

Micronutrients intake and cancer: Protective or promoters? A challenge for risk estimation.

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Introduction

- Cancer is a multicausal disease and it has been associated to environmental, biological and lifestyle conditions.
- Among these factors, diet components are central.
- Diet pattern in Argentina

- the logistic model.

$$\log\left(\frac{\pi}{1-\pi}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2$$

- The assumptions of not functionally related covariates
- Difficulties in micronutrients single effects estimation



collinearity

Objective

- To estimate the risk of colorectal cancer and urinary tract tumors, associated to micronutrients intake using different modelling strategies.

Methods

Study design

- Two case control studies in Córdoba, Argentina
- Central Argentina, capital of 1,280,000 inh..
- COLORRECTAL CANCER (ICD 18-adenocarcinomas)
 - 296 cases, 597 controls
 - 1993-2001
- URINARY TRACT TUMORS (ICD 64-68)urothelium)
 - 129 cases, 257 controls
 - 1999-2007

Instruments

- **Food Frequency Questionnaire**
 - NAVARRO, A; Osella, A; GUERRA, V; MUÑOZ, S; LANTIERI, M and EYNARD, A. Reproducibility and validation of a food-frequency questionnaire to assess dietary intakes and food habits in epidemiological cancer studies in Córdoba, Argentina. *J. Exp. Clin. Cancer Res.* 20:365-370, 2001.
 - 127 food items.
- **Food Atlas**
- Navarro, A; Cristaldo, PE; Andreatta, MM; Muñoz, . *Atlas de Alimentos*. ISBN: 978-950-33-0600-0, 2007.

Statistical methods

- Logistic model (LR)
 - Linear predictor : age, sex, bmi, social status, occupation, micronutrient intake
- Testing model assumptions (GLMM)
 - Link function (Pregibon(1979))
 - Linear predictor and systematic component (Wolfinger & O'Connell 1993)
 - Weighted logistic Model (WLM) using robust Mahalanobis distance
 - Monte Carlo resampling process for both models.
 - Maintaining case control 1:2 and n of original sample.

Ridge Regression

Normal equations

$$r_{XX} b^* = r_{XY} b^*$$

ridge equations

$$(r_{XX} + kI) b^r = r_{XY}$$

$$b^r = (r_{XX} + kI)^{-1} r_{XY}$$

- Mean square error

$$E \left\{ (b^r - \beta)^2 \right\} = \sigma^2 \{b^r\} + (E \{b^r\} - \beta)^2$$

RESULTS

Colorrectal cancer

Table 1: Correlation Matrix of vitamin intake.

Vitamins	A	B1	B2	Niacine	B6	C	E	K
A	1.00							
B1	0.32	1.00						
B2	0.23	<u>0.70</u>	1.00					
Niacine	0.08	0.41	0.27	1.00				
B6	0.33	0.49	0.34	<u>0.60</u>	1.00			
C	0.40	<u>0.67</u>	<u>0.68</u>	0.16	0.33	1.00		
E	0.21	0.18	0.17	0.11	0.33	0.25	1.00	
K	0.36	0.25	0.23	<u>0.72</u>	0.52	0.24	0.34	1.00

Table 2: Risk parameters and standard error estimations for vitamin intake and colorectal cancer employing the original data ($\hat{\beta}$) and Monte-Carlo resampling ($\hat{\beta}$), with the logistic weighted (W) and unweighted (NW) models.

vitamin	$\hat{\beta}$		$\hat{\beta}$		*Std.E. $\hat{\beta}$		Std.E. $\hat{\beta}$	
	NW	W	NW	W	NW	W	NW	W
A	<u>0.000088</u>	0.00010	0.000087	0.000084	0.00005	0.00006	0.000055	0.000058
B1	-0.1725	<u>-0.6015</u>	-0.17174	<u>0.021445</u>	<u>0.4591</u>	0.4757	0.477489	<u>0.503246</u>
B2	0.3792	0.5041	0.396834	0.372195	0.2001	0.2053	0.207052	0.217863
Niacine	0.0503	0.1023	0.052255	0.061594	0.0338	0.0354	0.035061	0.037171
B6	-0.0562	<u>-0.2076</u>	-0.05935	<u>0.035942</u>	0.2724	0.2773	0.281511	0.300084
C	<u>-0.00373</u>	-0.0031	-0.0039	-0.00374	0.00099	0.00097	0.001024	0.001077
E	0.0120	0.0477	0.012254	0.057778	0.0239	0.0235	0.024593	0.025750
K	<u>-0.00219</u>	-0.0029	-0.00226	-0.00239	0.00066	0.00069	0.000682	0.000715

$\hat{\beta}$ Logistic regression estimates from original data. $\hat{\beta}$ Logistic regression estimates from Monte Carlo samples. *Std E. Standard error. UW: unweighted, W: weighted.

Table 3: Risk estimation for colorectal cancer and vitamin intake using the classical model and **Ridge Regression**

Nutrient	Classical Model		Ridge Regression	
	OR _L	Ci 95%	OR _R	Ci 95%
VIT B1	0.444	0.199-1.191	0.776	0.515-1.168
VIT B2	<u>1.942</u>	1.359-3.176	<u>1.784</u>	1.357-2.344
NIACINE	1.051	0.895-1.110	<u>1.053</u>	1.006-1.102
VIT C	<u>0.906</u>	0.894-0.997	<u>0.995</u>	0.994-0.997
VIT. K	0.978	0.967-1.099	<u>0.998</u>	0.997-0.999

Variable	Categories*			Std. Error**.		P value	
		Unweighted	Weighted	Unweighted	Weighted	Unweighted	Weighted
Intercept		-1.04	-1.85	0.30	0.33	0.0005	<0001
Age (years)	<45	-	-	-	-	-	-
	45-55	-0.10	-0.07	0.28	0.31	0.7176	0.8168
	56-65	0.29	0.25	0.25	0.28	0.2540	0.3836
	66-75	0.19	0.21	0.25	0.29	0.4579	0.4477
	>75	0.65	0.78	0.65	0.39	0.0652	0.0458
BMI	normal	-	-	-	-	-	-
	overweighted	-0.01	-0.06	0.17	0.19	0.9354	0.7414
	obesity	0.20	0.19	0.24	0.27	0.4146	0.4859
Social Status	Low	-	-	-	-	-	-
	Medium	0.52	0.39	0.19	0.21	0.0071	0.0602
	Medium-high/ high	0.83	0.72	0.21	0.23	0.0001	0.0021
Vitamin A	1***	-	-	-	-	-	-
	2	-0.72	-0.76	0.19	0.21	0.0002	0.0004
	3	-0.32	-0.33	0.21	0.25	0.1450	0.1882
Vitamin B1	1	-	-	-	-	-	-
	2	0.47	0.65	0.27	0.29	0.0850	0.0249
	3	0.49	0.74	0.37	0.41	0.1934	0.0738
Vitamin B2	1	-	-	-	-	-	-
	2	-0.04	-0.03	0.24	0.26	0.8769	0.8994
	3	0.23	0.23	0.32	0.21	0.4711	0.5112
Niacine	1	-	XVIII Epi-2008.	-	-	-	13 -
	2	0.73	0.75	0.26	0.29	0.0054	0.0102
	3	1.00	1.06	0.20	0.44	0.0011	0.0000

RESULTS

Urinary tract tumors

Table 4 correlation matrix coefficients estimation
among micronutrients intakes

	VIT A	VIT E	VIT B6	VIT C	P	SE	ZN
VIT A	1						
VIT E	0.297	1					
VIT B6	<u>0.537*</u>	0.361*	1				
VIT C	0.204	0.021	0.181	1			
P	0.483*	0.341*	0.837*	0.167	1		
SE	0.369*	0.316	<u>0.667*</u>	0.159	<u>0.709*</u>	1	
ZN	0.382*	0.378*	<u>0.666*</u>	0.192	<u>0.698*</u>	<u>0.708*</u>	1

* Significants, $\alpha = 0.05$

Table 5
-Risk estimation for urothelial tumors and micronutrients intake
using the classical model and Ridge Regression.

Nutrient	Classical Model		Ridge Regression		
	OR _L	Ci 95%	OR _R	Ci 95%	p value
VIT A	1.000	1.000 – 1.000	0.999	0.999 – 1.000	0.909
VIT E	<u>0.962</u>	0.913 – 1.012	<u>0.947</u>	0.897 – 1.000	0.052
VIT B6	0.716	0.451 – 1.138	<u>0.730</u>	0.457 – 1.167	0.189
VIT C	1.000	0.998 – 1.001	0.999	0.996 – 1.000	0.157
P	1.000	1.000 – 1.001	1.000	0.999 – 1.001	0.264
Se	1.004	0.999 – 1.009	<u>1.005</u>	0.999 – 1.010	0.054
Zn	1.000	1.000 – 1.000	0.999	0.999 – 1.000	0.321

-All variables as continuous.

OR_L: Odds ratio of all micronutrients adjusted by confounders using logistic regression.

OR_R: Odds ratio of all micronutrients adjusted by confounders using Ridge regression.

Conclusions

Colorrectal cancer

- Vit C
- Vit K
- Niacine

Urinary tract tumors

- Vit E
- Vit. B6
- Se

- Micronutrients show different effect in each tumor type, and their risk estimations should be performed considering the multicollinearity in the model.
- Ridge regression estimation can offer a better approach for this kind of data.

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