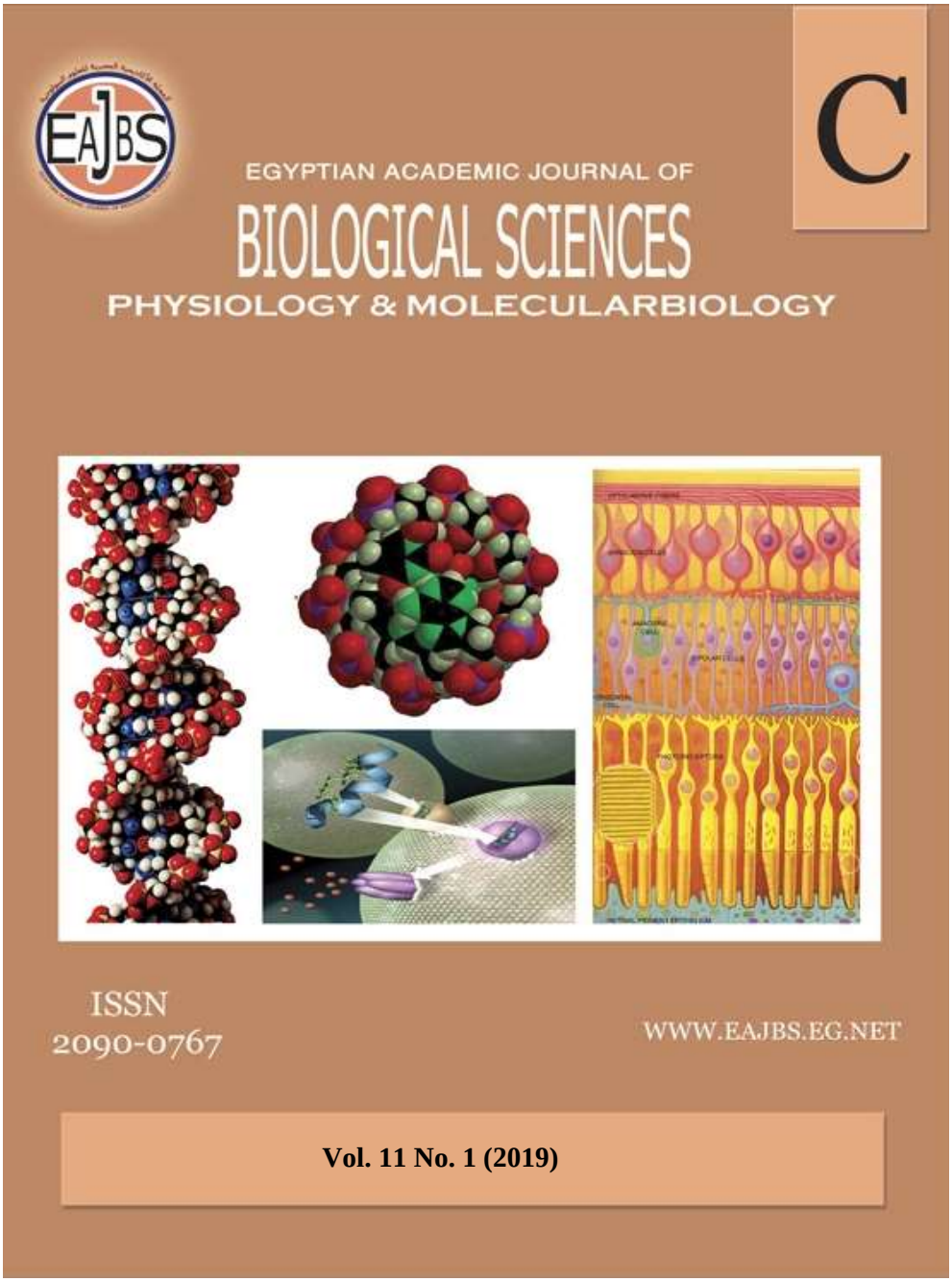

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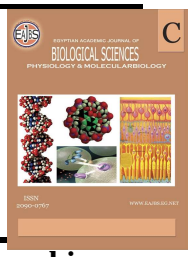

The Variant Allele Frequency of p53 Arg72Pro (rs1042522) Polymorphism: A Major Breast Cancer Susceptibility Factor in Saudi and Other Ethnic Groups

Naseem Akhter
Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University, Albaha- KSA
E.Mail : naseem.du@gmail.com; nakhter@bu.edu.sa

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ABSTRACT

Introduction: Codon 72 polymorphism (G> C; Arg> Pro) in p53, an important tumor suppressor gene, contribute to an elevated risk of many cancers including breast cancer. p53 alterations negatively impact cell cycle arrest, DNA damage repair, and apoptosis leading to cancer onset and development. The occurrence of *p53* exon 4 G>C polymorphism is different in diverse populations, but the information regarding its allelic distribution in the Saudi population is lacking.

Methods: PUBMED (Medline), the web of science and google database were used to search epidemiological studies conducted globally to compare the frequency distribution of variant allele in the Saudi population with that of diverse ethnic groups.

Results: The frequency of *p53* exon 4 variant allele (G) was found to be 51% in the Saudi population. A significantly different variant allele frequency was found for Japan ($p<0.0001$), Jordan ($p=0.0002$), China ($p<0.0001$), Iran ($p<0.0001$), India ($p=0.0023$), Turkey ($p<0.0001$) and Taiwan (0.0307) ethnic populations, upon comparison of Saudi Arabian frequency with that of other Asian populations. Furthermore, a significantly different MAF was found in every study in the Caucasian group except for Greece ($p=0.1451$) ethnic populations, when compared with Saudi Arabian frequency.

Conclusions: The allelic frequency distribution analysis of *p53* exon4 Arg72Pro SNP in Saudi population showed a unique pattern, significantly different from many populations in Asian subgroup and all but one populations in the Caucasian subgroup. The findings may help in large scale population screening for this cancer susceptibility factor.

INTRODUCTION

Breast cancer causes high morbidity and mortality in females, globally (Parkin *et al.* 2001). Age of breast cancer occurrence in the Saudi population is highly skewed when compared with the USA. The number of breast cancers developed before the age of 40 in the Saudi population is almost four times that of USA (Ezzat *et al.* 1999). An early study has shown that ≤ 40 years of age is an independent risk factor for relapse in operable Saudi breast cancer patients (Elkum *et al.* 2007).

The global cancer incidence variation is primarily caused by genetic and environmental factors including ionizing radiations causing DNA damage and the loss of genomic integrity coupled with defective DNA repair system leading to elevated cancer risk.

Genetic changes impacting host DNA repair system significantly contribute to cancer susceptibility (de Jong *et al.* 2002)**.** Single-nucleotide polymorphisms (SNPs) are the single base changes present in at least 1% population (Collins *et al.* 1999), having a minor individual effect but the additive impact of multiple SNPs over cancer onset and progression makes them a critical target for study (Perera and Weinstein 2000).

SNPs are known to reduce DNA repair capacity (DRC) rendering the host increasingly susceptible for cancer when compared with the population devoid of them (Wu *et al.* 2004).

The reports on inter-individual variations in diverse populations are valuable in identifying candidate susceptibility alleles/ genotype contributing to carcinogenesis.

A number of risk factors like genetic susceptibility and estrogen hormone exposure are associated with breast carcinogenesis, however, the precise molecular mechanisms remain to be elucidated (Veronesi *et al.* 2005; Yager and Davidson 2006).

Early reports suggest that tumorigenesis is an outcome of several changes in oncogenes and tumor suppressor genes (Porter-Jordan and Lippman 1994; Bartkova *et al.* 1995). Alterations in p53, regarded as the guardian of the genome, not only compromises a range of critical cellular processes including cell cycle arrest, DNA damage repair, apoptosis but may also promote cancer development (Bennett *et al.* 1999; Vogelstein *et al.* 2000; Brosh and Rotter 2009; Li *et al.* 2011). Not surprisingly, multiple reports show more than 50% of human tumors harboring p53 gene mutations (Bennett *et al.* 1999).Of 11 exons, the p53 tumor suppressor gene has the codon 72 polymorphism (rs1042522) located in exon 4 with a CGC to CCC transition, resulting in an arginine to proline amino acid substitution in amino acid position 72 (Arg72Pro). The two polymorphic variants have dissimilar biological effects and have been found linked with the carcinogenesis (Harris *et al.* 1986; Dumont *et al.* 2003; Zhou *et al.* 2007). This SNP, 1 among 25 SNPs, has the undetectably small individual effect but confers significant risk for breast cancer, cumulatively (Johnson *et al.* 2007).

SNPs have the potential to be used as next generation biomarkers, identifying the loci associated with

intricate diseases. They can also be used to study genetic variations in drug metabolic pathways influencing individual responses to drugs (Lander and Schork 1994; Lander 1996; Risch and Merikangas 1996) (Kruglyak 1997).

The present study investigated the frequency distribution of p53 exon 4 Arg72Pro, CGC to CCC transition, rs1045522 polymorphism in normal healthy individuals, age and sex-matched with breast cancer cases, from Saudi Arabia. The frequency distribution of the Saudi population was compared with diverse epidemiologic studies stratified along the Asian and Caucasian race performed globally. The findings of the study may facilitate the large scale population screening based on the prevalence of susceptibility factor.

MATERIALS AND METHODS

Selection of Studies:

PUBMED (Medline), the web of science and google database were used for research publications containing keywords "p53", "Arg72Pro", rs1045522 and ''polymorphism''. The inclusion criteria required case control or cohort studies conducted with human subjects, showing genotype frequencies for the control population.

Details like the name of the first author, year of publication, the number and race of the controls, inclusion/ exclusion criteria along with allelic/ genotypes distribution among controls were extracted.

Statistical Analysis:

MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium) was used for Pearson's $\chi 2$ and Hardy-Weinberg equilibrium test. Statistically, significant difference was considered at p-value ≤ 0.05.

RESULTS

Five studies (Siraj *et al.* 2008; Al-Hadyan *et al.* 2012; Al-Qasem *et al.* 2012; Alshatwi *et al.* 2012; Alsbeih *et al.* 2013) were used to extract data about the prevalence of *p53* exon 4 Arg72Pro polymorphism in Saudi Arabian population. Twenty (Kawajiri *et al.* 1993; Khaliq *et al.* 2000; Li *et al.* 2002; Huang *et al.* 2003; Katiyar *et al.* 2003; Mahasneh and Abdel-Hafiz 2004; Noma *et al.* 2004; Siddique *et al.* 2005; Ma *et al.* 2006; Gochhait *et al.* 2007; Khadang *et al.* 2007; Zhang *et al.* 2007; Lum *et al.* 2008; Rajkumar *et al.* 2008; Singh *et al.* 2008; Kazemi *et al.* 2009; Song *et al.* 2009; Kara *et al.* 2010; Koh *et al.* 2011; Leu *et al.* 2011) and twenty eight (Sjalander *et al.* 1996; Weston and Godbold 1997; Wang-Gohrke *et al.* 1998; Papadakis *et al.* 2000; Wang-Gohrke *et al.* 2002; Suspitsin *et al.* 2003; Menzel *et al.* 2004; Kalemi *et al.* 2005; Ohayon *et al.* 2005; Tommiska *et al.* 2005; Baynes *et al.* 2007; Franekova *et al.* 2007; Garcia-Closas *et al.* 2007; Johnson *et al.* 2007; Schmidt *et al.* 2007; Sprague *et al.* 2007; Cavallone *et al.* 2008; Costa *et al.* 2008; De Vecchi *et al.* 2008; Nordgard *et al.* 2008; Akkiprik *et al.* 2009; Denisov *et al.* 2009; Henriquez-Hernandez *et al.* 2009; Hrstka *et al.* 2009; Lang *et al.* 2009; Bisof *et al.* 2010; Ebner *et al.* 2010; Kara *et al.* 2010) studies were included for the comparative analysis of the Saudi population with Asian and Caucasian populations, respectively.

Two studies in the Saudi Arabian population were not found consistent with the Hardy–Weinberg equilibrium (HWE) analysis. The genotype distribution of *p53* (exon 4, Arg > Pro) in Saudi population showed the minor allele frequency (MAF) at 51% (Table 1).

Table 1. Observed and expected genotypic frequencies of p53 Arg72Pro polymorphism in the control group

S. no.	Study	Genotype observed (n) %			Genotype Expected (n)%			Chi square	p-value (HWE)
		Arg/Arg (GG)	Arg/Pro (GC)	Pro/Pro (CC)	Arg/Arg (GG)	Arg/Pro (GC)	Pro/Pro (CC)		
1.	Alsbeih et al., 2013	22	52	26	23	50	27	0.17	0.68
2.	Al Qasem et al, 2012	19	65	24	55	44	9	22.56	0.00*
3.	Alshatwi et al., 2012	32	51	17	33	49	18	0.19	0.66
4.	Al-Hadyan et al., 2012	71	110	70	63	125	62	3.83	0.05*
5.	Siraj et al., 2008	68	105	52	65	112	49	0.86	0.35
	Cumulative	212	383	189	208	390	185	0.26	0.61

HWE, Hardy Weinberg Equilibrium; GC, Arg/Pro; CC, Pro/Pro; GG, Arg/Arg;*not consistent with HWE.

The genotypic (Arg/ Arg, Arg/ Pro and Pro/ Pro) and allelic frequency distribution of the Arg72Pro polymorphism among Asian and Caucasian populations showed diverse minor allele frequency (Table 2 and 3).

Table 2. Genotype and allele frequency distribution of p53 Arg72Pro gene variant in various populations of Asian ethnicity and p-values in comparison to Saudi Arabian population

S. no.	Study	Country	(n)	Genotype			P value	MAF (%)
				Arg/Arg	Arg/Pro	Pro/Pro		
1.	Table 1 (5 studies)	Saudi Arabia	784	212	383	189	Ref	51
2.	Kawajiri et al, 1993	Japan	347	38	165	144	<.0001	35
3.	Khaliq et al, 2000	Pakistan	689	177	321	191	0.2865	49
4.	Li et al, 2002	China	50	14	26	10	0.8025	54
5.	Huang et al, 2003	Japan	282	30	138	114	<.0001	35
6.	Katiyar et al, 2003	India	41	8	24	9	0.4404	49
7.	Mahasneh et al, 2004	Iran	136	29	51	56	0.0002	40
8.	Noma et al, 2004	Japan	218	31	76	111	<.0001	32
9.	Siddique et al, 2005	China	265	38	120	107	<.0001	37
10.	Ma et al, 2006	China	472	100	222	150	0.0048	45
11.	Gochhait et al, 2007	India	333	97	160	76	0.7558	53
12.	Khadang et al, 2007	Iran	205	40	90	75	0.0009	41
13.	Rajkumar et al, 2008	India	500	141	224	135	0.3296	51
14.	Zhang et al, 2007	China	167	33	87	47	0.1333	46
15.	Lum et al, 2008	China	80	13	38	29	0.0233	40
16.	Singh et al, 2008	India	105	12	64	29	0.0023	42
17.	Kazemi et al, 2009	Iran	57	0	45	12	<.0001	39
18.	Song et al, 2009	China	1077	220	508	349	<.0001	44
19.	Koh et al, 2011	China	643	179	319	145	0.7827	53
20.	Kara et al, 2010	Turkey	169	72	80	17	<.0001	66
21.	Leu et al, 2011	Taiwan	321	104	129	88	0.0307	52

Table 3. Genotype and allele frequency distribution of p53 Arg72Pro gene variant in various populations of Caucasian ethnicity and p-values in comparison to Saudi Arabian population

S.no.	Study	Country	(n)	Genotype			P-value	MAF (%)
				Arg/Arg	Arg/Pro	Pro/Pro		
1.	Table 1 (5 studies)	Saudi Arabia	784	212	383	189	Ref	51
2.	Sjalander et al, 1996	Sweden	689	61	253	375	<.0001	27
3.	Weston et al, 1997	Mixed	117	3	42	72	<.0001	21
4.	Wang-Gohrke et al, 1998	Germany	305	21	117	167	<.0001	26
5.	Papadakis et al, 2000	Greece	59	6	41	12	0.0041	45
6.	Wang-Gohrke et al, 2000	Germany	543	40	203	300	<.0001	26
7.	Suspitsin et al, 2000	Russia	393	27	159	207	<.0001	27
8.	Menzel et al, 2000	Austria	302	30	114	158	<.0001	29
9.	Kalemi et al, 2005	Greece	51	9	32	10	0.1451	49
10	Ohayon et al, 2005	Israel	167	19	94	54	<.0001	40
11	Tommiska et al, 2005	Finland	733	52	278	403	<.0001	26
12	Baynes et al, 2007	Britain	2197	166	854	1177	<.0001	27
13	Garcia-Closas et al, 2007	Norway/ Poland	3251	228	1249	1774	<.0001	26
14	Franeková et al, 2007	Slovakia	156	9	55	92	<.0001	23
15	Johnson et al, 2007	Britain	2462	183	925	1354	<.0001	26
16	Schmidt et al, 2007	Mixed	6849	511	2677	3661	<.0001	27
17	Sprague et al, 2007	USA	1854	129	704	1021	<.0001	26
18	Akkiprik et al, 2009	Turkey	107	12	49	46	<.0001	34
19	Cavallone et al, 2008	French-Canadian	112	9	46	57	<.0001	29
20	Costa et al, 2008	Portugal	646	54	212	380	<.0001	25
21	De Vecchi et al, 2008	Italy	352	14	131	207	<.0001	23
22	Nordgard et al, 2008	Norway	121	14	34	73	<.0001	26
23	Lang et al, 2009	Sweden	142	5	58	79	<.0001	24
24	Denisov et al, 2009	Russia	275	29	99	147	<.0001	29
25	Henríquez et al, 2009	Spain	295	28	100	167	<.0001	26
26	Hrstka et al, 2009	Czech	108	45	8	55	<.0001	45
27	Bisof et al, 2010	Croatia	108	5	42	61	<.0001	24
28	Ebner et al, 2010	Germany	254	14	103	137	<.0001	26
29	Kara et al, 2010	Turkey	169	17	80	72	<.0001	34

A significantly different MAF was found for Japan ($p<0.0001$), Jordan ($p=0.0002$), China ($p<0.0001$), Iran ($p<0.0001$), India ($p=0.0023$), Turkey ($p<0.0001$) and Taiwan (0.0307) ethnic populations, upon comparison of Saudi Arabian frequency with that of other Asian populations.

Interestingly, a significantly different MAF was found in every study in the Caucasian group except for Greece ($p=0.1451$) ethnic populations, while compared with Saudi Arabian frequency.

DISCUSSION

The genes and/ or their polymorphisms identified through genome-wide/ genetic association studies have markedly influenced the development of effective disease prevention programs as well as their novel treatment (Pearson and Manolio 2008). p53 plays an important role in many cellular functions like gene transcription, DNA repair and programmed cell death and the SNPs of p53 likely have an association with cancer susceptibility including breast cancer (Zhang *et al.* 2010).

Among many SNPs of p53, Arg72Pro seems associated with an elevated breast cancer risk (Sjalander *et al.* 1996; Kalemi *et al.* 2005; Gochhait *et al.* 2007; Akkiprik *et al.* 2009). However, many reports also show no such association (Tommiska *et al.* 2005; Baynes *et al.* 2007; Khadang *et al.* 2007; Schmidt *et al.* 2007). The findings clearly suggest that susceptibility factor is influencing studied individuals and populations differently.

The discrepant findings are likely based on the human genome diversity, resulting from multiple evolutionary and demographic events like migration, isolation and natural selection, impacting individual susceptibility variably across the populations (Balaresque *et al.* 2007; Barbujani and Colonna 2010; Henn *et al.* 2012). Recent evidence showing that SNPs may act as candidate genes significantly contribute to the cancer susceptibility, emphasizes the importance of information about the prevalence of variant genetic alleles in diverse populations.

Early reports included in the current study to extract data of normal healthy subjects show significant differences in the distribution of p53 gene Arg72Pro polymorphism among diverse populations globally, stratified along Asian and Caucasian subgroups. Further, the present study showed significantly different MAF of p53 Arg72 SNP distribution in Saudi population when compared with other ethnic groups. Among Asian subgroup, significantly different MAF was found in Japan, Jordan, China, Iran, India, Turkey and Taiwan ethnic populations, when compared with the Saudi population.

Importantly, MAF of Saudi population was found significantly different from every population of the Caucasian group except for Greece population. The findings suggest that the susceptibility factor may behave differently in diverse populations and this fact needs to be considered when evaluating this genetic marker for risk, treatment or prognosis. The factors including racial difference, heterogeneity of the studied cohort and difference in sample sizes may be contributing to the difference in allele frequency of polymorphism.

The relative prevalence of the p53 Arg72 SNP in Asian and Caucasian subgroups also indicates population divergence and the interethnic differences, in addition to the elucidation of differential regulation of gene function among different populations.

The outcome of such studies may contribute to the development of the epidemiological database in Saudi Arabia helping in better clinical understanding and evaluation of enigmatic diseases like cancer. The allelic/ genotypes distribution data in healthy Saudi population in

comparison to other populations can be used for the screening of individuals at risk or prone to developing cancer. The finding has contributed to the information about the relative prevalence of studied polymorphism and thus can lead to the use of this SNP as a biomarker along with a better understanding of cancer etiology in the Saudi population.

CONCLUSION

In conclusion, the allelic frequency distribution analysis of *p53* exon4 Arg72Pro SNP in Saudi population showed significantly different prevalence in many populations in Asian subgroup and all but one populations in the Caucasian subgroup. However, the impact of this polymorphism influencing the cancer susceptibility or the prognosis in Saudi population needs future larger studies.

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CONFLICT OF INTERESTS

The author declares no conflict of interests.

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ARABIC SUMMERY

مدى نسبة حدوث البوليفورميزم p53 Arg72Pro (rs1042522) أحد العوامل الرئيسة للإصابة بسرطان الثدي في السعوديين وبعض الأعراض الأخرى

نسيم أخطر
المملكة العربية السعودية، جامعة الباحة، كلية العلوم الطبية التطبيقية، قسم طب المختبرات

إن تعدد أشكال كودون ٧٢ (G> C; Arg> Pro) في p53 ، وهو جين مهم لتثبيط الورم، يساهم في ارتفاع مخاطر الإصابة بالعديد من أنواع السرطان بما في ذلك سرطان الثدي. كما أن التغيرات في p53 تؤثر سلباً على إيقاف دورة الخلية، وإصلاح تلف الحمض النووي وموت الخلايا المبرمج مما يؤدي إلى بداية السرطان وتطوره. ويحدث تعدد أشكال p53 exon 4 G>C في الأعراق المختلفة، ولكن المعلومات المتعلقة بحدوثه في السعوديين غير موجودة. في هذه الدراسة تم استخدام PUBMED (ميدلاين)، وشبكة العلوم وقاعدة بيانات جوجل للبحث في الدراسات الوبائية التي أجريت على الصعيد العالمي لمقارنة مدى حدوث اختلاف توزيع الأليل في السكان السعوديين مع المجموعات العرقية المختلفة. إجمالاً، تم العثور على نسبة حدوث P53 exon 4 أليل (G) لتكون ٥١ ٪. وعند مقارنة حدوث التباين في توزيع الأليل المذكور بين السعوديين وبقية الأعراق الأسيوية فإنه وبشكل واضح إحصائياً، تم العثور على تباين في الأليل المذكور بشكل كبير مع اليابان(p <٠,٠٠٠١)، والأردن (p = 0.0002)، والصين (p <٠,٠٠٠١)، وإيران (p <٠,٠٠٠١)، والهند (p = 0.0023)، وتركيا (p <٠,٠٠٠١)، وتايوان (٠,٠٣٠٧). كما أنه تم العثور على MAF مختلفة بين السعوديين والأعراق القوقازية باستثناء اليونانيين.

كما أظهر تحليل p53 exon4 Arg72Pro SNP في المملكة العربية السعودية نمطًا فريدًا، يختلف اختلافًا كبيرًا عن العديد من المجموعات السكانية في المجموعة الفرعية الآسيوية وجميع السكان باستثناء مجموعة واحدة في المجموعة الفرعية القوقازية. وقد تساعد هذه النتائج في إجراء فحص سكاني على نطاق واسع لهذا العامل المسبب للإصابة بالسرطان.