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RESEARCH ARTICLE

ASSOCIATION OF CYTOCHROME P4502A VARIANTS WITH THE LIFE STYLE AND DIETARY HABIT INDUCED GASTRIC CANCER

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ABSTRACT

Background: Gastric malignancy constitutes the most common malignancy worldwide and continues to be an important contributor to the global burden of cancer. Gastric cancer is generally diagnosed in the advanced stages of the disease and exhibits an extremely poor prognosis, as patients with gastric cancer have unresectable, metastatic or recurrence. ***Methods:*** This case control type study was conducted in the department of General Surgery and Clinical Biochemistry, Sher e Kashmir Institute of Medical Sciences and SKIMS Medical College from June 2018 to September 2020 comprising of 82 cases of Gastric cancer. Data regarding socio-demographic characteristics like age, gender, place of residence, anthropometric measures, education and life style habits was collected from all cases. Qualitative and quantitative analysis of genomic DNA was done. ***Results:*** A total of 82cases were compared with 82 controls with male: female ratio of 2:1. The mean ages of cases and controls were 60.08 ±11.25years and 61.57 ±11.17years, respectively. In *CYP2A6a* genotype analysis, variant genotype, showed inverse but slightly insignificant association as compared to homozygous wild genotype (OR = 0.65; 95% CI = 0.42 – 1.06).*CYP2A6a* wild genotype showed an increased gastric cancer risk on limiting the analysis to smoking(OR = 2.66; 95% CI = 1.34 – 5.28).Positive history of any malignancy showed a stronger association with wild genotype carrying participants (OR = 8.87; 95% CI = 4.48 – 17.95) as compared to variant genotype (OR = 2.80; 95% CI = 1.15 – 7.75). In *CYP2A6b* genotype analysis, variant genotypes showed overall no change in the modification of gastric cancer risk (OR = 1.04;95% CI =0.67 – 1.60).*CYP2A6b*wild genotype harboring subjects showed a synergistically significant ESCC vulnerability in tobacco smokers (OR = 2.94; 95% CI = 1.25 – 6.91). However, with a family history of any malignancy, variant (OR = 8.21; 95% CI = 2.19 – 30.37) as well as wild (OR = 5.17; 95% CI = 2.76 – 9.66) genotype carrying subjects showed significantly a strong association towards gastric cancer development. Males turned out to be at higher risk than females on carrying a wild genotype (OR = 2.12; 95% CI = 1.00 – 4.78). **Conclusions:** The study suggests that polymorphism in major xenobiotic metabolizing enzyme CYP2A6, modify the gastric cancer risk.

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INTRODUCTION

Cancer constitutes a group of diseases with largely unknown etiology. Majority of global deaths are attributable to non-communicable diseases (1) and cancer is anticipated to rank as the major cause of worldwide mortality. Cancer alone is responsible for about 1 in every 6 deaths worldwide (2). By 2040, the global burden is expected to increase to 27.5 million new cancer cases and 16.3 million cancer deaths (3). Factors that contribute to differences in cancer incidence and mortality include variations in age structure, prevalence of the main risk factors for cancer, most of which are associated with the socioeconomic development & early detection tests. For example, cancers associated with infection are more prevalent in lower human development index (HDI) countries because of a higher rate of cancer-causing infections & lower socioeconomic development such as *Helicobacter pylori (H. pylori)* associated cancers like Gastric cancer. Infections are responsible for approximately 15% of cancers worldwide, the percentage is about three times higher in low and medium HDI countries than in very high-HDI countries (4). Gastric malignancy constitutes to be the most common malignancy worldwide and continues to be an important contributor to the global burden of cancer (5). Though, the rate of gastric cancer incidence and mortality rates are decreasing in developed world, it still remains the fifth most frequently diagnosed cancer (1033701 new cases in 2018) and the third leading cause of cancer death (782685 deaths) globally (6). This is attributed to improved socio-economic status (SES), better hygienic practices, change in environmental risk factors and more use of antibiotics (7).

In developing countries like India, due to poor socioeconomic status gastric malignancies continues to have higher incidence rates. Surgical resection and adjuvant chemotherapy or radiotherapy are used as therapeutic approaches for gastric cancer (8). In spite of advances in above techniques, the potential for this disease recurrence is still very high. Gastric cancer is generally diagnosed in the advanced stages of the disease and exhibits an extremely poor prognosis, as patients with gastric cancer have unresectable, metastatic or recurrence (9). Therefore, additional diagnostic and prognostic biomarkers are requisite for improving clinical outcomes. There is a dire requirement to extensively study the molecular mechanisms of gastric cancer. Nowadays the molecular epidemiology studies have focused on the status of polymorphic enzymes involved in xenobiotic metabolism. Though the influence of polymorphic forms of these XMEs in modulating the cancer risk could be small but it certainly does have a contributing role. Therefore, the genetic polymorphism analysis could allow us to have better understanding of the inherent predisposition of an individual to some types of specific cancers. activation and low detoxifying potentials could be expected to be more susceptible to cancer. Genetic polymorphisms of xenobiotic metabolizing enzymes (XMEs) like Cytochrome P450 *(CYP)1A1*, *CYP2E1*, *CYP2A6*, *CYP2A13*, *CYP2D6* etc. have been studied extensively and are associated with different malignancies like lung, gastric, esophagus, breast, etc. (10-14)

The study was conducted with the following main aims:

1. To weigh up the role of Phase-I xenobiotic metabolizing enzyme - *CYP2A6* in gastric cancer development in Kashmir.
2. Combinational effect of various variants of this gene i.e. gene-gene interactions on gastric cancer risk.
3. Modifying effect of various genotypes with environmental factors i.e. gene-environment interaction on gastric cancer risk in Kashmir.

METHODS

This study was a hospital-based case-control type conducted in the department of General and minimal invasive surgery and Clinical biochemistry, Sher-i-Kashmir Institute of Medical Sciences Srinagar, and SKIMS Medical College, Srinagar from June 2018 to September 2020 after receiving ethical clearance. Subjects with his to pathologically and endoscopically confirmed gastric cancer carcinoma were assessed and included as cases in the study. All the cases were more than 18 years old and had no history of any malignancy. While as controls are the non-malignant patients which are age (±5), sex and residence matching to their respective cases. Informed consent was obtained from all participants.

Inclusion criteria for cases

- Histopathologically and endoscopically proven cases of gastric cancer.
- Cases having Kashmir as their birth place.

Exclusion criteria for cases

- Patients who were suffering from any other malignancy also.
- Patients who had received chemotherapy for gastric cancer or any other malignancy.

Inclusion criteria for controls

- Absence of Gastric or any other malignancy.
- Not suffering from any such disease that affects the diet habits like diabetes mellitus.
- Subject belonging to Kashmir Valley.

Exclusion criteria for controls

- Individual suffering from any type of malignancy.
- Individual not belonging to Kashmir Valley.
- Individual having family history of any malignancy.

Data was collected from patients using a questionnaire that set forth information on known or apparently related factors of gastric cancer in detail, including information on socio-demographic characteristics like age, gender, place of residence, anthropometric measures, education and life style habits (tobacco smoking in different forms, snuff use and alcohol consumption). Qualitative and quantitative analysis of genomic DNA was done. Various Genotyping methods were used during study which include Primer designing, Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), Genotyping and restriction fragment length analysis. Statistical analysis was done using STATA software, version 14 (STATA Corp., College Station, TX, USA). Numbers and percentages by case status were calculated and presented for categorical variables. Conditional logistic regression models were used to calculate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs). Confounders were selected based on the previous knowledge on gastric cancer. However, for gene-gene or gene-environment interaction, analysis was restricted to wild genotype and a variant group (variant group has at least one defected or mutant allele i.e. heterozygous and homozygous mutant). Two-sided P values <0.05 were considered as statistically significant.

RESULTS

This study was conducted in the department of General and minimal invasive surgery and Clinical biochemistry, Sher-i-Kashmir Institute of Medical Sciences Srinagar, and SKIMS Medical College, Srinagar from June 2018 to September 2020.In this study 82 Gastric cancer cases and 82 controls, from Kashmir were recruited. These include 55 men and 27 women in each group with male to female ratio of 2:1. The mean ages (standard deviation) of cases and controls were 60.08 ±11.25years and 61.57 ±11.17years, respectively. In both groups 29(35.36%) patients belong to urban area and 53 (64.64%) belong to rural areas. There was history of smoking in 64(79.05%) in cases and 17(21.73%) in controls. 23 (28.04) patients had positive family history among cases and 04(04.88) had positive family history among controls. Salted tea use was seen in 80(97.56%) of cases and 74 (90.24%) of controls. Excessive use of red meat was seen in 38(46.34%) of cases and 32(39.02%) of controls. 40(45.78%) patients had excessive consumption of junk foods in cases and 42(51.22%) in controls. Excessive use of pickles was observed in 17(20.73%) of cases 19(23.17%) of controls. Pesticide exposure was seen in 35(42.68%) of cases and 30(36.58%) of controls (Table 1). Cases were uniformly distributed across different districts of Kashmir valley with 8 (09.75%) cases from Anantnag, 7(8.54%) from Bandipora, 7(8.54%) from Baramulla, 5(6.1%) from Budgam, 6(7.32%) from Ganderbal, 8(9.75%) from Kulgam, 4(4.88%) from Kupwara 7(8.54%) from Pulwama, 7(8.54%) from Shopian, 10 (12.20%) from Srinagar, 6(7.32%) from other areas (Table 2).

The CYP2A6a genotype analysis: PCR-RFLP results of *CYP2A6a*genotypes are shown in Figure 1 and analysis of these genotypes and their combinational effects on life style and different environmental exposures in modifying the gastric cancer risk are summarized in Table 3. Variant genotype, showed inverse but slightly insignificant association as compared to homozygous wild genotype (OR = 0.65; 95% CI = 0.42 – 1.06). On limiting the analysis to smoking, *CYP2A6a* wild genotype showed an increased gastric cancer risk (OR = 2.66; 95% CI = 1.34 – 5.28). Positive history of any malignancy showed a stronger association with wild genotype carrying participants (OR = 8.87; 95% CI = 4.48 – 17.95) as compared to variant genotype (OR = 2.80; 95% CI = 1.15 – 7.75). However, none of the genotypes or genotypic combinations of this gene could find any statistically significant relations with specific gender, neither was any gastric cancer modification seen by any of the genotypes with salted tea and meat consumption subjects.

Table 1. General characteristics of cases and controls

Characteristics	Cases n[a] (%)	Controls n[a] (%)	P value*
Total	82 (100)	82 (100)	>0.05
Age (Years mean ±S.D)	60.19±11.25	61.57±11.17	
Gender			
Male	55 (67.07)	55 (67.07)	<0.05
Female	27 (32.92)	27 (32.92)	
Place of residence			
Urban	29 (35.36)	29 (35.36)	>0.05
Rural	53 (64.64)	53 (64.64)	
Smoking			
Never	18 (21.95)	65 (79.27)	<0.05
Ever	64 (79.05)	17 (21.73)	
Family history			
Yes	23 (28.04)	04 (04.88)	<0.05
No	59 (71.96)	78 (95.12)	
Salt Tea			
Sweet or lepton tea	02 (03.44)	08 (09.76)	<0.05
Salted tea	80 (97.56)	74 (90.24)	
Red Meat			
Occasional (once a week)	44 (53.66)	50 (60.98)	>0.05
Excessive (2- 3 times a week)	38 (46.34)	32 (39.02)	
Junk food consumption			
Occasional or no use	15 (18.29)	25 (30.49)	P>0.05
Excessive usage	40 (45.78)	42 (51.22)	
Pickle Use			
No or occasional	57 (69.51)	55 (67.10)	>0.05
Excessive	17 (20.73)	19 (23.17)	
Pesticide Exposure			
No	45 (54.88)	48 (58.53)	>0.05
Yes	35 (42.68)	30 (36.58)	

Table 2. District wise distribution of cases

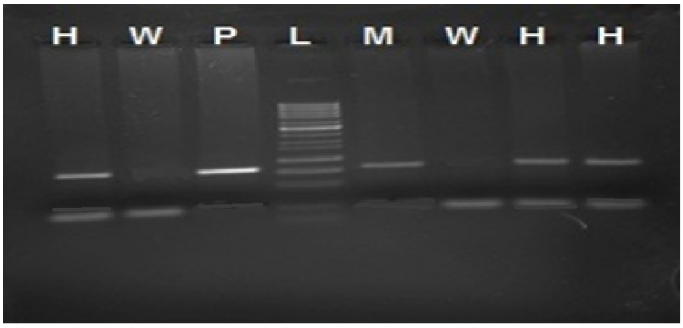
District	No. of Subjects (%)
Anantnag	08 (09.75)
Bandipora	07 (08.54)
Baramullah	07 (08.54)
Budgam	05 (06.10)
Ganderbal	06 (07.32)
Kulgam	08 (09.75)
Kupwara	04 (04.88)
Pulwama	07 (08.54)
Shopian	07 (08.54)
Srinagar	10 (12.20)
Other	06 (07.32)
Total	82 (100)

Table 3. OR and 95% CI of *CYP2A6a*genotypes in GC cases and controls stratified by smoking, family history and salted tea

Genotypes/variable	Cases N (%)	Controls N (%)	UA OR[1](95%CI)	A OR[2](95% CI)
Total	82(100)	82(100)	-	-
Wild	67 (81.70)	62 (75.61)	Referent	Referent
Heterozygous	13 (15.85)	19 (23.17)	0.57 (0.41 – 0.81)	0.61 (0.33 – 1.15)
Mutant	02 (2.43)	01 (1.21)	1.07 (0.44 – 2.60)	1.85 (0.35 - 9.73)
(Variant)[3]	15 (18.29)	20 (24.39)	0.61 (0.44 – 0.85)	0.65 (0.42 – 1.06)
Tobacco Smoking				
Variant + never smokers	05 (6.10)	10 (12.19)	Referent	Referent
Variant + ever smokers	09 (10.97)	10 (12.19)	1.86 (1.01 – 3.42)	1.60 (0.70 – 3.64)
Wild + never smokers	21 (25.61)	31 (37.80)	1.27 (0.77 – 2.10)	1.36 (0.69 – 2.68)
Wild + ever smokers	46 (56.10)	31 (37.80)	3.27 (1.98 – 5.41)	2.66 (1.34 – 5.28)
Salted tea				
Variant + other tea	01 (1.21)	01 (1.21)	Referent	Referent
Variant + salted tea	14 (17.07)	20 (24.39)	2.76 (0.30 – 25.22)	2.26 (0.22 – 23.69)
Wild + other tea	01 (1.22)	03 (3.66)	2.01 (0.19 – 21.18)	2.41 (0.17 – 33.58)
Wild + salted tea	66 (80.49)	58 (70.73)	4.45 (0.49 – 40.17)	3.42 (0.33 – 34.91)
Family history of any malignancy				
Variant + no FH	09 (10.97)	17 (23.20)	Referent	Referent
Variant + yes FH	05 (6.10)	02 (2.44)	3.88 (1.85 – 8.12)	2.80 (1.15 – 7.75)
Wild + no FH	44 (53.66)	57 (69.12)	1.46 (0.99 – 2.15)	1.34 (0.83 – 2.16)
Wild + yes FH	24 (29.27)	06 (07.32)	9.72 (5.47 – 17.26)	8.87 (4.48 – 17.95)
Gender				
Variant + male	14 (17.07)	22 (26.82)	Referent	Referent
Wild + male	68 (82.93)	60 (73.17)	1.84 (1.18 – 2.54)	1.39 (0.58 – 3.30)
Variant + female	15 (18.29)	17 (23.53)	Referent	Referent
Wild + female	67 (81.70)	65 (79.27)	1.39 (0.85 – 2.28)	1.42 (0.59 – 3.41)

Abbreviations: CI= confidence interval; FH= family history of any cancer; [1]UAOR= Unadjusted odds ratio; [2]AOR= adjusted odds ratio; [3] variant indicates combined genotype, which has at least one variant allele. ORs (95% CIs) were obtained from conditional logistic regression models. Numbers may not add up to the total numbers due to missing data in some variables. [2]Adjusted for age, gender, place of residence, tobacco smoking, family history of any cancer and salted tea. The variable under consideration was not additionally adjusted for it.

The *CYP2A6b* genotype analysis: Genotyping of *CYP2A6b*by PCR-RFLP method is shown in figure 2. The genotype analysis separately as well as in combination with positive gastric cancerrisk factors for their association if any, with gastric cancerpredisposition are described in Table 4. The variant genotypes showed overall no change in the modification of gastric cancerrisk (OR = 1.04;95% CI =0.67 – 1.60). Among the different risk determinants, *CYP2A6b*wild genotype harboring subjects showed a synergistically significant ESCC (Esophageal squamous cell carcinoma) vulnerability in tobacco smokers (OR = 2.94; 95% CI = 1.25 – 6.91). However, with a family history of any malignancy, variant (OR = 8.21; 95% CI = 2.19 – 30.37) as well as wild (OR = 5.17; 95% CI = 2.76 – 9.66) genotype carrying subjects showed significantly a strong association towards gastric cancer development. Importantly, as compared to females, males turned out to be at higher risk than females on carrying a wild genotype (OR = 2.12; 95% CI = 1.00 – 4.78). Salted tea and meat consumption could not show any alterations on the development of gastric cancer.



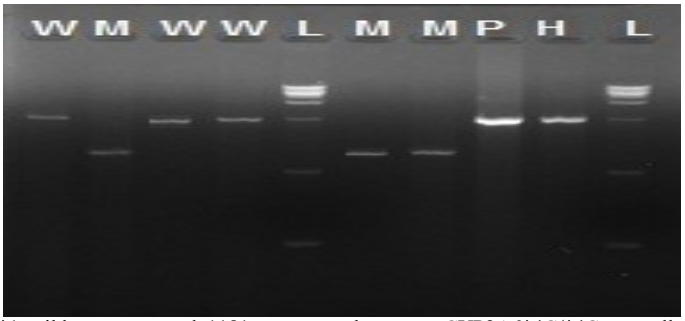
"P" is the PCR product, "W" represents the 116bp and 99bp*CYP2A6*1/*1* (homozygous wild) genotype; "M" represents the undigested parent band (215bp) indicating the*CYP2A6*1/*1* (homozygous mutant) genotype;"H" is the *CYP2A6*1/*6* (heterozygous) genotype which all the three bands i.e215bp, 116bp and 99bp and "L" represent the 50bp marker.

Figure 1. PCR-RFLP analysis of CYP2A6a polymorphism

Table 4. OR and 95% CI of *CYP2A6b*genotypes in ESCC cases and controls stratified by smoking, family history and salted tea

Genotypes/variable	Cases N (%)	Controls N (%)	UA OR[1](95% CI)	A OR[2](95% CI)
Total	82 (100)	82 (100)	-	-
Wild	64 (78.05)	61 (74.39)	Referent	Referent
Heterozygous	15 (18.29)	17 (23.20)	0.76 (0.55 – 1.04)	0.58 (0.32 – 1.09)
Mutant	02 (2.43)	04 (4.87)	1.02 (0.48 – 2.18)	1.79 (0.50 – 6.51)
(Variant)[3]	17 (20.73)	21 (25.61)	0.78 (0.58 – 1.06)	1.04 (0.67 – 1.60)
Tobacco smoking				
Variant + never smokers	08 (9.76)	10 (12.19)	Referent	Referent
Variant + ever smokers	10 (12.20)	11 (13.41)	1.39 (0.79 – 2.44)	1.36 (0.49 – 2.44)
Wild + never smokers	19 (23.18)	32 (39.02)	0.77 (0.49 – 1.24)	0.85 (0.35 – 2.04)
Wild + ever smokers	45 (51.65)	29 (35.36)	2.24 (1.41 – 3.54)	2.94 (1.25 – 6.91)
Salted tea				
Variant + no ST	0 (0.00)	01 (1.22)	Referent	Referent
Variant + yes ST	107 (21.75)	21 (25.61)	0	0
Wild + no ST	01 (1.22)	03 (3.66)	0	0
Wild + yes ST	63 (76.82)	58 (70.73)	0	0
Family history of any malignancy				
Variant + no FH	12 (14.63)	20 (24.39)	Referent	Referent
Variant + yes FH	06 (7.31)	01 (1.21)	10.63 (3.92 – 28.87)	8.21 (2.19 – 30.73)
Wild + no FH	41 (50.00)	55 (67.07)	1.30 (0.90 – 1.87)	1.01 (0.64 – 1.59)
Wild+ yes FH	23 (28.05)	31 (07.31)	6.44 (3.84 – 10.77)	5.17 (2.76 – 9.66)
Gender				
Variant + male	18 (21.95)	23 (28. 05)	Referent	Referent
Wild + male	64 (78.05)	59 (71.95)	1.50 (0.99 – 2.66)	2.12 (1.00 – 4.78)
Variant + female	18 (21.95)	19 (23.17)	Referent	Referent
Wild + female	64 (78.05)	63 (76.835)	1.03 (0.65 – 1.63)	1.04 (0.42 – 2.59)

Abbreviations: CI= confidence interval; FH= family history of any cancer
[1]UAOR= Unadjusted odds ratio; [2]AOR= adjusted odds ratio; [3] variant indicates combined genotype, which has at least one variant allele.
ORs (95% CIs) were obtained from conditional logistic regression models. Numbers may not add up to the total numbers due to missing data in some variables.
[2]Adjusted for age, gender, place of residence, tobacco smoking, family history of any cancer and salted tea. The variable under consideration was not additionally adjusted for it.



"W" represents the 1961bpCYP2A6*1/*1 wild genotype and 1181 represent the mutantCYP2A6*4C/*4C as well as the heterozygous CYP2A6**1/**4C genotype, depending upon the type of Primer pairs and "L" here represent the Ikb marker.

Figure 2. PCR-RFLP analysis of CYP2A6b polymorphism

DISCUSSION

Worldwide gastric cancer represents as one of the most common malignancies and continues to be an important contributor to the global burden of cancer deaths. In spite of advanced techniques, the potential for this disease recurrence is still very high. Therefore, additional diagnostic and prognostic biomarkers are requisite for improving clinical outcomes. The present study comprises of 82 (n=82) histopathologically confirmed gastric cancer cases and controls. Gender wise males comprise the maximum representation of cases and higher numbers of cases were older in age, living in rural areas and were physically very active. Most number of subjects were active smokers irrespective of their gender. *H. Pylori* infection seems to be less frequent among gastric cancer subjects in study population. Wild genotype of the study gene was significantly associated with the genesis of gastric cancer. With respect to different epidemiological and clinico-pathological factors there was an increased gastric cancer risk among subjects who were active smokers and harboured wild genotypes of the study gene. Variant genotypes of *CYP2A6*showed an inverse association with gastric cancer separately as well as when analysed together. The wild genotypes of *CYP2A6*gene, showed an increased risk with gastric cancer risk determining factors.

Our study is in agreement with the previous studies where increased cancer risk was found in wild genotypes as compared to variant genotypes of*CYP2A6*in esophageal (15) and lung malignancies (10,16).The synergistic association of the *CYP2A6* wild genotype on risk of gastric cancer in presence of smoking, could reflect the biological feature of *CYP2A6*variant, which exhibits a decreased catalytic efficiency toward NNK (Nicotine derived nitrosoamine ketone) as compared with that of *CYP2A6 wild genotype*. The retention of protective effect due to combination of *CYP2A6a* with *CYP2Ab* gene variant in our study is consistent previous studies. (17) In our study there was a very strong association of specific genotypes (wild or variant) with family history. Although, family history itself is having a strong association with the development of gastric cancer, reports from high-risk areas have suggested a high level of genetic instability in gastric cancer and have indicated that certain chromosomes may harbor a tumor susceptibility gene which could run in families. Some recent studies were consistent with these findings.(18-20) However, presence of any malignancy among family members may not always reflect shared genetic susceptibility; but could also be due to sharing environmental and lifestyle risk factors similar with other family members over a long period of time(21).

In our study, most of the vulnerable gene variants were more common among males as compared to females. The combination of smoking in males with susceptible gene variants put them at higher risk and hence male predominance towards gastric cancer. Reduction in the consumption of smoking among the carriers of variant alleles of *CYP2A6*gene (22) could also be the probable reason for male dominance in *CYP2A6* wild genotype carrying subjects and hence dominant risk than female subjects. In our study, small percentage of gastric cancer subjects were infected with *H. Pylori*. Though the possible role of which is yet to be known but correlation between gastric cancer and *H. Pylori* could be a possible target of gastric cancer intervention (23,24).In our study, there was higher prevalence of gastric cancer among very active subjects. Though, most of the studies are contradictory to this finding but a recent study from Kashmiri population showed a higher risk of esophageal squamous cell carcinoma risk among subjects who are physically more active (25). The plausible reason for this finding could be linked to very high energy demand that warrants excessive aerobic metabolism. During excessive respiration there is almost a 200-fold uptake and utilization of muscle oxygen, which results in increased flux of electron through the rapidly respiring mitochondria and possibility of electron leakage and subsequent reactive oxygen species (ROS) production, which is over and above the capacity of the antioxidant scavenging system of the cell (26-28).

CONCLUSION

The study suggests that polymorphism in major xenobiotic metabolizing enzyme *CYP2A6,* modify the gastric cancer risk. In combination with risk predisposing genotypes, potent environmental risk factors particularly smoking, synergistically enhance the gastric cancer risk in our population. Similarly, the risk susceptible genotypes in presence of family history of any cancer, have added effects on gastric malignancy

Declarations

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

Ariyoshi, N., *et al*., Genetic polymorphism of CYP2A6 gene and tobacco-induced lung cancer risk in male smokers. Cancer Epidemiol Biomarkers Prev, 2002. 11(9): p. 890-4.

Blaser, M.J. and S. Falkow, What are the consequences of the disappearing human microbiota? Nature Reviews Microbiology, 2009. 7(12): p. 887-894.

Bollschweiler, E., *et al*., Treatment of early gastric cancer in the Western World. World Journal of Gastroenterology: WJG, 2014. 20(19): p. 5672.

Bray, F., *et al*., Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 2018. 68(6): p. 394-424.

Cheung, W.Y., *et al*., Single nucleotide polymorphisms in the matrix metalloproteinase gene family and the frequency and duration of gastroesophageal reflux disease influence the risk of esophageal adenocarcinoma. Int J Cancer, 2012. 131(11): p. 2478-86.

Chevion S, M.D., Heled Y, *et al*., Plasma antioxidant status and cell injury after severe physical exercise. Proceedings of the National Academy of Sciences, 2003. 100(9): p. 5119-23.

Davies KJ, Q.A., Brooks GA, Packer L, Free radicals and tissue damage produced by exercise. Biochemical and biophysical research communications, 1982. 107(4): p. 1198-205.

Ding, K., *et al*., GSE1 predicts poor survival outcome in gastric cancer patients by SLC7A5 enhancement of tumor growth and metastasis. Journal of Biological Chemistry, 2018. 293(11): p. 3949-3964.

Fujieda, M., *et al*., Evaluation of CYP2A6 genetic polymorphisms as determinants of smoking behavior and tobacco-related lung cancer risk in male Japanese smokers. Carcinogenesis, 2004. 25(12): p. 2451-8.

Gonzalez CA, M.F., Buissonniere A, *et al*, Helicobacter pylori infection assessed by ELISA and by immunoblot and non cardica gastic cancer risk in a prospective study: the Eurgast-EPIC project. Ann Onco, 2012. 23(5): p. 1320-1324.

Guo, W., *et al*., Decreased expression of WWOX in the development of esophageal squamous cell carcinoma. Mol Carcinog, 2013. 52(4): p. 265-74.

Humans., I.W.G.o.t.E.o.C.R.t., Lyon, 7-14 June 1994. Schistosomes, Liver Flukes and Heli-cobacter pylori. IARC Monogr Eval Carcinog Hum, 1994. 61: p. 1-241.

Idrees Ayoub Shah, G.A.B., Rumaisa Rafiq, Najma Nissa, Mansha Muzaffar, Malik Tariq Rasool, Abdul Rouf Banday, Mohd Maqbool Lone, Gulam Nabi Lone, Paolo Boffetta, Nazir Ahmad Dar, Strenous occupational physical activity-potential association with esophageal squamous cell carcinoma risk. Cold spring harbor Laboratory BioRxiv 2019.

Islami, F., *et al*., Exposure to Polycyclic Aromatic Hydrocarbons Among Never Smokers in Golestan Province, Iran, an Area of High Incidence of Esophageal Cancer - a Cross-Sectional Study with Repeated Measurement of Urinary 1-OHPG in Two Seasons. Front Oncol, 2012. 2: p. 14.

J, F., World Health Organization International Agency for Research on Cancer. GLOBOCAN 2018, 2018.

Kato, I., S. Tominaga, and T. Suzuki, Correspondence in cancer history between husbands and wives. Jpn J Cancer Res, 1990. 81(6-7): p. 584-9

Khlifi, R., *et al*., Association of CYP1A1 and CYP2D6 gene polymorphisms with head and neck cancer in Tunisian patients. Mol Biol Rep, 2014. 41(4): p. 2591-600.

Kumondai, M., *et al*., CYP2A13 Genetic Polymorphisms in Relation to the Risk of Bladder Cancer in Japanese Smokers. Biol Pharm Bull, 2016. 39(10): p. 1683-1686.

Miyamoto M, U.Y., Dosaka-Akita H, Sawamura Y, Yokota J, Kunitoh H, *et al*. , CYP2A6 gene deletion reduces susceptibility to lung cancer. . Biochem Biophys Res Commun, 1999. 261: p. 658-60.

Munafo, M., *et al*., The genetic basis for smoking behavior: a systematic review and meta-analysis. Nicotine Tob Res, 2004. 6(4): p. 583-97.

Organization, W.H., Global Health Observatory. Geneva: World Health Organization. 2018

Plummer, M., *et al*., Global burden of cancers attributable to infections in 2012: a synthetic analysis. The Lancet Global Health, 2016. 4(9): p. e609-e616.

Reid MB, H.K., Franchek KM, Valberg PA, Kobzik L, West MS, Reactive oxygen in skeletal muscle. I. Intracellular oxidant kinetics and fatigue in vitro. Journal of applied physiology (Bethesda, Md : 1985), 1992. 73(5): p. 1797-804.

Sjodin B, H.W.Y., Apple FS Biochemical mechanisms for oxygen free radical formation during exercise. Sports medicine (Auckland, NZ), 1990. 10(4): p. 236-54.

Society, A.C., Global Cancer Facts & Figures 4th Edition. 2018.

Tsukino, H., *et al*., Effects of cytochrome P450 (CYP) 2A6 gene deletion and CYP2E1 genotypes on gastric adenocarcinoma. Int J Cancer, 2002. 100(4): p. 425-8.

Van Cutsem, E., *et al*., Gastric cancer. The Lancet, 2016. 388(10060): p. 2654-2664.

Wen Tan, G.-F.C., De-Yin Xing, Chun-Ying Song, Fred F. Kadlubar and Dong-Xin Lin, Frequency Of CYP2A6 gene deletion and its relation to risk of lung and esophageal cancer in the Chinese Populations. Int. J. Cancer, 2001. 95: p. 96-101

Zhou, R.M., *et al*., PLC-epsilon1 gene polymorphisms significantly enhance the risk of esophageal squamous cell carcinoma in individuals with a family history of upper gastrointestinal cancers. *Arch Med Res,* 2012. 43(7): p. 578-84.

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