

## Case Control Study

## Cigarette smoking, dietary habits and genetic polymorphisms in *GSTT1*, *GSTM1* and *CYP1A1* metabolic genes: A case-control study in oncohematological diseases

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**Supported by** The “Consejo Nacional de Investigaciones Científicas y Técnicas” (PIP-634 to Richard S and Scholarship Grant to Cerliani MB); and the “Instituto Nacional del Cáncer” (grant No. R.M. 493: Asistencia financiera a proyectos de investigación en cáncer de origen nacional II, to Pavicic W).

**Institutional review board statement:** The study was reviewed and approved by the “Instituto Multidisciplinario de Biología Celular” Institutional Review Board.

**Informed consent statement:** All study participants provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** No conflicts of interests.

**Data sharing statement:** Technical appendix and dataset available from the corresponding author at [srichard@imbice.gov.ar](mailto:srichard@imbice.gov.ar). The presented data are anonymized.

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**Manuscript source:** Invited manuscript

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**Received:** June 24, 2016

**Peer-review started:** June 24, 2016

**First decision:** August 5, 2016

**Revised:** September 7, 2016

**Accepted:** September 21, 2016

**Article in press:** September 23, 2016

**Published online:** October 10, 2016

### Abstract

#### AIM

To analyze the association between oncohematological diseases and *GSTT1/GSTM1/CYP1A1* polymorphisms, dietary habits and smoking, in an Argentine hospital-based case-control study.

#### METHODS

This hospital-based case-control study involved 125 patients with oncohematological diseases and 310 control subjects. A questionnaire was used to obtain sociodemographic data and information about habits. Blood samples were collected, and DNA was extracted using salting out methods. Deletions in *GSTT1* and *GSTM1*

(null genotypes) were addressed by PCR. *CYP1A1 MspI* polymorphism was detected by PCR-RFLP. Odds ratio (OR) and 95%CI were calculated to estimate the association between each variable studied and oncohematological disease.

### RESULTS

Women showed lower risk of disease compared to men (OR 0.52, 95%CI: 0.34-0.82,  $P = 0.003$ ). Higher levels of education (> 12 years) were significantly associated with an increased risk, compared to complete primary school or less (OR 3.68, 95%CI: 1.82-7.40,  $P < 0.001$  adjusted for age and sex). With respect to tobacco, none of the smoking categories showed association with oncohematological diseases. Regarding dietary habits, consumption of grilled/barbecued meat 3 or more times per month showed significant association with an increased risk of disease (OR 1.72, 95%CI: 1.08-2.75,  $P = 0.02$ ). Daily consumption of coffee also was associated with an increased risk (OR 1.77, 95%CI: 1.03-3.03,  $P = 0.03$ ). Results for *GSTT1*, *GSTM1* and *CYP1A1* polymorphisms showed no significant association with oncohematological diseases. When analyzing the interaction between polymorphisms and tobacco smoking or dietary habits, no statistically significant associations that modify disease risk were found.

### CONCLUSION

We reported an increased risk of oncohematological diseases associated with meat and coffee intake. We did not find significant associations between genetic polymorphisms and blood cancer.

**Key words:** Cancer; Oncohematological disease; Case-control study; Lifestyle; Diet; Tobacco; Xenobiotic metabolizing genes; *GSTT1*; *GSTM1*; *CYP1A1*

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**Core tip:** Cancer is considered as a multi-factorial disease. Except certain genetic abnormalities, viruses, environmental exposures and chemotherapeutic agents, it is not well defined which are the risk factors for these diseases (leukemia, lymphoma, multiple myeloma, among others). Here, we analyzed lifestyle and genetic polymorphisms as risk factors for blood cancer. We reported an increased risk of disease associated with meat and coffee intake. No significant associations were found between metabolic gene polymorphisms and disease. Our study offers relevant insights into diverse aspects of oncohematological diseases etiology, particularly genes and environmental factors, in an Argentinean population.

Cerliani MB, Pavicic W, Gili JA, Klein G, Saba S, Richard S. Cigarette smoking, dietary habits and genetic polymorphisms in *GSTT1*, *GSTM1* and *CYP1A1* metabolic genes: A case-control study in oncohematological diseases. *World J Clin Oncol* 2016; 7(5): 395-405 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v7/i5/395.htm> DOI: <http://dx.doi.org/10.5306/wjco.v7.i5.395>

## INTRODUCTION

Xenobiotic metabolizing enzymes (XME), coded by a family of xenobiotic metabolizing genes (XMG), transform endo and exogenous compounds in hydrophilic by-products, which are more easily excreted from the tissues<sup>[1]</sup>. It is well known since decades that genetic differences in the metabolism of drugs and environmental chemicals exist<sup>[2]</sup>. These differences are due to pharmacogenetic polymorphisms, which are allele variants that occur with a relatively high frequency in the population, and are generally associated with anomalies in gene expression or enzymatic function. Moreover, pharmacogenetic polymorphisms have been associated with an increased risk of some types of cancer, due to: (1) an impaired ability to inactivate endogenous or exogenous mutagenic molecules; or (2) the conversion of metabolites into highly reactive and toxic compounds. Both polymorphisms and the levels of exposure to their substrates, may impact on cancer susceptibility.

The cytochrome P450 family of enzymes is responsible for catalyzing phase I metabolism reactions. CYP1A1 is a member of the CYP family and plays an important role in the metabolism of estrogen and polycyclic aromatic hydrocarbons (PAHs), catalyzing the activation of pro-carcinogenic PAHs<sup>[3]</sup>. Dysfunction of CYPs enzymes can cause damage to DNA, lipids and proteins, leading to carcinogenesis<sup>[4,5]</sup>. A commonly studied single nucleotide polymorphism (SNP) in *CYP1A1* gene is the T3801C (also named *MspI* polymorphism, \*2A or m1), a T to C mutation in the 3' flanking region of the gene. The C variant becomes more highly inducible than the T variant<sup>[6]</sup>, which may cause enhanced enzymatic activity, thus modifying susceptibility to adduct formation and cancer risk<sup>[7]</sup>. In fact, T3801C polymorphism was associated with leukemia and cervical, hepatocellular, lung, prostate, and head and neck cancer<sup>[8]</sup>.

Glutathione S-transferases (GSTs) constitute a superfamily of phase II detoxification enzymes which play a key role in cellular protection against environmental carcinogens, drugs, toxins and by-products of oxidative stress. GSTs catalyze the conjugation of reduced glutathione (GSH) to a wide variety of electrophilic compounds to facilitate their cellular excretion. In addition, as non-enzymatic proteins, GSTs can modulate signaling pathways that control cell proliferation, cell differentiation, apoptosis, anti- and pro-inflammatory functions and DNA damage processing, among other processes<sup>[9]</sup>. Genetic polymorphisms in *GST* genes are common in the human population. *GSTM1* and *GSTT1* exhibit variations in copy number due to complete gene deletion, resulting in the loss of enzymatic activity. The absence of enzyme has been associated with lung, breast and gastrointestinal cancer, among others<sup>[10]</sup>, and also with adverse side effects and toxicity in chemotherapies<sup>[11]</sup>.

Lifestyle and dietary habits are additional risk factors for cancer. Diet is known to modulate the immune system, and it may also influence cancer susceptibility through changes in the energy balance and in the levels of carcinogens and anticarcinogens<sup>[12]</sup>. Cigarette smoke contains more than 7000 chemicals and compounds, from which more than 70 are associated with cancer<sup>[13]</sup>. Benzene, present in tobacco smoke, is a strong carcinogen associated with leukemia and lymphoma development<sup>[14]</sup>, and has long been recognized as hematotoxic<sup>[15]</sup>.

It should not be forgotten that cancer susceptibility results from genetic and environmental factors, individually or in combination. According to this, it is expected that genetic, dietary and lifestyle factors interact with each others.

Several studies have inquired the epidemiologic risk factors associated with leukemia, lymphoma and/or myeloma. Except certain genetic abnormalities, viruses, environmental exposures and chemotherapeutic agents, little is known about risk factors that develop these onco-hematological diseases.

Argentina is within the range of countries with medium to high incidence of cancer, according to the International Agency for Research on Cancer (IARC) data for 2012. They estimated an incidence of 14.2 new cases/year/100000 persons for Hodgkin lymphoma (HL), leukemia, non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) all together<sup>[16]</sup>. During 2012, nearly 3830 patients have died because of these diseases according to the Statistics and Health Information Office<sup>[17]</sup>. Between 2007 and 2011, oncohematological diseases account for the 6.5% of all cancer deaths<sup>[18]</sup>.

The aim of this study was to analyze the association between oncohematological diseases and genetic polymorphisms in *GSTT1*, *GSTM1* and *CYP1A1*, dietary habits and cigarette smoking, in an argentine hospital-based case-control study.

## MATERIALS AND METHODS

### Subjects

A hospital-based case-control study was performed, involving 125 patients with oncohematological diseases and 310 control subjects. Participants were recruited between June 2013 and March 2015 at the Unit of Diagnosis, Treatment and Support for Hematological Diseases of the Acute Care General Hospital "Prof. Dr. Rodolfo Rossi" (La Plata, Buenos Aires, Argentina). The study was approved by the hospital's Ethics Committee. The International Classification of Diseases for Oncology information was not available.

Cases were patients diagnosed with acute lymphoblastic leukemia (ALL,  $n = 10$ ), acute myeloblastic leukemia (AML,  $n = 18$ ), chronic lymphoblastic leukemia (CLL,  $n = 10$ ), chronic myeloblastic leukemia (CML,  $n = 20$ ), MM ( $n = 29$ ), HL ( $n = 18$ ) and NHL ( $n = 20$ ). Controls included patients frequently visiting the Unit for routine checks of disorders unrelated to cancer or

preoperative blood analyses (*i.e.*, for ophthalmic surgeries, pre-employment medical examinations, anemia, among others). All participants reside in Argentina. Cases and controls with previous history of cancer or pathologies closely related to oncohematological diseases were excluded from the study.

Patients were invited to participate in the study and signed an informed consent. A questionnaire was used to obtain sociodemographic data and information about habits, such as cigarette smoking (never, former and current smoker), and consumption of grilled/barbecued meat (times per month), canned food (times per week), alcohol (times per week) and coffee (cups per day). No other food or beverage items were asked. The survey also included weight, height, medication, working conditions, family history of cancer, history of disease (only in cases), and functionality data (quality of sleep, fatigue, changes in appetite and mood, *etc.*). The overall case and control response rate was higher than 90% for both groups.

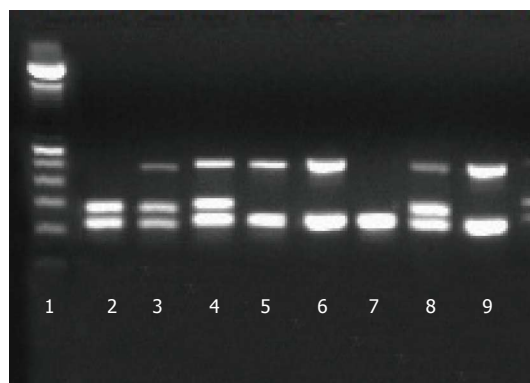
All surveys were addressed by the same person. Blood samples were collected and kept in Vacutainer tubes with K2-EDTA (3.6 mg), and DNA was extracted from whole blood using salting out methods.

### *GSTT1* and *GSTM1* genotype assay

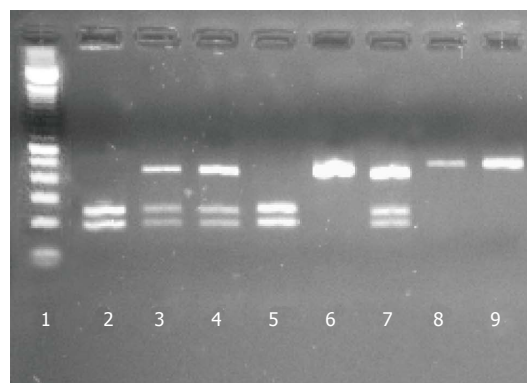
*GSTT1* and *GSTM1* gene deficiency resulted from the deletion of the loci (null alleles). The detection was performed by a multiplex PCR, using *GSTT1* forward primer 5'-TTC CTT ACT ggT CCT CAC ATC TC-3' and *GSTT1* reverse primer 5'-TCA CCG gAT CAT ggC CAG CA-3' (459 bp product), *GSTM1* forward primer 5'-CTg CCC TAC Ttg ATT gAT ggg-3' and *GSTM1* reverse primer 5'-CTg gAT TgT AgC AgA TCA TgC-3' (273 bp product), and a third pair of primers, forward 5'-TCC AgC AgT TTC ATg AgA TgC-3' and reverse 5'-gAg gTC ATT TCA Tag CTg AgC-3' for a 221 bp product of the gene *CLOCK*, as an internal control of the reaction (Figure 1). PCR conditions were as follows, in a final volume of 15  $\mu$ L: 1  $\times$  buffer, 50 ng DNA, 0.25  $\mu$ mol/L each primer, 200  $\mu$ mol/L dNTPs, 2 mmol/L MgCl<sub>2</sub>, 0.45 U Taq Platinum Polymerase (Invitrogen, Life Technologies) and H<sub>2</sub>O up to 15  $\mu$ L. PCR cycling consisted in an initial denaturation at 94  $^{\circ}$ C for 5 min, followed by 35 cycles of 1 min at 94  $^{\circ}$ C, 1 min at 59  $^{\circ}$ C and 1 min at 72  $^{\circ}$ C, with a final extension at 72  $^{\circ}$ C for 5 min. Verification of PCR products, and subsequent identification of genotype, were performed using 2% agarose gels stained with GelRed (Biotium Inc., CA, United States). The absence of PCR product defines the null allele.

### *CYP1A1* genotype assay

*MspI* polymorphism was detected by PCR-RFLP. A product of 420 bp was amplified by PCR in a final volume of 15  $\mu$ L, containing buffer 1  $\times$ , 2 mmol/L MgCl<sub>2</sub>, 250 nmol/L each primer, 200  $\mu$ mol/L dNTPs, 0.4 U Taq DNA Polymerase Recombinant (Invitrogen), 30 ng DNA and H<sub>2</sub>O up to 15  $\mu$ L. Primers were: forward



**Figure 1** Gel electrophoresis showing PCR products of GSTT1 (459 bp), GSTM1 (273 bp) and CLOCK (221 bp). Numbered lanes represents: 1: 100 bp molecular weight marker; 3, 4, 8: T\*/M\*; DNA from samples with positive GSTT1 and GSTM1 alleles, plus control CLOCK gene band; 7: T\*/M\*; Double null genotype of GSTM1 and GSTT1 (in the presence of CLOCK PCR product); 5, 6, 9: T\*/M\*; GSTT1 positive/GSTM1 null; 2: T\*/M\*; GSTT1 null/GSTM1 positive.



**Figure 2** Gel electrophoresis showing PCR-RFLP product of CYP1A1 gene digested with MspI restriction enzyme. CYP1A1 gene T3801C variant gives the following digestion band patterns: TT, 420 bp; TC, 420 bp and 237 bp + 183 bp; and CC, 237 bp + 183 bp. Numbered lanes represents: 1: 100 bp molecular weight marker; 2, 5: CC homozygous type; 3, 4, 7: TC heterozygous type; 6, 8, 9: TT homozygous type.

5'-ACC CCA TTC TgT gTT ggg TT-3' and reverse 5'-TAG AgA ggg CgT AAg TCA gCA-3'. Cycling conditions were as follows: An initial denaturation at 94 °C for 5 min, followed by 35 cycles of 30 s at 94 °C, 30 s at 58 °C and 40 s at 72 °C, with a final extension at 72 °C for 5 min.

After checking amplification in 2% agarose gel stained with Gel Red, 7 µL of PCR product were digested with 5U of *MspI* enzyme (Thermo Scientific), buffer and H<sub>2</sub>O up to 15 µL. Incubation time was 5 h at 37 °C. Verification of digested products was carried out in 2% agarose gels stained with Gel Red. The C variant has the restriction site, generating 237 and 183 bp products (Figure 2).

### Statistical analysis

Odds ratio (OR) and 95%CI were calculated to estimate the association between each variable studied and oncohematological disease.  $\chi^2$  test was applied to obtain the statistical significance of the association. Analyses were performed with the softwares STATA 11.1<sup>[19]</sup> and Epidat 4.0<sup>[20]</sup>. Genotype and allele frequencies were calculated and tested for Hardy-Weinberg Equilibrium using the software GenAIEx 6.5<sup>[21]</sup>. The sample size of this survey achieved 80% power to detect an OR = 2. *P*-values ≤ 0.05 were considered statistically significant. The statistical review of the study was performed by a biomedical statistician (Gili JA, one of the authors).

## RESULTS

### Study population

In this association study, a total of 125 cases were compared to 310 controls, all of them patients from the Acute Care General Hospital "Prof. Dr. Rodolfo Rossi". Demographic characteristics are listed in Table 1, and were already published by our group in Cerliani *et al.*<sup>[22]</sup>. Missing data for each variable were not included in the analysis, nor are detailed in the tables. The maximum number of missing data in a variable was 18,

representing 4.14% of the samples. Of all variables in the questionnaire, only height and weight were excluded due to > 10% missing data. There was no significant difference in the mean age of cases and controls. Women showed lower risk of disease compared to men (OR 0.52, 95%CI: 0.34-0.82, *P* = 0.003). Higher levels of education (> 12 years) were significantly associated with an increased risk, compared to complete primary school or less (OR 3.68, 95%CI: 1.82-7.40, *P* < 0.001 adjusted for age and sex). Marital status did not show association with the disease.

### Tobacco, dietary habits and XMG polymorphisms

With respect to tobacco, none of the smoking categories showed association with oncohematological diseases. Regarding dietary habits, consumption of grilled/barbecued meat 3 or more times per month showed significant association with an increased risk of disease (OR 1.72, 95%CI: 1.08-2.75, *P* = 0.02). Daily consumption of coffee also was associated with an increased risk (OR 1.77, 95%CI: 1.03-3.03, *P* = 0.03). Since control patients with gastrointestinal problems could create a spurious OR (given that they may be abstaining from coffee), patients from the Gastroenterology Unit of the hospital were removed from the analysis, as well as control patients under treatment with gastric protectors or medication prescribed for other gastrointestinal issues. Therefore 19 controls were excluded from the analysis; nevertheless, coffee consumption still remains statistically correlated with disease, showing the same OR range (OR 1.01-3.02). No association was observed with consumption of canned food or alcohol. When assessing the risk associated with consumption of coffee and grilled/barbecued meat, within each of the pathologies, results showed no differences between groups for coffee consumption, but CML and MM cases exhibited a significant association with consumption of grilled/barbecued meat 3 or more times per month, adjusted for age, sex and educational

**Table 1** Demographic characteristics of the population under study *n* (%)

	Cases <i>n</i> = 125	Controls <i>n</i> = 310	OR (95%CI)	<i>P</i>
Age mean (SD)	48.5 (16.6)	51 (18.5)	-	0.507
Sex				
Male	74 (59.2)	134 (43.2)	Ref.	0.003
Female	51 (40.8)	176 (56.8)	0.52 (0.34-0.82)	
Education				
≤ 7 yr (complete primary school or less)	174 (56.31)	55 (44)	Ref.	
12 yr (complete secondary school)	115 (37.22)	48 (38.4)	1.2 (0.73-1.95)	< 0.001 <sup>1</sup>
> 12 yr (complete college)	20 (6.47)	22 (17.6)	3.68 (1.82-7.4)	
Marital status				
Single	79 (25.48)	27 (21.6)	Ref.	
In couple/married	162 (52.26)	86 (68.8)	1.7 (0.99-2.95)	0.05 <sup>1</sup>
Divorced/separated	27 (8.71)	5 (4)	0.64 (0.21-1.9)	0.42 <sup>1</sup>
Widowed	42 (13.55)	7 (5.6)	0.75 (0.27-2.13)	0.59 <sup>1</sup>
Type of malignancy				
ALL	10 (8)			
AML	18 (14.4)			
CLL	10 (8)			
CML	20 (16)			
MM	29 (23.2)			
HL	18 (14.4)			
NHL	20 (16)			

<sup>1</sup>Adjusted for age and sex. *P* < 0.05 considered statistically significant. ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; CLL: Chronic lymphoblastic leukemia; CML: Chronic myeloblastic leukemia; MM: Multiple mieloma; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; Ref: Reference category; SD: Standard deviation.

**Table 2** Allele and genotype frequencies for *CYP1A1* \*2A polymorphism, and *GSTT1/GSTM1* null polymorphisms

	Cases <i>n</i> = 125	Controls <i>n</i> = 310
Allele frequencies		
<i>CYP1A1</i>		
T	0.7	0.65
C	0.3	0.35
Genotype frequencies ( <i>n</i> )		
<i>GSTT1</i> *null	0.18 (22)	0.18 (55)
<i>GSTM1</i> *null	0.5 (61)	0.47 (140)
<i>CYP1A1</i>		
TT	0.53 (64)	0.47 (140)
TC	0.34 (42)	0.37 (113)
CC	0.13 (16)	0.16 (47)

level (data not shown). With regard to *GSTT1*, *GSTM1* and *CYP1A1* polymorphisms, results showed no significant association with oncohematological diseases. *CYP1A1 MspI* polymorphism was not in Hardy-Weinberg equilibrium. Allele and genotype frequencies are detailed in Table 2. Results from the association analysis between tobacco, dietary habits, XMG polymorphisms and oncohematological diseases are described in Table 3. When analyzing the interaction between XMG polymorphisms and tobacco smoking or dietary habits, no statistically significant associations that modify disease risk were found (data not shown).

## DISCUSSION

Carcinogenesis is considered as a multi-step and multi-factorial process that implied different genetic alterations

and several biological pathways. Thus, it is expected that cancer risk factors interact with each others. Genetic polymorphisms may play different roles in cancer susceptibility according to the genetic background, environmental exposures and lifestyles<sup>[8]</sup>. Despite this, we did not find evidence of interaction between genetic and lifestyle factors, probably because the sample size is not big enough for this type of analysis.

Regarding tobacco use and dietary habits, we reported an increased risk of oncohematological diseases associated with grilled/barbecued meat intake 3 or more times per month, and with daily consumption of coffee, after adjustment for age, sex and educational level. Moreover, for both factors that showed an increased risk when analyzing all malignancies combined, we have also assessed the risk associated with each of the major groups within the case category. While for coffee consumption results showed no differences between groups, grilled/barbecued meat intake (3 times or more per month) has shown a significant correlation with CML and MM cases. However, it has to be considered that the sample size becomes small when divided by each pathology. Therefore, the real effect of each risk factor for a specific type of leukemia, lymphoma or myeloma might be determined in future studies by analyzing a larger set of samples.

Although cigarette smoke has been associated with mutagenic/carcinogenic effects, inflammation and immune suppression in animals and humans<sup>[23,24]</sup>, previous studies on cigarette smoking and its association with blood cancers have generated inconsistent findings. Regarding NHL, studies reported little or no association

**Table 3 Association between tobacco, dietary habits, xenobiotic metabolizing genes polymorphisms, and oncohematological diseases n (%)**

	Cases n = 125	Controls n = 310	OR (95%CI)	P
Tobacco smoking status				
Never	49 (39.8)	142 (46.4)	Ref.	
Former	47 (38.2)	100 (32.7)	1.36 (0.84-2.19)	0.202
Current	27 (22)	64 (20.9)	1.22 (0.70-2.13)	0.478
Consumption of canned food				
0-2 times/wk	121 (96.8)	292 (94.8)	Ref.	0.370
3 or more times/wk	4 (3.2)	16 (5.2)	0.60 (0.14-1.92)	
Consumption of grilled/barbecued meat				
0-2 times/mo	69 (55.2)	217 (70.7)	Ref.	0.021 <sup>1</sup>
3 or more times/mo	56 (44.8)	90 (29.3)	1.72 (1.08-2.75)	
Alcohol drinking				
0-3 times/wk	110 (88)	268 (86.5)	Ref.	0.665
4 or more times/wk	15 (12)	42 (13.5)	0.87 (0.43-1.68)	
Consumption of coffee				
< 1 cup/d	90 (72)	259 (83.5)	Ref.	0.037 <sup>1</sup>
1 or more cups/d	35 (28)	51 (16.5)	1.77 (1.03-3.03)	
GSTT1				
Presence	100 (82)	245 (81.7)	Ref.	0.942
Null	22 (18)	55 (18.3)	0.98 (0.54-1.74)	
GSTM1				
Presence	61 (50)	160 (53.3)	Ref.	0.534
Null	61 (50)	140 (46.7)	1.14 (0.73-1.78)	
CYP1A1				
TT	64 (52.5)	140 (46.7)	Ref.	0.280
TC + CC	58 (47.5)	160 (53.3)	0.79 (0.51-1.24)	

<sup>1</sup>Adjusted for age, sex, and educational level. P < 0.05 considered statistically significant. Ref.: Reference category.

with use of cigarettes/tobacco, or patterns related with duration or intensity of exposure (detailed in<sup>[25-27]</sup>). In a case-control study from Sweden, the effects of smoking on the risk of AML were weak and no significant<sup>[28]</sup>. However, a cohort study from the same country showed a 50% increased risk of AML for current smokers<sup>[29]</sup>; this study also indicated no association between current and former smokers with CML, ALL, CLL or MM. An Indian case-control study reported an increase of 2.1 fold in the risk of leukemia in the cigarette smokers, compared to non-smokers<sup>[30]</sup>. A US cohort study that evaluated risk factors for AML, showed hazard ratios of 1.79, 2.42 and 2.29 for former smokers of > 1 pack/d, current smokers of ≤ 1 pack/d, and current smokers of > 1 pack/d, respectively<sup>[31]</sup>. A meta-analysis done by Fircanis *et al.*<sup>[32]</sup> including over 7500 cases of AML, found an increased risk of disease associated with smoking, regardless of sex, geographical region, study design and quality of studies. They also reported a higher risk with higher intensity and longer duration of smoking.

It is possible that the exposure to agents present in the smoke varies given the different usage patterns, exposure pathways and manufacturing processes.

A recent study done by Rubinstein *et al.*<sup>[33]</sup> showed that 29.7% of the general population of Argentina, Chile and Uruguay (n = 7524) smoke cigarettes. The CARMELA study (Cardiovascular Risk Factor Multiple Evaluation in Latin America), performed between 2003 and 2005, reported that Buenos Aires (Argentina, n =

1482) and Santiago (Chile, n = 1655) have the highest smoking prevalence among the seven Latin American cities studied, with no gender differences (38.6% and 45.4% respectively)<sup>[34]</sup>. Our study reports that 20.9% of the controls and 22% of the cases are current smokers, with higher percentages for former smokers (32.7% for controls and 38.2% for cases). These results are probably due to that this study is based on hospital population, which strongly encourages quitting. Considering the high proportion of people exposed to tobacco in these countries, it would be interesting to continue assessing its impact on the development of blood cancer, given the limited information available.

Diet, probably among the most modifiable environmental factors, contributes to the development of 30%-35% of cancers<sup>[35]</sup>. Association studies in the field may be inconsistent due to differences in the frequency of food intake, varieties of available food, and different methods of preparation among populations.

According to a recent publication of the IARC Monograph Working Group, consumption of processed meat was classified as "carcinogenic to humans" (group 1), and consumption of red meat as "probably carcinogenic to humans" (group 2A)<sup>[36]</sup>. Meat processing can result in formation of N-nitroso compounds and PAH, while cooking it can produce heterocyclic aromatic amines and PAH. High-temperature cooking, such as grilling and barbecuing, produces the highest amounts of these carcinogens. Barbecued red meat is a frequent dish

among the Argentinean population, where there is a high consumption of animal protein and fats obtained mainly from red meat<sup>[37,38]</sup>. Several epidemiologic studies from Córdoba, an Argentinean province, report significant associations between consumption of red meat, or dietary patterns that contains it, and breast, colorectal, prostate, and urinary tract cancers<sup>[37-42]</sup>. According to Navarro *et al.*<sup>[38]</sup>, all meats were associated with an increased risk for colorectal cancer when barbecued, a similar result to that observed in our study. In two other surveys, the Southern Cone dietary pattern (red meat, starchy vegetables and wine consumptions) was associated with higher risk of urinary tract tumors<sup>[39]</sup> and colorectal cancer<sup>[37]</sup>. In a case-control study from Uruguay, red meat, lamb, and boiled meat were associated with the risk of squamous cell carcinoma of the esophagus<sup>[43]</sup>.

In relation to oncohematological diseases, there are no studies in Argentina concerning diet and lifestyle as risk factors. Several studies from other countries evaluated this possible association, with inconsistent results. Most of them reported no association between meat consumption and increased risk of NHL or CML<sup>[44-46]</sup>. A case-control study from US done by Li *et al.*<sup>[47]</sup> reported a positive association between an increased risk of AML and beef intake among women. Our results are the first to report a significant association between oncohematological diseases and consumption of barbecued/grilled meat in our population. However, some bias could exist since portion size was not assessed, and the questionnaire does not differentiate between red and white meat. Despite this, our results are relevant given the fact of a high and frequent consumption of these foods in Argentina.

It has been suggested that light to moderate alcohol consumption has beneficial effects due to advantageous host cellular and humoral immune responses<sup>[48]</sup>. On the other hand, ethanol was classified as carcinogenic to humans by the IARC. Regarding hematologic malignancies, a pooled analysis from the International Lymphoma Epidemiology Consortium reported that ever or current drinking were associated with a lower risk of NHL, compared with non-drinkers<sup>[49]</sup>. However, they did not find a dose-response relation or a stronger trend with longer duration. A meta-analysis performed with 18 studies, including 5694 cases with MM and 7142 with leukemia, did not find any association between alcohol drinking and MM or leukemia risks<sup>[50,51]</sup>. As with beef consumption, Li *et al.*<sup>[47]</sup> reported a positive association between beer and wine intake and AML, only among women. An Italian case-control study showed no clear association between leukemia or NHL and alcohol consumption<sup>[27]</sup>. In line with some of these reports, we found no association between alcohol consumption and oncohematological diseases in the Argentinean population under study.

Regarding coffee consumption, there is no consistent evidence suggesting protective or deleterious effects. On the one hand, coffee may decrease the risk of cancer through antioxidant, antihormonal, and anti-inflammatory mechanisms<sup>[52]</sup>. On the other hand, caffeine and Topo II inhibitors may elevate cancer risk. A United States cohort

study reported no association between coffee intake and risk of all cancers combined, but they observed a decrease in the risk of endometrial cancer for women drinking 1 or more cups per day<sup>[53]</sup>. Although some studies on solid tumors have reported a protective effect (*i.e.*, on liver, colorectal, breast and endometrial cancer<sup>[54-57]</sup>), studies on hematopoietic malignancies in adults are rare. In our study, daily consumption of coffee was associated with an increased risk of disease. An Indian case-control study showed a 40% reduction in the risk of leukemia for coffee drinkers<sup>[30]</sup>, while an Italian one reported an increase in the risk of NHL<sup>[58]</sup>. Other studies found no significant associations between coffee consumption and hematologic cancer<sup>[44,59,60]</sup>. In 1991, the IARC Working Group classified coffee as possibly carcinogenic to humans (group 2B). Given the large number of studies published on the subject since that IARC publication, the IARC Advisory Group recommends a review of the evidence, giving to this exposure high priority for its inclusion in the monographs to be published between 2015 and 2019<sup>[61]</sup>.

Genetic variations in XMG may be important factors in the etiology of onco-hematological diseases. Although they have low penetrance, they are highly prevalent in most populations, giving the chance to identify potential carcinogens and populations at higher risk of cancer<sup>[62]</sup>. These polymorphisms also interact with other polymorphisms and/or particular environmental factors, which vary between and within ethnic groups<sup>[8]</sup>. The increased activity/inducibility of CYP1A1\*2A may contribute to the accumulation of genetic changes due to an increased production of mutagenic agents. In a similar way, the decreased activity of GSTs due to gene deletions may lead to a more intense cellular oxidative stress, increasing the level of DNA damage.

Regarding CYP1A1 *MspI* polymorphism, allele frequencies vary between ethnic groups, being 0.058, 0.149 and 0.218 for the C allele (\*2A) in Caucasians, Asians and Africans, respectively<sup>[63]</sup>. Roco *et al.*<sup>[64]</sup> reported a \*2A allele frequency of 0.37 for a Chilean population. In this study, \*2A allele frequencies were 0.34 for controls and 0.30 for cases, similar to that described for the Chilean population and away from that reported for Caucasians. Our genotypic data about this polymorphism deviate from Hardy-Weinberg equilibrium; this may be because the sample does not represent the entire population variability, or due to genotyping errors that create a bias towards increased homozygosity.

Our association analysis between *MspI* polymorphism and blood cancer showed an OR = 0.79 (95%CI: 0.51-1.24), with no statistical significance. Association studies between CYP1A1 *MspI* polymorphism and cancer have been inconsistent. A meta-analysis from 268 studies performed by He *et al.*<sup>[8]</sup> showed that the variant \*2A was associated with an increased risk of leukemia, cervical, hepatocellular, head and neck, lung and prostate cancer, but not with other cancer types. Another meta-analysis done by Han *et al.*<sup>[65]</sup> reported a higher risk of leukemia associated with this variant, which remains significant for Caucasians when stratified by ethnicity.

They also reported an increased risk for ALL and AML, especially in childhood ALL in Caucasians. Among Asians, Lu *et al.*<sup>[66]</sup> showed that the presence of the *MspI* polymorphism increased the risk of AML. On the other hand, a meta-analysis performed by Zhuo *et al.*<sup>[67]</sup> did not find significant associations between CYP1A1 variant and AML risk.

Many studies have analyzed the possible association between hematological cancer and the deletions of *GSTT1* and *GSTM1*, with disparate results. In this study, frequencies for null genotypes were 0.18 in cases and controls for *GSTT1*, and 0.5 and 0.47 for *GSTM1*, in cases and controls respectively. Reported frequencies for *GSTT1*\*null in controls were 0.13-0.26 for Caucasians<sup>[63]</sup>, 0.10-0.12 for Chilean and Argentinean populations<sup>[64,68-70]</sup>, and 0.09-0.24 for Native American Argentineans<sup>[71]</sup>. *GSTM1*\*null has higher frequencies, with values of 0.42-0.60 for Caucasians<sup>[63]</sup>, 0.36-0.46 for Chilean and Argentinean populations<sup>[64,68-70]</sup>, and 0.29-0.49 for Native American Argentineans<sup>[71]</sup>. Our study showed an OR = 0.98 (95%CI: 0.54-1.74) for the *GSTT1* deletion, and an OR = 1.14 (95%CI: 0.73-1.78) for *GSTM1* deletion. He *et al.*<sup>[62]</sup> carried out a meta-analysis, showing that *GSTM1*\*null genotype significantly increased the risk of AML in East Asians, while *GSTT1*\*null increased it in Caucasians. Double-null genotypes were associated with AML in both ethnic groups. Several case-control studies reported significant associations between *GSTT1*\*null genotype and AML, CML, CLL and acute leukemia<sup>[72-78]</sup>. Conversely, other studies did not find such associations with all leukemia, acute leukemia, CML, AML or MM<sup>[79-82]</sup>. A similar scenario occurs with *GSTM1*\*null genotype: many studies showed a significant increased risk of NHL, CLL, AML, MM, CML, and acute leukemia associated with the null genotype<sup>[72,73,76,78,83,84]</sup>, while other ones reported no differences in cancer risk between controls and CML, AML, MM, acute leukemia and all leukemia cases<sup>[74,75,77,79-82]</sup>. In general, studies reported moderate OR, with values from 1 to 3; however, values up to 7 were reached in some assays, with OR values even greater when analyzing double null genotypes. It should be noted that these case-control studies are from different countries with different ethnic backgrounds, and with a variable number of participants.

Our study has strengths that are worth mentioning. Face-to-face interviews were performed by the same person, with all cases and controls, thus addressing reliable data about personal information, habits and lifestyle. Furthermore, although sample size is small, it has the power to detect an OR = 2, a value close to that reported in similar case-control studies. Even though cases and controls were not age- and gender-matched, statistical adjustment were used to minimize potential biases. It should be recall that hospital-based studies may have some bias, due to controls that might have benign diseases which are prone to turn malignant. This study design could reduce the generalization of the results to the general population. Additionally, hematological malignancies are heterogeneous illnesses,

with potentially different causes. A larger number of samples will allow us to conduct studies of risk factors for each pathology independently.

There is a lack of studies for oncohematological diseases etiology in an argentinean population, particularly for genes and environmental factors. Taking that into account, our goal through the study was to address and offers relevant insight into diverse aspects for these pathologies in our population.

## ACKNOWLEDGMENTS

We thank the hospital's technical staff for their help in attending the patients for sampling. Ignacio Miguel is thanked for helping in processing some DNA samples.

## COMMENTS

### Background

Risk factors for oncohematological diseases are not completely defined. As in other cancer pathologies, blood cancer susceptibility is related to both lifestyle and genetic factors. In regards to the Argentinean population, these pathologies are barely studied, even in relation to highly frequent risk factors for this population.

### Research frontiers

In the latest years, although specific diet patterns for Argentina have been evaluated as risk factors related to cancer development by many studies, hematological cancer was not included. Moreover, studies about tobacco, alcohol and coffee as risk factors for oncohematological diseases are still not conclusive; furthermore, the results can vary between different populations and study designs. On the other side, genetic variants in coding genes for enzymes associated to carcinogenic compounds metabolism are known genetics risk factors linked to cancer. Allelic frequencies for these enzymatic variants are different between populations; therefore, it becomes difficult to extrapolate an estimated risk from one population to another. For Argentina, genetic frequencies for metabolizing enzymes are already known; however, available data are limited to just a few cities and, mostly, for healthy population.

### Innovations and breakthroughs

In that regards, in this work the authors reported an association between oncohematological diseases with coffee and meat intake. With respect to the latter risk factor, the result becomes extremely relevant given the fact of high meat consumption in Argentina. The results are the first one showing a possible association in the authors' population. Moreover, Argentina has a medium-high cancer incidence; every research implying an evaluation of different risk factors frequently found in the population, could help in contributing with new information, in order to dilucidate which specific factors are really involved in the actual incidence of blood related cancer diseases.

### Applications

The result could be joined with the whole set of studies looking to evaluate the impact of genetics and lifestyle factors in cancer development. The results reported for coffee and barbecued/grilled meat intake, could be taken into account to go deeply in future studies by evaluating specific kinds of meat, portion size, other cooking methods, *etc.* This could allow researchers to classify, more specifically, which particular characteristics related to nutrition patterns are associated with cancer development in a population. Additionally, each oncohematological pathology could be also analyzed individually from the main group, due to the fact that each specific genetic or lifestyle factor could be involved in different pathways and/or specific disease stages, independently.

### Terminology

Odds ratio (OR), in statistics, the OR is a way to quantify how strongly the presence or absence of property A is associated with the presence or absence



of property B in a given population. Oncohematological diseases or hematology-oncology, the diagnosis, treatment and prevention of cancer developed in blood cells, and the research associated to them. Hematology-oncology includes diseases such as leukemias and lymphomas, as well as other blood disorders (*i.e.*, iron deficiency anemia, hemophilia, sickle cell disease, and thalassemias).

### Peer-review

The study indicates an increased risk of oncohematological diseases associated with meat and coffee intake. Overall the manuscript was written in a clear and concise manner.

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