to 4 μM BPDE in vitro, the lymphocytes were harvested for cytogenetic study. The average of simple chromatid breaks per cell (b/c) from a total of 50 metaphases per subject was used for statistical comparisons. Overall, cases had a greater mean b/c value (mean±SD, 0.53±0.22) than controls did (0.41±0.16). The difference was statistically significant (P<0.001). Using the control median b/c as the cut-off value for high and low sensitivity, high sensitivity was associated with a four-fold increased risk (Odds ratio, 4.00; 95% confidence interval, 1.61-9.97; adjusted for age and ethnicity). This preliminary finding suggests that increased sensitivity to tobacco carcinogens may play a role in the etiology of breast cancer. (Supported in part by HIH grant CA70264, CA55769, and CA70334).

#820 *WAF-1 (P21)* AND *P53* POLYMORPHISMS IN BREAST CANCER. Channa K C Keshava, B. L Frye, M. S Wolff, and A. Weston, *Mount Sinai Med Ctr, New York, NY, and Niosh,, CDC, Morgantown, WV*

Previous studies have indicated that certain *p53* polymorphisms confer an increased risk of breast cancer (ORs and 95%CIS = 2.9, 1.4 – 6.3 *Carcinogenesis* 17: 1313, 1996; 2.5, 1.3 – 4.8 *Cancer Epidemiology, Biomarkers and Prevention* 6:105, 1997; 1.5, 1.1 – 2.0, *Anticancer Research* 18: 2095, 1998). *p53* is a transcription factor for *Waf-1/p21* a cyclin-dependent kinase inhibitor, which is also polymorphic. To test the hypothesis that minor variants (F = 0.10 Caucasians, 0.27 Latinas, 0.34 African Americans) of a codon 31 polymorphism of *Waf-1* are involved in this process, genotypes were determined by PCR/RFLP for 355 women (122 cases and 233 controls) enrolled in a breast cancer case-control study. No increased breast cancer risk was associated with inheritance of minor variants of *Waf-1* (OR = 1.1, 95%CI = 0.7 – 1.6). Similarly, analysis by both race and menopausal status was unable to find any association. Finally, despite an increased risk for Caucasians associated with the *p53* genotype (*CEBP* 1997), no risk was found to be associated with *Waf-1* alleles independently or in combination with *p53* alleles (OR = 1.1, 95%CI = 0.3 – 4.7).

#821 CHARACTERISTICS OF P53, HER/*NEU* AND *BCL-2* IN A LOW RISK BREAST CANCER POPULATION OF CHINESE PATIENTS FROM MAINLAND CHINA. XiaoTan Qiao, Karen S Fiderici, Zeng Si, ChangBan Gong, GongHa Zhou, Yan Li, Lin Wang, KeFeng Dou, Kenneth S van Golen, Sofia D Merajver, and Charles D Mackenzie, *BenXi Gen Hosp, BenXi, People's Rep of China, China-Japan Friendship Hosp, BeiJing, People's Rep of China, Michigan State Univ, East Lansing, MI, Univ of Michigan, Ann Arbor, and XiJing Hosp, Xian, People's Rep of China*

Reliable epidemiological data reveal striking differences in breast cancer risk between the North American Caucasian and Chinese Asian populations. We hypothesize that these differences in risk reflect in part, different pathways of breast carcinogenesis, which may, in turn be due to epigenetic or environmental variables. To begin to test this hypothesis, we investigated a cohort of 178 patients breast cancer samples from mainland China. The tumors were analyzed for descriptional parameters such as age, stage, ER/PR status, and grade as well as molecular genetic alterations in p53, HER-2/*neu*, and Bcl-2. For p53, HER2/*neu* (*c-erbB-2*), and Bcl-2, 14.2%, 23.1% and 66.4% stained positively by immunohistochemistry. HER2/*neu* gene amplification was detected by differential polymerase chain reaction methods and 29.1% of specimens were positive. Sixty-four samples were evaluated for p53 gene point mutations in exon 5 to 9 by PCR-single strand conformation polymorphism assay, followed by gene sequence analysis: only 1/64 (1.56%) was found to be positive for a missense transition mutation at codon 151, a CpG site. The results demonstrated that the Western (high breast cancer risk group) and Chinese (low risk group) populations have similar phenotypic features and also similar proportions of genetic alterations in these 3 key molecular markers.

#822 BREAST CANCER INCIDENCE AMONG A COHORT OF WOMEN WITH BENIGN BREAST DISEASE. Angela C Blount, Usha Raju, Judith Abrams, Michelle Jankowski, S David Nathanson, Sandra R Wolman, Maria J Worsham, and Christine C Johnson, *Henry Ford Health System, Detroit, MI, Uniformed Service Univ of the Health Sci, Bethesda, MD, and Wayne State Univ, Detroit, MI*

The risk of developing breast cancer has been reported to be increased among women with a history of benign breast disease (BBD). A cohort of women diagnosed with BBD from 1981-1994 was established to investigate this relationship in a large health care system. Women were eligible for entry with an initial index BBD biopsy performed during this time period. A diagnosis of breast cancer prior, concurrent or within 6 months of the index BBD biopsy ruled women ineligible for the cohort. The archived pathology reports of all breast biopsies were retrieved and reviewed by an expert breast pathologist to identify specimens containing only BBD lesions. The slides were microscopically reviewed for confirmation of the diagnosis utilizing a universal diagnostic terminology system. All cohort members were followed from their index BBD biopsy for the subsequent occurrence of breast cancer. During cohort establishment, 5254 women were found to be eligible and 116 ineligible. Slide review revealed the lesions were primarily proliferative (65%), with 30% non-proliferative, and 4% atypical ductal or lobular hyperplastic. The cohort yielded 167 cases of breast cancer detected through July 1999. With 48,201 person-years of follow-up, the average incidence rate was 346.5 per 100,000 (95% confidence interval [CI], 295.9-400.8), ranging from 298.3 (95% CI, 148.9-534.0) in the 1981 cohort year to 530.8 in 1994 (95% CI, 254.8-976.6). In comparison to 1991-1995 SEER rates of 353.8 nationally and 363.6 per 100,000 for the metropolitan Detroit area among women aged 50 and older, breast cancer incidence in this BBD cohort does not appear to differ from the general population.

#823 EVALUATION OF PROPHYLACTIC OPTIONS FOR ASHKENAZI JEWISH WOMEN WITH A BRCA MUTATION: A DECISION ANALYSIS. Lesley-Ann Natasha Miller, and Mendel E Singer, *Case Western Reserve Univ Sch of Medicine, Cleveland, OH*

Ashkenazi Jewish women have a high prevalence (about 2.5%) of three specific BRCA1/2 mutations that are associated with an increased risk of developing breast or ovarian cancer. The authors developed a Markov decision model and used Monte Carlo simulation to evaluate the implications of various prophylactic options for a 40 year old woman who tests positive for any one of these mutations. Prophylactic options considered included prophylactic mastectomy (PM), prophylactic oophorectomy (PO), both PM and PO, tamoxifen chemoprevention, and increased screening. Parameter estimates were taken from SEER cancer statistics and the published literature. Outcomes considered were additional life expectancy and quality-adjusted life years (QALYs). We assumed that PO would reduce the risk of ovarian cancer (OC) by 46% and breast cancer (BC) by 25%, PM would reduce the risk of BC by 90%, and tamoxifen would reduce the risk of BC by 44%. Increased screening was defined as biennial mammography and clinical breast exam. We postulated that this increased screening would lead to beneficial gains associated with an earlier stage of diagnosis. The results indicate that the strategy of both PM and PO offered the greatest benefit in terms of increased life expectancy. However, after adjusting for quality of life (QOL), increased screening becomes the preferred strategy. For all surgical or chemopreventive strategies, the loss in QOL more than offset the benefit of the associated risk reduction. Time discounting of future life years had no impact on the results. QOL considerations may have a profound impact on choosing the optimal BC/OC prophylaxis.

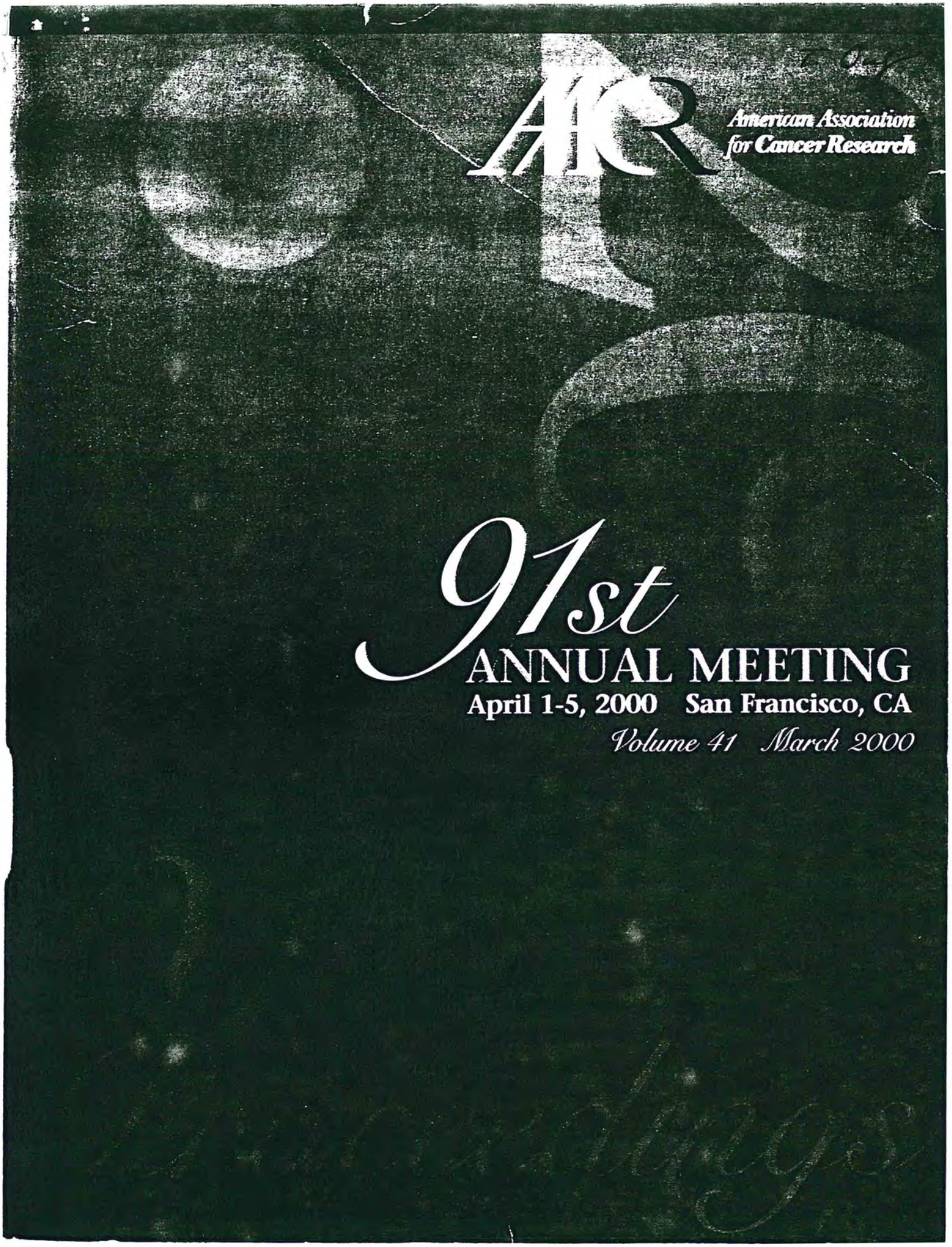
#824 ASSOCIATION BETWEEN BREAST CANCER AND THE THREE DIFFERENT VITAMIN D RECEPTOR GENE POLYMORPHISMS TAQI, BSMI AND APAI. Diana Lueftner, M. Schweigert, K. Engellandt, P. Petrides, I. Roots, K. Possinger, and I. Cascorbi, *Humboldt Univ Berlin, Berlin, Germany*

Breast cancer (BRCA) growth is influenced by vitamin D. We investigated the distribution of the *TaqI* (T/t), *BsmI* (B/b) and *ApaI* (A/a) VDR gene polymorphisms in 247 BRCA patients and 248 age-matched controls. After DNA extraction from white blood cells, VDR genotypes were determined by polymerase chain reaction (PCR) amplification followed by restriction enzyme digestion of the PCR product. The mean age for BRCA patients (and controls) was 60.4 (60.1) years with a range from 31–90 (31–91) years. The VDR genotype distribution for BRCA patients (in comparison to controls) was as follows: BB: 17.8% (17.3%); Bb: 46.6% (48%); bb: 35.6% (34.7%); AA: 26.7% (26.6%); Aa: 49.8% (53.6%); aa: 23.5% (19.8%); TT: 37.7% (39.1%); Tt: 47.4% (51.6%); tt: 15.0% (9.3%). The VDR genotype distribution was statistically not different between BRCA patients and controls for the *BsmI* and *ApaI* genotypes. However, for *TaqI* an increase of the genotypes TT + Tt vs. tt could be found (odds ratio: 1.72; CI: 0.99–2.99, p=0.052). Combined analysis adjusted for age and considering all genotypes revealed a relative risk of TT vs. tt of 3.02 (CI: 1.19-7.71, p=0.02) to develop breast cancer. This finding is important for the screening of risk families and for replacement therapy in hospitalized patients who generally show a decreased vitamin D level.

CELL AND TUMOR BIOLOGY 6: Proteases I

#825 RAPID TRAFFICKING OF MT1-MMP TO THE CANCER CELL SURFACE FROM A POST-GOLGI STORAGE POOL RESULTS IN EXPLOSIVE CELL SURFACE ACTIVATION OF LATENT MMP-2. Stanley Zucker, Michelle H Hymowitz, Cathleen E Conner, and Jian Cao, *SUNY - Stony Brook, Stony Brook, NY, and VA Med Ctr, Northport, NY*

Pericellular matrix degradation during cancer invasion is dependent on activation of proMMP-2 by Membrane Type 1-Matrix Metalloproteinase (MT1-MMP). We herein report that concanavalin A (con A) or phorbol (PMA) treatment of HT-1080 fibrosarcoma cells is followed by MT1-MMP induced activation of proMMP-2 on the cell surface within 30 min. Surface biotinylation, immunoprecipitation, and ^{125}I-TIMP-2 binding techniques were employed to characterize MT1-MMP appearance on the cell surface. Con A-induced trafficking of MT1-MMP from a post-Golgi compartment (endosomal/secretory) to the cell surface occurred within 10 min. Rapid MT1-MMP trafficking was accelerated by brefeldin A, a Golgi inhibitor and chloroquine, a lysosome inhibitor; cycloheximide, a protein synthesis inhibitor, had minimal early effect. Rechallenge of HT-1080 cells with con A 3 hr later demonstrated a requirement for new protein synthesis and transit through the Golgi (inhibited by cycloheximide/brefeldin A). Con A enhancement of MT1-MMP mRNA synthesis was not noted before 18 hr. After binding to cell surface MT1-MMP, ^{125}I-TIMP-2 is internalized and secreted as an intact protein after 3 hr. These results are consistent with an intracellular recycled storage pool for MT1-MMP which is readily available to invasive cancer cells.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