*2138

PROPHYLACTIC MASTECTOMY (PM) AND OOPHORECTOMY (PO) IN WOMEN UNDERGOING BRCA1/2 TESTING. *D. Schrag, K.J. Kalkbrenner, T.L. Light, K.A. Schneider, J.E. Garber. Dana Farber Cancer Institute, Boston, MA.*

Women tested for BRCA1/2 mutations may consider PM and/or PO based on the results of genetic testing for predisposing mutations. A cohort of 88 women with at least 10% risk of inherited breast/ovarian cancer provided information about attitudes towards PM and PO before testing and again at mean 5.5 months following results disclosure. 46 women had prior breast/ovarian cancer (CA); 42 women had not had cancer (NC). Before genetic testing, 8 women had had PM, 12 PO and 5 therapeutic oophorectomy. At baseline, 37/80 had discussed PM with a physician and 33/71 had discussed PO 8/80 were considering PM and 24/71 PO. Following BRCA disclosure, 6 women underwent PM (3 CA, 3 NC) and 5 had PO (2 CA, 3 NC); one woman (NC) had both procedures. Mutations were identified in all women having prophylactic surgery following results disclosure except for 2 who had PM with indeterminate results but abnormal breast biopsies. In addition, 13 were still considering PM (8+, 4?) and 19 were considering PO (12+, 6?, 1−) For the entire cohort, no cancers have been detected at PM; one borderline ovarian cancer was found at PO. PM and PO are often considered by women who have BRCA1/2 mutation testing even with indeterminate test results.

*2139

LY231514 (MTA): RELATIONSHIP OF VITAMIN METABOLITE PROFILE TO TOXICITY. *C. Niyikiza, J. Walling, D. Thornton, D. Seitz, and R. Allen. Eli Lilly and Company, Indianapolis, IN, and Univ of Colorado Health Science Center, Denver, CO.*

LY231514 (MTA) is a new generation multitargeted antifolate antimetabolite with inhibitory activity against thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase. Of a total of 246 patients (pts) in phase II trials treated with MTA (600 mg/m^2 IV over 10 minutes once every 21 days) 118 pts also had vitamin metabolites measured. Because earlier studies with other antifolates had suggested that nutritional status may play a role in the likelihood that a patient will experience severe toxicity, levels of the vitamin metabolites homocysteine, cystathionine and methylmalonic acid were measured at baseline and once each cycle thereafter. A multivariate statistical analysis of the data was conducted in order to determine which among a set of pre-specified predictors (creatinine clearance, albumin levels, liver enzyme levels, and vitamin metabolites) might correlate with toxicity. There was a strong correlation between baseline homocysteine levels and the development of the following toxicities at any time during the study: CTC Grade 4 neutropenia (57 pts, $p < 0.0001$), Grade 4 thrombocytopenia (13 pts, $p < 0.0001$), Grade 3 or 4 mucositis (8 pts, $p < 0.0003$), and Grade 3 or 4 diarrhea (8 pts, $p < 0.004$). Cystathionine levels did not correlate with hematologic toxicity or mucositis but were moderately correlated with fatigue ($p < 0.04$). Maximum cystathionine levels doubled from baseline during treatment with MTA. No correlation between toxicity (CTC Grades as defined above) and the remaining pre-specified predictors was seen. Toxicity was seen in all patients with homocysteine levels above a threshold concentration of 10 μM. A correlation over time between homocysteine levels and CTC Grade 4 neutropenia and thrombocytopenia and CTC Grade 3 or 4 mucositis was also observed, but only in the first two cycles of treatment. Maximum homocysteine levels did not appear to change from baseline during treatment with MTA.

*2140

PHASE I CHEMOPREVENTION CLINICAL TRIAL OF CURCUMIN *A.L. Cheng, J.K. Lin, M.M. Hsu, T.S. Shen, J.Y. Ko, J.T. Lin, B.J. Lin, M.S. Wu, H.S. Yu, S.H. Jee, G.S. Chen, T.M. Chen, C.A. Chen, M.K. Lai, Y.S. Pu, M.H. Pan, Y.J. Wang, C.C. Tsai, C.Y. Hsieh. National Taiwan University College of Medicine, Taipei, Taiwan; and Kaohsiung Medical College, Kaohsiung, Taiwan.*

Curcumin (diferuloylmethane), a yellow substance from the root of the plant Curcuma longa Linn., has been demonstrated to inhibit murine carcinogenesis of skin, stomach, intestine and oral cavity. A phase-I clinical trial was conducted to examine the toxicology, the pharmacokinetics and the biologically effective dose of curcumin in humans. Five types of high-risk individual were eligible: 1. recently-resected urinary bladder cancer (BC), 2. arsenic Bowen's disease (BD), 3. uterine cervical intraepithelial neoplasia (CIN), 4. oral leukoplakia (OL), and 5. intestinal metaplasia of gastric mucosa (IM). The starting dose was 500 mg/day, taken orally for 3 months. If no any ≥ Grade II toxicity was noted in at least 3 p'ts, the dose was escalated successively to 1000 (level II), 2000 (level III), 4000 (level IV), and 8000 mg/day (level V). Lesion sites were biopsied before and 3 months after taking curcumin. Serum curcumin was quantitated by HPLC method. In a total of 25 p'ts enrolled, no treatment-related toxicity was noted up to 8000 mg/day (level V). Serum concentration usually peaked at 1 to 2 hours after oral intake, and gradually declined within 12 hours. The average peak serum concentrations after taking 4000 mg, 6000 mg and 8000 mg of curcumin were 0.41 ± 0.07 μM, 0.57 ± 0.05 μM, and 1.75 ± 0.80 μM, respectively. Although 3 of 25 p'ts proceeded to develop frank malignancies, histological improvement of the precancerous lesions was seen in 1 (level III) of the 2 p'ts with BC, 2 (both level IV) of 7 p'ts with OL, 1 (level II) of 6 p'ts with IM, 1 (level I) of 4 p'ts with CIN, and 2 (level I and III) of 6 p'ts with BD. Although curcumin is probably non-toxic even up to more than 8000 mg/day, the bulky volume of drug tablets became a limiting factor itself. Therefore, for future phase II studies, doses close to 8000 mg/day may be recommended.

*2141

FACTORS INFLUENCING THE DECISION TO UNDERGO BRCA1/2 GENE TESTING: A STUDY OF ASHKENAZI JEWISH WOMEN WITH A PERSONAL HISTORY OF BREAST CANCER (BC), ENROLLED IN AN ONTARIO CANCER GENETICS NETWORK PROTOCOL. *K.A. Phillips, J. Hunter, E. Warner, W. Meschino, G. Glendon, I.L. Andrulis and P.J. Goodwin. Mt Sinai Hospital, Princess Margaret Hospital, Toronto-Sunnybrook Regional Cancer Center, North York General Hospital, Toronto, Ontario, Canada.*

The purpose of this study was to examine the contribution of demographic, medical, psychosocial, and cultural/religious factors in decision making regarding testing for BRCA1 and BRCA2 mutations, in Canadian Jewish women with BC, unselected for family history. A self-administered questionnaire was developed and distributed, (after genetic counseling), to 134 individuals enrolled in a research-based testing program for Ashkenazi women. Data for the first 52 participants are presented. The response rate was 40 (77%). Respondents had the following demographic features: age 40–75 years (median = 59), married 83%, had children 92%, post-secondary education 55%, practicing Jew 88%, extra health insurance 77%, median age of BC diagnosis = 50. No patient had ovarian cancer (OC). 45% had at least one 1st degree relative with BC or OC (median perceived risk for being a gene carrier 50%). 35% had no affected relatives (median perceived risk for being a carrier = 15%). The 5 factors most frequently identified as "definitely an important factor in my decision making" were, desire to contribute to research (90%), curiosity (77%), potential benefit to other family members (64%), potential for personal cancer prevention (59%), and impact on ovarian cancer screening practice (41%). 53% and 38% of women respectively, identified a potential change in their perspective on prophylactic oophorectomy and mastectomy as at least "somewhat important." Main concerns related to insurance discrimination (35%), confidentiality (30%), accuracy and interpretability of results (33%), potential impact on marriage prospects for family members (20%), and focus on the Jewish community (15%). Potential employer discrimination and impact on life planning were "not a factor" for most (90%,82%). The focus on factors unrelated to personal physical health is notable. The generalisability of these results to women not affected by BC requires further study. Final results for the 134 patients will be presented.