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Lifestyle and Environmental Factors on Prostate Cancer Risk in South America

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ABSTRACT

South America constitutes a region of great diversity in geography, population, and socioeconomic development. Though, even when epidemiologic and nutritional transitions are at different stages across countries, there are some common characteristics including the increasing prevalence of chronic non transmissible diseases as prostate cancer. This disease has a complex etiology, with biological and environmental factors implicated, whose study deserves addressing multiple dimensions, both at individual and contextual levels.

In this chapter a review of the epidemiological studies on lifestyle and environmental factors and risk of prostate cancer focusing on those carried out in countries of South America was carried out. Also, the main results about this topic of the Group of Environmental Epidemiology of Cancer in Córdoba (Argentina) are here presented.

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There is some suggestion that high intake of dairy products, red and processed meat, as well as dietary patterns characterized by higher intakes of red and processed meat, eggs, refined grains and sugary beverages, may play some role in the development of prostate cancer. Obesity, tobacco smoke and occupational exposure, mainly combined with other risk factors could also be associated with total and advanced prostate cancer. There is no clear association with the intake of vegetables and fruits, lycopene, fats, different types of fatty acids or arsenic exposure through drinking water.

The evidence on diet and other environmental factors on prostate cancer risk are still inconclusive in South America. Particular attention must be paid to the study of prostate cancer risk in countries of South America because of the singularly risky scenario with exposure of its population to multiple and combined factors.

INTRODUCTION

Prostate Cancer **(PC)** is the second most commonly diagnosed cancer in men and overall. In 2012, the number of new cases was estimated at over 1 million worldwide, being most frequently diagnosed in high-income countries, where PSA (prostate specific antigen) utilization and screening is common. However, rates have also increased in less developed countries, as those of South America, where screening is still not widely available [1]. The increasing trends in the incidence counteracted by an overall decrease in mortality from this disease have made PC an important health problem because of its high prevalence [2].

In terms of incidence and mortality of PC, there are significant geographical differences according to age, family history, ethnicity with higher influence in African-Americans [3]. These, and other related environmental conditions have been demonstrated to play an important role in the biology of PC and tumorigenesis. The importance of environmental factors is highlighted by data showing that when individuals from a low incidence/mortality region move to a high incidence/mortality region, the disease becomes more common. A considerable proportion of PC cases were attributable to environmental exposures.

South America constitutes a region of great diversity in geography, population, and socioeconomic development, and includes Bolivia, Colombia, Ecuador, Peru, Venezuela, Brazil, Argentina, Chile, Paraguay, Uruguay, Guyana, Surinam and Trinidad and Tobago. These countries are experiencing different stages of the nutrition transition. Besides, the prevalence of under nutrition is declining at different rates, and the prevalence of chronic Non Transmissible Diseases **(NTDs)** is dramatically increasing, associated with an elevated longevity and a decrease in infectious diseases [4]. Although the South American countries have different health profiles, cancer are among the main causes of mortality in all of them [1].

While most of the information available about the role of dietary and other lifestyles profiles and environmental factors in cancer have come from studies conducted in high income, developed countries, evidence from developing countries has been increasing during the last years.

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Since 2005, the Group of Environmental Epidemiology of Cancer in Cordoba **(GEECC)** has been studying, global and specific issues (at individual, group and regional levels) of the causal network of the most prevalent cancers in Argentina. The Group has described the cancer mortality trends, initiated the study of the spatio-temporal distribution of incidence and conducted several population-based epidemiological studies in order to identify and assess the effect of biological, social and environmental features that determine its occurrence in Argentinean territory. After analyzing published evidence about dietary and environmental factors related to PC risk with focus in results from South America, we will describe the main results of GEEC on this topic.

DIETARY FACTORS AND PC RISK

A large number of epidemiologic studies have investigated dietary habits and several dietary components in relation to the etiology and progression of PC. Decades ago, some ecological studies suggested that PC was associated with a western diet that includes high consumption of saturated and trans fats, fatty meats, and dairy products [5-7]. Since then, a large number of observational and experimental studies were conducted to address the influence of dietary factors in the etiology of PC.

In this chapter, we gave particular attention to studies from South America. This region is characterized by large disparities in food access and food consumption patterns within and between populations. At the same time, there is evidence that nutritional transition have affected food patterns of South American population since the 1980s, contributing to increased prevalence of nutrition-related chronic disease [8-10].

Few years ago, a review about dietary habits related to PC focusing on South America was published [11]. The epidemiologic evidence for some of the principal dietary factors possibly associated with risk for PC evaluated are here updated, enriched with our own research works on PC and examined relating to current literature.

Meat

The consumption of red meat in some countries of South America is among the highest in the world. Traditionally, in populations of the sub-region known as the Southern Cone (which includes Argentina, Uruguay, Paraguay and Chile), the contribution of meat (especially red meat) to energy intake has been of considerable magnitude, providing in some cases about 20 percent of total daily energy [9,12,13].

Several observational studies found that higher intakes of total meat as well as red and processed meat were associated with the occurrence of PC when they were analyzed as an individual food group or as a characteristic of a dietary pattern. Results of a recent pooled analysis of 15 prospective cohort studies do not support a substantial effect of total red, unprocessed red and processed meat for all PC outcomes, except for a modest positive association for tumors identified as in advanced stage at diagnosis [14]. The AICR/WCRF expert panel came as well to the

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conclusion that evidence about a promoting effect of total and processed meat regarding PC risk is "limited-suggestive" and these findings remained unchanged after updating the analyses with new data identified in the PC systematic literature review in 2014 [15].

In South America, studies where meat and PC were investigated have been carried out in Uruguay [16-21] and Argentina [12]. All of them reported that intakes of meat overall, as well as red, fatty or salted meat have a positive relation with PC, showing ORs of 1.5 or higher.

The basis of the association between PC and high consumption of red meat is still unknown. A possible explanation is the high zinc content of red meat. This mineral is essential for testosterone synthesis and may also have other effects on the prostate [22]. Red meat is also one of the major sources of saturated fatty acids, which have already been reported associated with PC. In fact, meat is the major contributor to fat intake in the Southern Cone diet.

On the other hand, cooking at high temperatures results in a high formation of heterocyclic amines including 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). Furthermore, when meats are cooked on charcoal grilling, rendered fat is pyrolized by the coals, leading to the deposition of polycyclic aromatic hydrocarbons, such as benzo(a)pyrene which are also carcinogenic in animals [22]. The charcoal grilling and the griddle, the most common methods for cooking meat in Argentina and the Southern Cone [12], often cause a crust with the formation of heterocyclic compounds on the surface of the meat [23]. According to studies conducted by the GEECC, the habitual meat intake in this population is in average 320 g/day, from which 150 are of meat with crust. Considering the amount of PhIP found in meats, and habitual dietary intake of Argentinean population, it is estimated that an Argentinean person eats around 12268.0 ng/day of PhIP if meats are overcooked [23]. This value -only from PhIP- are highly above those reported for dietary heterocyclic aromatic amines as a whole in other countries, and is twenty times higher than the 497 ng/day proposed by Layton et al (1995) as the acceptable levels of total heterocyclic amines [24].

Fruits and Vegetables

Consumption of vegetables and fruits is highly variable in South America. These food groups, as contributors to total energy, have declined in Bolivia, and it is stabilized in Uruguay and Argentina last decade with a contribution of around 50 Kcal/day per cápita. Nowaday, Chile and Peru showed the higher levels of vegetable intake, while Ecuador and Paraguay, the lowest values per cápita. Fruit intake is higher in more tropical countries as Colombia and Ecuador with more than 200 Kcal/day, and low in countries of the Southern Cone, where the daily intake does not reach 100 calories from this food [13].

The Second Expert Report [25] concluded that non-starchy vegetables probably protect against selected cancer sites. However, specifically for PC, the evidence was judged as 'limited-no conclusion', as well as in the updated report [15].

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In South America, three Uruguayan studies found that higher intake of fruits [21], or fruits and vegetables combined [17,26], was associated with a decreased risk of total and PC. These inverse associations were mainly observed in men with high intake of meat, alcohol drinking and smoking. Given that Argentinian and Uruguayan eat salads, frequently made of fresh lettuce, tomato and onions, or fried potatoes always accompanying grilled or roasted beef [27], which are possibly linked to increase risk for PC, the interpretation of epidemiological data regarding vegetable consumption became difficult en these countries.

Lycopene, a carotenoid widely present in fruits and vegetables, and tomato, its main dietary source, have been studied frequently in relation to PC occurrence.

It has been suggested that lycopene can function as an antioxidant. Since antioxidants reduce oxidative stress damage, may thereby prevent chronic diseases such as cancer and cardiovascular disease [28]. Other proposed mechanisms include regulation of gene function, cell-cell communication via gap junctions, modulation of hormone and immune activity, and metabolism of carcinogens [29].

One of the most significant epidemiologic results comes from the US Health Professionals Follow-up Study [30], which evaluated the intake of various carotenoids in relation to risk of PC. The estimated intake of lycopene and tomato sauce was inversely related to the risk of PC. The protective effect was even stronger when more advanced or aggressive PC was considered.

A case-control carried out in Uruguay [17] observed a no significant association. In a small case-control from Argentina [31] controls consumed significantly more lycopene per day than cases. In Trinidad and Tobago a randomized clinical trial was carried out to determine whether lycopene supplementation lowered serum PSA in men with elevated PC risk. As a result, serum PSA was nearly identical in both treatment groups, with this declining during the first month of treatment, but returned to randomization level by month 4 [32]. In summary, the role of lycopene in PC remains to be established.

Dairy Products and Calcium

Dairy products and calcium have been reported to increase the risk of PC in a few epidemiological studies. A multicountry ecological study showed that the nonfat portion of milk could be a risk factor for PC mortality [33]. Related to incidence, Chan and Giovannucci (2001) concluded that consumption of dairy products is one of the most consistent dietary predictors for PC [34]. The Health Professionals Follow-up Study, found positive associations for advanced and fatal PC independently for both dietary and long-term supplemental calcium [35].

Total dairy products showed a significant increased risk per 400 g per day according to the PC report of WCRF. For milk, there was evidence of a non-linear dose-response.

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The hypothesized mechanisms concerning the association between dairy product/calcium consumption and PC risk are focused on the presence of estrogens and insulin like growth factor (IGF-I) in milk. Further, high calcium consumption lowers the level of circulating 1,25(OH)2D3 (the active form of vitamin D3), an inhibitor of prostate carcinogenesis [34-36].

In Uruguay, De Stefani et al [16] found an increased risk associated with milk intake, though, Deneo-Pellegrini et al [17] found no association with dairy products, and subsequently, a positive association between whole milk and PC [21].

Fat

Average intake of total fat is highest in most urbanized and industrialized regions. As a general trend, consumption of fats is increasing in middle- and low-income countries [25]. Dietary fat has been the focus of several investigations since it is linked to various chronic degenerative diseases such as obesity, type 2 diabetes, coronary heart disease, and cancers of some sites.

The role of dietary fats in the pathogenesis of PC is under scrutiny. The main hypothesis is that increased fat intake might lead to increased testosterone levels and this might, eventually, lead to increased cell division and activation of proto-oncogenes and deactivation of tumor suppressor genes [37,38]. In addition, increasing evidences showed that imbalance in the quality of Polyunsaturated Fatty Acids **(PUFAs)** may produce a pro-inflammatory environment in prostate gland tissue [39].

However, results from epidemiologic studies are controversial with respect to the relation between dietary fat consumption and PC risk. Most case-control studies have found a positive association between intake of total fat and PC. Instead, most findings from cohort studies found weak associations or no relationship with total fat intake. When considering nutritional quality of fatty acids from oils and fats, intake of saturated or animal fat showed stronger associations than total fat [11].

In the prospective study performed by Giovannucci et al, [30] a high dietary intake of α-linolenic acid (a metabolic precursor of ω3-EPA) was found to be related to incident (total) and low grade PC risk. This may be explained by the fact that the capacity for the conversion of α-linolenic acid to the two long-chain ω-3 fatty acids in humans is limited, and even more, in cancer cells [40].

In a case-control study conducted Mendoza, Argentina, total fat, as well as saturated, monounsaturated and polyunsaturated fat intake was higher in cases than in controls [31]. Other two studies, performed in Uruguay, found positive associations with total fat intake, though not significant [17,41]. When specific fatty acids were analyzed, the only fatty acid associated with a significant increased PC risk was α-linolenic acid and even stronger associations were found after controlling for total energy intake and other types of fat [41].

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Dietary Patterns

Most of the studies have examined the role of single micronutrients, macronutrients and foods intakes on PC risk. However, populations ingest mixed foods and meals and only in rare occasions eat isolated foods for long periods of time. For this reason, the dietary eating pattern method could be more useful than the traditional method, based on the analysis of isolated foods and nutrients.

In South America, a constant characteristic of recent dietary changes is the inclusion of more refined foods and less complex carbohydrate. These modifications in food consumption patterns are linked to globalization and the rapidly increasing accessibility to "modern" highly processed foods, which are easily moved across regions.

In a multisite case–control study conducted in Uruguay on advanced PC [42] four dietary patterns were identified. The traditional (loaded on lamb, dairy foods, cooked vegetables, and all tubers) and western patterns (loaded on beef, processed meat, boiled eggs, fried eggs, and total grains) were directly associated with risk of PC, with the former pattern presenting even more risk than the later.

NATURAL AND ANTHROPOGENIC ENVIRONMENTAL POLLUTANTS

Arsenic is a metalloid widely distributed in the Earth´s crust. It is present in igneous and sedimentary rocks and can be easily solubilized in groundwater depending on pH, redox conditions, temperature and solution composition [43,44]. In Latin America, pollution of drinking water by arsenic affects about 14 million of people especially in the poorest regions of numerous countries (Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Peru and Uruguay) where high concentrations of arsenic in the water come from natural and anthropogenic sources [45,46]

There is considerable evidence that long-term exposure to arsenic is associated with several chronic diseases including several types of cancer [47,48]. The working group of the International Agency for Research on Cancer classified arsenic into Group 1: carcinogenic to humans [49]. Arsenic can produce increased oxidative stress, genotoxic damage, chromosomal abnormalities and epigenetic mechanisms that alter DNA methylation [50] and may also precipitate events leading to androgen imbalance and impacting in PC cell progression [51].

Most of epidemiological studies were carried out in areas with high arsenic concentrations in drinking water and reported higher incidence or mortality rates of various cancers (bladder, lung, liver and kidney) [52-59]. However, few studies have examined the association between PC risk and arsenical water exposure [55,60-63].

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Another Public Health problem in South America is the increasing pesticide exposure of general and occupationally exposed population. The prevailing agricultural production model, characterized by a great expansion of planted surface, is accompanied by an increased use of agrochemicals with a significant environmental impact and a potential toxic effect in animals and humans [64-66]. In Argentina, the cultivated area has almost tripled in the last 20 years [67]. Chronic occupational exposure is most often a problem in agricultural settings and can increase the risk of developing several cancers and other illnesses [68-71]. The wide use of pesticides in agricultural activity result in continuous human exposure [72] being the agricultural workers a fraction of the population highly vulnerable to the toxicological effects of pesticide exposure [64,65,73]. Epidemiological studies have shown the association of several types of pesticides with increased cancer incidence of lung, pancreas, colon, bladder, prostate, brain and leukemia in pesticides applicators [72-75].

There are difficulties in interpreting the risk of cancer related to pesticide exposure, due to the existence of hundreds of active principles, as well as their chronic and multiple low doses from direct and especially indirect exposure sources as food, water, air and environment [76].

TOBACCO SMOKE

Latin America has a millenary story of tobacco smoke exposure and Argentina has long belonged to its trade routes. Córdoba province particularly, was always been in the middle of the goods traffic between Atlantic and Pacific oceans during the Viceroyalty period and, after the Independence war, continued as a central point for collection and distribution [77]. As in the rest of the world, in Argentina tobacco smoke is legalized and it is a socially tolerated practice. However, because it is well known that tobacco smoking is a major cause of dead and premature disability, several programs have been implemented to remove smoking habit.

Tobacco smoking is a widespread source of exposure worldwide and it is associated with at least 15 types of cancer [78]. Some of the 5000 chemical compounds identified in tobacco have been evaluated by IARC as showing “sufficient evidence for carcinogenicity” in humans or in animal models [78]. Genotoxic agents in cigarette smoke induce DNA damage and promote tumorigenesis by several mechanisms: gene point mutation, deletions, insertions, recombinations, rearrangements, and chromosomal aberrations [79]. Previous epidemiologic and experimental investigations suggest that polycyclic aromatic hydrocarbons (one of the most abundant genotoxic component of tobacco smoke) may be related with PC [80-82] through various mutagenic and non mutagenic mechanisms [83,84]. However, there is not convincing epidemiological evidence for an increased risk of PC due to cigarette smoke habit. Nevertheless, tobacco smoke may act modifying the effect of a second exposure agent, as diet, on cancer risk [85-86], as shown in results of our group, which will be described below.

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BODY FATNESS

The last decades the world has been living an accelerate increase in obesity prevalence, with this becoming a major public health concern. This phenomenon has beginning in developed countries, but nowadays, it is also common in many other regions over the world, as Asia and Latin America.

There are several observational studies linking adiposity and the risk of several adult cancers, mainly colorectal, breast, endometrial, gastric and prostate cancers. Epidemiologic evidence is conflicting and has usually failed to show significant associations between obesity and the risk of total or non-advanced PC. However, the evidence was consistent for a dose-response relationship between body fatness and advanced PC, as stated by the WCRF on its updated report.

Insulin and leptin are elevated in obese people, and can promote the growth of cancer cells [87]. In men, obesity is related to lower serum testosterone levels. Decreased levels of this hormone may facilitate the growth of a less differentiated, aggressive PC phenotype [88].

In parallel, increasing evidence links obesity, inflammation and the development of cancer. Obese adipose tissue is characterized by macrophage infiltration and the production of pro-inflammatory factors. The resulting low-grade chronic inflammatory state can promote cancer development [89].

The Pan American Health Organization reports that in South America more than 15% of the population is obese and above the 50% of the population is overweight, affecting a greater proportion of those in urban areas and of low socioeconomic status [90].

A recent population-based prevalence study (Córdoba Obesity and Diet Study, **CODIES)** investigating the association of social and other factors with overweight and obesity was conducted in Argentina. The findings showed 52% of the subjects to be overweight and 17% to be obese [91].

Results of other study in Argentina showed a direct correlation between BMI and tumor aggressiveness, suggesting that obesity may promote the PC progression rather than being a risk factor [31].

MAIN RESULTS OF THE GEECC IN ARGENTINA

Córdoba is the second most populated Argentinean province (3,067,000 inhabitants, mainly Caucasians), located in the center of the country. The capital, Córdoba city, is the second largest city of Argentina with a population of about 1,280. Overall 80% of Córdoba province population is urban, but most of its surface is rural. This means that housing areas coexist with agricultural areas without clearly defined borders [64]. Several works have assumed Córdoba province as representative of the Argentinean urban population because of the characteristics such as high-density population counties versus rural regions with a very small population size, including areas

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with diverse cultural traditions and different economic activities (strong agricultural activity along with others, with clusters of industrial activity) [92].

From 2005 the GEECC have conducted in Córdoba diverse ecologic, case-control and prospective studies about dietary and other environmental exposures related to the cancers of highest incidence. In this occasion, we will describe the main results of studies addressing the relation between lifestyle (mainly dietary) and environmental factors and PC risk.

In PC case-control study, cases were men with incident, histologically confirmed PC (ICD-10th Edition, ICIE10: C61) with no previous diagnosis of cancer in other sites. They were identified in public and private health institutions registered at the Córdoba Tumor Registry. Two controls per case, frequency matched by age (± 5 years) and area of residence, were randomly chosen only after verifying the absence of any neoplastic or related condition. A total of 147 men with PC aged 48-89 (median age 72) and 300 controls aged 46-89 years (median age 71) were included. A structured questionnaire was completed including information about socio-economic characteristics, occupational history, smoking habits, alcohol consumption, anthropometric characteristics, physical activity and family history of cancer. To assess dietary exposure, a validated food frequency questionnaire was completed.

The characteristics of subjects studied are shown in Table 1. Cases and controls had a similar distribution of socioeconomic status, smoking habits, physical activity, energy intake and BMI. On the contrary, occupational exposure and low educational level displayed higher percentages among cases compared with controls.

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Table 1: Characteristics of cases and controls, Córdoba, Argentina (2008-2012).

	Cases (n= 147) n (%)	Controls (n= 300) n (%)
Age *(years)*		
≤ 60	17 (11.56)	40 (13.33)
61 – 70	48 (32.65)	109 (36.33)
71 – 80	63 (42.8 6)	115 (38.33)
≥ 81	19 (12.93)	36 (12.00)
Socioeconomic status		
Low	61 (41.50)	114 (38.00)
Middle	50 (34.01)	103 (34.33)
High	36 (24.49)	83 (27.67)
Educational level		
Low	34 (23.13)*	47 (15.82)*
Middle	70 (47.62)	141 (47.47)
High	43 (29.25)	109 (36.70)
Occupational exposure[a]		
No	99 (67.35)	219 (73.24)
Yes	48 (32.65)*	80 (26.76)*
Smoking habits		
No	51 (34.69)	92 (30.67)
Yes	96 (65.31)	208 (69.33)
Lifetime physical activity		
Low	79 (53.74)	178 (59.33)
Middle	51 (34.69)	100 (33.33)
High	17 (11.56)	22 (7.33)
BMI		
≤ 24.9	34 (24.44)	84 (27.66)
25 – 29.9	87 (57.78)	150 (49.65)
≥ 30	26 (17.78)	66 (22.70)
Energy intake[b]		
Low	40 (27.21)	100 (33.33)
Middle	48 (32.65)	100 (33.33)
High	59 (40.14)	100 (33.33)

**Proportion values significantly different (p≤0.1). [a]Exposure to chemical contaminants for 2 years or longer.[b]Categories based on tertiles of intake in controls.*

Multiples analytical approaches were proposed to analyze the association between the different exposures assessed and PC risk. See Pou et al. (2014), Román et al. (2014) and Niclis et al. (2015) for additional information about the details of the study design and statistical analysis [10,93,94].

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Multilevel logistic regression models, adjusting by smoking habit, age, BMI and total energy intake, were used to estimate the risk of PC related to intake of food groups. They were fitted in smokers and nonsmokers separately. Our results showed differential effects of nonstarchy vegetables, fat meat, and total fat intake on the risk of PC among smokers and non-smokers (Table 2). Intake of nonstarchy vegetables over 200g/day were inversely associated with a risk of PC in nonsmokers (OR 0.55, 95%CI 0.20–1.48), whereas in smokers, there was no association. Smokers with high intakes of fat meat had an increased risk of PC (OR 1.56, 95%CI 0.81-3.05). higher intakes of fat and oils showed a positive association in smokers (OR 1.95, 95%CI 1.09-3.50), but no association was found in nonsmokers [93].

Table 2: Prostate cancer risk by smoking habits for different food groups considering family history of prostate cancer as a covariate or as a clustering variable.

PROSTATE CANCER						
	All		Nonsmoker		Smoker	
	Cases (%)	OR (CI95%)[a]	Cases (%)	OR (CI95%)[a]	Cases (%)	OR (CI95%)[a]
Dairy products						
<200g/day	65	1	34	1	46	1
≥ 200g/day	35	1.01 (0.64-1.59)	66	1.24 (0.51-2.99)	54	1.03 (0.60-1.75)
Lean meat						
< 120 g/day	56	1	68	1	68	1
≥ 120 g/day	44	0.76 (0.48-1.19)	32	1.19 (0.51-2.75)	32	0.97 (0.55-1.69)
Fat meat						
< 200 g/day	59	1	61	1	57	1
≥ 200 g/day	41	1.32 (0.77-2.28)	39	1.42 (0.50-3.98)	43	1.56 (0.81-3.05)
Nonstarchy vegetables						
< 200 g/day	56	1	59	1	68	1
≥ 200 g/day	44	0.66 (0.43-1.03)	41	0.55 (0.20-1.48)	32	1.03 (0.58-1.83)
Fruits						
< 200 g/day	44	1	40	1	42	1
≥ 200 g/day	56	1.35 (0.87-2.09)	60	1.18 (0.52-2.71)	58	1.42 (0.83-2.42)
Fat and oils						
<30 g/day	56	1	54	1	54	1
≥30 g/day	44	1.56 (0.96-2.54)	46	1.11 (0.45-2.76)	46	1.95 (1.09-3.50)
Sweet drinks						
<250 cc/day	61	1	59	1	61	1
≥250 cc/day	39	1.10 (0.67-1.79)	41	0.97 (0.41-2.31)	39	1.30 (0.72-2.34)
Ethanol						
<20 g/day	53	1	57	1	50	1
≥20 g/day	47	0.71 (0.44-1.15)	43	0.73 (0.29-1.83)	50	0.72 (0.41-1.28)

OR, odds ratio; CI, confidence interval. [a]Multilevel analyses include age, body mass index, total energy intake, dairy products, lean meat, fatty meat, nonstarchy vegetables, fruits, total fat, sweet drinks and ethanol as covariates, with family history of prostate cancer as level 2 variable (clustering variable).

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Dietary patterns approach was also proposed. A principal component factor analysis was applied on 300 male controls to characterization of dietary patterns and a two-level logistic model was applied to risk analysis, considering family history of cancer as a second level of aggregation.

Initially, we identified four characteristic dietary patterns in male population. The Traditional Pattern (positively loaded for fatty red meats, eggs and cereals/starchy vegetables) and Sugary Beverages Pattern (high loadings for sodas and juices) were significantly associated with PC risk (OR 2.00; 95%CI 1.634-2.943 and OR 1.52; 95%CI 1.094-2.751, respectively) [10]. More recently, in an updated analysis with a higher number of subjects, the Traditional (fatty red meats, offal, processed meat, starchy vegetables, added sugars and sweets, candies, fats and vegetable oils), Carbohydrate (sodas/juices and bakery products), Prudent (non-starchy vegetables, whole grains), and Cheese Patterns (cheeses) were identified. The Traditional Pattern correlates positively with all macro and micronutrients ($p<0.05$), and more strongly with total energy intake ($r=0.753$), intake of carbohydrates ($r=0.667$), lipids ($r=0.627$), cholesterol ($r=0.542$) and vitamin E ($r=0.622$). Carbohydrate intake was also strongly correlated with the Carbohydrate Pattern ($r=0.592$). On the other hand, Prudent Pattern had negative correlations with ethanol ($r=-0.449$).

The Traditional and Carbohydrate Patterns were significantly associated with PC risk (OR 2.54; 95%CI 1.491-4.342 and OR 2.10; 95%CI 1.400-3.164, respectively), while the Prudent and Cheese Patterns were not associated (OR 1.31; 95%CI 0.493-3.508 and OR 1.02; 95%CI 0.538-1.932, respectively) (Table 3). Remarkably, two of the most characteristic patterns that emerged in this population had a promoting effect for PC occurrence, possibly due to the presence of high loadings of fatty, processed, refined or high-sugar foods, coupled with a complete absence of fresh and non starchy vegetables and fruits [94].

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Table 3: Prostate cancer risk on dietary patterns estimates from multilevel logistic modeling[a], Córdoba, Argentina (2008-2012).

	Number of cases	OR (CI 95%)[a]	p value	p for trend
Traditional Pattern				
quartile I	24	1	-	
quartile II	39	1.60 (0.970-2.660)	0.065	
quartile III	37	1.73 (1.167-2.575)	0.006	
quartile IV	47	2.54 (1.491-4.342)	0.001	0.048
Prudent Pattern				
quartile I	41	1	-	
quartile II	28	0.70 (0.396-1.264)	0.243	
quartile III	34	0.84 (0.540-1.310)	0.445	
quartile IV	44	1.31 (.493-3.508)	0.584	0.926
Carbohydrate Pattern				
quartile I	22	1	-	
quartile II	36	1.76 (1.254-2.479)	0.001	
quartile III	48	2.67(0.975-7.349)	0.056	
quartile IV	41	2.10 (1.400-3.164)	<0.001	0.069
Cheese Pattern				
quartile I	33	1	-	
quartile II	40	1.48(0.690-3.202)	0.310	
quartile III	37	1.34 (0 .842-2.155)	0.213	
quartile IV	37	1.02 (0.538-1.932)	0.950	0.720

OR, odds ratio; CI, confidence interval. [a]Age, BMI, energy intake, and occupational exposure were included in the MLR as covariates at first level, and family history of cancer at second leve.

Epidemiological studies conducted by the GEECC showed no association between BMI and total PC [10,93,94]. However, significant interactions between weight status (normal weight - overweight) and adherence to Traditional Pattern was found. A two level logistic regression model was fitted including interaction terms as covariates at level 1. Overweight subjects who simultaneously strongly adhere to the Traditional Pattern, showed an increased risk of PC (OR 2.73; 95%CI 0.97-7.67). There were no interactions among smoking habit and weight status on PC risk. When stratifying by smoking habit, a greater risk of PC in smokers with overweight and high adherence to the Traditional Pattern (OR: 3.52; 95%CI: 0.97-12.76) was found (Table 4) (Unpublished data).

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Table 4: Prostate cancer risk by smoking habits for interaction terms of weight status and Traditional Dietary Pattern from a Multilevel Logistic regresion Model [a].

NON SMOKERS		
	OR (95% CI)	**p value**
Normal weight x Tertile I Traditional Pattern	-	-
Normal weight x Tertile II Traditional Pattern	1.15 (0.14 – 9.30)	0.891
Normal weight x Tertile III Traditional Pattern	2.01 (0.26 – 15.13)	0.498
Overweight x Tertile I Traditional Pattern	0.88 (0.11 – 6.02)	0.860
Overweight x Tertile II Traditional Pattern	1.66 (0.25 – 10.84)	0.565
Overweight x Tertile III Traditional Pattern	2.17 (0.32 – 14.68)	0.427
SMOKERS		
Normal weight x Tertile I Traditional Pattern	-	-
Normal weight x Tertile II Traditional Pattern	1.03 (0.22 – 4.52)	0.966
Normal weight x Tertile III Traditional Pattern	2.49 (0.61 – 10.15)	0.204
Overweight x Tertile I Traditional Pattern	1.59 (0.51 – 5.03)	0.422
Overweight x Tertile II Traditional Pattern	1.40 (0.42 – 4.63)	0.582
Overweight x Tertile III Traditional Pattern	3.52 (0.97 – 12.75)	0.056

OR, odds ratio; CI, confidence interval. [a]Age, energy intake, and occupational exposure were included in the MLR as covariates at first level, and family history of cancer at second level.

In order to consider environmental characteristics of the context, we also examined exposure to anthropic and natural contaminants related to PC in addition to dietary factors.

Arsenic level in drinking water was measured in randomly selected subjects of case-control study. Results of multilevel model, using age, occupational exposure (without, rural, transport, industry), dietary patterns (traditional, sweet beverages) and arsenic in drinking water as covariates in 1-level and family history of cancer as the variance component (2-level) indicated that exposure to high levels of arsenic (>10 μg/l) combined to occupational exposure in agricultural workers constitutes a strong significant risk increase of PC occurrence (OR 3.55; 95% IC 1.59-7.94) [95].

CONCLUSION

Although the South American countries have different health profiles, cancer incidence is increased in all of them and constitutes a major cause of mortality. PC occurrence has variations across these countries and there are many contextual factors to consider in the possible explanation of this picture. There are areas rich in natural pollutants like arsenic as in Chile and the Argentine Pampas, and higher anthropic culture-related activities mainly in the east countries.

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On this environmental scene, even when some lifestyle and dietary habits can vary across the countries, there are some common features identifiable through eminent component foods of the characteristic dietary patterns. One is the high caloric intake, mainly because of the traditional preference for high glycemic charge foods like corn, manioc and potatoes, and low fiber ones. In the Southern Cone countries this is also accompanied with high intakes of rich-fat red meat cooked using traditional methods like griddle, or asado. In front of this situation, risk assessment shows weak evidence. It is not clear if that is because there are not strong associations or because the highly homogeneous and conservative nature of South American habits make it difficult to discriminate among exposed and not exposed people. The accelerate increase in obesity prevalence in the region would contribute per se, but mainly combined with other risk factors to the risk scenario in this region. Perhaps, collaborative studies among broader set of countries should be favored. Yet, Public health measures can be still preciously valid. Being PC a high prevalent cancer and considering a South American average incidence rate of around 70/100000, detecting and controlling even a 1% increased risk, it would save almost 300000 men in one year. Efforts should be done to regulate cigarette consumption and to promote a healthy weight and dietary habits with predominance of fresh vegetables and minimally processed food in order to contribute to PC prevention.

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