

## REVIEW

# Allele Frequencies of 25 Polymorphisms Pertaining to Cancer Risk for Japanese, Koreans and Chinese

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## Abstract

Allele frequencies are rather constant among different ethnic groups in many genetic polymorphisms, but some polymorphisms vary in the allele frequency depending on the time when the germ-line base exchanges occurred in the history of humans and on the adaptability of the phenotypes to given environment. This review documented the allele frequencies of polymorphisms pertaining to cancer risk for Japanese, Koreans, and Chinese. Twenty-five polymorphisms of 21 genes whose allele frequencies were available for at least two out of the three ethnic groups were selected. They were *ALDH2* Glu487Lys, *COMT* Val158Met, *CYP1A1* MspI and Val/Ile, *CYP1B1* Leu432Val, *CYP2E1* RsaI, *CYP17* T-34C, *ER* C975G, *GSTM1*, *GSTT1*, *GSTP1* Ile105Val, *IL-1B* C-511T, *IL-1RN* 86-bp VNTR (variable number of tandem repeats), *MTHFR* C677T and A1298C, *NAT1*, *NAT2*, *NQO1* Pro187Ser, *OGG1* Ser326Cys, *p21* Ser31Arg, *p53* Arg72Pro, *TNF-A* G-308A and G-238A, and *XRCC1* Arg194Trp and Arg399Gln. The allele frequencies were found for 24 in Japanese, 16 in Koreans, and 24 in Chinese. All of the polymorphisms had similar allele frequencies for these ethnic groups, except the following polymorphisms; *ALDH2* Glu487Lys whose Lys allele was more common for Japanese and Taiwanese, *COMT* Val158Met whose Met allele was more common for Japanese, and *NAT2* rapid/slow whose slow alleles were more common for Chinese. When compared with the allele frequencies among Caucasians, the following minor alleles were more frequent among Japanese/Koreans/Chinese; *ALDH2* 478Lys, *CYP1A1* m1 and m2, *CYP2E1* c2, *ER* 975G, *GSTT1* null, *NAT1* \*10, *NQO1* 187Ser, *OGG1* 326Cys, p21 31Arg, and *XRCC1* 194Trp, and less frequent in *COMT* 158Met, *GST-P1* 105Val, *IL-1RN* non-4R, *MTHFR* 1298C, and *TNF-A* -308A. The differences in genetic background may affect the impact on the lifestyle factors and/or genotypes examined in epidemiological studies. However, the influences of the variations in the allele frequency seemed to be limited among Japanese, Koreans, and Chinese. The substantial differences in the allele frequency from Caucasians could modify the influences of lifestyle factors and polymorphism genotypes, resulting in the inconsistent results of epidemiologic studies.

**Key Words:** cancer - polymorphisms – allele frequency – Japanese – Koreans - Chinese

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## Introduction

A large number of studies have been conducted on the associations between cancer risk and genetic polymorphisms (Vineis et al., 1999). It is not rare that the studies provide inconsistent associations among ethnically/regionally different populations (Rebbeck, 1997; Houlston, 1999, Houlston, 2000; Kiyohara, 2000). The main reasons for the inconsistent findings seem to be derived from the gene-environment interactions and/or gene-gene interactions (Hamajima et al., 1999), although studies with a small sample size have been providing the source of the inconsistent results due to random error.

There is no doubt that the differences in environment exposures/lifestyle influence the genetic susceptibility to cancer. *Aldehyde dehydrogenase 2 (ALDH2)* Gln487Lys polymorphism has no roles in disease susceptibility among non-drinkers, while it confers a markedly elevated risk for drinkers with the heterozygous genotype (Matsuo et al., 2001a; Matsuo 2002). The combinations of genotypes may also play an important role in the elevation of cancer risk, such as polymorphisms of *CYP1A1* and *GSTM1* (Nakachi et al., 1993). Accordingly, the impact of a polymorphism varies depending on the proportion of the counterpart genotype among the population under study.

In order to understand the impact of genetic

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polymorphisms for disease risk, information on the allele frequencies for each ethnic group is essential. Some polymorphisms distribute similarly among different ethnic groups, while others do not (Garte et al., 2001), depending on the time when the germ-line base exchanges occurred and on the adaptability of the phenotypes to given environment. For the populations in Asian Pacific regions, data on the allele frequencies are relatively scarce and documented in separated reports. This paper summarizes the allele frequencies of 25 polymorphisms of 21 genes pertaining to cancer risk whose allele/genotype frequencies were available at least in two ethnic groups of Japanese in Japan, Koreans in Korea and China, and Chinese in the main land of China, Taiwan, and Singapore. The frequencies for Caucasians were also documented to contrast the differences between Japanese/Koreans/Chinese and Caucasians.

## Materials and Methods

The PubMed was used for searching papers on the polymorphisms. As of June 11, 2002, 38 and 229 papers were found with the keywords, "Koreans, polymorphism, cancer" and "Chinese, polymorphism, cancer", respectively. Among them, the eligible reports on the polymorphism studies for Koreans and Chinese were adopted. Studies for Japanese were searched by PubMed using the polymorphism names found for Koreans/Chinese. When the eligible polymorphisms were found in the process of study selection, they were enrolled in the present review. The allele frequencies were obtained mainly from controls in case-

control studies. The studies were not included when the allele frequencies for the controls were not described in the abstracts of PubMed and the original papers were not available.

For each polymorphism, the allele frequencies for Caucasians were selected from a few studies with a larger sample size. When the genotype frequencies were obtained, Hardy-Weinberg equilibrium was examined by a Pearson chi-square test using STATA Version 7 (STATA Corp., College Station, TX).

In this paper, italic words are used to mean the names of genes and alleles/genotypes, and not italic for the gene products (enzymes or receptors). For example, ALDH2 is an enzyme, but *ALDH2* is the gene encoding ALDH2. The abbreviations for genes are listed in the Appendix.

## Results and Discussion

In 25 selected polymorphisms, the allele/genotype frequencies were not found for 1 polymorphism for Japanese, 9 for Koreans and 1 for Chinese. Table 1 shows the names of polymorphism, location in chromosome, main function of the gene, and allele name with high or low/null activity/expression. Table 2 lists the allele frequencies in an alphabetical order of gene abbreviations.

*ALDH2* Glu487Lys is deterministic for drinking habit. Individuals with *Lys/Lys* genotype cannot drink alcohol because they lack the ability to detoxicate acetaldehyde derived from ethanol. The *Lys* allele is found for Japanese/Koreans/Japanese and Caboclos in Brazil, but very rare for

**Table 1. Polymorphisms Concerning Cancer Risk for Japanese, Koreans, and Chinese**

Gene	Chromosome	Main function	Activity/expression	
			High	Low/null
<i>ALDH2</i>	12q24	Aldehyde catabolism	<i>487Glu</i>	<i>487Lys</i>
<i>COMT</i>	22q11.2	Estradiol catabolism	<i>158Val</i>	<i>158Met</i>
<i>CYP1A1</i>	15q22-24	Carcinogen activation	<i>m1, m2</i>	<i>wt</i>
<i>CYP1B1</i>	2p22-21	Carcinogen activation	<i>432Val</i>	<i>432Leu</i>
<i>CYP2E1</i>	10q24.3-qter	Carcinogen activation	Controversial for <i>c1/c2</i>	
<i>CYP17</i>	10q24.3	Estradiol synthesis	<i>-34C</i>	<i>-34T</i>
<i>ER</i>	6q25.1	Estrogen receptor	Unknown for C975G	
<i>GST-M1</i>	1p13.3	Carcinogen detoxification	Present	Null
<i>GST-T1</i>	22q11.2	Carcinogen detoxification	Present	Null
<i>GST-P1</i>	11q13	Carcinogen detoxification	<i>105Ile</i>	<i>105Val</i>
<i>IL-1B</i>	2q14	Proinflammatory cytokine	Contraversial for C-511T	
<i>IL-1RN</i>	2q14	IL-1 $\beta$ antagonist	<i>2R</i>	<i>4R</i>
<i>MTHFR</i>	1p36.3	Folate metabolism	<i>677C, 1298A</i>	<i>677T, 1298C</i>
<i>NAT1</i>	8p23.1-21.3	Carcinogen activation	Fast ( <i>wt</i> )	Slow ( <i>M1-M4</i> )
<i>NAT2</i>	8p23.1-21.3	Carcinogen detoxification	<i>*10</i>	others
<i>NQO1</i>	16q22.1	Carcinogen detoxification	<i>609C</i>	<i>609T</i>
<i>OGG1</i>	3p25	Repair enzyme for 8-OhdG	<i>326Ser</i>	<i>326Cys</i>
<i>p21</i>	6p21.2	Cyclin-dependent kinase inhibitor	No difference between <i>31Ser</i> and <i>31Arg</i>	
<i>p53</i>	17p13	Tumor suppressor gene	<i>72Arg</i>	<i>72Pro</i>
<i>TNF-A</i>	6p21.3	Proinflammatory cytokine	<i>-308A</i>	<i>-308G</i>
<i>XRCC1</i>	19q13.2	Base excision DNA repair	Unknown for G-238A Unknown for Arg194Trp <i>399Arg</i>	<i>399Gln</i>

other ethnic groups (Goedde et al., 1992). A study showed a lower *Lys* allele frequency for Koreans than Japanese (Lee et al., 1997a), and another study reported that Chinese in Taiwan had a similar *Lys* allele frequency to that in Japanese (Chao et al., 2000). It was reported that the *Lys* allele was 0.360 for 50 Koreans residing in the main land of China and

**Table 2. Allele Frequencies for Japanese, Koreans, Chinese and Caucasians**

Gene	Polymorphism	Japanese		Koreans		Chinese		Caucasians	
		N <sup>a)</sup>	Allele frequency	N	Allele frequency	N	Allele frequency	N	Allele frequency
<i>ALDH2</i>	Glu487Lys	Takeshita et al., 1993		Goedde et al., 1992		Goedde et al., 1992 <sup>M</sup>		Goedde et al., 1992 <sup>G,SW</sup>	
		264 0.710 0.290		218 0.849 0.151		132 0.841 0.159		292 1.000 0.000	
<i>COMT</i>	Val158Met or H/L	Matsuo et al., 2001a		Lee et al., 1997a		Chao et al., 2000 <sup>T</sup>			
		241 0.722 0.278		481 <sup>^</sup> 0.840 0.160		105 0.714 0.286			
		Ohara et al., 1998		Yim et al., 2001		Huang et al., 1999 <sup>T</sup>		Millikan et al., 1998 <sup>US</sup>	
<i>CYP1A1</i>	<i>MspI</i> RFLP or T6235C or wt1/m1	135 0.648 0.352		163 <sup>**</sup> 0.761 0.239		125 0.748 0.252		379 0.475 0.525	
		Hamajima et al., 2001a						Thompson et al., 1998 <sup>US</sup>	
		165 0.670 0.330						289 0.510 0.490	
		Nakachi et al., 1991		Hong et al., 1998		Huang et al., 1999 <sup>T</sup>		Garte et al., 2001 <sup>MA</sup>	
<i>CYP1A1</i>	Ile462Val or A4889G or wt2/m2	375 0.668 0.332		63 0.706 0.294		133 0.605 0.395		4,453 <sup>**</sup> 0.906 0.094	
		Inoue et al., 2000		Kim et al., 1999		Song et al., 2001a <sup>M</sup>			
		205 0.639 0.361		48 <sup>^</sup> 0.615 0.385		404 0.645 0.355			
		Oyama et al., 1997a		Hong et al., 1998		Song et al., 2001a <sup>M</sup>		Garte et al., 2001 <sup>MA</sup>	
<i>CYP1B1</i>	Leu432Val	622 0.777 0.223		63 <sup>***</sup> 0.508 0.492		404 <sup>***</sup> 0.744 0.256		4,790 <sup>***</sup> 0.948 0.052	
		Murata et al., 2001		Kim et al., 1999		Chen et al., 2001 <sup>M</sup>			
		200 0.785 0.215		48 <sup>^</sup> 0.750 0.250		106 0.816 0.184			
		Watanabe et al., 2000		No studies reported		Tang et al., 2000 <sup>M</sup>		Tang et al., 2000 <sup>US</sup>	
<i>CYP2E1</i>	<i>RsaI</i> c1/c2	324 0.846 0.154				109 <sup>^</sup> 0.83 0.17		189 <sup>^</sup> 0.57 0.43	
						Zheng et al., 2000 <sup>M</sup>			
						200 <sup>***</sup> 0.463 0.537			
		Watanabe et al., 1995		Lee et al., 1997a		Tan et al., 2000 <sup>M</sup>		Garte et al., 2001 <sup>MA</sup>	
<i>CYP17</i>	T-34C or A1/A2	503 0.809 0.191		481 <sup>^</sup> 0.808 0.192		150 <sup>**</sup> 0.697 0.303		1,454 0.962 0.038	
		Oyama et al., 1997b		Lee et al., 1997b		Gao et al., 2002 <sup>M</sup>			
		612 0.799 0.201		31 0.839 0.161		196 0.776 0.224			
						333 0.751 0.249			
<i>ER</i>	Pro325Pro C975G			No studies reported		Huang et al., 1999 <sup>T</sup>		Dunning et al., 1998 <sup>UK</sup>	
		Miyoshi et al., 2000				126 0.472 0.528		591 0.622 0.378	
		195 0.518 0.482						Haiman et al., 1999 <sup>US</sup>	
<i>GST-M1</i>	Present/Null <sup>d)</sup>	Hamajima et al., 2000		Kang et al., 2002		No studies reported		618 0.600 0.400	
		166 <sup>*</sup> 0.551 0.449		155 <sup>b)</sup> 0.500 0.500				Southey et al., 1998 <sup>A</sup>	
		Hoshino et al., 2000						294 0.791 0.209	
<i>GST-T1</i>	Present/Null <sup>d)</sup>	306 <sup>*</sup> 0.480 0.520						Herrington et al., 2002 <sup>US</sup>	
								301 <sup>c)</sup> 0.739 0.261	
		Kihara et al., 1994		Hong et al., 1998		Setiawan et al., 2001a <sup>M</sup>		Slattery et al., 1998 <sup>US, f)</sup>	
		201 0.547 0.453		63 0.476 0.524		417 0.492 0.508		1,949 0.454 0.546	
<i>GST-P1</i>	Ile105Val or A313G	Oyama et al., 1997a		Park et al., 2000		Chen et al., 2001 <sup>M</sup>		Garte et al., 2001 <sup>MA</sup>	
		622 0.487 0.513		181 0.475 0.525		106 0.632 0.368		10,514 0.469 0.531	
		Inoue et al., 2000		Kim et al., 2000		Zhao et al., 2001 <sup>SN</sup>			
		220 0.441 0.559		220 0.441 0.559		187 0.364 0.636			
<i>IL-1B</i>	C-511T	Katoh et al., 1996		Park et al., 2000		Setiawan et al., 2001a <sup>M</sup>		Garte et al., 2001 <sup>MA</sup>	
		126 0.556 0.444		181 0.580 0.420		417 0.544 0.456		5,577 0.803 0.197	
		Murata et al., 2001		Kim et al., 2000		Zhao et al., 2001 <sup>SN</sup>			
		200 0.480 0.520		220 0.541 0.459		187 0.455 0.545			
<i>IL-1B</i>	C-511T			No studies reported		Wong et al., 2002 <sup>T</sup>			
						333 0.538 0.462			
		Morita et al., 1998		No studies reported		Tan et al., 2000 <sup>M</sup>		Millikan et al., 2000 <sup>US</sup>	
<i>IL-1B</i>	C-511T	164 0.835 0.165				150 0.783 0.217		348 0.648 0.352	
		Kihara et al., 1999				Setiawan et al., 2001b <sup>M</sup>			
		257 0.842 0.158				419 0.844 0.156			
		Hamajima et al., 2001b		No studies reported		Tseng et al., 2001 <sup>T</sup>		Mansfield et al., 1994 <sup>UK</sup>	
<i>IL-1B</i>	C-511T	239 0.559 0.441				145 0.479 0.521		242 0.624 0.376	
		Kato et al., 2001				Hsieh et al., 2001 <sup>T</sup>		El-Omar et al., 2000 <sup>P</sup>	
		335 0.509 0.491				103 0.515 0.485		429 0.699 0.301	

Gene	Polymorphism	Japanese		Koreans		Chinese		Caucasians	
		N <sup>a)</sup>	Allele frequency	N	Allele frequency	N	Allele frequency	N	Allele frequency
<i>IL-1RN</i>	86-bp VNTR 2,3,4, and 5R		<i>4R</i> <i>2R</i>	No studies reported		<i>4R</i> <i>2R</i>		<i>4R</i> <i>2R</i>	
		Hamajima et al., 2001b	241    0.946    0.041			Tseng et al., 2001 <sup>T</sup>	145    0.931    0.014	Mansfield et al., 1994 <sup>UK</sup>	261    0.734    0.241
		Nishimura et al., 2000	111    0.960    0.027			Hsieh et al., 2001 <sup>T</sup>	103    0.951    0.039	El-Omar et al., 2000 <sup>P</sup>	429    0.721    0.269
<i>MTHFR</i>	Ala223Val C677T	Morita et al., 1997		Zuo et al., 1999		Shen et al., 2001 <sup>M</sup>		Chen et al., 1998 <sup>US</sup>	
		778    0.667    0.333	124 <sup>***</sup> 0.597    0.403	166    0.602    0.398	713    0.680    0.320				
	Matsuo et al., 2001b	243    0.593    0.407	94 <sup>^</sup> 0.532    0.468	360    0.589    0.411	369 <sup>**</sup> 0.707    0.293				
	Glu430Ala A1298C	Matsuo et al., 2001b		No studies reported		Shen et al., 2001 <sup>M</sup>		Skibola et al., 1999 <sup>UK</sup>	
		243    0.809    0.191				166    0.819    0.181		362    0.673    0.327	
						Song et al., 2001b <sup>M</sup>			
						360 <sup>*</sup> 0.829    0.171			
<i>NAT1</i>	*10/others	Katoh et al., 1998		No studies reported		Hsieh et al., 1999 <sup>T</sup>		Taylor et al., 1998 <sup>US</sup>	
		122    0.418    0.582				171 <sup>^</sup> 0.418    0.582		382 <sup>^</sup> 0.18    0.82	
		Yang et al., 2000b	110    0.532    0.468					Fronhoffs et al., 2001 <sup>G</sup>	
<i>NAT2</i>	Rapid/Slow <sup>e)</sup>	Oyama et al., 1997c		Kim et al., 2000		Seow et al., 1999 <sup>SN</sup>		Slattery et al., 1998 <sup>US, D)</sup>	
		376    0.698    0.302	219    0.662    0.338	141    0.528    0.472	1,955    0.237    0.763				
		Morita et al., 1998				Hsieh et al., 1999 <sup>T</sup>		Gertig et al., 1999 <sup>US</sup>	
		164 <sup>*</sup> 0.735    0.265				183 <sup>^</sup> 0.526    0.474		466    0.244    0.756	
		Katoh et al., 1998				Lee et al., 2000 <sup>T</sup>			
		122    0.721    0.279				254    0.524    0.476			
<i>NQO1</i>	Pro187Ser C609T	Naoe et al., 2000		No studies reported		Lin et al., 1999 <sup>T</sup>		Smith et al., 2001 <sup>UK</sup>	
		150 <sup>*</sup> 0.617    0.383				95 <sup>^</sup> 0.49    0.51		838    0.812    0.188	
		Hamajima et al., 2002b	241    0.579    0.421					Krajcinovic et al., 2002 <sup>CA</sup>	323    0.822    0.178
<i>OGG1</i>	Ser326Cys	Sugimura et al. 1999 <sup>e)</sup>		No studies reported		Xing et al., 2001 <sup>M</sup>		Wikman et al., 2000 <sup>G</sup>	
		197    0.591    0.409				196 <sup>**</sup> 0.592    0.408		105    0.776    0.224	
		Ito et al., 2002b	240    0.529    0.471				Takezaki et al., 2002 <sup>M</sup>		Le Marchand et al., 2002 <sup>US</sup>
<i>p21</i>	Ser31Arg or C to A	Hachiya et al., 1999		Roh et al., 2001		Shih et al., 2000 <sup>T</sup>		Sjalander et al., 1996 <sup>SW</sup>	
		55 <sup>*</sup> 0.591    0.409	98    0.592    0.408	189    0.508    0.492	761    0.953    0.047				
						Tsai et al., 2002 <sup>T</sup>			
						119    0.429    0.571			
<i>p53</i>	Arg72Pro	Minaguchi et al., 1998		Baek et al., 2000		Wang et al., 1999 <sup>T</sup>		Pierce et al., 2000 <sup>US</sup>	
		110    0.596    0.404	103    0.602    0.398	152    0.556    0.444	173    0.723    0.277				
		Hamajima et al., 2002c		Kim et al., 2001		Lee et al., 2000 <sup>T</sup>		Fan et al., 2000 <sup>US</sup>	
		239    0.598    0.402	100    0.705    0.295	254    0.598    0.402	510    0.673    0.327				
						Guimaraes et al., 2001 <sup>M</sup>		Zehbe et al., 2001 <sup>SW</sup>	
						57    0.368    0.632		188    0.694    0.306	
<i>TNF-A</i>	G-308A	Kamizono et al., 2000		Yea et al., 2001		Sheu et al., 2001 <sup>T</sup>		Kunstmann et al., 1999 <sup>G</sup>	
		575 <sup>*</sup> 0.983    0.017	113    0.969    0.031	246    0.919    0.081	384 <sup>**</sup> 0.837    0.163				
		Hamajima et al., 2002c					Tsai et al., 2002 <sup>T</sup>		Rasmussen et al., 2000 <sup>D</sup>
		240    0.988    0.012				139    0.952    0.048		325    0.811    0.189	
								Rasmussen et al., 2000 <sup>D</sup>	
		575    0.980    0.020		Yea et al. 2001		246    0.984    0.016		309    0.937    0.063	
<i>XRCC1</i>	Arg194Trp C26304T	No studies reported		Kim et al., 2002		Shen et al., 2000 <sup>M</sup>		Sturgis et al., 1999 <sup>US</sup>	
				205    0.659    0.341	166    0.654    0.346	424    0.928    0.072			
							Lunn et al., 1999 <sup>T</sup>		Lunn et al., 1999 <sup>US</sup>
						120    0.733    0.267		169    0.941    0.059	
								Sturgis et al., 1999 <sup>US</sup>	
		Hamajima et al. 2002c		Kim et al., 2002		Shen et al., 2000 <sup>M</sup>			
		241    0.701    0.299	205 <sup>*</sup> 0.685    0.315	166    0.744    0.256	424    0.659    0.341				
						Wong et al., 2002 <sup>T</sup>		Lunn et al., 1999 <sup>US</sup>	
						333 <sup>*</sup> 0.736    0.266		169    0.630    0.370	

<sup>a)</sup>N is the number of subjects. <sup>b)</sup>Including 110 breast cancer cases. <sup>c)</sup>Postmenopausal women with established coronary artery. <sup>d)</sup>Genotype. <sup>e)</sup>"Rapid" is type 1 allele (*wt* or *NAT2\*4*), and "slow" is the others. <sup>f)</sup>Caucasians were 91.4%. <sup>g)</sup>Data from Okinawa. <sup>M</sup> Conducted in main land of China, <sup>T</sup> in Taiwan, <sup>SN</sup> in Singapore, <sup>US</sup> in the United States, <sup>CA</sup> in Canada, <sup>UK</sup> in the United Kingdom, <sup>D</sup> in Denmark, <sup>G</sup> in Germany, <sup>P</sup> in Poland, <sup>SW</sup> in Sweden, <sup>A</sup> in Australia, and <sup>MA</sup> for meta-analysis. \*  $p < 0.05$ , \*\*  $p < 0.01$  and \*\*\*  $p < 0.001$  for a Hardy-Weinberg equilibrium test, and <sup>^</sup> not examined for the test because the original genotype data were not available.

0.229 for 48 Chinese in the same area (Shen et al., 1997). The interpretation for the allele frequency should be careful because of the limited number of subjects and a separated Korean group. In Japan, the odds ratio of alcohol drinking was found to be larger among those with *Glu/Lys* genotype than among those with *Glu/Glu* genotype, for cancers of the esophagus (Matsuo et al., 2001a) and rectum (Matsuo et al., 2002).

Catechol-O-methyltransferase (COMT) metabolizes estradiol. *Met (L)* allele, a low activity allele of *COMT* Val158Met seemed less frequent among Koreans and Chinese than among Japanese. It is more frequent in Caucasians. The association between this polymorphism and breast cancer risk is very controversial. A significantly increased risk was found for high BMT (body mass index) postmenopausal Caucasians with *Met/Met* genotype (54 cases and 47 controls) by Lavigne et al (Lavigne et al., 1997), while postmenopausal Caucasians with *Met/Met* genotype had a significantly low risk in a study (140 cases and 155 controls) by Thomson et al (Thompson et al., 1998). Millikan et al. (Millikan et al., 1998) reported no associations for Caucasians (389 cases and 379 controls) and African-Americans (265 cases and 263 controls) and for premenopausal women (331 cases and 297 controls) and postmenopausal women (323 cases and 344 controls). For Mongoloids, a significant elevation of OR was reported for Koreans (163 cases and 163 controls) (Yim et al., 2001) and postmenopausal Chinese (65 cases and 72 controls) (Huang et al., 1999), but no association was found for Japanese (150 cases and 165 controls) (Hamajima et al., 2001a).

Cytochrome P-450 (CYP) are a superfamily of enzymes for oxidative, peroxidative, and reductive metabolism of diverse compounds (Kawajiri and Fujii-Kuriyama, 1991; Nelson et al., 1996). CYP1A1, CYP1B1, and CYP2E1 are regarded to work mainly for carcinogen activation. The minor alleles, *CYP1A1 MspI* RFLP *m1* and *462Val m2*, *CYP2E1 RsaI c2*, in Japanese/Koreans/Chinese are more frequent than in Caucasians. *CYP1B1 432Val* reported by Watanabe et al for Japanese (Watanabe et al., 2000) and by Tang et al (Tang et al., 2000) for Chinese were less common than for Caucasians, but the *432Val* frequency by Zheng et al (Zheng et al., 2000) for Chinese women in Shanghai whose Hardy-Weinberg equilibrium was highly significant ( $p=0.0001$  for 29 *Leu/Leu*, 127 *Leu/Val*, and 44 *Val/Val*) was high similar to that for Caucasians. The reports by Hong et al (Hong et al., 1998) and Song et al (Song et al., 2001a) for *CYP1A1 Ile462Val*, and by Tan et al (Tan et al., 2000) for *CYP2E1 RsaI c1/c2* were also not in Hardy-Weinberg equilibrium. There are a great number of papers on the association between these *CYP* polymorphisms and cancer risk (Bartsch et al., 2000).

CYP17 is an enzyme needed for estrogen synthesis, so that high expression alleles seemed carcinogenic for breast cancer (Feigelson et al., 1997; Miyoshi et al., 2000), though majority of the studies have been reporting no associations (Dunning et al., 1998; Haiman et al., 1999; Hamajima et al., 2000). The *CYP17 -34C (A2)* allele are slightly frequent for

Japanese/Chinese than for Caucasians. Different functions of estrogen receptor (ER) are expected to influence breast cancer susceptibility, although the association with *ER C975G* polymorphism is controversial (Roodi et al., 1995; Southey et al., 1998; Kang et al., 2002). The polymorphism has different allele frequencies between Japanese/Koreans and Caucasians.

Glutathione S-transferase (GST) is a detoxification enzyme with four isozymes; *GST-μ*, *GSTθ*, and *GST-π* whose gene polymorphisms have been reported, as well as *GST-α*. The null or lower enzyme activity is regarded to be high risk for cancers. *GSTM1* null allele are common and there are no differences in the genotype frequency among Japanese, Koreans, Chinese, and Caucasians, while *GSTT1* null genotype in Japanese/Koreans/Chinese are more common in comparison with Caucasians. Although *GSTT1* null genotypes in Japan (n=167) was reported to be significantly fewer than the combined data from Korea (n=165) and Singapore (n=244) by Garte et al (Garte et al., 2001); 0.353, 0.515, and 0.519, respectively, the data from other researchers did not indicate the difference. A low activity allele, *GSTP1 105Val*, are less frequent in Japanese/Chinese than in Caucasians.

Interleukin (IL) 1β is a proinflammatory cytokine with a potent gastric acid inhibitory activity. Polymorphisms of *IL-1B* encoding IL-1β and *IL-1RN* encoding IL-1 receptor antagonist were reported to have significant associations with stomach cancer (El-Omar et al., 2000). *IL-1B T-31C T* allele tightly linked *IL-1B C-511T C* allele was consistently associated with the elevated risk of persistent *Helicobacter pylori* infection (Hamajima et al., 2001b, Hamajima, et al., 2002a). IL-1β combines estrogen receptor α, resulting in transcriptional activation. A recent study found a significant association with breast cancer, especially postmenopausal women (Ito et al., 2002a). *IL-1B C-511T T* minor allele is more frequent for Japanese/Chinese than for Caucasians. *IL-1RN* 86-bp VNTR (variable number of tandem repeat) polymorphism has 4 alleles; 2, 3, 4, and 5 repeat allele. Among them, 4 repeat allele (4R) dominates Japanese/Chinese.

*MTHFR* encodes methylenetetrahydrofolate reductase, an enzyme metabolizing folate. The tightly linked polymorphisms C677T and A1298C affect the enzyme function. It was reported that the 677T allele distribution was significantly different among six ethnic groups; 0.124 for 185 African Americans, 0.101 for 89 Asian Indians in the United States, 0.266 for 192 Caucasians, 0.415 for 82 Hispanic, 0.468 for 94 Koreans in Seoul, and 0.287 for 87 Native Americans (Hessner et al., 1999). As shown in Table 2, Japanese/Koreans/Chinese have a slightly higher frequency of 677T allele than Caucasians, but lower frequency of 1298C allele. These polymorphisms have been examined for the associations with esophageal cancer (Song et al., 2001b), gastric cancer (Shen et al., 2001), colorectal cancer (Ma et al., 1997), malignant lymphoma (Matsuo et al., 2001b), leukemia (Skibola et al., 1999), and so forth.

N-acetyl transferases (NAT) acetylate arylamines,

carcinogens included tobacco smoke, at liver with NAT2, and N-hydroxylated arylamines at bladder with NAT1. While N-acetylated arylamines with NAT2 is non-reactive, the metabolites O-acetylated with NAT1 is reactive (Kadlubar and Badawi, 1995). Accordingly, slow-acetylation alleles of NAT2 (*M1*, *M2*, *M3*, and *M4*) and high-acetylation allele of NAT1 (*NAT1\*10*) are expected to increase the risk of cancers. The point estimates for the NAT2 allele frequency showed that the slow acetylator alleles were the lowest in Japanese, then in Koreans and in Chinese, and the highest in Caucasians, while *NAT1\*10* allele was higher for Japanese/Chinese than for Caucasians. There are many studies on the associations with these polymorphisms (Hein et al., 2000; Yang et al., 2000a). The interactions with smoking or between the two NATs have been reported for cancers of the bladder (Taylor et al., 1998; Hsieh et al., 1999), breast (Ambrosone et al., 1996), and lung (Wikman et al., 2001).

NAD(P)H: quinone oxidoreductase 1 (*NQO1*) is a detoxification enzyme. The encoding gene *NQO1* has a null activity allele *187Ser* (*609T*) as well as *187Pro* (*609C*) with a full enzyme activity. The allele frequency from a study for 95 Chinese was 0.51 for *187Ser*, which was higher than those obtained from two Japanese studies (Naoe et al., 2000; Hamajima et al., 2002b). Caucasians have been reported to have a lower *187Ser* allele frequency (Smith et al., 2001; Krajcinovic et al., 2002). The significantly elevated risk of *187Ser* allele have been reported for leukemia (Nao et al., 2000; Smith et al., 2001; Krajcinovic et al., 2000), lung (Lin et al., 1999), and a possible interaction with smoking for cancers of lung and esophagus (Rosvold et al., 1995; Hamajima et al., 2002b).

The reported *Cys* allele frequency for *OGG1* Ser326Cys varied from 0.146 for Melanesians in Vanuatu (n=55) to 0.607 for Chinese in Jiangsu (n=98) (Sugimura et al., 1999). The *Cys* allele frequency derived from other datasets listed in Table 2 also demonstrated a substantial difference between Caucasians and Japanese/Chinese. A study in Hawaii reported that the *Cys* allele was 0.420 among 150 Japanese Americans, 0.448 among 96 Hawaiians, and 0.217 among 159 Caucasians (Le Marchand et al., 2002). Since the *Cys* is a low-expression allele conferring a higher risk for cancers relating to 8-hydroxyguanine, it means that Japanese/Chinese are more susceptible than Caucasians. This polymorphisms have been examined for lung cancer (Sugimura et al., 1999; Wikman et al., 2000; Ito et al., 2002b; Le Marchand et al., 2002), esophageal cancer (Xing et al., 2001), stomach cancer (Takezaki et al., 2002)

*p21* is a molecule of *p53* family, which plays important roles in apoptosis. The *p21* 31Arg allele was reported common in Japanese/Koreans/Chinese (Hachiya et al., 1999; Roh et al., 2001; Shih et al., 2000), but rare in Caucasians (Sjalander et al., 1996). The difference in *p53* Arg72Pro allele frequencies among Japanese, Hawaiians, and Caucasians was documented by a study in Hawaii; the Arg allele was highest for 173 Caucasians (0.723), lowest for 103 Hawaiians (0.519), intermediate for 170 Japanese

(0.674) (Pierce et al., 2000). The allele frequencies listed in Table 2 is rather close among Japanese, Koreans, and Chinese, except that by Guimaraes et al in Linxian with a high prevalence for esophageal cancer (Guimaraes et al., 2001). It is not clear whether the low frequency of Arg allele is real in that area or due to random variation for 57 individuals. The apoptotic function was reported to be higher in Arg/Arg genotype than in Pro/Pro genotype (Thomas et al., 1999). The significant associations with *p53* 72Pro have been reported for lung cancer (Wang et al., 1999; Fan et al., 2000)

Tumor necrosis factor (TNF)  $\alpha$  is a proinflammatory cytokine, which is encoded by *TNF-A*. As shown in Table 2, the minor alleles of *TNF-A* G-308A and G-238A polymorphisms are rare for Japanese/Koreans/Chinese, which cannot be evaluated for the association with disease risk based on a large statistical power. The -239A allele is similarly rare among Caucasians, but -308A for Caucasians is slightly more frequent. A small-sized study showed a significant association between -308A and malignant tumor (44 malignant lymphoma cases, 40 breast cancer cases, and 40 other miscellaneous cancer cases) (Chouchane et al., 1997). Another study on nasopharyngeal carcinoma showed no significant association with the G-308A polymorphism (Tsai et al., 2002).

*XRCC1* is a base excision DNA repair enzyme. *XRCC1* 194Trp allele is common among Koreans/Chinese, but less common among Caucasians. On the contrary, *XRCC1* Arg399Gln polymorphism has a similar allele distribution among Japanese, Koreans, Chinese, and Caucasians, as shown in Table 2. These polymorphisms have been examined for lung cancer (Butkiewicz et al., 2001), breast cancer (Kim et al., 2002), stomach cancer (Shen et al., 2000), and cancers of the head and neck (Sturgis et al., 1999).

In this paper, the polymorphisms reported for at least two out of Japanese/Koreans/Chinese populations. Other than the polymorphisms listed in Table 2, the substantial differences in the allele frequencies between Japanese and Caucasians have been reported for several polymorphisms. For example, *Seroid 5- $\alpha$  reductase type II* (*SRD5A2*) Val89Leu *Leu* allele was reported to be 0.426 in 284 Japanese, 0.364 in 360 Latenos, 0.319 in 240 Caucasians, and 0.245 in 411 African Americans (Pearce et al., 2002). *IL-1A* T-889C *T* allele was 0.085 in 241 Japanese (Hamajima et al., 2001b), while it was 0.283 for 242 Caucasians in England (Mansfield et al., 1994) and 0.331 for 400 Caucasians in Finland (Hulkkonen et al., 2000).

In conclusion, the differences in the allele frequency among Japanese, Koreans, and Chinese were found to be rather small. The possible differences may be for *ALDH2* Glu487Lys, *COMT* Val158Met, and *NAT2* polymorphisms. Since those polymorphisms have a large difference in the allele frequency from that for Caucasians, the documented differences among the three ethnic groups may be a part of the gradient from Caucasians. It is quite natural that the differences in the allele frequencies are small among the three ethnic groups, just like among subgroups in Caucasians.

Some reports of polymorphisms for Japanese/Koreans/Chinese might fail to be collected, but this paper provides useful information when we consider the inconsistent results from epidemiologic studies on lifestyle factors and/or genotypes.

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## Appendix: Abbreviations for the Genes

*ALDH2*: aldehyde dehydrogenase 2, *COMT*: catechol-O-methyltransferase, *CYP*: cytochrome P-450, *ER*: estrogen receptor, *GST*: glutamine S-methyltransferase, *IL*: interleukin, *MTHFR*: methylenetetrahydrofolate reductase, *NAT*: N-acetyl transferase, *NQO1*: NAD(P)H:quinone oxidoreductase 1, *OGGI*: 8-oxoguanine DNA glycosylase 1, *TNF*: tumor necrosis factor, and *XRCC1*: X-ray repair cross-complementing 1.

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