BMC Research Notes

CrossMark

Effect of genetic ancestry to the risk of susceptibility to gastric cancer in a mixed population of the Brazilian Amazon

Ellen Moreno da Silva[1,2,4*†], Marianne Rodrigues Fernandes[1,2†], Darlen Cardoso de Carvalho[1,2], Luciana Pereira Colares Leitao[1], Giovanna Chaves Cavalcante[2], Esdras Edgar Batista Pereira[1], Antônio André Conde Modesto[1,2], João Farias Guerreiro[2], Paulo Pimentel de Assumpção[1,2,3], Sidney Emanuel Batista dos Santos[1,2] and Ney Pereira Carneiro dos Santos[1,2]

Abstract

Background: Global literature describes differences in the incidence of gastric cancer among populations. For instance, Europeans have lower incidence rates of gastric cancer in relation to Latin and Asian populations, particularly Korean and Japanese populations. However, only a few studies have been able to verify the occurrence of gastric cancer in admixed populations with high interethnic degree mix, such as the Brazilian Amazon region.

Results: We observed an increase in European ancestry in the control group compared to the case group (47% vs. 41%). Using increments of 10%, compared to categorical distribution of European ancestry in the sample, we found a difference in the contribution between cases and controls (p = 0.03). Multiple logistic regression was performed to determine the influence of European ancestry in susceptibility to gastric cancer in the sample. According to the adopted model, for each 10% increase in European ancestry, there is a 20% decrease chance of developing gastric cancer (P = 0.0121; OR = 0.81; 95% CI 0.54–0.83).

Conclusion: Overall, the results suggest that a greater contribution of European ancestry can be a protective factor for the development of gastric cancer in the studied Amazon population. It can help to establish protocols able to predict susceptibility to gastric cancer in admixed populations.

Background

Stomach cancer, also known as gastric cancer, is the third leading cause of cancer death worldwide [1]. The incidence of stomach cancer is the sixth highest in the world [2] and is among the highest incidences in Latin America [3].

The literature reports differences in the incidence of gastric cancer among populations. For example, Europeans have lower rates of gastric cancer incidence when

compared to Latin and Asian populations, especially Japanese and Korean [4, 5]. These differences in incidence can be attributed to risk factors associated with lifestyle, such as diet, obesity, stress and physical inactivity. In addition, other studies suggest that the lower incidence of gastric cancer in the European population may be related to lower frequency of genes associated with gastric cancer susceptibility [5, 6].

In this context, it is conceivable that heterogeneity among populations and different genetic ancestries can contribute to the varying levels of susceptibility to cancer development. This is especially important in admixed populations, such as the Brazilian population, which is known to be one of the most heterogeneous populations in the world, with contributions from three main parental groups: Amerindian, European and African [7–9].

*Correspondence: Ellenmoreno.biomed@gmail.com
†Ellen Moreno da Silva and Marianne Rodrigues Fernandes contributed equally to this work
[4] Instituto de Ciências Biológicas, Laboratório de Genética Humana e Médica, Cidade Universitária Prof. José da Silveira Netto, Rua Augusto Corrêa, 01, BOX: 8615, Belém, PA CEP 66.075-970, Brazil
Full list of author information is available at the end of the article

da Silva *et al. BMC Res Notes* (2017) 10:646

Page 2 of 5

Literature demonstrates the influence of genetic ancestry and the risk of developing various types of cancer, such as breast [10–12], colorectal [13], leukemia [14] and ovarian cancer [15]. More specifically, there is a work that explores the influence of genetic ancestry in the risk of developing gastric cancer among Brazilian populations [12].

Therefore, the objective of this study is to investigate the influence of genetic ancestry in susceptibility to gastric cancer in a population of the Amazon region with a high degree of interethnic admixture.

Methods
Cases and control
The participants of the research were chosen based on a case–control study. Participants from both case and control groups were recruited from free services in public institutions, were from the same socioeconomic level, and belonged to the same geographic area.

The case group constituted of 137 individuals that were diagnosed with gastric adenocarcinoma, attended by the Unified Health System (SUS), in a public hospital that is reference in the treatment of this kind of neoplasm (Hospital Universitário João de Barros Barreto, Pará, Brazil). Most patients involved in the study (80%) presented advanced tumor staging—grade III and IV according to Borrmann classification.

The control group constituted of 262 cancer-free individuals, attended in the Laboratório de Exercício Resistido e de Saúde (LERES), from a public university of the region (Universidade Estadual do Pará, Pará, Brazil).

Ethical approval
The protocol used in the study was approved by the Ethics Committee of the University Hospital João de Barros Barreto (Protocol Number 3505/2004). All patients in the present study signed a consent form.

Analysis of genetic ancestry
The analysis of genetic ancestry was performed using a panel of 48 ancestry informative markers (AIM) developed by Santos et al. [16]. Amplification was performed using three multiplex PCR reactions with 16 markers each. PCR separation and analysis was performed by capillary electrophoresis using the ABI PRISM 3130 sequencing and GeneMapper ID Software v3.2. Individual proportions of ancestries of Europeans, Africans and Amerindians were estimated using the STRUCTURE software v2.3.3, with three parental populations (European, African and Amerindian).

Parental populations involved individuals that were representative of three great ancestral groups: 222 Amerindian from nine tribes in the Brazilian Amazon (Tiriyó,

Waiãpi, Zoé, Urubu-Kaapor, Awa-Guajá, Parakanã, Wai Wai, Gavião and Zoró), 211 African (Angola, Mozambique, Congo Republic, Cameroon and Ivory Coast) and 268 European (Portugal and Spain). More details on these populations can be found in [17].

Statistical analysis
All statistical analyses were performed using the statistical program SPSS v.20.0 (SPSS, Chicago, IL. USA). Chi squared test in pairs was applied for group comparisons of categorical variables (sex), while Student's t-test was used for the analysis of quantitative variables (age). For comparisons of ancestry among the samples, we used the Mann–Whitney test. Multiple logistic regression analyses were performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs). In these analyses, variables considered confounding factors (age, sex) were corrected. All statistical tests were two-tailed and based on $P < 0.05$ probability to be significant.

Results
We analyzed 137 patients with gastric cancer and 262 cancer-free individuals. Table 1 shows the demographic characteristics of these groups. The case group showed a predominance of men while the control group showed a predominance of women. The results were statistically significant between the case and control groups regarding the following variables: age ($P < 0.001$), sex ($P < 0.001$) and European ancestry ($P = 0.001$).

According to the ancestry analyses conducted in this study, the ethnic composition of the case group was 41% European, 26% African and 33% Amerindian. By comparison, the control group's ancestry contributions was 47% European, 23% African and 30% Amerindian (Table 1). The results revealed that there was a higher contribution of European ancestry in the control group compared to the case group (47% vs. 41%). Using increments of 10%, we compared the categorical distribution of

Table 1 Demographic variables for patients with gastric cancer and the control group

Variable	Case	Control	*P*
Age, years[a]	52.81 ± 18.89	46.80 ± 24.48	< 0.001
Sex (women/men)	34/103	156/106	< 0.001
Genetic ancestry[b]			
European ancestry	0.415 ± 0.143	0.466 ± 0.158	0.001
African ancestry	0.259 ± 0.140	0.232 ± 0.117	0.089
Amerindian ancestry	0.326 ± 0.142	0.302 ± 0.137	0.079

[a] Values are as expressed as mean (± SD = standard deviation). Significance determined by Student's *t*-test

[b] Values are as expressed as mean ± SD. Significance determined by Mann–Whitney test

da Silva *et al. BMC Res Notes* (2017) 10:646

Page 3 of 5

European ancestry in the sample and found a difference in this ancestry contribution between cases and controls (P = 0.03) (Table 2).

Multiple logistic regressions were performed to determine the influence of European ancestry in the susceptibility to gastric cancer in the sample (Table 3). According to the adopted model, for each 10% increase in European ancestry there is a 20% lower chance of developing gastric cancer (P = 0.0121; OR = 0.81; 95% CI 0.68–0.95).

Discussion

In our analyses, the case group presented a greater proportion of men (75%), while in the control group, the proportion was greater among women (60%). The incidence of gastric cancer, as well as other gastrointestinal neoplasms, was greater in men than in women. This finding has been observed in different populations worldwide [18–22]. The justification for this disparity in incidence between men and women goes beyond the explanation of sex differences for exposure to known risk factors. Many studies have suggested a protective effect of estrogen in the development of gastric cancer [22, 23].

To better comprehend the sex difference in the susceptibility to gastric cancer, we performed new statistical tests, which included isolated analyses for men (Additional file 1) and for women (Additional file 2). In both men and women, the European ancestry was the most prevalent, being more frequent in the control group than in the case group.

In the analyses involving only men (Additional file 1), European ancestry was statistically different between case and control (P = 0.009). Logistic regression analysis showed a reduction of 94% in the chances of developing gastric cancer (P = 0.004; OR = 0.059; 95% CI 0.008–0.414).

In the analyses involving only women (Additional file 2), there was no statistically significant difference of European ancestry between case and control groups (P = 0.052). We believe that the absence of significance

Table 2 Categorical distribution of European ancestry in patients with gastric cancer in the comparison with the control group

Genetic ancestry (%)	Case no. (%)	Control no. (%)
European ancestry		
10–20	8 (6)	14 (5.3)
20–30	24 (17.5)	32 (12.2)
30–40	30 (21.8)	40 (15.2)
40–50	38 (27.7)	60 (23)
50–60	21 (15.3)	61 (23.2)
> 60	16 (11.6)	55 (21)
P	0.03	

Table 3 Odds ratio (OR) and 95% confidence intervals (CIs) in the logistic regression model of European ancestry
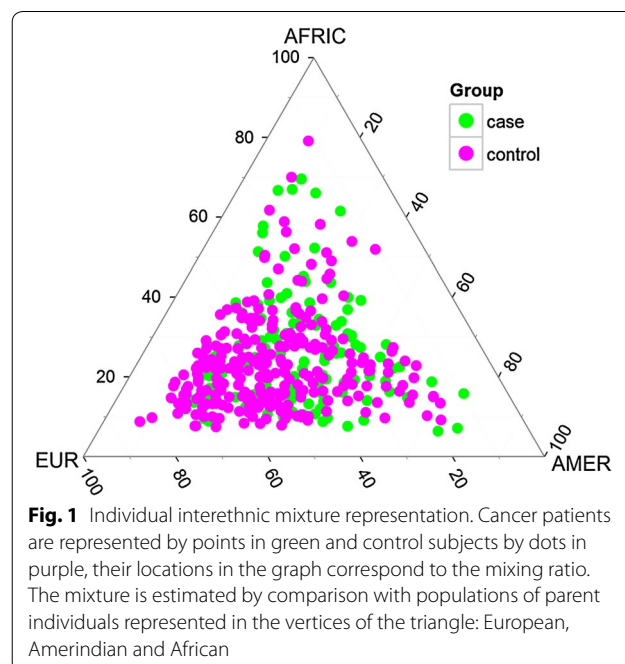
Genetic ancestry	Case mean	Control mean	OR[a]	95% CI[a]	*P*[a]
European ancestry	0.415 ± 0.143	0.466 ± 0.158	0.807	0.682–0.953	0.0121

[a] Logistic regression adjusted for sex and age. Odds-ratio of the analysis of 10% ethnicity increase

may be due to the low sample number of women in the case group (N = 34), which may not allow reliable statistical associations.

Brazilian population is one of the most heterogeneous populations worldwide and it is formed by an admixture of Amerindians, Europeans and Africans. The admixture process occurred through different means in the Brazilian geographic regions. Our sample presented a variety in its composition, with a higher prevalence of European ancestry, followed by Amerindian and African ancestries in both case and control groups (Fig. 1). Previous data have demonstrated that the European ancestry is predominant in four regions in Brazil—North (68.8%), Northeast (60.1%), Southeast (74.2%) and South (79.5%). The African proportion was highest in the Northeast (30.3%) and the Amerindian proportion was highest in the North (19.4%) [16, 24].

Our results demonstrated that European ancestry is more represented in the control group than it is in the case group (Table 1) and that genetic ancestry modifies the risk of developing gastric cancer. The 10% increase in

Fig. 1 Individual interethnic mixture representation. Cancer patients are represented by points in green and control subjects by dots in purple, their locations in the graph correspond to the mixing ratio. The mixture is estimated by comparison with populations of parent individuals represented in the vertices of the triangle: European, Amerindian and African

da Silva *et al. BMC Res Notes* (2017) 10:646

Page 4 of 5

European ancestry was associated with decreased risk of developing gastric cancer (Table 3). There are only a few works in literature on the association of genetic ancestry and gastric cancer susceptibility [12, 25].

The work by [12] has investigated the susceptibility to gastric and breast cancer together, in a different population from the North region of Brazil, and found a protection association between European ancestry and the development of these neoplasms. Each increase of 10% in the European ancestry was inversely correlated to the risk of developing cancer (OR = 0.186), corroborating with our results.

A work developed by [25] has investigated the contribution of genetic ancestry in the risk of developing gastric cancer in an admixed population from Lima (Peru). European ancestry was correlated to a negative effect in the development of gastric cancer, supporting our results.

In addition, other studies have analyzed the association of genetic ancestry and cancers around the world. For example, African ancestry was associated with colorectal cancer [13] and with prostate cancer [26]. Amerindian ancestry was associated with the development of acute lymphoblastic leukemia (ALL) [27].

Our results showed that genetic ancestry may modify the risk of developing gastric cancer. European ancestry was related to a reduction in the chances of developing this neoplasm. Further studies must be carried out to identify genetic polymorphisms that are more frequent in populations with high European ancestry and that may confer a protective effect to this ancestry regarding the development of gastric cancer.

Conclusion

Our results corroborate with studies that suggest that the lower incidence of gastric cancer in the European population may be related to lower frequency of alleles related to high susceptibility of developing gastric cancer [5, 6]. Therefore, a higher European ancestry contribution may be considered a protection factor to gastric cancer in the studied Amazon population. More studies are needed to confirm such results, but this work presented significant findings that contribute to a greater knowledge of the influence of genetic ancestry in the development of gastric cancer.

Additional files

Additional file 1. Demographic variables for men in both groups (gastric cancer and control). To better comprehend the sex difference in the susceptibility to gastric cancer, we performed new statistical tests, which included isolated analyses for men.

Additional file 2. Demographic variables for women in both groups (gastric cancer and control). To better comprehend the sex difference in the susceptibility to gastric cancer, we performed new statistical tests, which included isolated analyses for women.

Author details
[1] Núcleo de Pesquisas em Oncologia, Hospital Universitário João de Barros Barreto, Universidade Federal do Pará, Belém, Brazil. [2] Laboratório de Genética Humana e Médica, Universidade Federal do Pará, Belém, PA, Brazil. [3] Hospital Universitário João de Barros Barreto, Universidade Federal do Pará, Belém, PA, Brazil. [4] Instituto de Ciências Biológicas, Laboratório de Genética Humana e Médica, Cidade Universitária Prof. José da Silveira Netto, Rua Augusto Corrêa, 01, BOX: 8615, Belém, PA CEP 66.075-970, Brazil.

References
1. International Agency for Research on Cancer—IARC. International Agency for Research on Cancer: Biennial Cancer Report. IARC; 2013. http://governance.iarc.fr/. Accessed 20 Jan 2015.
2. Globocan. Estimated cancer incidence, mortality, prevalence and disability-adjusted life years (DALYs) worldwide in 2008. International agency for research of cancer—World Health Organization; 2013. http://globocan.iarc.fr/. Accessed 25 Jan 2015.
3. Bonequi P, Meneses-González F, Correa P, Rabkin CS, Camargo MC. Risk factors for gastric cancer in latin-america: a meta-analysis. Cancer Causes Control. 2014;24(2):217–31.
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer Incidence and Mortality

da Silva *et al. BMC Res Notes* (2017) 10:646

Page 5 of 5

Patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–403.

5. Saeki N, Sakamoto H, Yoshida T. Mucin 1 gene (muc1) and gastric-cancer susceptibility. Int J Mol Sci. 2014;15(5):7958–73.

6. Kim J, Kim Y, Lee K. Ethnic differences in gastric cancer genetic susceptibility: allele flips of interleukin gene. World J Gastroenterol. 2014;20(16):4558–65.

7. Salzano F, Sans M. Interethnic admixture and the evolution of Latin American population. Genet Mol Biol. 2014;37(Suppl 1):151–70.

8. Henderson BE, Lee NH, Seewaldt V, Shen H. The influence of race and ethnicity on the biology of cancer. Nat Rev Cancer. 2012;12(9):648–53.

9. Wang S, Ray N, Rojas W, Parra MV, Bedoya G, Gallo C, Poletti G, Mazzotti G, Hill K, Hurtado AM, Camrena B, Nicolini H, Klitz W, Barrantes R, Molina JA, Freimer NB, Bortolini MC, Salzano FM, Petzl-Erler ML, Tsuneto LT, Dipierri JE, Alfaro EL, Bailliet G, Bianchi NO, Llop E, Rothhammer F, Excoffier L, Ruiz-Linares A. Geographic patterns of genome admixture in Latin American Mestizos. PLoS Genet. 2008;4(3):e1000037.

10. Fejerman L, Hu D, Huntsman S, John EM, Stern MC, Haiman CA, Pérez-Stable EJ, Ziv E. Genetic ancestry and the risk of mortality among US Latinas with breast cancer. Cancer Res. 2013;73(24):7243–53.

11. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, Troester MA, Tse CK, Edmiston S, Deming SL, Geradts J, Cheang MC, Nielsen TO, Moorman PG, Earp HS, Millikan RC. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006;295(21):2492–502.

12. Vieira PC, Burbano RM, Fernandes DC, Montenegro RC, Dos Santos SE, Sortica VA, Assumpção PP, Ribeiro-Dos-Santos ÂK, Carvalho AA, Dos Santos NP. Population stratification effect on cancer susceptibility in an admixed population from Brazilian Amazon. Anticancer Res. 2015;35(4):2009–14.

13. Hernandez-Suarez G, Sanabria MC, Serrano M, Herran OF, Perez J, Plata JL, Zabaleta J, Tenesa A. Genetic ancestry is associated with colorectal adenomas and adenocarcinomas in Latino populations. Eur J Hum Genet. 2014;22(10):1208–16.

14. Carvalho DC, Wanderley AV, Amador MA, Fernandes MR, Cavalcante GC, Pantoja KB, Mello FA, de Assumpção PP, Khayat AS, Ribeiro-Dos-Santos Â, Santos S, Dos Santos NP. Amerindian genetic ancestry and INDEL polymorphisms associated with susceptibility of childhood B-Cell Leukemia in an admixed population from the Brazilian Amazon. Leuk Res. 2015. https://doi.org/10.1016/j.leukres.2015.08.008.

15. Raska P, Iversen E, Chen A, Chen Z, Fridley BL, Permuth-Wey J, Tsai YY, Vierkant RA, Goode EL, Risch H, Schildkraut JM, Sellers TA, Barnholtz-Sloan J. European american stratification in ovarian cancer case control data: the utility of genome-wide data for inferring ancestry. PLoS ONE. 2012;7(5):e35235.

16. Santos NP, Ribeiro-Rodrigues EM, Ribeiro-Dos-Santos AK, Pereira R, Gusmão L, Amorim A, Guerreiro JF, Zago MA, Matte C, Hutz MH, Santos SE. Assessing individual interethnic admixture and population substructure using a 48-insertion-deletion (INSEL) ancestry-informative marker (AIM) panel. Hum Mutat. 2010;31(2):184–90.

17. Amador MA, Cavalcante GC, Santos NP, Gusmão L, Guerreiro JF, Ribeiro-dos-Santos Â, Santos S. Distribution of allelic and genotypic frequencies of IL1A, IL4, NFKB1 and PAR1 variants in Native American, African, European and Brazilian populations. BMC Res Notes. 2016. https://doi.org/10.1186/s13104-016-1906-9.

18. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. JAMA. 2002;288(7):872–81.

19. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. Cancer Incidence in five Continents. In: IARC Scientific Publication No. 155. International Agency for Research on Cancer; 2002. http://www.iarc.fr/en/publications/pdfs-online/epi/sp155/. Accessed 23 Feb 2017.

20. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, Rodabough RJ, Rosenberg CA, Taylor VM, Harris R, Chen C, Adams-Campbell LL, White E, Women's Health Initiative Investigators. Estrogen plus progestin and colorectal cancer in postmenopausal women. New Engl J Med. 2004;350(10):991–1004.

21. Chandanos E, Lagergren J. Oestrogen and the enigmatic male predominance of gastric cancer. Eur J Cancer. 2008;44(16):2397–403.

22. Nikfarjam Z, Massoudi T, Salehi M, Salehi M, Khoshroo F. Demographic survey of 4000 patients with 10 common cancers in north eastern Iran over the past three decades. Asian Pac J Cancer Prev. 2014;15(23):10193–8.

23. Jukic Z, Radulovic P, Stojković R, Mijic A, Grah J, Kruslin B, Ferencic Z, Fucic A. Gender difference in distribution of estrogen and androgen receptors in intestinal-type gastric cancer. Anticancer Res. 2017;37(1):197–202.

24. Pena SD, Di Pietro G, Fuchshuber-Moraes M, Genro JP, Hutz MH, Kehdy Fde S, Kohlrausch F, Magno LA, Montenegro RC, Moraes MO, de Moraes ME, de Moraes MR, Ojopi EB, Perini JA, Racciopi C, Ribeiro-Dos-Santos AK, Rios-Santos F, Romano-Silva MA, Sortica VA, Suarez-Kurtz G. The genomic ancestry of individuals from different geographical regions of Brazil is more uniform than expected. PLoS ONE. 2011. https://doi.org/10.1371/journal.pone.0017063.

25. Pereira L, Zamudio R, Soares-Souza G, Herrera P, Cabrera L, Hooper CC, Schneider S. Socioeconomic and nutritional factors account for the association of gastric cancer with Amerindian ancestry in a Latin American admixed population. PLoS ONE. 2012;7(8):41200.

26. Yamoah K, Johnson MH, Choeurng V, Faisal FA, Yousefi K, Haddad Z, Ross AE, Alshalafa M, Den R, Lal P, Feldman M, Dicker AP, Klein EA, Davicioni E, Rebbeck TR, Schaeffer EM. Novel biomarker signature that may predict aggressive disease in African American men with prostate cancer. J Clin Oncol. 2015;33(25):2789–96.

27. Yang JJ, Cheng C, Devidas M, Cao X, Fan Y, Campana D, Yang W, Neale G, Cox NJ, Scheet P, Borowitz MJ, Winick NJ, Martin PL, Willman CL, Bowman WP, Camitta BM, Carroll A, Reaman GH, Carroll WL, Loh M, Hunger SP, Pui CH, Evans WE, Relling MV. Ancestry and pharmacogenomics of relapse in acute lymphoblastic leukemia. Nat Genet. 2011;43(3):237–41.