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Interracial Comparative Study of Prostate Cancer in the United States, China, and Japan

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Abstract The interracial differences of prostate cancer progression have long been documented; however, underlying molecular and cellular mechanisms remain obscure. This study focuses on the histopathologic, immunohistochemical, biochemical, and molecular characterization of prostate cancer tissues unselectively obtained from US, Chinese, and Japanese men. Histopathologic analyses indicate that 74.5% of the prostate cancers in Chinese patients were poorly differentiated, compared with 28.6 and 32.8% of the prostate cancers in US and Japanese men, respectively. These differences cannot be attributed to patient age, clinical stage of disease, or methods of tissue sampling. Furthermore, the high proportion of poorly differentiated prostate cancer tissues in the Chinese group was not related to the patients' access to medical service or their geographic origins within China. We found significantly higher levels of tumor angiogenesis (2- to 4-fold), serotonin (2- to 20-fold), and bombesin (7- to 16-fold), but not chromogranin A, in tissue specimens obtained from Chinese prostate cancer patients compared with those from US and Japanese patients. We also found marked differences in p53 protein accumulation among various ethnic groups. The p53 protein was frequently detected in prostate cancer tissue specimens from Chinese (90.2%), but less frequently in US black (3.7%), US white (17.4%), and Japanese (7.1%) men. Further analysis of 31 prostate cancer tissues from Chinese men indicated that mutational changes in the *p53* gene occurred between exons 5 and 8. J. Cell. Biochem. Suppls. 28/29:182–186.

Key words: prostate cancer in Chinese men; angiogenesis; neuroendocrine factors; p53 protein; *ras* oncogene; androgen receptor

Prostate cancer is the most prevalent cancer among men in the United States (US) and many Western countries [1]. The clinically detected rates of prostate cancer vary distinctly around the world [1]. China and Japan are among countries with the lowest incidence rates of clinical prostate cancer [1]. Zhao et al. reported a comparative study on clinical staging and histological grading of prostate cancers in Chinese and Japanese men [2]. The results indicated that 79% (80/111) of the Chinese patients presented as stages B and C at first diagnosis, while 52% (239/460) of the Japanese patients were stage D. The majority (61%, 68/111) of Chinese patients were poorly differentiated. In comparison, 51% (235/460) of the Japanese patients were moderately differentiated. However, no immunohistochemical or biochemical data documented a possible molecular basis of interracial differences of prostate cancer. In recent years, several groups reported differences in *ras* oncogene and androgen receptor mutations in prostate cancer tissues obtained from US and Japanese men.

The reported incidence of *ras* oncogene mutations associated with prostate cancer in US patients is between 0 and 12.5%. However, 24% each of latent (11/44) [3] and clinical (16/68) [4] prostate cancer tissues from Japanese patients had *ras* mutations. The majority of mutation codons in latent clinical cancer are at K*ras*12 and at H*ras*61 [3].

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Androgen and its receptor (AR) play an integral role in the growth and differentiation of the prostate gland. Mutations in the AR gene were identified in both primary and metastatic prostate cancer tissues. The majority of analyses involved DNA-binding and hormone-binding domains (i.e., exons B to H). Takahashi et al. [5] reported a 14% (10/74) incidence of AR mutations in latent prostate cancer in Japanese patients. In the same study, they found no AR mutations in US latent prostate cancer, nor in either US or Japanese clinical prostate cancer.

Recognizing the rapid changes in both diet and living environment in China and the increasing trend of clinical prostate cancer in both China and Japan, we launched a comparative study that contrasted the occurrence of certain risk factors between these ethnic groups; we also studied the same factors in US blacks (known to have 2 to 3-fold higher incidence of prostate cancer, as compared to their white counterparts) and US whites. We believe this type of approach will eventually yield important insights into the intrinsic biochemical and molecular differences in prostate cancers among diverse ethnic groups, enhancing our understanding of prostate cancer biology.

RESULTS

Histopathology

We analyzed 112 tissue specimens from US prostate cancer patients, 180 specimens from Chinese, and 460 from Japanese patients [6]. Histopathologically (Table I), the US and Japanese prostate cancers were predominantly moderately differentiated. In contrast, the Chinese prostate cancers were typically poorly differentiated with Gleason scores of 8 to 10. These differences were statistically highly significant (chi square test, $P < 0.001$). No regional differences of tumor differentiation were noted in the subpopulations of Chinese living in the north (Jilin) vs. central China (Sichuan). The differences in tumor differentiation cannot be attributed to clinical stages. The great majority of US and Chinese specimens were clinical stages B and C, while the majority of Japanese were stage D.

Tumor Angiogenesis

Tumor angiogenesis quantified by microvessel density count correlates with advanced prostate cancer and was proposed as a prognostic marker [7,8]. The microvessel counts in prostate cancer tissues from Chinese patients were significantly higher than those in US blacks, whites, and Japanese (Table II). When microvessel counts were compared separately by each Gleason score, the interracial differences were also significant statistically. However, within each race group, microvessel counts were not correlated with Gleason score.

Neuroendocrine Factors

Neuroendocrine factors have been implicated in prostatic cell growth and differentiation, and were shown to correlate with poor survival of prostate cancer patients [9–11]. We analyzed serotonin expression by the actual counts of positively stained cells per specimen in normal stromal and basal cells, as well as cancerous stromal, basal, and epithelial compartments. We found significant interracial differences in serotonin expression in all tissue compartments except the cancerous basal area (Fig. 1). Chinese patients have the highest positive cell counts in the normal basal area. US blacks and Japanese have low overall counts. Similar analyses were done for bombesin. Striking dif-

TABLE I. Comparison of Tumor Differentiation Among US, Chinese, and Japanese Prostate Cancer Cases

	No. (%) specimens in each tumor differentiation category			
Specimen	Well	Moderate	Poor	Total
US	4 (3.6)	76 (67.8)	32 (28.6)	112 (100)
Chinese	6 (3.3)	40 (22.2)	134 (74.5)	180 (100)
Japanese	74 (16.1)	235 (51.1)	151 (32.8)	460 (100)

TABLE II. Comparison of Microvessel Scores in Prostate Cancer Tissues From US Blacks, U.S. Whites, Chinese, and Japanese

Groups	Gleason score	No. of specimens	Mean no. of microvessels ± SD
US blacks	5,6	3	24 ± 14
	7	5	27 ± 19
	8–10	5	38 ± 16
US whites	5,6	21	30 ± 17
	7	34	30 ± 20
	8–10	18	44 ± 22
Chinese	5,6	3	50 ± 19
	7	10	80 ± 25
	8–10	46	86 ± 46
Japanese	5,6	2	26 ± 16
	7	4	22 ± 13
	8–10	13	23 ± 15

ferences in bombesin expression were also found in normal stromal and basal areas, and in cancerous stroma (Fig. 2). Tissues from Chinese prostate cancer patients also had the highest bombesin-positive cells in all five tissue compartments. US blacks had the overall lowest positive cell counts. The Japanese group was not analyzed. However, we did not detect significant interracial differences in the expression of chromogranin [6].

p53 Protein Accumulation

p53 tumor suppressor gene mutation is implicated in a number of human malignancies, in-

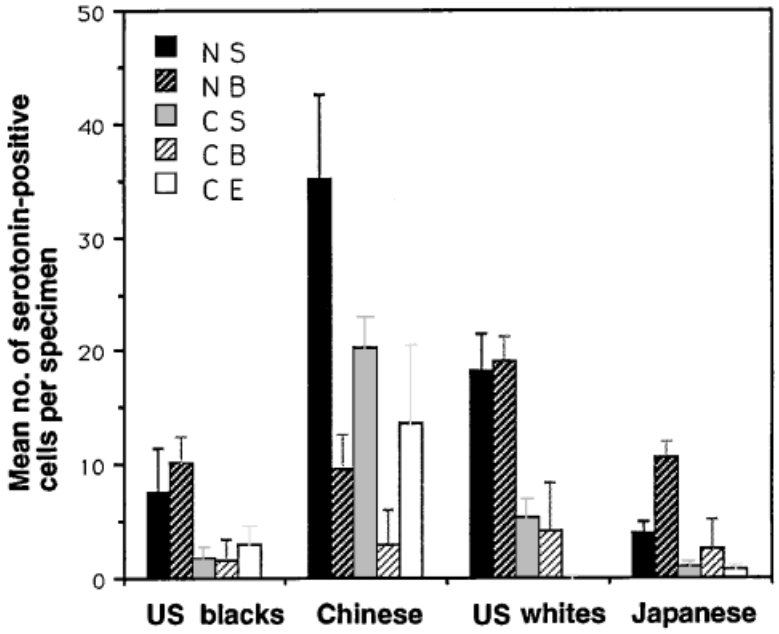

Fig. 1. Interracial differences of the average number of serotonin-containing cells [+ standard error (SE)] in stromal (NS) and basal (NB) compartments of normal prostate tissue areas and in stromal (CS), basal (CB), and epithelial (CE) compartments of cancerous tissue area.

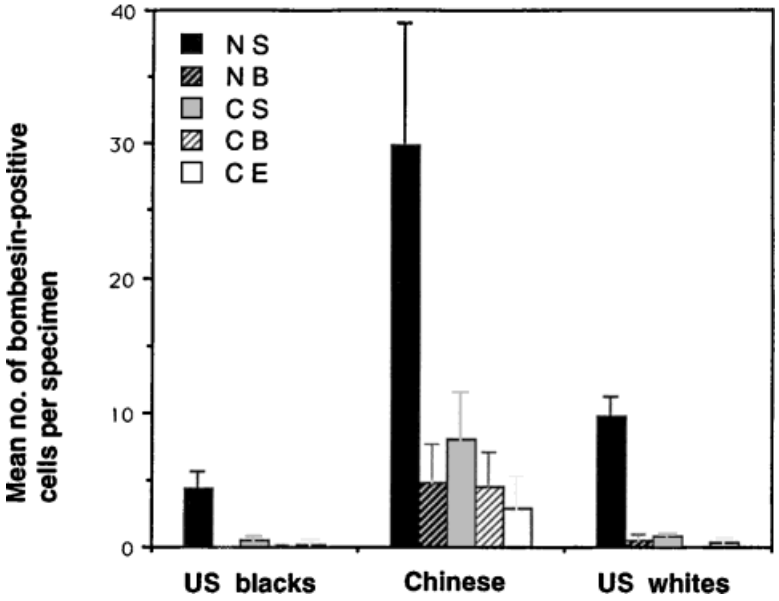

Fig. 2. Interracial differences of the average number of bombesin-containing cells (+ SE) in prostate tissues among different cell compartments. (See legend to Figure 1 for abbreviations.)

cluding prostate cancer [12–14]. Mutations were most studied and commonly found between exons 5 and 8 [12]. The accumulation of p53 nuclear protein was detected by immunohistochemical staining of paraffin tissue sections using a monoclonal antibody, pAb 1801 or DO1. Strikingly high numbers of Chinese prostate cancer tissues contain p53 nuclear protein (90.2%, 37/41), as compared to 7.14% (2/28) in Japanese, 3.7% (1/27) in US blacks, and 17.4% (4/23) in US whites. Half of the tissue specimens from Chinese patients were identified with p53 protein accumulation and confirmed by aberrant profiles of PCR-SSCP products within exons 5 to 8. Direct DNA sequencing of the aberrant PCR-SSCP products was confirmed in 44% of the cases. Further analyses of the *p53* mutation showed that, unlike tissue specimens from Japanese patients, those from US and Chinese patients have predominantly transitional GC→AT mutations. In contrast to tissue specimens from Japanese and US patients, mutations in tissue specimens from Chinese patients were limited only to the GC region. We analyzed all exons (1 to 11) of the *p53* gene by single-strand conformation polymorphism in 31 tissue specimens from Chinese patients. The *p53* mutations were localized only in exons 5 to 8.

Summary and Implications

We have demonstrated that the majority of Chinese prostate cancer tissues in this series are poorly differentiated. Substantial differences exist in degree of angiogenesis, number and distribution of cells that express neuroendocrine factors, and protein accumulation and mutational spectra of the *p53* gene in prostate cancer tissues from different ethnic groups. The results of our study imply that genetic or genetic/epigenetic interactions may account for the rapid progression of a subset of Chinese prostate cancer patients. Also, the lower incidence of clinical prostate cancers in China may be due to lack of the "multihits" believed necessary for development of clinical prostate cancers. Studying racial and geographic differences in clinical prostate cancer may help identify the subtypes of cancers with different progression rates and the clinically relevant biomarkers for cancer occurrence and progression. These biomarkers will be valuable in conducting chemopreventive trials in men with prostate cancer. From this analysis, it would appear that the neuroendocrine factors serotonin and bombesin merit further investigation as potential surrogate endpoint biomarkers.

Incidence rates of clinical prostate cancer in China and Japan are increasing. The rapid westernization of diet and lifestyle and increasing industrialization, which affects both urban and rural communities, may make prostate cancer the predominant cancer of Asian men in the 21st century. This emphasizes the importance of identifying causative prostate cancer progression factors and effective strategies to prevent the disease.

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