RESEARCH ARTICLE

Changes in Median Ages at Death from Selected Cancer Types in Relation to HLA-DRB1/DQB1

Wan-Xin An[1,2], Ya-Xin Fan[1], Xiao-Hua Liang[1], Hui Liu[2]*

Abstract

The median ages at death from cancers between 1985 and 2005 were calculated to demonstrate that inherent anticancer mechanisms may be a common pathway for different cancers. Seventy-eight patients with gastric, liver and lung cancers, were recruited in the solid cancer group. The leukemia group consisted of 31 patients with three main types of leukemia. The controls were 100 healthy individuals. The samples were typed using an HLA-DR/DQ PCR-SSP typing kit. The results showed that the median ages at death from all causes were 64.7 years in 1985 and 70.1 years in 2005. The range of the median ages at death from all cancers was similar to the corresponding value for deaths attributed to all causes. The frequency of DRB1*03 was 9.6% in the solid cancer group and 3.0% in the control group ($p<0.05$). The frequency of DRB1*04 in the leukemia group were significantly lower than that of the control ($p<0.05$). DRB1*13 and DQB1*06 frequencies in the leukemia group were significantly higher than those of the controls ($p<0.05$). It is suggested that inherent anti-cancer mechanisms may be a common pathway for different cancers and are associated with the immune system and HLA.

Keywords: Cancer - HLA - death statistics - China

Asian Pac J Cancer Prev, **15 (10)**, 4125-4128

Introduction

Cancer is multigenic, with several susceptibility genes acting together with environmental factors to produce an abnormal phenotype, and anti-cancer mechanisms have evolved to contend with the consequences of cancer (Monteiro et al., 2013; Shames et al., 2014). The healthy state (i.e., absence of cancer) is one of the inherent anti-cancer mechanisms, such as the immune system's intrinsic ability to fight against cancer, and the final result of cancer depends on rehabilitative efficacy with nature or with the medical help from cancer. It is necessary to evaluate a basal kind of instinct to repair cancer. From experience, we know that the instinct to repair cancer or anti-diseases have increased because of the increase in life expectancy in China since 1980. In this research, we calculated the median age at death from cancer during the last 20 years to demonstrate that the instinct to repair cancer may be a common pathway of an anti-cancer mechanism for different cancers.

Human leukocyte antigen complex (HLA) genes are located on the short arm of chromosome 6 and the most polymorphic loci within the human genome. The primary function of HLA is to allow the immune system to identify infectious pathogens and eliminate them. HLA alleles play a significant role in immune responses and immunologic tolerance (Fischer et al., 2001). Hence, HLA genes are the most significant genetic predisposition factor or genetic markers on chromosome 6 for diseases and cancers affecting the immune system (Shugart et al., 2011; Hildesheim et al., 2012). Since HLA class II loci have a distinctive role in diseases, associations are usually observed with HLA-DR and DQ genes (Sugihara, 2012; Zhao et al., 2012; Pratesi et al., 2013). We are also interested in understanding whether the HLA class II DR /DQ allelic polymorphism is a common risk factor in the development of cancer with the instinct to repair cancer or not. There is very little information about this hypothesis.

Materials and Methods

Original death data of the population and cancer

The population deaths and cancer by age during the interval 2000 through 2006, is shown in Table 1 (Xiudan et al., 2004; Department of population and employment statistics national bureau of statistics of China, 2006; Shiming et al., 2007; Jing, 2008). The population deaths and cancer by age during the interval, 1980 through 1989, is shown in Table 2 (Chengxiao et al., 1987; Changming, 1988; Department of population and employment statistics national bureau of statistics of China, 1988; Yijian, 1988). For mortality statistics, the underlying causes of death are classified according to ICD-10 coding.

Subjects

Two hundred nine individuals of the northern Han Chinese living in Dalian during 2004-2007 who expressed an interest to take part in the study were included in this

*[1]Dalian Blood Center, [2]Department of Clinical Immunology, Dalian Medical University, Dalian, China *For correspondence: liuhui_60@163.com*

Table 1. The Death of Population by Age in China Mainland During 2000-2006

Age group	Number of death (Cumulative percent)					
	All causes	All cancers	Gastric cancer	Liver cancer	Lung cancer	Leukemia
0-4	3025 (2.97)	69 (0.23)	-	-	10 (0.10)	26 (3.25)
5-14	1002 (3.95)	82 (0.50)	-	2 (0.05)	2 (0.12)	43 (8.63)
15-24	1811 (5.73)	144 (0.97)	7 (0.18)	10 (0.28)	7 (0.19)	57 (15.76)
25-34	2999 (8.68)	280 (1.89)	21 (0.72)	61 (1.71)	33 (0.54)	39 (20.64)
35-44	5638 (14.22)	1707 (7.5)	179 (5.29)	419 (11.55)	329 (3.98)	101 (33.28)
45-54	9423 (23.48)	4031 (20.74)	403 (15.75)	822 (30.85)	1069 (15.16)	119 (48.17)
55-64	13938 (37.18)	4932 (36.94)	615 (31.26)	832 (50.38)	1477 (30.60)	99 (60.56)
65-74	25421 (62.17)	10904 (72.75)	1530 (70.3)	1255 (79.84)	3887 (71.25)	176 (82.59)
>75	38482 (100)	8302 (100)	1164 (100)	859 (100)	2749 (100)	139 (100)
Age at death	70.13	68.65	69.8	64.81	69.77	56.45

Table 2. The Death of Population by Age in China Mainland During 1980-1989

Age group	Number of death					
	All causes	All cancers	Gastric cancer	Liver cancer	Lung cancer	Leukemia
0-4	6078 (10.48)	73 (0.46)	-	7 (0.23)	-	31 (6.77)
5-14	1361 (12.83)	105 (1.12)	-	5 (0.39)	-	48 (17.25)
15-24	2615 (17.34)	245 (2.65)	15 (0.38)	55 (2.16)	4 (0.20)	79 (34.50)
25-34	2153 (21.05)	536 (6.01)	35 (1.26)	245 (10.04)	24 (1.41)	64 (48.47)
35-44	2578 (25.49)	1176 (13.37)	165 (5.40)	521 (26.80)	86 (5.74)	49 (59.17)
45-54	4830 (33.82)	2103 (26.54)	486 (17.6)	477 (42.14)	260 (18.82)	51 (70.31)
55-64	9700 (50.54)	4564 (55.11)	1227 (48.41)	891 (70.80)	628 (50.41)	54 (82.10)
65-74	13905 (74.51)	4842 (85.42)	1402 (83.61)	632 (91.13)	702 (85.72)	65 (96.29)
>75	14782 (100)	2328 (100)	653 (100)	277 (100)	284 (100)	18 (100)
Age at death	64.68	63.21	65.46	57.75	64.88	36.76

Table 3. The Ratio of Age at Death from 4 Leading Cancers (%)

Year	All	Gastric cancers	Liver cancer	Lung cancers	Leukemia cancers
2005	97.89	99.5	92.41	99.49	80.51
1985	97.73	101.21	89.29	100.31	56.83

study. Seventy-eight patients (46 males and 32 females; mean age, 61±16 years) with different cancers, including 17 gastric, 18 liver, and 20 lung cancers, and 23 other cancers, such as colon carcinoma, rectal cancer, and gynecologic cancer, were recruited as the solid cancer group (as evidenced by surgical intervention). The leukemia group consisted of 31 patients (17 males and 14 females; mean age, 32±5.5 years) with acute lymphoblastic leukemia, acute non-lymphocytic leukemia, or chronic myelocytic leukemia (as evidenced by pathologic findings). The control population was comprised of 100 healthy blood donors (50 males and 50 females; mean age, 38±9.5 years) from the same geographic area.

HLA-DRB1/DQB1 allele typing

Genomic DNA was extracted from white blood cells using standard techniques for HLA typing. The samples were typed using an HLA-DR/DQ "low resolution" PCR-SSP typing kit (Pel-Freez Clinical Systems), including allele-specific primers for DRB1*01, DRB1*03, DRB1*04, DRB1*07, DRB1*08, DRB1*09, DRB1*10, DRB1*11, DRB1*12, DRB1*13, DRB1*14, DRB1*15, DRB1*16, DQB1*02, DQB1*03, DQB1*04, DQB1*5, and DQB1*6. All commercial tests were run according to the manufacturer's instructions. Products were separated by electrophoresis in 2% agarose and visualized by ethidium bromide staining and UV transillumination. Automated gel reading was performed using Pel-Freez software.

Statistical analysis

The median ages at death were calculated with a frequency table. The ratio of age at death (the ratio of median ages at deaths from a disease to that from all causes in same period) was obtained.

Genotype and allele frequencies in the different groups were obtained. Frequencies in the solid cancer and leukemia groups were compared to the control group by the (chi) 2 test or Fisher's exact test (when the expected frequencies were too small). Differences were considered significant when p values were <0.05.

All analyses were performed using the SPSS 11.0 statistical software package.

Results

The median ages at death from all causes and each of the 4 leading cancers are shown in Table 1, 2. The ratios of age at death for each of the 4 leading cancers are shown in Table 3. There were no major differences, with the exception of leukemia, between the ratio of ages at death in 2005 and 1985.

The raw data of alleles in HLA-DRB1/DQB1 of the total study population and subgroups are listed in Tables 4, 5. Quantitative comparisons between the solid cancer group, leukemia group, and control population were performed. The frequency of DRB1*03 was 9.6% in the

Table 4. Allele Distributions for Locus HLA-DRB1 in Different Groups f% (*p* values)

DRB1*	Solid cancer	Leukemia	Control
01	3.8 (0.798)	3.2 (1.000)	4.5
03	9.6 **(0.012)**	1.6 (1.000)	3.0
04	10.9 (0.741)	0.0 **(0.001)**	12.5
07	10.3 (0.449)	9.7 (0.595)	7.5
08	7.1 (0.841)	12.9 (0.311)	8.0
09	14.1 (0.753)	19.4 (0.210)	12.5
10	0.6 (0.391)	1.6 (1.000)	2.0
11	3.8 (0.345)	6.5 (1.000)	6.5
12	10.9 (0.096)	11.3 (0.322)	17.5
13	6.4 (0.481)	12.9 **(0.034)**	4.5
14	4.5 (0.785)	3.2 (1.000)	3.5
15	14.7 (1.000)	16.1 (0.841)	15.0
16	3.2 (1.000)	1.6 (1.000)	3.0
N[a]	156	62	200

N[a], Number of chromosomes analyzed; Bold-faced values indicate significant difference at the 5% level

Table 5. Allele Distributions for Locus HLA-DRB1 in Different Groups f% (*p* values)

DRB1*	Solid cancer	Leukemia	Control
02	16.0 (0.274)	6.5 (0.341)	11.5
03	41.7 (1.000)	38.7 (0.661)	42.0
04	5.8 (0.174)	4.8 (0.305)	10.0
05	12.8 (1.000)	12.9 (1.000)	12.5
06	23.7 (1.000)	37.1 **(0.043)**	24.0
N[a]	156	62	200

N[a], Number of chromosomes analyzed; Bold-faced values indicate significant difference at the 5% level

solid cancer group and 3.0% in the control population, which represented a significant difference ($p<0.05$). The frequency data of DRB1*04 was lower in the leukemia group, reaching statistical significance compared to the control population ($p<0.05$). A significant increase was found in the DRB1*13 frequency of the leukemia group compared to the control population ($p<0.05$). The frequency of DQB1*06 was recorded in 37.1% of the leukemia group and 24.0% of the control population ($p<0.05$).

Discussion

The quality of life in China has shown a marked improvement since 1980. The life expectancy at birth was 68.9 years in 1985 and 73.0 years in 2005. In this study, we chose the Chinese literature published in scientific journals since 1980 and obtained the values for the number of deaths attributed to cancer in different age groups. The median ages at death were calculated. The median ages at death from all causes was 64.68 years in 1985 and 70.13 years in 2005 (Table 1, 2). These results were in parallel with the increase in life expectancy at birth since 1980 and implied that the data obtained in this study were sufficiently representative.

The median ages at death from all cancers were 63.21 years in 1985 and 68.65 years in 2005. The range of the median ages at death from all cancers was similar to the corresponding value for deaths attributed to all causes. These findings indicate that a change in basal health status may have played a more significant role than development of medicine in the observed enhancement of the median age at deaths from cancer.

The numbers of deaths from cancer were mainly attributed to gastric cancer, liver cancer, and lung cancer, and represented >50% of all cancer deaths in China (Department of population and employment statistics national bureau of statistics of China, 1988, 2006). Therefore, the present study focused on those three cancers as representative of solid cancers. The results showed that the differences in the median ages at death from the three cancers between 2005 and 1985 were similar with the exception of leukemia and the ratio of age at death from 3 solid cancers in 2005 and 1985 were almost equal (Table 3). These findings suggest the presence of a common inherent anticancer pathway. These considerations led us to establish a solid cancer group and a leukemia group to explore the regularity of cancer occurrence and development.

For most sporadic cancers, genetic susceptibility results from the additive effect of multiple genetic variants, each of which contributes a modest risk individually (Monteiro et al., 2013; Shames et al., 2014). Genetic polymorphisms in functionally critical genes have been suggested as risk factors for the development of a variety of cancers. Candidate genes may be involved in DNA damage repair, carcinogen metabolism, cell-cycle control, apoptosis, and immune response (Meyer et al., 2008). Particularly important is the anti-cancer adaptive immune response. It is widely accepted that the anti-cancer adaptive immune response is the T lymphocyte. T lymphocyte activation requires the completion of a carefully orchestrated series of specific steps that can be pre-empted or disrupted by any number of critical events (Inman et al., 2007; DeNardo et al., 2008). It is now recognized that antigen presentation by HLA class II molecules plays an important role in this process. Specifically, persistent pro-tumor immune responses, now generally accepted as potentiating primary tumor development, are also recognized as mediators of cancer metastasis (Kim et al., 2008; Mangalam et al., 2008; Sun et al., 2008). Clearly, the immune response is an important inherent defense mechanism against cancer. Therefore, the study of polymorphisms of HLA may help explain the differences in individual cancer susceptibility and may assist in identifying novel markers of risk that can be utilized to create more effective and tailored cancer prevention strategies. HLA class I and II alleles polymorphisms have been shown to associate with many cancers (Yang et al., 2011; Bonamigo et al., 2012; Xiao et al., 2013).

Quantitative comparisons between the solid cancer group, the leukemia group, and the control group were performed. We found that the frequency of DRB1*03 was 9.6% in the solid cancer group and 3.0% in the control population ($p<0.05$). It is suggested that there may be common susceptibility genes in solid cancer. The frequency data of DRB1*04 was lower in the leukemia group than in the control population ($p<0.05$). A significant increase was found in both DRB1*13 and DQB1*06 of the leukemia group compared to the control population ($p<0.05$). These findings indicated that there may be

common susceptibility or resistance genes which are different from solid cancer in different kinds of leukemia.

Another possibility is that the role of HLA-DRB1/DQB1 alleles implicated in this study is due to linkage to the neighboring genes of HLA-DRB1/DQB1 alleles, which may be involved in a common pathway of anti-cancer mechanism for different cancers. Whether our findings are a matter of haplotype or whether they suggest a direct role for HLA-DRB1/DQB1 alleles needs to be investigated further. The hypothesis proposed in this study may allow focusing research on the involvement of quality of life, nutritional status, life style, and other factors in a common anticancer mechanism; the results of these studies may assist in identifying novel targets that can be used to create more effective and personalized cancer-prevention strategies. We expect increasing integration of genetics, epidemiology, and clinical trials through valuable data among laboratories leading to genetically informative designs that will not only identify cancer genes, but also clarify how they interact with each other and how the environment influences their effects.

References

Bonamigo RR, Carvalho AV, Sebastiani VR, Silva CM, Pinto AC (2012). HLA and skin cancer. *An Bras Dermatol*, **87**, 9-16.

Changming G (1988). Analysis of the Death Caused by Malignant Carcinoma in 1986 in Jiangsu province of China. *J Oncol*, **1**, 55-9.

Chengxiao H, Darong SH (1987). Analysis of the Death Caused by Malignant Carcinoma in 1984 in Yiwu county of China. *J Oncol*, **1**, 13-24.

DeNardo DG, Johansson M, Coussens LM (2008). Immune cells as mediators of solid tumor metastasis. *Cancer Metastasis Rev*, **27**, 11-8.

Department of population and employment statistics national bureau of statistics of China (1988). China population statistics yearbook 1988.

Department of population and employment statistics national bureau of statistics of China (2006). China population statistics yearbook 2006.

Fischer GF, Mayr WR (2001). Molecular genetics of the HLA complex. *Wien Klin Wochenschr*, **113**, 814-24.

Hildesheim A, Wang CP (2012). Genetic predisposition factors and nasopharyngeal carcinoma risk: a review of epidemiological association studies, 2000-2011: Rosetta Stone for NPC: genetics, viral infection, and other environmental factors. *Semin Cancer Biol*, **22**, 107-16.

Inman BA, Frigola X, Dong H, Kwon ED (2007). Costimulation, coinhibition and cancer. *Curr Cancer Drug Targets*, **7**, 15-30.

Jing Q (2008). Analysis of the Death Caused by Malignant Carcinoma in Zhangjiagang City during 2002-2006. *Occup Health*, **24**, 966-8.

Kim S, Sunwoo JB, Yang L, et al (2008). HLA alleles determine differences in human natural killer cell responsiveness and potency. *Proc Natl Acad Sci USA*, **105**, 3053-8.

Mangalam A, Luckey D, Basal E, et al (2008). HLA-DQ6 (DQB1*0601)-restricted T cells protect against experimental autoimmune encephalomyelitis in HLA-DR3.DQ6 double-transgenic mice by generating anti-inflammatory IFN-gamma. *J Immunol*, **180**, 7747-56.

Meyer LA, Westin SN, Lu KH, Milam MR (2008). Genetic polymorphisms and endometrial cancer risk. *Expert Rev Anticancer Ther*, **8**, 1159-67.

Monteiro AN, Freedman ML (2013). Lessons from postgenome-wide association studies: functional analysis of cancer predisposition loci. *J Intern Med*, **274**, 414-24.

Pratesi F, Petit Teixeira E, Sidney J, et al (2013). HLA shared epitope and ACPA: just a marker or an active player? *Autoimmun Rev*, **12**, 1182-7.

Shames DS, Wistuba II (2014). The evolving genomic classification of lung cancer. *J Pathol*, **232**, 121-33.

Shiming D, Biao C, Qianjin L, Xianzhong L (2007). Analysis on mortality distribution of malignant tumor from 2002 to 2005 in Chongqing city of China. *Chin J Prev Contr Chron Non-commun Dis*, **15**, 66-7.

Shugart YY, Wang Y, Jia, WH, Zeng YX (2011). GWAS signals across the HLA regions: revealing a clue for common etiology underlying infectious tumors and other immunity diseases. *Chin J Cancer*, **30**, 226-30.

Sugihara S (2012). Genetic susceptibility of childhood type 1 diabetes mellitus in Japan. *Pediatr Endocrinol Rev*, **10**, 62-71.

Sun Y, Song M, Jager E, et al (2008). Human CD4+ T lymphocytes recognize a vascular endothelial growth factor receptor-2-derived epitope in association with HLA-DR. *Clin Cancer Res*, **14**, 4306-15.

Xiao X, Liu L, Li WJ, Liu J, Chen DJ (2013). HLA-A, HLA-B, HLA-DRB1 polymorphisms and risk of cervical squamous epithelial cell carcinoma: a population study in China. *Asian Pac J Cancer Prev*, **14**, 4427-33.

Xiudan P, Shaofan P, Xun L (2004). Analysis on mortality distribution of malignant tumor from 2002 to 2005 in Shenyang city of China. *Chin J Prev Contr Chron Non-commun Dis*, **12**, 273-5.

Yang XX, Pan HZ, Li PY, et al (2011). HLA class II variants in Chinese breast cancer patients. *Asian Pac J Cancer Prev*, **12**, 3075-9.

Yijian ZH (1988). Analysis of the Death Caused by Malignant Carcinoma in 1987 in Xianju county of China. *J Oncol*, **3**, 33-6.

Zhao Y, Wang J, Tanaka T, et al (2012). Association between HLA-DQ genotypes and haplotypes *vs Helicobacter pylori* infection in an Indonesian population. *Asian Pac J Cancer Prev*, **13**, 1247-51.