new and established Se species, compounds, proteins, and biomarkers to determine kinetic pathways, health effects, and population consumption patterns (Rayman et al., 2018).

Selenoneine, a novel Se-containing compound and a strong antioxidant, is a major form of Se in bluefin tuna and other marine species, and is found in the red blood cells human populations that consume these foods (Yamashita et al., 2010; Yamashita et al., 2011; Yamashita et al., 2013a). Selenoneine is a Se analogue of ergothioneine and can be transported via the carnitine/organic cation transporter (OCTN1), which is especially abundant in red blood cell (RBC) membranes (Yamashita et al., 2013a). Once in RBCs, selenoneine binds to hemoglobin and prevents iron oxidation (Yamashita and Yamashita, 2010). Results from animal studies suggest that selenoneine may play a crucial role in MeHg detoxification (Yamashita et al., 2013b). It is therefore necessary to study this form of Se to determine its local sources and health functions, particularly among those populations with high marine food consumption.

We recently reported high concentrations of selenoneine in RBCs of Inuit residing in communities along the Hudson Strait in Nunavik, northern Quebec (Achouba et al., in review). We also found very high selenoneine concentrations in beluga *mattaaq* (primarily in the skin), a delicacy highly praised by Inuit and consumed across Nunavik but primarily in the Hudson Strait region (Achouba et al., in review). Here we report on the RBC selenoneine concentrations from all participants of the *Qanuippitaa*? (How are we?) study, a comprehensive health survey conducted in 2004 in 14 communities in Nunavik. In addition, we present correlations between selenoneine and other biomarkers of Se and Hg exposure. Finally, we examine associations between RBC selenoneine and several sociodemographic, lifestyle, and dietary factors.

2. Methods

2.1. Study population

From August through October of 2004, the *Qanuippitaa*? (How are we?) Nunavik Inuit Health Survey was conducted in 14 communities in all three regions (Eastern Hudson Bay, Hudson Strait, and Ungava Bay) of Nunavik in Northern Quebec, Canada (Fig. 1). The full study design and methodology have been published elsewhere (Rochette and Blanchet, 2007). Briefly, two-stage stratified random sampling was used to recruit Inuit residents between the ages of 18 and 74. In the first stage, a proportional random sample of Inuit households was selected, taking into consideration the village size. In the second stage, all eligible members of the selected household were asked to participate. Data collection primarily took place onboard *The Amundsen*, a Canadian Coast Guard ship that was refitted for scientific research. Participants were invited on board the ship, where they attended a clinical session and were administered an extensive survey, including a food frequency questionnaire (FFQ). During the clinical session, several clinical and anthropometric measurements were collected and blood samples were provided. Blood samples were immediately frozen, stored at −80 °C on the ship until the end of the study period, after which they were transferred and stored at −80 °C at the *Institut national de santé publique du Quebec* (INSPQ) until time of analysis.

2.2. Analysis of blood samples

Concentrations of selenoneine, methylselenoneine and total Se were measured in RBCs using high performance liquid chromatography (Agilent 1260-HPLC) coupled to inductively coupled plasma mass spectrometry (Agilent 8800-ICP-MS), according to the method described by Achouba et al. (in review). Briefly, 50 µL of RBCs were homogenized with 450 µl of of a 50 mM dithiothreitol aqueous solution for 1 h. A 100-µl aliquot of the homogenate was diluted with 400 µL of water and filtered through a 10 kDa cut-off centrifugal filter. The filtrate was then diluted in the mobile phase and analyzed by HPLC-ICP-MS. Levels of detection (LODs) were 2 µg Se/L and 4 µg Se/L for selenoneine and methylselenoneine respectively. Total Se content of RBCs was determined by isotope dilution calibration technique (Reyes et al., 2003) using an ICP-MS/MS (Agilent 8800). A 50-µL aliquot of RBCs was diluted and spiked with the appropriate amount of ^{77}Se. The (^{78}Se/^{77}Se) isotope ratio was used to determine the Se concentration; the LOD was 8 µg Se/L.

The measurement of total whole blood Hg concentrations was performed by ICP-MS at the toxicology laboratory of INSPQ and the complete analytic method was detailed elsewhere (Valera et al., 2008). Prior to analysis, blood samples were diluted 20-fold in a solution containing ammonium hydroxide and the LOD was 0.12 µg/L.

Fig. 1. Map of Nunavik and all sample communities for *Qanuippitaa*? study (August–September 2004).

2.3. Analysis of plasma samples

The full description of the method used to determine total Se and Se-containing proteins in plasma was published elsewhere (Achouba et al., 2016). Briefly, concentrations of Se linked to Se-containing proteins (GPx-3, SelP and SeAlb) were measured by post-column isotope dilution after separation on an ultra-performance liquid chromatography system (UPLC, Waters) equipped with two affinity columns. Signal detection was achieved with a NexION 300 s ICP-MS (Perkin-Elmer) and LODs were 0.7 µg Se/L for GPx-3, 1.1 µg Se/L for SelP and 2.2 µg Se/L for SeAlb. Total Se concentrations in plasma samples were obtained by summing concentrations of all the Se-containing proteins.

2.4. Processing food frequency questionnaire data

Detailed methodology for data processing of dietary consumption variables from the FFQ are described elsewhere (Rochette and Blanchet, 2007). Briefly, average daily food intake values (g/day) were calculated

Table 1
Characteristics of study participants (n = 885).

Variable	Men (n = 387) %	Women (n = 488) %	p-Value*
Age category			
17–30	39.2	37.7	
31–40	27.7	26.4	
41–50	14.2	16.6	
51–60	9.8	10.6	
61 +	9.1	8.3	0.65
Region			
Eastern Hudson Bay	36.5	40.9	0.18
Hudson Strait	25.2	24.1	0.70
Ungava Bay	38.4	35.0	0.18
Body mass index			
Underweight (< 18.5 kg/m^2)	1.2	1.6	0.77
Normal weight (18.5 kg/m^2–24.9 kg/m^2)	41.8	36.8	0.14
Overweight (25.0 kg/m^2–29.9 kg/m^2)	30.3	29.7	0.86
Obese (≥ 30.0 kg/m^2)	26.7	31.9	0.095
Alcohol consumption			
Often (≥ 3 drinks/week)	7.9	9.4	0.50
Occasionally (< 3 drinks/week)	81.4	76.9	0.15
Never	10.7	13.7	0.23
Smoking			
Daily	66.9	71.6	
Occasionally	6.2	6.2	
Never	26.1	21.5	0.14

* p-Value represents Pearson's chi-square test statistic value for comparing proportions between men and women.

by multiplying the consumption frequency of each food by the portion size in grams. Country (traditional) foods were grouped according to wildlife animal class (e.g. marine mammals, fish and seafood, big game, and small game), although individual foods were analyzed in some cases (e.g. beluga *mattaaq*, beluga meat). Market foods were grouped according to food groups in Canada's Food Guide for First Nations, Inuit, and Métis (Health Canada, 2007). To ensure models including dietary variables were not skewed by extreme observations, dietary variables were winsorized, such that observations with values higher than those in the 99th percentile were adjusted to the 99th percentile value.

2.5. Statistical analyses

All statistical analyses were performed in Stata® Version 13.0 (Statacorp, College Station, TX). Since many biomarkers were not normally distributed, we present geometric means and non-parametric statistics (e.g. Spearman's correlation coefficients [r_s]) where appropriate. Descriptive statistics were computed by sex for all variables of interest and Se and Hg biomarkers, including percentage (for categorical variables) and mean, 95% confidence interval, and range (for continuous variables). Correlations were assessed between RBC selenoneine concentration and all other Se biomarkers using Spearman's correlation coefficients, scatterplots with overlaid linear predictions, and simple linear regression models. We then examined sex-specific Se biomarkers and dietary intake of food categories by tertile of RBC selenoneine concentration using Wilcoxon rank sum test and Sidak post-hoc pairwise comparisons. Unadjusted and adjusted linear regression models were used to assess associations between dietary intake of food groups (both country foods and store-bought foods) and blood Se biomarkers.

We conducted a backwards step-wise linear regression model building process to determine sociodemographic, lifestyle, and dietary factors associated with RBC selenoneine concentration (Dohoo et al., 2003). First, univariate associations were assessed using a *p*-value cut-off < 0.2 and included in an initial multivariable model. Variables were systematically eliminated at $p > 0.05$ based on highest *p*-value, and after elimination, all previously-excluded variables were re-introduced and assessed for significance in the multivariable model. Confounding was considered present if coefficients of remaining variables changed by > 20% following elimination of each variable. Interaction variables were tested if there was a priori knowledge or hypotheses about potential interaction effects. Diagnostics on the final model included Shapiro-Wilks test for normality of residuals using and Cook-Weisberg test for homoscedasticity. All non-parametric variables were log-transformed, which resulted in improved model diagnostics over the untransformed model. We also report standardized β values for each coefficient for ease of comparison. Due to the complex study design of *Qanuippitaa*?, population weights were incorporated into the regression analysis, which assigned a weight to each participant based on probability of sample selection, non-response rate, and observed differences between the sampled population and source population. Population weights were adjusted for age, sex, and community, and correspond to the number of individuals in the source population represented by the sample (Rochette and Blanchet, 2007).

As a final step, we assessed correlations between beluga *mattaaq* consumption and Se biomarkers for men and women. Gender-stratified geometric mean concentrations of RBC selenoneine, RBC Se, and plasma Se were calculated for each tertile of beluga *mattaaq* consumption. Means were adjusted for covariates identified in the multivariable regression analysis. We employed Wilcoxon rank sum tests to determine if median biomarker concentrations were significantly different across tertiles, using the lowest tertile as the referent. For all statistical analyses, a cut-off *p*-value < 0.05 was used to determine significance. 95% confidence intervals were reported wherever possible.

3. Results

The overall participation rate for the *Qanuippitaa*? Study was 52%, with 889 participants completing the clinical session and submitting blood samples (Rochette and Blanchet, 2007). Of these participants, 756 completed a FFQ. A total of 885 samples (387 men and 488 women) were analyzed for whole blood Se and RBC selenoneine and 858 samples (390 men and 468 women) were analyzed for plasma seleno-proteins and Hg. Descriptive characteristics of participants by sex are displayed in Table 1.

Geometric mean values of Se biomarkers in blood samples are presented by sex in Table 2. Median whole blood Se concentration was 261 μg/L. Selenoneine was found in all RBC samples (range: 1 μg/L to 3226 μg/L), and accounted for a large proportion of total Se in RBCs (geometric mean: 26%; although values reached up to 92%). RBC Se, and RBC selenoneine concentrations were higher among women ($p < 0.001$), while plasma Se concentrations were higher among men ($p < 0.001$). However, whole blood Se concentrations were not statistically different between sexes. RBC selenoneine concentrations were considerably higher ($p < 0.001$) in Hudson Strait communities (geometric mean (range) for men: 199.8 μg/L (3–3226 μg/L); women: 356.1 μg/L (11–2708 μg/L)) when compared to communities in Hudson Bay (men: 52.6 μg/L (1–1780 μg/L); women: 97.5 μg/L (5–1409 μg/L)) and Ungava Bay (men: 87.0 μg/L (2–1826 μg/L); women: 140.1 μg/L (1–2170 μg/L)).

RBC selenoneine was highly correlated with RBC Se ($r_s = 0.96$, $p < 0.001$) and whole blood Se ($r_s = 0.89$, $p < 0.001$) but only weakly correlated with plasma Se ($r_s = 0.13$, $p < 0.001$) (Fig. 2). The RBC selenoneine: RBC Se ratio was positively correlated with RBC Se ($r_s = 0.82$; $p < 0.001$; Fig. 2), indicating that in the study population, as RBC Se rises, an increasing proportion of Se is found as selenoneine. However, this association was non-linear, with RBC selenoneine: RBC Se ratio plateauing around 0.8. RBC selenoneine was also highly correlated with whole blood Hg ($r_s = 0.66$; $p < 0.001$) and MeHg

Table 2
Summary statistics of blood compounds among participants of the *Qanuippitaa*? 2004 study.

Variables	N	Geometric Means			*p*-Value*
		Men [95% confidence interval]	Women [95% confidence interval]	Overall (range)	
Se and associated compounds	885				
Total Se – whole blood (μg/L)		283.3 [271.5, 295.6]	301.5 [289.2, 314.3]	293.1 (118.5–3555)	0.057
Total Se – RBCs (μg/L)		414.2 [391.7, 438.0]	495.3 [469.6, 522.5]	457.1 (174.7–3892.6)	< 0.001
Total selenoneine – RBCs (μg Se/L)		87.6 [75.2, 102.1]	150.3 [133.3, 169.4]	118.0 (0.99–3226.3)	< 0.001
Methylated selenoneine – RBCs (μg Se/L)		5.5 [4.9, 6.1]	7.3 [6.6, 8.1]	6.4 (1.97–124.28)	< 0.001
RBC selenoneine:RBC Se ratio		0.21 [0.19, 0.24]	0.30 [0.28, 0.32]	0.24 (0.003–0.92)	< 0.001
Total Se – plasma	858	135.5 [134.0, 137.0]	143.9 [142.4, 145.5]	139.3 (87.4–228.8)	< 0.001
Se bound to GPx-3[a] (μg Se/L)		35.7 [35.2, 36.3]	34.1 [33.6, 34.7]	34.9 (19.6–77.5)	< 0.001
Se bound to SelP (μg Se/L)		75.2 [74.4, 76.0]	69.2 [68.5, 69.9]	71.8 (45.9–109.7)	< 0.001
Se bound to SeAlb (μg Se/L)		32.4 [31.8, 33.0]	31.6 [31.0, 32.1]	32.0 (19.2–75.6)	0.076

RBC = red blood cell.
* *p*-Value represents one-way analyses of variance for comparison of means between men and women.
[a] GPx-3 and unretained small molecules containing Se.

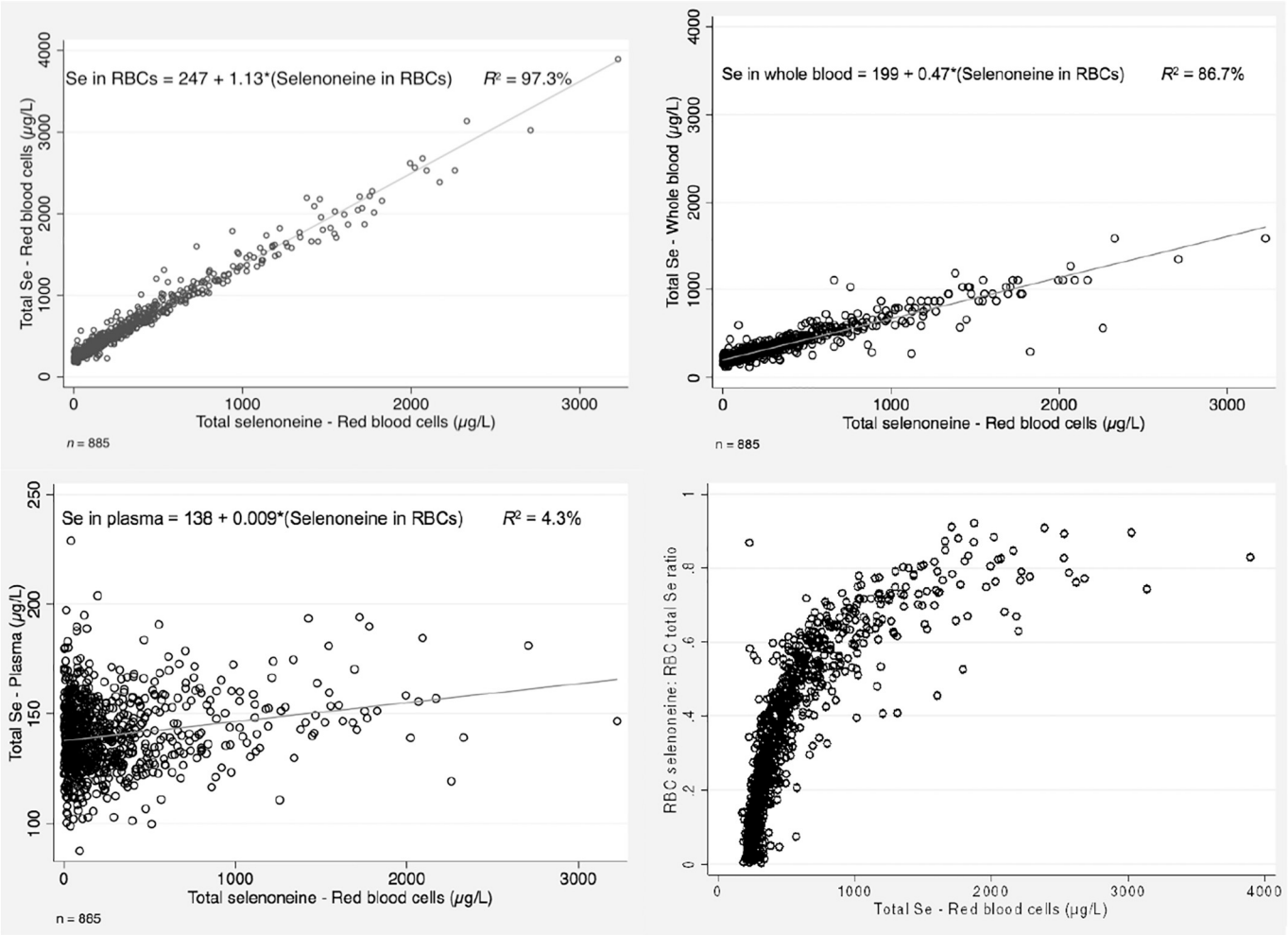

Fig. 2. Scatterplots with overlaid linear prediction plots showing associations between selenoneine measures and other Se biomarkers in blood samples from participants of the *Qanuippitaa*? 2004 study.

Table 3
Geometric means [95% confidence intervals] of blood markers and dietary intake by tertile of red blood cell selenoneine concentration by sex among participants of the *Qanuippitaa*? 2004 study.

Marker		Q1	Q2	Q3	*p*-Value for trend*
Total selenoneine – RBCs (μg Se/L)	M	15.2 [13.1, 17.7]	96.1 [90.1, 102.5]	465.2 [418.3, 517.3]	–
	W	33.7 [29.4, 38.5]	162.8 [154.4, 171.7]	202.9 [158.4, 260.0]	–
Se and associated compounds (n = 885)					
Total Se – whole blood (μg/L)	M	202.4 [197.5, 207.4]	246.5 [240.4, 252.8]	456.7 [426.6, 488.8]	< 0.001[a,b,c]
	W	202.6 [198.1, 207.2]	268.3 [260.2, 276.6]	506.1 [476.0, 538.0]	< 0.001[a,b,c]
Total Se – RBCs (μg/L)	M	253.7 [247.0]	349.4 [339.1, 359.9]	804.6 [745.5, 868.4]	< 0.001[a,b,c]
	W	280.5 [273.6, 287.5]	436.8 [422.9, 451.2]	931.8 [931.8, 1065.2]	< 0.001[a,b,c]
RBC selenoneine: RBC Se ratio	M	0.06 [0.051, 0.069]	0.28 [0.26, 0.29]	0.58 [0.56, 0.60]	< 0.001[a,b,c]
	W	0.12 [0.11, 0.14]	0.38 [0.36, 0.39]	0.63 [0.61, 0.64]	< 0.001[a,b,c]
Total Se – plasma (μg/L)	M	143.0 [139.9, 146.0]	143.0 [140.5, 145.6]	145.8 [143.1, 148.5]	0.31
	W	132.6 [130.0, 135.2]	134.1 [131.7, 136.5]	139.7 [137.2, 142.3]	< 0.001[b,c]
Se bound to GPx-3 (μg Se/L)	M	34.3 [33.3, 35.2]	34.8 [34.1, 35.6]	38.1 [36.9, 39.3]	< 0.001[b,c]
	W	31.6 [30.9, 32.4]	33.2 [32.6, 33.9]	37.8 [36.7, 38.8]	< 0.001[b,c]
Se bound to Selenoprotein P (μg Se/L)	M	75.1 [73.6, 76.6]	75.7 [74.3, 77.2]	74.7 [73.3, 76.1]	0.54
	W	68.9 [67.6, 70.2]	69.2 [68.0, 70.5]	69.5 [68.4, 70.6]	0.87
Se bound to Selenoalbumin (μg Se/L)	M	33.1 [32.0, 34.3]	31.9 [31.0, 32.9]	32.3 [31.4, 33.2]	0.20
	W	31.6 [30.6, 32.6]	31.2 [30.3, 32.2]	31.9 [31.0, 32.9]	0.57
Dietary consumption (g/day) (n = 756)					
Store-bought meats	M	158.2 [136.3, 183.7]	160.7 [136.5, 189.3]	114.4 [95.4, 137.2]	0.016[c]
	W	126.9 [111.6, 144.2]	107.4 [92.2, 125.0]	97.5 [83.8, 113.4]	0.24
Fruits and vegetables	M	379.4 [298.8, 481.9]	435.1 [356.5, 530.9]	414.3 [330.8, 519.0]	0.76
	W	412.1 [350.2, 484.9]	444.7 [366.8, 539.2]	440.7 [367.2, 528.8]	0.59
Milk products	M	95.9 [69.2, 132.9]	79.0 [58.1, 107.4]	80.5 [59.3, 109.2]	0.15
	W	78.8 [62.7, 99.0]	80.1 [61.5, 104.4]	63.3 [49.1, 81.6]	0.93
Cereals	M	200.1 [170.9, 234.3]	173.7 [147.7, 204.3]	161.1 [135.9, 191.1]	0.38
	W	146.8 [130.6, 164.9]	153.4 [132.7, 177.4]	129.3 [113.1, 147.7]	0.08
Country foods, total	M	82.3 [63.8, 106.1]	113.0 [93.0, 137.4]	126.9 [105.5, 152.9]	0.92
	W	79.1 [64.8, 96.5]	98.7 [83.4, 116.8]	109.6 [01.2, 131.6]	0.10
Beluga *mattaaq***	M	1.14 [0.85, 1.52]	2.12 [1.61, 2.82]	3.90 [2.85, 5.33]	< 0.001[a,b,c]
	W	1.01 [0.77, 1.33]	1.23 [0.92, 1.65]	3.75 [2.80, 5.02]	0.006[b,c]

M = men; W = women; RBC = red blood cell.
* *p*-value represents results of Wilcoxon rank sum tests; numeric superscripts represent $p < 0.05$ of Sidak pairwise comparisons.
** All country food categories and items were assessed, but only beluga *mattaaq* is presented due to its association with tertile of RBC selenoneine.
[a] Q1 vs Q2.
[b] Q1 vs Q3.
[c] Q2 vs Q3.

($r_s = 0.66$; $p < 0.001$). Concentrations of various blood markers and dietary intake variables by tertile of RBC selenoneine concentration are listed in Table 3. Table S1 (supplementary materials) summarizes the results of unadjusted and adjusted multivariable linear regression models assessing associations between several FFQ food groups and several blood Se biomarkers. Consumption of store-bought meats and game birds were negatively associated with RBC selenoneine, while marine mammal consumption was positively associated with RBC selenoneine in adjusted models.

Several sociodemographic, lifestyle, and dietary factors were

Table 4
Multiple linear regression model of RBC selenoneine among participants of the *Qanuippitaa*? 2004 study.

Variable	Standardized β [95% confidence interval]	Robust standard error	*p*-Value
Age	0.24 [0.16, 0.32]	0.04	< 0.001
Female sex	0.10 [0.03, 0.18]	0.037	0.001
Body mass index (kg/m^2)	0.078 [0.008, 0.15]	0.035	0.033
Beluga *mattaaq* consumption (g/day)	0.19 [0.09, 0.27]	0.053	< 0.001
Hudson Strait (compared to other regions)	0.38 [0.27, 0.49]	0.057	< 0.001
Market meat consumption (g/day)	−0.068 [−0.11, 0.029]	0.039	0.012
Coefficient	0.066 [−0.01, 0.14]	0.039	0.089

Adjusted R-squared: 0.29.

associated with RBC selenoneine in a multivariable model (Table 4). Increased age, higher body-mass index (BMI), and female sex were positively associated with RBC selenoneine. Beluga *mattaaq* consumption was the only country food variable positively associated with RBC selenoneine. Individuals from the Hudson Strait had significantly higher RBC selenoneine concentrations than individuals from Hudson Bay and Ungava Bay. Finally, consumption of market meats was negatively associated with RBC selenoneine. We found no significant interactions between any of the tested variables and age or sex.

Beluga *mattaaq* consumption was common; 83.5% of FFQ participants consumed at least 0.2 g/day and average consumption was 7.3 g/day. Consumption was not significantly different between sexes ($p = 0.18$). Self-reported consumption of beluga *mattaaq* was positively associated with whole blood Se ($r_s = 0.41$; $p < 0.001$), RBC selenoneine ($r_s = 0.42$; $p < 0.001$), and RBC selenoneine: RBC Se ratio ($r_s = 0.43$; $p < 0.001$), and these associations were not significantly different between sexes. As shown in Fig. 3, for both sexes, each increasing tertile of beluga *mattaaq* consumption had significantly higher geometric mean concentrations of RBC selenoneine and whole blood Se ($p < 0.001$), but not plasma Se. Indeed, beluga *mattaaq* consumption was not associated with total plasma Se in women ($r_s = -0.023$; $p = 0.65$) or men ($r_s = 0.022$; $p = 0.69$), and was even negatively associated with SelP in women ($r_s = -0.11$; $p = 0.03$) but not men ($r_s = -0.038$; $p = 0.50$).

4. Discussion

We determined RBC selenoneine concentrations in a random sample of 885 Inuit adults from Nunavik, northern Quebec, Canada. To our knowledge, this is the first study to determine RBC selenoneine concentrations in a large cross-sectional sample from a human population. We found that selenoneine is a major Se compound in RBCs from Nunavik Inuit, accounting for up to 92% of Se in RBCs (geometric mean: 26%). In the only other report of selenoneine in human RBCs, Yamashita et al. (2013a) found higher geometric mean but a lower range of RBC selenoneine concentrations in a small non-random sample from a fish-eating population in Japan (geometric mean = 212 μg/L; range: 6–2380 μg/L; n = 167) than those reported here (geometric mean = 118 μg/L; range: 1–3226 μg/L). While there have been no studies on selenoneine in general populations, it is likely that RBC selenoneine concentrations are considerably elevated among Inuit populations compared to non-Inuit due to consumption of foods high in selenoneine, such as beluga *mattaaq* (Achouba et al., in review).

This study is the first to compare RBC selenoneine concentrations by sex. Geometric mean RBC selenoneine concentration in women (150.3 μg/L) was almost double that of men (87.6 μg/L), and this difference was significant even after controlling for age, region, and dietary factors in the multiple linear regression model ($p < 0.001$). Elevated selenoneine concentrations likely account for the higher RBC Se among women compared to men ($p < 0.001$), findings that correspond with Greenlandic Inuit populations (Hansen et al., 2004), but not fish-eating populations in Japan (Imai et al., 1990). While higher RBC selenoneine among women may reflect potential differential response bias in FFQs, it is also possible that biological sex differences exist in the sequestration and functions of selenoneine. However, given that selenoneine has been reported to bind to heme proteins (hemoglobin and myglobin) (Yamashita and Yamashita, 2010), which tend to be found in lower concentrations in women, these findings are perplexing and require further examination. Alternatively, it is possible that selenoneine intake differs between men and women due to gender-specific dietary habits. For example, there is some preliminary evidence to suggest that, among Inuit in Nunavik, traditional practices dictate that women consume raw *mattaaq*, meat, and cartilage from the tail of beluga whales following a beluga hunt, whereas men never consume these products (unpublished data from 11 interviews). A detailed examination of gender-based dietary differences and selenoneine accumulation in specific body parts of beluga whales and other country foods is therefore currently underway to shed light on this hypothesis.

As previously reported, this population exhibited one of the highest mean and the largest ranges of whole blood Se concentrations in the world (median = 261 μg/L, geometric mean = 293 μg/L, range: 118–3555 μg/L) (Achouba et al., 2016; Lemire et al., 2015). These findings confirm previous research from Nunavik (Muckle et al., 2001) and correspond with similarly high whole blood Se concentrations found among Inuit populations in Nunavut (Hu et al., 2017) and Greenland (Hansen et al., 2004). Indeed, Inuit from Nunavik, Nunavut, and Greenland have considerably higher whole blood Se concentrations than Native populations in Alaska (median = 185.4 μg/L, range: 145–339 μg/L) (Dr. James Berner, personal communication), a subsample of First Nations and Inuit women from the Northwest Territories (median = 120 μg/L, range: 67–184 μg/L) (Butler Walker et al., 2006), First Nations populations in southern Canada (median = 182 μg/L, 95th percentile: 235 μg/L) (AFN, 2013), and general populations in Canada (median = 199 μg/L, 95th percentile: 160 μg/L) (Health Canada, 2010), USA (median = 189 μg/L, 95th percentile: 236 μg/L) (Jain and Choi, 2015), and Europe (Batáriová et al., 2005). As recently reported by Achouba et al. (2016), despite high whole blood Se levels among Nunavik Inuit, plasma Se and selenoproteins were not remarkably elevated and in the same range as southern populations. Additionally, a non-linear association was observed between whole blood Se and plasma Se, with plasma Se concentrations reaching a plateau around 200 μg/L. Hansen et al. (2004) reported a similar trend among Inuit in Greenland. Such findings contrast with those from inland populations in Brazil (Lemire et al., 2012), Malawi (Stefanowicz et al., 2013), and the United Kingdom (Stranges et al., 2010), which exhibit a linear association between whole blood Se and plasma Se.

We propose that elevated RBC and whole blood Se among Arctic Inuit populations, as well as non-linear associations between whole blood Se and plasma Se found in Nunavik and Greenland, are primarily due to accumulation of selenoneine in RBCs resulting from consumption of traditional marine country foods. In particular, such trends may result from high consumption of beluga *mattaaq* and possibly other toothed-whale *mattaaq* such as narwhal *mattaaq*, which is eaten in Nunavut and Greenland but not Nunavik. Beluga *mattaaq* from different regions in the Arctic has been previously reported as very high in Se (Blanchet et al., 2000; Lockhart et al., 2005), however, it was only recently discovered that a large proportion - upwards of 50% - of this Se exists as selenoneine (Achouba et al., in review). Other local marine mammal foods in Nunavik, such as walrus meat, contain selenoneine but in lower quantities (Dufour et al., personal communication, November 14, 2017), and more studies are needed to better identify other

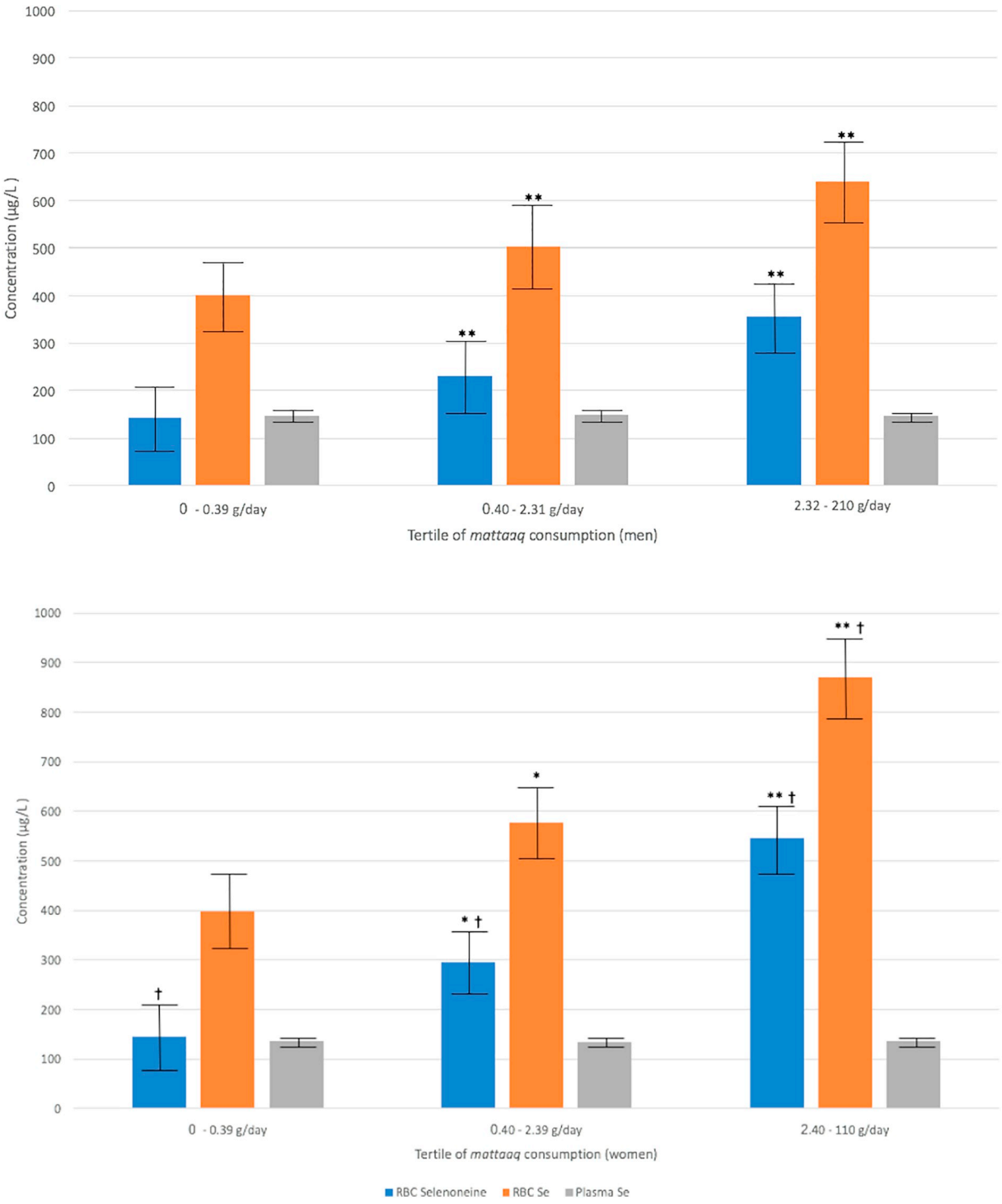

Fig. 3. Geometric means of RBC selenoneine, RBC Se, and plasma Se concentrations by tertile of beluga *mattaaq* consumption stratified by gender and adjusted for BMI, region of residence, and market meat consumption [color figure]; Wilcox rank-sum test used to determine significant differences between categories. *p-value < 0.01 compared to sex-specific lowest tertile; **p-value < 0.001 compared to sex-specific lowest tertile; †different at $p < 0.05$ compared to tertile-matched men.

possible sources of selenoneine in the diet in Nunavik and elsewhere. In the present study, self-reported beluga *mattaaq* consumption was highly correlated with RBC selenoneine ($p < 0.001$) after controlling for age, sex, region, and other dietary factors. Furthermore, differential intake of beluga *mattaaq* may be responsible for the associations between RBC selenoneine and market meat consumption (e.g. market meat consumers eat less beluga *mattaaq*), region (e.g. Hudson Strait communities have increased access to beluga since beluga hunting is more common in this region), and age (e.g. older Inuit often consume more beluga *mattaaq* and selenoneine may bioaccumulate in older individuals if there exists a kinetic reservoir) (Kuhnlein et al., 1996; Lemire et al., 2015).

Until now, epidemiological research has primarily measured hair, toenail, plasma, or whole blood total Se to determine Se status in human populations (AMAP, 2015; Hu et al., 2017; Park et al., 2011; Van Oostdam et al., 2005). Additionally, randomized trials assessing Se

supplementation most commonly administer SeMet to the intervention group and studies on selenosis often measure total Se exposure, while reports on the health effects of different Se species and compounds are lacking (Qin et al., 2012; Sutter et al., 2008). Such epidemiological studies on Se, which often occur outside of the Arctic context, form the basis for policy and public health recommendations for Inuit populations. For example, Health Canada (Government of Canada, 2016) and other public health organizations (IOM, 2000; WHO, 2011) published recommended dietary allowances (RDAs) and upper tolerable intakes (UTLs) for total Se intake based on evidence from a seleniferous agricultural region of China (Yang and Zhou, 1994). Research and policy have thus inadequately recognized and examined the different functions and biomarkers of various dietary Se species and compounds. Such oversights are underscored by conflicting or inconsistent evidence on the health impacts of high Se exposure (Hu et al., 2017; Rayman, 2012; Rayman et al., 2018; Vinceti et al., 2018) and findings suggesting that populations in Greenland (Hansen et al., 2004), Japan (Yamashita et al., 2010), and Brazil (Lemire et al., 2012) exhibit little evidence of selenosis despite very high Se dietary intake. Our results show that selenoneine is a major Se compound in Nunavik Inuit adult blood due to beluga *mattaaq* consumption, which indicates that this population - and possibly other coastal populations consuming marine foods - is unique in its exposure to Se. There is therefore a need for further research on routes of exposure (e.g. ingested versus inhaled), kinetics, and health implications of various Se species and compounds to develop population- and region-specific risk assessments and subsequent RDAs and UTLs (Xia et al., 2010).

Inuit populations experience high methylmercury (MeHg) exposure and higher whole blood Hg concentrations than general Canadian populations (Achouba et al., 2016; Laird et al., 2013). Evidence suggests that concomitant high dietary intake of Se may mitigate MeHg toxicity in humans (Ayotte et al., 2011; Boucher et al., 2010; Fillion et al., 2013; Hu et al., 2017; Lemire et al., 2010; Lemire et al., 2011; Valera et al., 2009). In addition to its antioxidant activity, a few recent studies provide evidence that selenoneine may play a role in this mechanism, as selenoneine is capable of demethylating MeHg in vitro and reduces Hg accumulation in animal models (Palmer and Parkin, 2015; Khan and Wang, 2010; Yamashita et al., 2010; Yamashita et al., 2013a, 2013b). In the present study, RBC selenoneine was highly correlated with whole blood Hg and MeHg, likely due to their co-occurrence in marine country food sources. Future studies will examine if selenoneine-mediated in situ demethylation occurs. If such a mechanism exists, and if selenoneine is a non-toxic form of Se as proposed by Yamashita et al. (2010), such information will contribute to an evidence base for public health recommendations that weigh the potential benefits and risks of consuming traditional country foods that are simultaneously high in selenoneine (and other Se compounds), MeHg, and other nutrients and contaminants.

This study has certain limitations. Due to the cross-sectional nature of the *Qanuippitaa*? study, we are unable to determine causation. Response rate was 52%, which increased the possibility of selection bias. Red blood cell samples were analyzed for selenoneine after being frozen at −80 °C since 2004, which may have affected the accuracy and precision of laboratory analyses. However, after conducting a two-stage freeze-thaw stability test on blood samples, no signs of degradation were present (Achouba et al., in review). Additionally, although the FFQ is considered a valid form of dietary assessment, the limitations of FFQs are well-documented, and include a tendency to over-estimate food intakes and a susceptibility to social desirability and social approval biases (Hebert et al., 1995).

5. Conclusion

Selenoneine is found in high concentrations in RBCs and accounts for a large proportion of whole blood Se among Inuit adults in Nunavik. Accumulation of selenoneine in the RBCs of this population contributed to high RBC and whole blood Se concentrations, as well as the non-linear association between plasma and whole blood Se concentrations in this population. Beluga *mattaaq* consumption was one of the most important predictors of RBC selenoneine concentrations, and, women had higher RBC selenoneine concentrations than men, possibly due to dietary or biological sex differences. Future studies will examine the underlying mechanisms explaining sex-differences among Inuit populations. Furthermore, research is needed to assess the potential adverse and beneficial health impacts of selenoneine exposure, including its potential in moderating MeHg toxicity.

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Declarations of interest

None.

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