RESEARCH COMMUNICATION

Do Cross-Registry Comparisons of Black and White Americans Provide Support for N-Acetylation as an Important Determinant for Urinary Bladder and Other Tobacco-related Cancers?

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Abstract

Tobacco smoking is an unequivocal risk factor for cancers of the larynx, lung, pancreas and urinary bladder. Whereas African-Americans demonstrate higher laryngeal, lung and pancreatic cancer rates than their Caucasian-American counterparts, they paradoxically have only approximately half of the urinary bladder incidences. One possible explanation is their N-acetyltransferase (NAT) status, since this enzyme is responsible for metabolism of arylamines in smoke and blacks are reported to have a higher rate for rapid acetylation than whites. However, other tobacco-related cancers are also linked to slow acetylation so that African-Americans might therefore also be expected to have lower incidences of other tobacco-related cancers. The present investigation was conducted with data from Cancer Incidence in Five Continents Vol VIII to assess whether there might be correlations between incidence rates for four major cancers across registries in the United States. Cluster analysis demonstrated clear separation of the white and black populations for all states, and significant correlations were observed between bladder and laryngeal cancers, and also for lung and laryngeal cancers, for both Blacks and Whites. Striking similarities in the plots for urinary bladder incidence against all three of the other cancers suggests the existence of a factor specific to the bladder. A review of black-white ratios for cancer incidences in all major body sites in both sexes and the published literature for NAT polymorphisms provided evidence that this might indeed be arylamine exposure, although other factors could also be involved.

Key Words: Smoking-associated cancers - larynx - lung - pancreas - urinary bladder - ethnic variation

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Introduction

Tobacco smoking is an unequivocal risk factor for cancers of the upper alimentary and respiratory tracts, pancreas and urinary bladder in males (IARC, 1996). The most recent Cancer Incidence in Five Continents separate data for African-Americans and whites in the United States show that the black populations are generally more at risk of such tobacco-related cancers, with the notable exception of the urinary bladder (Parkin et al., 2002). This is an intriguing anomaly, particularly in consideration of the evidence that prostate and bladder cancers may be linked. Thus the rate of bladder cancer in patients with prostate cancer was found to be 18 times higher and the rate of prostate cancer in those with bladder cancer 19 times higher than expected in one series (Chun et al., 1997). In the World Cancer Research Fund overview in 1997, the importance of tobacco for different cancers was acknowledged and other factors were considered for their impact. In all tobacco-related sites, protection was concluded for vegetables and fruits, as well as for carotenoids and vitamin C in many cases. The other major risk factor in the esophagus and larynx is alcohol, which does not appear to have an influence in at least two of the sites, the pancreas and urinary bladder.

One explanation porposed (Yu et al., 1994) for the low urinary bladder cancer rate in blacks is their rapid N-acetyltransferase status (Lin et al., 1994; Loktionov et al., 2002), although one study found no variation for NAT-2 (Rodriguez et al., 1993), this enzyme being responsible for detoxification of arylamine carcinogens found in tobacco smoke (Hein, 1988; Hein et al., 2000). It is well documented that risk of bladder cancer development is elevated in individuals with NAT-2 polymorphisms leading to low acetylation, independent of the racial background (Hanssen et al., 1987;Dewan et al., 1995; Hsieh et al., 1999; Tsukino et al., 2004; Hung et al., 2004), but there is evidence that this is also the case for the pharynx, larynx (Drozdz et al., 1987; Morita et al., 1999; Lei et al., 2002; Varzim et al.,

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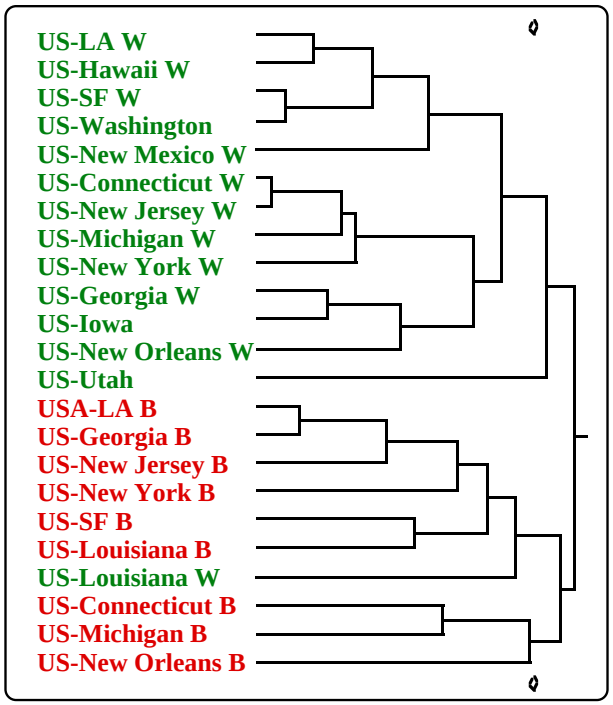

Figure 1. Ward's Cluster Analysis of ASR Rates for Laryngeal, Lung, Pancreatic and Urinary Bladder Cancers in US Registries for Black and White Males

2002) and esophagus (Morita et al., 1998; Shibuta et al., 2001). The situation appears unclear for the pancreas and lung (Philip et al., 1988; Martinez et al. 1995;Oyama et al., 1997; Zhou et al., 2002). The relationships between relative incidences of these tobacco-related cancers in different black and white populations is therefore of interest and the present cross-registry correlation study was performed with data from high quality registries from across the United States to cast light on this question. Here we focus on the larynx, lung, pancreas and urinary bladder, omitting the oesophagus because of the complication of major variation between the squamous cell carcinoma and adenocarcima incidences between males and females (Parkin et al., 1997). In addition, consideration was given to relative risks for all the major sites in both sexes of African-Americans and whites, to assess the fit with epidemiological data for influence of NAT polymorphisms.

Methodology

ASR incidence data were accessed from the IARC/WHO Cancer Incidence in Five Continents (Vol. VIII) (Parkin et al., 2002) and percentage distributions of microscopically verified cases from Vol VII (Parkin et al, 1997). The registries investigated were California Los Angeles, Black and Non-Hispanic White, San Francisco, Black and Non-HispanicWhite, Connecticut, Black and White, Atlanta Gerogia, Black and White, Iowa (considered as White), Louisiana, Black and White, New Orleans, White and Black, Detroit Michigan, Black and White, New Jersey, Black and White, New Mexico, Non-Hispanic White, New York State, Black nd White, Utah and Seattle (both considered as White). In additional to hierarchical cluster analysis after Ward (1963), correlations between organ sites were made with the JMP statistical package, version 3.1 (SAS Institute, Cary, NC) on a Macintosh computer. Simple correlation co-efficients were generated for blacks and whites separately.
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Results

Results of the cluster analysis with male larynx, lung, pancreas and urinary as variables are shown in Figure 1. With the exception of Louisiana Whites, the two racial communities form two clearly separate groups. Within the white registries, those on the West coast and Hawaii form one sub-group and those on the North-East another. With the blacks, there was no such obvious geographical grouping. Correlations between urinary bladder and larynx, lung and pancreas, as well as lung and larynx are illustrated graphically in Figure 2a-d. Clear separation of the two racial groups is evident with distributions of urinary bladder cancer relative to larynx, pancreas and lung cancers, with markedly different slopes between blacks and whites. However, in all three cases a very similar distribution of urinary bladder

Table 2. Ratios of SEER Black to White Cancer Rates*

Body Site	Male Black	Male White	Male Ratio	Female Black	Female White	Female Ratio
Mouth	4.9	2.5	1.9:1	1.6	1.4	1.1:1
Oesophagus**						
SCC	12.6	2.0	6.3:1	3.5	0.8	4.4:1
AC	0.5	2.2	0.2:1	0.2	0.8	0.3:1
Stomach	13.4	6.6	2.0:1	5.3	2.6	2.0:1
Colon	31.6	25.5	1.2:1	26.0	19.4	1.3:1
Rectum	11.5	12.2	0.9:1	7.4	7.3	1.0:1
Anus	1.1	0.7	1.6:1	0.9	0.9	1.0:1
Liver	7.1	3.8	1.9:1	2.1	1.4	1.5:1
Gall	1.4	1.4	1.0:1	1.5	1.5	1.0:1
Pancreas	12.5	7.3	1.7:1	9.1	5.5	1.7:1
Pharynx	7.5	3.4	2.2:1	1.8	1.0	1.8:1
Larynx	9.6	5.3	1.8:1	2.0	1.2	1.7:1
Lung**						
SCC	33.8	18.8	1.8:1	8.9	6.4	1.4:1
AC	28.5	18.8	1.5:1	14.5	13.0	1.1:1
Pros/Breast	185	107	1.7:1	83.1	92.1	0.9:1
Kidney**						
SCC	1.4	2.1	0.7:1	0.6	1.1	0.6:1
RCC	9.3	7.9	1.2:1	4.7	4.0	1.2:1
Pelvis	0.6	0.7	0.9:1	0.3	0.4	0.8:1
Ureter	0.1	0.5	0.2:1	0.1	0.2	0.5:1
U Bladder	11.3	23.3	0.5:1	4.2	6.2	0.7:1
Test/Ovary	1.0	5.6	0.2:1	8.8	13.2	0.7:1
Endometrium				12.0	18.4	0.7:1
Cervix				10.2	6.8	1.5:1
Vagina				0.8	0.4	2.0:1

* Data are ASR Incidence Rates (/100,000) from Parkin et al., 2002 or ** Parkin et al., 1997

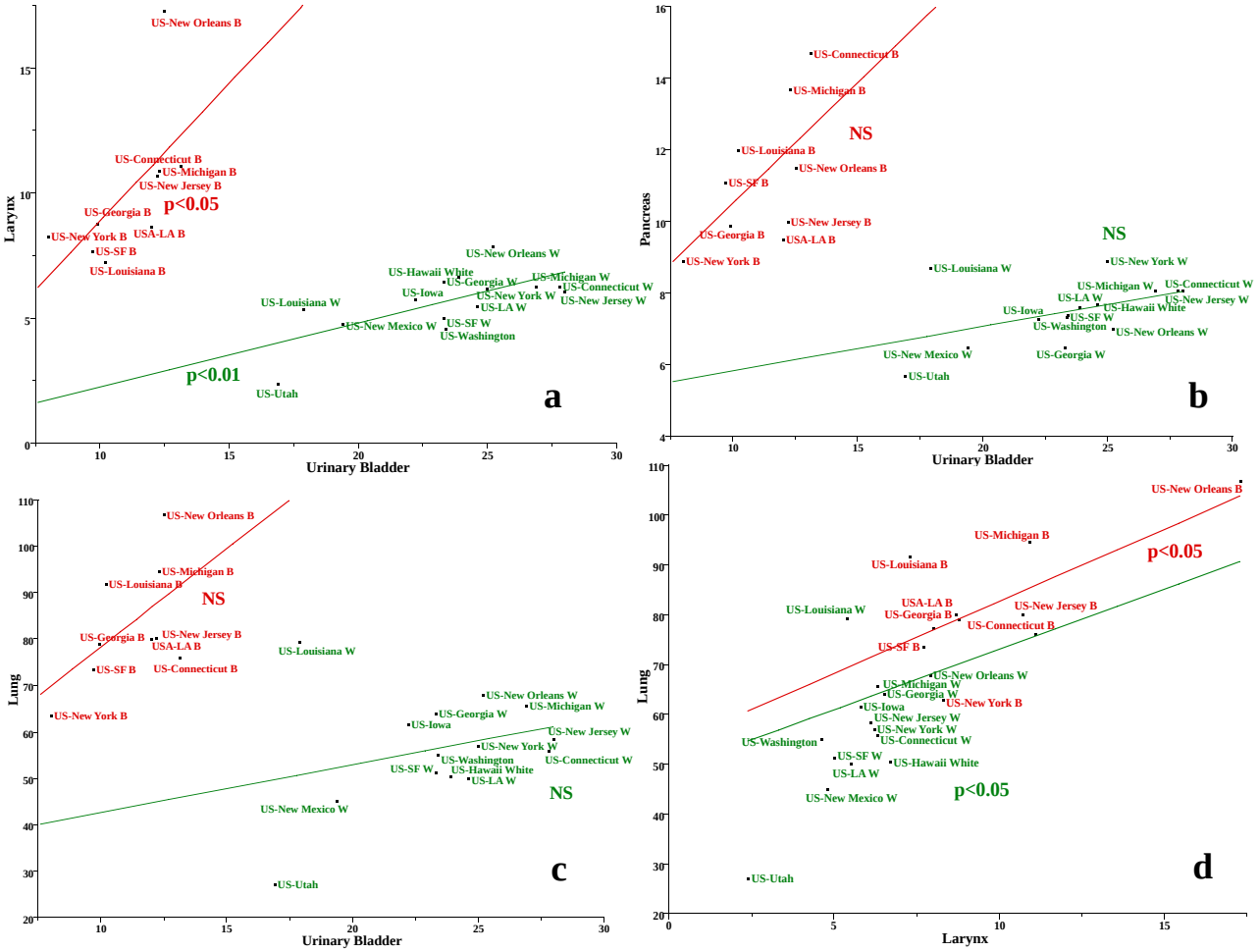

Figure 2. Plots of Cancer Incidence Rates for Tobacco-related Cancers in Black and White Americans (Data are ASR Incidence Rates (/100,000) from Parkin et al., 2002 **)**

relative to the other tobacco-related cancers was observed. Slopes were similar between the two groups for the relations between larynx and lung, these cancer sites correlating significantly, and also for pancreas with the larynx and lung (data not shown).

Data for ratios of Black to White cancers from SEER data in 2002 or 1997 (the latter chosen for availability of data for histological diagnosis for both sexes) are summarized in Table 1. Organ sites where SCC predominate, or for this tumor type within the oesophagus and lung, demonstrate clearly higher rates for blacks of both sexes, particularly in the oesophagus. In contrast, ACs of the oesophagus and testis cancers are much more prevalent in whites, as well as ureter and urinary bladder transitional cell carcinomas, and to a lesser extent cancers of the ovary and endometrium.

Discussion

The present results provide an intriguing picture of variation between the black and white populations of the United States regarding cancer incidence rates which are particularly suggestive regarding the urinary bladder and esophagus. Thus the lower urinary tract is a clear exception in the cancers generally most closely associated with tobacco consumption, although the positive correlation noted between male bladder and laryngeal cancers would indicate that smoking is a major factor also in blacks, in line with the hypothesis of rapid acetylation as the reason for low incidence rates (Yu et al., 1994). The fact of slow acetylation being linked to squamous cell carcinomas of the pharynx, larynx and esophagus, all three sites in which African-Americans have higher rates than Caucasian-Americas is in clear contradiction to the hypothesis, although the possibility that NAT2 may be involved in the activation of one or more pro-carcinogens associated with alcohol consumption might provide an explanation (Chen et al. 2001). It is unclear why the oral cavity should demonstrate no link with acetylation (Hahn et al., 2002). It has been argued that variation in the responsible carcinogens in tobacco smoke are a deciding factor, DNA adducts in the larynx being derived predominantly from polycyclic aromatic hydrocarbons, while in the urinary bladder putative aromatic amine (AA)-DNA adducts are predominant (Badawi et al., 1996). For the lungs, a recent case-control study demonstrated similar overall odds ratios (ORs) for blacks and whites, except among the heaviest smoking males, in whom ORs for blacks were considerably greater (Stellman et al., 2003). There is

evidence that blacks of both sexes are more susceptible to cigarette smoking risk than whites (Burns and Swanson, 1991) and this appears to be the case for both SCCs and ACs, from the comparison in Table 1. The report that slow acetylation is a risk factor for lung adenocarcinoma (Oyama et al., 1997) is interesting in this context.

Regarding other organ sites, individuals with high NAT2 enzyme activity may be at increased risk of developing gastric carcinoma (Ladero, et al., 2002), in line with the higher incidence rate in blacks. NAT2 does not appear to play a major role in colorectal cancer risk (Hubbard et al., 1997) and incidence rates overall are similar for both racial groups. In the liver, two studies provided evidence of slow acetylation as a risk factor (Farker et al., 2003; Gao et al., 2003) and in a third rapid acetylators demonstrated a trend for increased HCC risk with high red meat intake (Huang et al., 2003).

While there is a marked predominance of prostate in black Americans, slow NAT-2 acetylation has been shown to be a risk factor in a preliminary study (Hein et al.2002) However, in Japan NAT 1 rapid is a risk factor (Fukutome et al., 1999) and a rapid NAT2 genotype was found to correlate significantly with development of double prostate-bladder cancers (Wang et al., 2002). Many studies have shown no link between N-acetylation and breast cancer (Agundas et al., 1995; Kocabas et al., 2004), but in both Taiwan and the US, the NAT2 slow acetylator genotype has been associated with an increased risk (Alberg et al., 2004). However, the type of tobacco-related carcinogen may again be important, and a slow NAT2 status is only positively associated with active smoking, rather demonstrating an inverse influence with passive exposure (Chang-Claude et al., 2002). Slow acetylation is a risk factor in cervical cancer (Costa et al., 2002), but blacks have a higher incidence than whites. There is thus evidence both for and against the rapid acetylation hypothesis for bladder cancer and other possibilities should be considered.

Regarding excess risk in the lung, African-Americans are known to have a higher incidence of smoking than whites although the overall dosage is lower (Richardson, 1997). They are well documented to prefer menthol flavored cigarettes, but these were recently found to give no greater risk for lung cancer than unflavored brands (Brooks et al., 2003). The reported racial differences in glucuronidation of a carcinogen in tobacco would best be reconciled with excess risk of urinary bladder cancer in blacks (Richie et al., 1997). Any link between human papilloma virus infection and bladder cancer (Chan et al., 1997), would also be expected to lead to greater incidence rates in blacks, given the relative rates for cancers of the buccal cavity and cervix. There does not appear to be a reduced sensitivity of the urothelium to carcinogens overall, since elevated bladder cancer mortality among African American males and females has been documented for several occupational groups with exposure to suspected bladder carcinogens (Schulz and Loomis, 2000).

One finding of possible relevance is that serum levels of cotinine, a metabolite of nicotine, are higher among black smokers than among white or Mexican American smokers (Caraballo et al., 1998). This might reflect both slower clearance and higher intake of nicotine per cigarette, providing a possible explanation for ethnic differences in smoking-related disease risks (Perez-Stable et al., 1998). It has been proposed that tobacco-related cancers may be partly attributable to immunomodulatory properties of chronic nicotine exposure by dampening Th1 immunity and enabling tumoral evasion of immune surveillance (Yun et al., 1995). Nicotine does have a specific action on the urinary bladder since it is a diuretic (Pawlik et al., 1985), and it is known that total fluid intake is inversely related to lower urinary tract cancer (Wilkens et al 1996; Cantor et al., 1987; Lu et al., 1999). Although it should be borne in mind that beer may be a risk factor (Probert et al., 1998), high liquid throughput might result in lower concentrations of carcinogens in the urine or shorter periods of exposure (Moore, 2000). Whether there might be significant variation between African-Americans and other racial groups in the United States in consumption of drinks, including coffee, another possible risk factor for urinary bladder neoplasia (World Cancer Research Fund, 1997), is unclear.

While incidences of colon, rectum and gallbladder adenocarcinomas appear to be approximately the same in the two racial groups, there does appear to be a remarkable difference in relative risk for development of adenocarcinoma of the esophagus (Kubo and Corley, 2004). This is again intriguing, since the accepted risk factor is obesity (World Cancer Research Fund, 1997; Nguyen et al., 2003; Znaor et al., 2003) and African-Americans do not generally have lower total body fatness than whites (Summerson et al., 1996), although they tend to have lower visceral adipose tissue accumulation and high HDL cholesterol levels (Depres et al., 2000). Together with low triglycerides this might explain the lower risk of coronary heart disease experienced by black males compared with whites and black females (Zoratti, 1998). In contrast they appear to demonstrate a higher prevalence of hypertension and diabetes (Ahluwalia et al., 2003). Interestingly, abdominal obesity was found to be associated with 44, 90 and 98% increased odds of prehypertension in male Whites, Blacks and Hispanics, respectively, and 112, 198 and 104% in females (Okosun et al., 2004). Whether there are racial differences in other risk factors for esophageal adenocarcinoma, such as hiatal hernia, linked to body size, in combination with other reflux conditions and symptoms, (Wu et al 2003) remains to be determined.

The present ecological approach clearly can not provide answers to many of the questions raised by registry data. However, pointers for future research may be gleaned from an awareness of the marked variation between particular registries. For example, why do whites in Louisiana have only half the urinary bladder risk of their counterparts in the state capitol, New Orleans, while demonstrating considerably higher pancreatic, and greater incidences of lung but not laryngeal cancer? This is presumably related to

the present findings from hierarchical clustering. Similar anomalies are just as evident for the African-Americans in these two populations (see Fig 2). Comparisons of groups with similar ethnic and cultural backgrounds may provide aids to developing new hypotheses. Whether cross-sectional studies focused on particular populations are warranted to provide more detailed profiling, perhaps with involvement of cancer registries in more complex data collection, is clearly worthy of greater attention (Moore and Tajima, 2004).

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