Environmental Exposure to Trace Elements and Prostate Cancer in Three New Zealand Ethnic Groups

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Abstract: A stratified random sample of 176 men was taken from a larger community prostate study group of 1405 eligible subjects from three ethnic groups in the Wellington region of New Zealand, in order to examine ethnic differences in exposure to cadmium (Cd), selenium (Se) and zinc (Zn) and possible associations of blood levels of Cd, Se and Zn with the prevalence of elevated serum Prostate Specific Antigen (PSA); a marker of prostate cancer. Maori and Pacific Islands men were found likely to have higher Cd exposure than New Zealand Europeans through diet, occupation and smoking. However, there was no significant difference between ethnic groups in mean blood Cd levels. Pacific Islands men had significantly higher levels of blood Se than both New Zealand European men and Maori men. Maori men had significantly higher levels of blood Zn than both New Zealand European men and Pacific Islands men. A positive association was found between blood Cd and total serum PSA. Se and Zn levels were not associated with elevated PSA. Maori and Pacific Islands men have higher prostate cancer mortality rates than New Zealand European men. Ethnic differences in mortality could be contributed to by differences in rates of disease progression, influenced by exposure and/or deficiency to trace elements. However, results did not reflect a consistent ethnic trend and highlight the complexity of the risk/protective mechanisms conferred by exposure factors. Further research is needed to ascertain whether the associations found between Cd and PSA levels are biologically important or are merely factors to be considered when interpreting PSA results clinically.

Keywords: Cadmium, selenium, zinc, serum prostate specific antigen, prostate cancer, ethnicity.

Introduction

Prostate Cancer and Environmental Trace Elements

It is well accepted that genetic variation alone does not explain the observed differences in incidence of prostate cancer [1]. A 120-fold difference in rates of prostate cancer among different countries indicates that there is substantial variation in occurrence of this disease, and suggests that environmental factors are of importance [2]. The Health Research Council of New Zealand [3] highlights that the role of putative environmental and dietary factors (such as low soil Se) in causing prostate cancer is still unknown. Whether such environmental

exposures are associated with increased rates or progression of prostate cancer remains to be explored.

Within the New Zealand population there is significant ethnic variation in cancer incidence and mortality [4]. WHO age-standardized prostate cancer rates in 1998-1999, showed that at 86.1 per 100,000, Maori males had the lowest incidence, followed by Pacific Islands males at 115.2 per 100,000 and other (chiefly New Zealand European) males the highest incidence at 118.9 per 100,000 [5]. Conversely, the prostate cancer WHO age-standardized mortality rates for Pacific Islands males and Maori males in 1998-1999 (52.3 and 39.3 per 100,000 respectively) were higher than rates for other males (22.8 per 100,000) [5, 6].

The ethnic disparity between incidence and mortality is likely to reflect reduced health care utilisation by Maori and Pacific Islands men, as well as underreporting in ethnic health data collection in New Zealand [7-9]. Recent research has shown that prostate cancer incidence for Maori and Pacific Islands men is likely to be at least as high as that shown for New Zealand European men [10]. The higher mortality rates shown for Pacific Islands and Maori men may reflect the health utilisation issues of later diagnosis and treatment, as well as ethnic differences in disease progression, influenced by exposure to risk factors.

Ecological and migrant studies world-wide have implicated environmental factors as risks for prostate cancer [11]. Since many environmental factors are modifiable, they lead to important implications for the prevention of prostate cancer. Three environmental trace elements, cadmium (Cd), selenium (Se) and zinc (Zn) have been highlighted in the literature in relation to prostate disease [12, 13] and are important elements within the New Zealand environment [14, 15].

Cd is readily found in New Zealand soil [16, 17]. Certain foods in New Zealand are high in Cd, including watercress, shellfish and offal meats [15]. Zn is a nutrient element found in high concentrations in the prostate gland and is necessary for healthy prostate function [12]. Cd and Zn compete for binding to protein ligands in tissues and Zn antagonises the toxicity of Cd [18]. Both Cd and Zn may affect the amount of both testosterone and dihydrotestosterone (DHT) in the prostate, which are essential for the progression of both benign prostate hyperplasia (BPH) and prostate cancer [19, 20].

The role of Se as a promising anti-carcinogen for prostate cancer is being researched internationally in clinical trials using dietary supplements [12]. Dietary intakes of Se in New Zealand are low by international comparisons [14]. The New Zealand specific characteristics of these three trace elements may mean that New Zealand males are particularly susceptible to environmentally induced prostate disease. Furthermore, there are known ethnic differences in diet, occupation and smoking levels, which may affect exposure to these trace elements.

Blood Cd reflects both recent and cumulative exposures [21]. Therefore, the older the person the higher the blood Cd level is likely to be. It has also been suggested that, as populations age, their intake of Se and Zn decreases due to age-related changes in diet [22]. As prostate cancer risk increases with age, these changes in trace element exposure may further increase prostate cancer risk.

Risk Factor - Cadmium

The human body burden of Cd has increased over the last 100 years due to an increase in environmental and industrial pollutants [15]. Environmental Cd pollution occurs in New Zealand through a combination of land contamination (through fertilisers and sludge application) and water contamination (through irrigation and industry), and is subsequently introduced into the food chain. In New Zealand, soil Cd levels are increasing [16, 17]. Excess consumption of lamb, kidney, alcohol, grains, and oysters can increase the body burden and industry can provide direct occupational exposure [15].

Studies have attempted to find a link between Cd exposure and prostate cancer with equivocal results. Cd exposure has been positively associated with elevated prostate cancer rates in a number of occupational and laboratory studies [13, 23-26]. Research into environmentally exposed populations to Cd, do not indicate an increased relative risk of cancer [27]. However, biological studies have found evidence of carcinogenic properties in prostatic cells [28], and that the carcinogenic effect of Cd can be hormonally mediated [13, 29].

Protective Factors - Selenium and Zinc

Se is an essential trace element found in varying concentrations in the soil. Primary sources of Se in the diet are meats, eggs, dairy products and bread. Kidney, liver, and seafood are also rich in Se. In these foods, Se occurs mostly as organic compounds [30].

Ecologic studies have established an inverse correlation between soil Se levels and prostate cancer mortality [31, 32]. The Nutritional Prevention of Cancer Study found that men taking Se supplements for five years had a 65% reduction in the incidence of prostate cancer [14]. However, another large study (the Alpha-tocopherol, Beta-Carotene Cancer Prevention Study) found no association between baseline Se and prostate cancer during nine years of follow-up [33]. Though clinical studies have focused on Se supplementation as a protective factor in reducing prostate cancer incidence [34, 35], the effect of low Se on potentially increasing prostate cancer risk has not been addressed.

A case-control study on 9345 Japanese-American men found an inverse association between blood Se levels and prostate cancer incidence [36]. This Japanese study showed that subjects had less chance of prostate cancer if baseline blood Se was greater than 147µg/L. The association was mainly present in current or past cigarette smokers [36]. This lends support to the possibility that Se may help to combat the toxic effect of cigarette compounds, such as Cd [12]. A smaller (3059 men) USA case/control study's results were consistent with this finding and reported a steady reduction in prostate cancer risk with serum Se >135µg/L [37].

Because Se concentrations in food depend on local soil conditions, intakes vary geographically. Some populations, living in parts of the world that depend on domestic food production, ingest very little Se and are at risk of Se deficiency [37]. New Zealand is low in soil Se, particularly in some areas of the South Island and this is reflected in low Se levels in some foods that are domestically grown [14].

A report by Thomson and Robinson [38] concluded that the Se status of New Zealanders had improved since the first reports in the early 1970s. This improved Se status was attributed to the importation of Australian wheat and cereal because of its higher Se content, as well as an increased consumption of fish and poultry [38].

However, both the 1997/98 New Zealand Total Diet Survey and the 1997 National Nutrition Survey found that the dietary intakes of Se were well below the recommended daily allowances in other countries [39]. Intake estimates from the 1997 National Nutrition Survey were only two-thirds the Australian recommended daily intake. More recent studies in younger New Zealand adults still indicate an insufficient Se intake for full expression of glutathione peroxidase (GPx) and do not confirm the earlier findings of 1996 [22].

Furthermore, in the South Island, 100% New Zealand grown wheat is used in bread making, whereas in the North Island, between 50 and 100% imported wheat is used [22]. As older people are prone to low Se status and because intakes of Se are strongly correlated with those of total energy and protein [40], de Jong et al. [22] conclude that this places the elderly living in the South Island of New Zealand at particular risk.

Zn is a homeostatically regulated essential mineral, present in red meat, poultry, grains, dairy, legumes and vegetables. It is a component of numerous metalloenzymes and is important for cell growth and replication, osteogenesis and immunity. Zn may also act as an antioxidant by stabilizing membranes in some cell types. Some studies have found an association of lower Zn intakes in patients with certain cancers, whilst others have observed no association [12].

Zn is regarded as a 'cellular growth protector' for the prostate. Normal human prostate accumulates the highest levels of Zn of any soft tissue in the body [41]. In contrast, the Zn level in prostate cancer cells is markedly decreased from the level detected in non-prostate tissues [42]. Studies have found evidence that Zn inhibits human prostate cancer cell growth; possibly due to induction of cell cycle arrest and apoptosis [42]. It is thought that the loss of a unique capability to retain high levels of Zn is an important factor in the development and progression of malignant prostate cells [42]. In-vitro Zn helps to maintain intra-prostatic balance of testosterone and DHT [41].

Based on these cellular activities, it could be expected that Zn levels would be inversely associated with prostate cancer. However, epidemiologic findings for Zn and prostate cancer incidence and mortality have not been consistent. At this time the evidence for a beneficial effect of Zn on prostate cancer incidence is insufficient to warrant undertaking randomized chemoprevention trials [12].

Reduction in red meat and an increase in cereals in the diet may compromise the intake and bioavailability of Zn in New Zealanders diet [43]. Both dietary and biochemical data suggest that current 'Western' diets of the elderly may induce a considerable risk of Zn deficiency. The detrimental effect of a marginal Se status on immune function may be further aggravated by inadequate Zn intake [43].

A study by Feustel et al. [44] found a distinct biological antagonistic effect between Zn and Cd in the human prostate gland. They found an increasing amount of Zn in cases of benign prostatic hyperplasia (BPH) but a decrease in prostate cancer. In contrast, they found a lower Cd concentration in the normal prostate compared

to prostate cancer. Studies in the late 1980s confirmed that elevated total PSA (>4.0ng/mL) could be used to identify patients with prostate cancer [45]. A recent study has found a relationship between Zn in prostate tissue and PSA levels in blood [46].

Ethnic differences in prostate cancer mortality could be contributed to by differences in rates of disease progression, influenced by exposure to trace elements. The aim of this study was to examine ethnic differences in exposure to Cd, Se and Zn and possible associations of blood levels of these trace elements with the prevalence of elevated PSA in three ethnic groups.

Materials and Methods

From January 2000 to February 2002, a total of 1617 males were recruited into the Wellington Regional Community Prostate Study (WRCPS) co-ordinated through the Wellington School of Medicine and Health Sciences of the University of Otago. In order to ensure an adequate representation of Maori and Pacific Islands men, participants were enrolled by two separate procedures. Initially subjects were identified in census area units containing at least 5% Maori and 5% Pacific Islands populations. Males aged between 40 and 69 years were invited to attend a local clinic where a blood sample was taken and a detailed questionnaire was completed (Phase 1). The total number recruited into Phase 1 was 698.

The second mode of recruitment was through the identification of individuals who had been screened as part of the Wellington hepatitis and diabetes-screening programme for Maori and Pacific Islands populations. After ethics approval, blood samples were retrieved from the Hepatitis Foundation of New Zealand and subjects were contacted and asked to complete the study questionnaire (Phase 2). The total number recruited into Phase 2 was 919.

A 10ml tube of blood was collected, and centrifuged within 4 hours of sampling. Serum was stored at -70C until assayed. Sera from each subject were tested for total PSA, complexed PSA (cPSA) and free PSA (fPSA). Laboratory blood analysis for PSA and free PSA was carried out using an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany) assay [47]. Assays were performed according to manufacturer's specifications.

Questionnaires were self-administered and covered occupation, education, medical history and diet. Most dietary information was obtained via a subset of questions from a food frequency questionnaire (FFQ) previously validated in another New Zealand study [48].

Ethnicity was determined on a self-identification basis [49]. Subjects also completed an International Prostate Symptom Score Sheet (IPSS) [50] and declared if they have ever had any evidence of prostate disease. Subjects with total PSA levels of >4.0ng/mL were referred back to their general practitioner for further evaluation and exclusion of prostatic malignancy.

In order to ensure subjects were affiliated to the three ethnic groups in question and aged between 40-69, age and ethnicity selection criteria were applied to the combined Phase 1 and Phase 2 group (1617). Subjects were also excluded on the basis of suspected prostate cancer (through PSA testing, GP diagnosis or prostate

biopsy). A stratified random sample was taken from the remaining 1405 eligible subjects.

Sampling was undertaken as follows; 150 randomly chosen New Zealand European, Maori and Pacific Islands men (50 from each group), plus all 26 men who screened positive for elevated PSA (total PSA >4.0ng/mL) were selected to be tested for Cd, Se and Zn. Due to some results being below the detection limits, data were only available for 157 subjects; 51 New Zealand European, 60 Maori and 46 Pacific Islands men.

Laboratory Analyses

Several methods have been used for the analysis of Zn, Cd and Se in biological samples and environmental samples including flame and graphite furnace atomic absorption (FAA and GFAA), Inductively Coupled Plasma Emission Spectrometry (ICP-OES) as well as Inductively Coupled Plasma Mass Spectrometry (ICP-MS) [51]. ICP-MS and GFAA are most commonly used for the clinical application. The levels for Cd and Se in blood are in µg/L, whereas for Zn the levels are in mg/L (or µg/mL) of blood [52]. The detection limits for both techniques for all three elements are below these levels (low µg/L for GFAA and ng/L for ICP-MS) [51]. However, GFAA suffers from short dynamic range and each analyte requires a separate analysis [51]. The advantages of ICP-MS are short analysis time, multi-element capability and linear response over several orders of magnitude (from low ng/L to mg/L within the same run) for each of the elements studied [51, 53]. For these reasons ICP-MS was the selected method for the current study.

Cd, Se and Zn measurements were carried out using ICP-MS at the Division of Biophysical Toxicology Pathology, U.S. Armed Forces Institute of Pathology in Washington DC [54]. We used open vessel microwave digestion (MDS 2000, CEM Corporation, Mathews, NC, USA) for the New Zealand blood samples, using internal standards for all three elements (^{74}Se, ^{68}Zn and ^{106}Cd). Finally, the samples were dissolved in concentrated nitric acid and diluted accordingly for ICP-MS measurement and analysis [54]. The analysis was performed on Perkin Elmer Sciex Elan 6100 DRC instrument (Perkin Elmer, Norwalk, CT, USA).

Certified reference materials (National Institute of Standards and Technology, Gaithersburg, MD) of the same matrix, at known concentrations, were used as quality controls and these were used at intervals of every batch of 10-15 samples per analysis. This method provided percent recoveries for each of the analytes between 95-105%.

Statistical Analyses

Statistical analyses were performed with SPSS version 10.1. Two separate sets of analyses were performed; first to examine the ethnic-specific levels of Cd, Se and Zn, second to investigate the relationship between these trace elements and PSA.

Ethnic Differences in Trace Elements

As blood levels of Cd, Se and Zn are associated with age, a standard multivariate regression model was used to estimate the age-adjusted mean levels in µg/L (or µg/mL for Zn) of the trace elements for each ethnic group.

Occupational data were sorted into two categories; those who currently work in high Cd exposure risk jobs and those who do not. Linear regression analyses were undertaken to examine the relationship between the blood trace element values, diet, high Cd exposure risk occupation (such as metal work) and smoking data. Ethnic differences in consumption of foods were investigated [55]. Life in New Zealand (LINZ) Activity and Health Unit [56] results were used to assess likely sources of trace elements from food.

Zn and Se results were compared with other available New Zealand studies [22, 57, 58] and major overseas studies [36, 37, 59, 60]. No comparable studies were available for Cd.

PSA Levels and Trace Element Associations

Because Cd was significantly associated with total PSA levels, weighting by WRCPS group proportions of elevated PSA was undertaken in order to standardize for differences in the structure of elevated PSA prevalence between the sample group and the larger WRCPS group.

Cd levels were categorized according to the percentile blood Cd results of a large sample of subjects >20 years old (4207) in the US NHANES between 1999 and 2000 [21]. Three categories were developed for the New Zealand population; low = <LOD-0.60 µg/L, medium=0.60-1.00 µg/L and high >1.00 µg/L. These Cd categories were used to determine the extent of PSA increase with increased levels of blood Cd.

Linear models were undertaken to estimate the effect of all the trace elements on total PSA, complexed PSA (cPSA), free PSA (fPSA) and the ratio of free to total PSA (%fPSA). Because PSA, cPSA, fPSA, Cd, Se and Zn were found to be log-normally distributed, the logarithm of all biomarkers was used in analyses. A logistic regression model was developed to test whether the prevalence of elevated PSA varied significantly by levels of Cd, Se and Zn.

To test for possible bias in the stratified sampling method, a comparison of p-values in regression models was undertaken after the removal of all men with elevated PSA (>4.0ng/mL). Backwards Stepwise Regression models were developed to examine if the association between trace elements, initially found to correlate to PSA (and its various molecular derivatives) on a bivariate level, was due to confounding alone [61].

Potential confounding factors for elevated PSA such as age, smoking, body mass index, lower urinary tract symptoms, selected dietary factors and occupation were controlled for within the models. Due to the non-random sampling method in the WRCPS, the potential for selection bias was investigated and partially controlled for by including factors within the model likely to be associated with participation, such as Phase of recruitment.

Results

Statistical tests for potential confounding and selection bias were undertaken. There was no change in the significance of p-values after the removal of men with

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elevated PSA (>4.0ng/mL) indicating that the stratified sampling method (of including all men who had elevated PSA levels) was not likely to bias the results.

Standardization of mean blood Cd levels by weighting by population proportions of elevated PSA was undertaken. Results indicated that the actual blood Cd mean was 1.03 and weighted mean was 1.04 (with overlapping 95%CI). As the standardized rate did not differ greatly from the crude rate, the confounding effect of differences in the structure of elevated PSA prevalence between the sample group and the larger group was small [62].

Ethnic Differences in Exposure to Trace Elements

Tables 1 and 2 show that, in mean blood Cd levels, there was no significant differences between the ethnic groups. Pacific Islands men have significantly higher levels of blood Se (164.14μg/L) than both New Zealand European men (p<0.001, 117.87μg/L) and Maori men (p<0.001, 122.30μg/L). Zinc levels were significantly higher in Maori men (6.94μg/mL) than both New Zealand European (p=0.002, 6.38μg/mL) and Pacific Islands men (p=0.003, 6.36μg/mL).

Table 1: Age-adjusted mean blood level for total study group and each ethnic group.

Trace Element	Total		New Zealand European Men	Maori Men	Pacific Islands Men
Cd μg/L	1.04^{*a} (0.86-.22)	1.03 (0.50-.08)	0.93 (0.79-1.08)	1.04 (0.90-1.21)	1.15 (0.98-1.36)
Se μg/L	131.72 (129.71-133.73)		117.87 (109.07-127.38)	122.30 (113.71-131.53)	164.14** (151.02-178.40)
Zn μg/mL	6.58 (1.98-8.57)		6.38 (6.13-6.63)	6.94* (6.69-7.20)	6.36 (6.10-6.64)
Zn/Cd Ratio	7.57 (6.82-8.31)		7.98 (6.66-9.29)	7.62 (6.41-8.84)	7.04 (5.65-8.42)

^{*a} Mean Cd standardized for prevalence of elevated PSA.
 95% CI are shown in brackets.

Table 2: Difference in blood trace element mean level between the three ethnic groups (p-value)

Trace Element	New Zealand European vs Maori	New Zealand European vs Pacific Islands	Maori vs Pacific Islands
Cd	0.261	0.055	0.363
Se	0.495	*<0.001**	*<0.001**
Zn	*0.002*	0.956	*0.003*
Zn/Cd ratio	0.699	0.334	0.932

All least significant differences are reported and significant differences (p-values) determined using the Holm multiple comparison procedure [p1 = 0.05 / (n-i+1)].

Table 3 shows that New Zealand European and Maori men had blood Se levels lower than those shown for the three ethnic groups in the USA (all between 132-140µg/L) [36, 37]. Pacific Islands men have comparable blood Se levels (within the 95%CI) to the highest shown for American Europeans (140µg/L, 95%CI 85-195µg/L) [37]. Results were significantly higher than found in a Finnish population in 1990 (62.2µg/L, 95%CI 33.1-91.3µg/L) [60]. Mean Se results were generally higher than other New Zealand studies. However, results for New Zealand Europeans and Maori were within the 95%CI of the results reported for Otago women (114µg/L, 95%CI 66-162µg/L) and Otago women > 70 years old (97µg/L, 95%CI 49-145µg/L) [22]. Pacific Islands men's mean blood Se results were significantly higher than results reported for Otago women >70 years old.

Table 4 shows that all three ethnic groups had blood Zn levels significantly lower than those shown for the US NHANES (8.56µg/L, 95%CI 8.55-8.57µg/L) [56]. All three ethnic groups were comparable to a Spanish study, which found adjusted mean blood Zn levels to be 6.95µg/mL (95%CI 5.87-8.03µg/mL) [63]. Mean results were shown to be generally higher than other New Zealand studies, although total mean blood Zn levels (6.58µg/mL, 95%CI 1.98-8.87µg/mL) were within the 95%CI (1.05-1.65µg/mL) of the study on Otago women [43]. Some Se and Zn study comparisons are not based on analyses of the same blood derivatives therefore may be indicative of differences rather than precise comparisons (see tables for study blood derivative details).

Table 3: Blood Se level by ethnicity of the WRCPS, compared with other community-based studies.

Study	WRCPS [c*]				Robinson et al. [57] [c*]	de Jong et al. [22] [d*]		Voght et al. [37] [e*]		Nomura et al. [36] [e*]	Knekt et al. [60] [e*]
Ethnic group	All	New Zealand European	Maori	Pacific Islands	New Zealand (Otago)	New Zealand (Otago Women)	New Zealand (Otago Women >70 yrs)	African American	American European	Japanese American	Finland
n	157	51	60	46	146	Not published	103	112	121	9345	39,268
Se µg/L	132 [a*]	118 [a*]	122 [a*]	164 [a*]	54	114 [b*]	97 [b*]	134	140	132	62.2

[a*] *These are age-adjusted values.*
[b*] *Values have been converted from µmol/L to µg/L by the formula µg/L = (µmol/L x 1000)/8.90*
[c*] *Se levels have been determined on whole blood:* [d*] *Se levels have been determined on plasma.*
[e*] *Se levels have been determined on serum.*

Table 4: Blood Zn level by ethnicity of the WRCPS, compared with other community-based studies.

Study	WRCPS [c*]				McKenzie [58] [d*]	Gibson et al. [43] [d*]	de Jong et al. [22] [d*]	Hotz et al. [59] [d*]	Moreno et al. [63] [c*]
Ethnic group	All	New Zealand European	Maori	Pacific Islands	New Zealand (Otago Women)	New Zealand (Otago Women >70 yrs)	New Zealand (Otago Women >70yrs)	USA NHANES	Spanish
n	157	51	60	46	49	330	103	14,770	82
Zn µg/mL	6.58 [*a]	6.38 [*a]	6.94 [*a]	6.36 [*a]	2.09	1.35	1.39	8.56	6.95

[*a] These are age-adjusted values.
[b*] values have been converted from µmol/L to µg/mL by the formula µg/L = µmol/L/8.90
[c*] Zn levels have been determined on whole blood.
[d*] Zn levels have been determined on serum.

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Exposures - Diet, Smoking and Occupation

Ethnic differences in consumption of foods were investigated [55]. The most significant difference in dietary practice was between New Zealand European and Pacific Islands men. The age group studied (40-69 years) probably influenced the magnitude of this difference. Other studies have shown that this generation of Pacific Islands people have traditional diets, eating more taro, shellfish and fresh vegetables, and drinking less alcohol than New Zealand Europeans [64]. The dietary pattern of Maori found in the WRCPS more closely resembled that of New Zealand European men, which may be because Maori now live a more 'Westernised' rather than traditional lifestyle [65].

Blood Cd was significantly positively associated with shellfish intake (p=0.039) when adjusting for smoking status. As discussed later in this section, Pacific Islands and Maori men have significantly higher intakes of shellfish than New Zealand European men.

More Maori and Pacific Islands men (31% and 31% respectively) were current smokers than New Zealand European men (17%). Current smokers had significantly higher blood Cd levels (1.77µg/L, 95%CI 1.58-1.96µg/L) than former smokers (p<0.001, 0.977µg/L, 95%CI 0.817-1.14µg/L) and never smokers (p<0.001, 0.886µg/L, 95%CI 0.707-1.07µg/L).

More (39.4%) Pacific Islands men currently work in occupations deemed within the literature to be high Cd exposure risk than New Zealand European (17.6%) and Maori men (20%). 83.4% of those who currently worked in high Cd exposure risk occupations had been in this work for more than 2 years. For these men, the average amount of time spent working in these occupations was 17 years. However, blood Cd levels were not associated with working in a high Cd exposure risk occupation (p=0.161).

Pacific Islands males had significantly higher intakes of combined fish/shellfish than Maori and New Zealand European men (p<0.001), and Maori higher intakes of combined fish/shellfish than New Zealand European (p<0.001). Pacific Islands and Maori males had significantly higher intakes of pork, lamb and vegetables than New Zealand Europeans (p<0.001).

PSA Levels and Trace Element Associations

A positive association was found between blood Cd and total PSA (p<0.001, *r*=0.226), which remained significant within the multivariate model. This association also remained significant after removal of men with elevated PSA.

A positive association was found between being in the elevated PSA group and blood Cd levels. For example, having a blood Cd level <1.00µg/L was associated with an 83% reduction in elevated PSA risk (OR 0.17, 95%CI 0-1.68, p=0.024). No association was found between Se and Zn levels and elevated PSA.

The mean PSA level in the low blood Cd level category was 0.85ng/mL (95%CI 0.12-1.33 ng/mL), medium category was 0.90ng/mL (95%CI 0.09-1.23 ng/mL) and high blood Cd level category was 1.64ng/mL (95%CI 0.40-2.52 ng/mL). There was a significant difference in PSA levels between the low and high blood Cd level (p<0.001).

Discussion

Ethnic Differences in Exposure to Trace Elements

There was no significant difference in blood Cd levels between the three ethnic groups. However, a difference in Cd levels was expected, as Maori and Pacific Islands men both have higher exposure to factors significantly associated with increased blood Cd levels (such as diet, occupation and smoking).

Shellfish in New Zealand are high in Cd [15], and our data indicated that shellfish intake was significantly higher in Maori and Pacific Islands men than New Zealand European men. Blood Cd was found to be significantly associated with shellfish intake. In addition, more (39.4%) Pacific Islands men currently work in high Cd exposure risk occupations, and more Maori and Pacific Islands men are current smokers (both 31%). Nevertheless, these factors did not result in a significant difference in blood Cd levels between the three ethnic groups.

Luoma et al. [66] found that the Cd concentration of smokers was three times that of non-smokers (1.85 µg/L vs. 5.5µg/L). Even though differences in blood Cd according to smoking status were smaller than found in Luoma et al.'s [66] study, our results showed that current smokers (at 1.77µg/L) had 1.9 times the blood Cd level of former smokers (0.977µg/L) and twice the level of never smokers (0.886µg/L).

It is possible that ethnic difference in Cd did not reach a significant level because New Zealand European men are exposed to other sources of Cd (not accounted for within this research), and/or because there is an ethnic difference in metabolizing this metal and/or interactions between trace elements.

Whether blood Cd at the levels reported in this study is a cause for health concern is not known. Finding a measurable amount of Cd in the blood does not automatically lead to an adverse health effect. Occupational Safety and Health organisations world-wide, have developed (or adopted) criteria for evaluating occupational chronic workplace exposures. In the USA the blood Cd criterion is >5.00µg/L [21]. This cut-off provides an upper occupational limit in which to assess this study group from. There were no men in this study whose blood Cd level reached this limit, with the 95th percentile being 2.42µg/L.

A Belgian study tested blood Cd levels from both low and high environmental exposure areas [67]. Cd levels found in blood (0.96µg/L vs. 1.24µg/L respectively) were significantly (p<0.001) raised in the two high exposure areas compared with the two low exposure areas (p<0.001) [67]. This indicates that, despite levels in this study not being high enough to be deemed chronic occupational exposure, there may be higher environmental exposure in the Pacific Islands group at 1.15µg/L (0.98-1.36) (Table 1).

There is no reason to suspect that environmental Cd is significantly higher in the Wellington region than any other large urban area in New Zealand, therefore the data

presented here provide a reference range that could help to determine whether people are exposed to higher levels of Cd than what could be considered normal for New Zealand.

Data showed that Pacific Islands men have significantly higher levels of blood Se than both New Zealand European men and Maori men (Tables 1 & 2). Tinned fish was positively associated with blood Se levels. The LINZ Activity and Health Unit (1999) reported that the top contributor to Se intake in 45-74 year old New Zealand males is fish/seafood (32%). As intake of tinned fish was shown to be significantly higher in Pacific Islands men, it is possible that their significantly higher blood Se levels were contributed to by their high consumption of tinned fish, as well as other seafood.

It is acknowledged that there are limitations in directly comparing this current study with the trace element results of other studies, because of the previously discussed possibility of different Se and Zn intakes due to geographical location and/or age. Women may also have different intakes of Se and Zn than men. Regardless, comparisons provide an important indication of trace element status in New Zealand.

With regards to Se, New Zealand European and Maori men had blood Se levels lower than those shown for the three ethnic groups in the USA (Table 3) [36, 37]. However, results were higher than found in a Finnish population in 1990 [60]. In comparison with other countries, Finland is known to be a low Se region, likely due to geological conditions [68].

Mean Se results for this current study were generally higher than other New Zealand studies compared, especially for Pacific Islands men. Pacific Islands men's mean blood Se results were significantly higher than results reported for Otago women >70 years old and Pacific Islands men have comparable blood Se levels to the highest shown for American Europeans (Table 3) [37].

A comparison of the 1997 New Zealand National Nutrition Survey [56] with the US 1988-1994 NHANES found that the dietary intake of Zn for the New Zealand population was higher than that for the US, however, seniors (>71years old) in both surveys had the lowest Zn intakes [69].

Mean Zn results for this current study were generally higher than the other New Zealand studies compared. Data show that all three ethnic groups had blood Zn levels comparable to a Spanish study [63] and, contrary to the findings of the dietary intake estimate study [69], significantly lower than those shown for the US NHANES (Table 4) [59].

Zn levels were significantly higher in Maori men than both New Zealand European and Pacific Islands men (Tables 1 & 2). This may in part be due to their higher intake of pork, lamb and vegetables, which are the next highest contributors of Zn (approx. 15% total) after beef, bread and milk for 45-74 year old New Zealand males [56]. Despite these differences in blood Zn levels, it appears that blood Zn levels found in this current study, for all ethnic groups, are suggestive of adequate Zn levels for general health. For example, Pilch and Senti [70] suggest that serum levels <10.7μmol/L (or 1.2μg/mL) indicate Zn deficiency. No men in this study were below this level (Table 4), however, it is unclear if the levels reported in this study are adequate for prostate health.

PSA Levels and Trace Element Associations

In New Zealand, more Pacific Islands and Maori men die from prostate cancer than New Zealand European men [5]. It is presently unknown whether the ethnic difference in mortality is influenced by exposure to trace elements. This aspect of the study aimed to explore whether ethnic differences in blood levels of Cd, Se and Zn and a marker of prostate cancer, PSA, might explain differences in prostate cancer mortality.

In our study, a positive association was found between blood Cd and total PSA, and an association was found between having an elevated PSA and increased blood Cd levels. The effect of Cd on PSA levels could be due to direct prostate cellular changes towards cancer [13, 29] or via hormonal pathways involving androgens. PSA expression is differentially regulated by androgens acting on prostate cells [45] and androgenic activity has been shown to be influenced by Cd [71]. For example, a study that treated human prostate cancer cells with Cd stimulated cell growth, found that Cd decreased the concentration of the androgen receptor protein and mRNA (80 and 60% respectively) and increased the expression of PSA (6-fold). Cd blocked the binding of androgen to the receptor but did not alter its affinity, suggesting that the metal is an inhibitor of hormone binding [71].

Regardless of the mechanism, if elevated PSA indicates higher risk for prostate cancer, the increased odds of being in the elevated PSA group with higher levels of blood Cd could indicate that Cd exposure is a risk factor for prostate cancer. This finding highlights that the potentially high level of Cd exposure of New Zealand men, in general, may be reflected in the high rate of prostate cancer in New Zealand by world standards. Ethnic differences in Cd exposure may influence New Zealand ethnic differences in prostate cancer rates.

Despite other studies describing a potential protective relationship between Se and Zn and prostate cancer [31, 32, 37, 72], this current study found no association between blood Se levels and PSA. Perhaps, Se and Zn protect prostate cells against cancer, without influencing the expression of PSA in normal prostate tissue, because these trace elements have a direct cellular (rather than humoral) effect.

It is possible that an ethnic difference in genetics influences the toxicology of trace elements and in turn, the degree of protection offered by these trace elements. For example, a study that compared prostate cancer tissue from African American men with American European men (for the ability to express two major human Zn transporters, hZIP1 and hZIP2) found that the degree of Zn expression was higher in the American European men than the African men. The study also found a significant downregulation of Zn transporters in normal prostate tissues from African American men [73]. Rishi et al. [73] suggest that because Africa is

mineral-rich and Zn levels in the water and diets are high, Africans have genetically downgraded Zn absorption capacity in order to avoid possible Zn toxicity. Furthermore, important interactions of Se and Zn with other trace elements, such as Cd, may influence prostate cancer rates, as with Wasowicz et al. [74], who found an inverse linear correlation between blood Se and Cd concentrations in workers exposed to Cd ($p<0.001$; $r= -0.449$).

In New Zealand ethnic prostate cancer incidence rates are inaccurate because of under-reporting in health data for Maori and Pacific Islands men. There are ethnic differences in mortality rates, with Pacific Islands and Maori men shown to have higher rates than New Zealand Europeans [6]. Under-utilisation of the health system is a likely influence in the increased mortality rates for Pacific Islands and Maori males [7]; however, ethnic differences in disease progression may also contribute. Given the probable inaccuracy of the incidence rates, it appears important to examine mortality as an indication of increased disease burden for Pacific Islands and Maori men.

A large proportion of Pacific Islands men blood Se levels were over the level reported to be protective for prostate cancer. Even though Maori men had a high blood Zn status, no studies have indicated a threshold blood Zn level that may be protective of prostate cancer. This high Se and Zn status in Pacific Islands men and Maori men respectively appears to be inconsistent with their higher mortality rates in comparison to New Zealand Europeans.

The strength of this study was the recruitment of a large number of Maori and Pacific Islands men, allowing for insight to be gained into differing dietary and occupational patterns, and blood levels of Cd, Se and Zn. Standardization of mean blood Cd levels resulted in similar mean levels (Table 1). Therefore, results gained through the stratified random sample were not expected to differ markedly from those from a simple random sample. There were limitations, including the potential inaccuracy involved with dietary assessment. In this case, through the brief FFQ which did not cover total dietary intake; thus, it was not possible to control for other dietary factors. However, it is reassuring that the dietary patterns found in this study were generally consistent with those found in the 1997 New Zealand National Nutrition Survey [64]. Furthermore, there was consistency between the blood results and dietary intake estimates, which provides reassurance about the validity of blood Se and Zn measures as an indication of regular intakes of the trace elements.

It is acknowledged that Se consumed in food exists in a number of different organic and inorganic forms including selenomethionine, selenocysteine, selenate and selenite. Studies have established that the bioavailability and body distribution of Se depends upon the chemical form. For example, selenomethionine is retained in tissue proteins to a greater extent than selenocysteine and other inorganic forms. A number of other factors may influence Se bioavailability, including other dietary components; therefore, Se speciation along with the measurement of GPx activity is important considerations in further research [38].

Conclusions

Ethnic differences in mortality could be contributed to by differences in rates of disease progression,

influenced by exposure to the trace elements examined. The discovery of a significant ethnic difference in levels in Se and Zn warrants further investigation. However, results did not reflect a consistent ethnic trend and highlight the complexity of the risk/protective mechanisms conferred by exposure factors. The body burden of Cd is likely to increase with age and the intake of Se and Zn decrease. As prostate cancer risk increases as men get older, these age-related changes in trace element exposure may be an important factor to consider in prostate cancer risk. Further research is needed to ascertain whether the associations found between Cd and PSA levels are biologically important or are merely factors to be considered when interpreting PSA results clinically.

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