Association of Galactose-1-Phosphate Uridyltransferase Activity and N314D Genotype with the Risk of Ovarian Cancer

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Deficiency in the galactose-1-phosphate uridyltransferase (GALT) enzyme results in accumulation of galactose and its metabolites in the ovary (Am J Epidemiol 1989;130:904–10). Galactose may raise gonadotropin levels, resulting in proliferation of ovarian epithelium. In 1993–1999, the authors conducted a population-based case-control study of ovarian cancer in Hawaii and Los Angeles, California, to examine the hypothesis that reduced GALT activity is associated with an increased risk of ovarian cancer. A total of 239 ovarian cancer cases and 244 population controls were interviewed. A blood sample was collected to measure levels of GALT and to assay for the N314D (A940G) polymorphism of the GALT gene. Covariate-adjusted mean GALT activity was similar between cases (23.8 µmol per hour/g hemoglobin (Hb)) and controls (23.7 µmol per hour/g Hb) (p = 0.83). No evidence was found for a dose-response relation between the odds ratios for ovarian cancer and GALT activity or the ratio of lactose intake to GALT activity. The risk associated with the presence of at least one variant Asp314 allele was 0.77 (95% confidence interval: 0.42, 1.41). This study did not support the hypothesis that reduced galactose metabolism is a risk factor for ovarian cancer, although increased GALT activity attenuated the inverse association of oral contraceptive pill use with risk.

Abbreviations: CI, confidence interval; GALT, galactose-1-phosphate uridyltransferase, Hb, hemoglobin.

The reduced incidence of ovarian cancer among Asian and Pacific Islander women compared with White women in the United States may result from differences in dairy product intake. An international correlation study showed a positive association of milk consumption and lactase persistence with the incidence of ovarian cancer (1). Aside from differences in eating patterns, lactase persistence—or the ability to digest lactose—is much higher among adult northern Europeans (78–97 percent) and Whites in the United States (94 percent) than among Japanese and other Asian populations (0–10 percent) (2). As a consequence, dairy product intake and exposure to lactose are lower among Asians (and Pacific Islanders) than among Whites.

An association of lactose intake and metabolism with the risk of ovarian cancer is biologically plausible. High concentrations of circulating galactose, which is separated from glucose during digestion of lactose, may impair ovarian feedback to the pituitary, increasing gonadotropin secretion. Excess gonadotropin stimulation of the ovaries has been reported in galactosemic women who are deficient in the galactose-1-phosphate uridyltransferase (GALT) enzyme. Hypogonadism or ovarian failure occurs frequently among women with classic galactosemia, an inherited polymorphism in the GALT gene (3). Cramer et al. (4) hypothesized that women with galactosemia may be at increased risk of ovarian cancer because an excess concentration of gondo-
tropin, including luteinizing hormone and follicle-stimulating hormone, may increase estrogenic stimulation of ovarian inclusion cysts, resulting in proliferation of ovarian epithelium. In support of this hypothesis, Cramer et al. (4) reported significantly lower GALT activity in ovarian cancer cases than in community controls. A significant positive trend in risk associated with a ratio of lactose intake to GALT activity was also found.

Conversion of galactose to glucose via the Leloir pathway involves several enzymes, including galactokinase, GALT, and uridine diphosphate galactose 4’-epimerase (5, 6). Although metabolic disorders may arise from deficiencies in the activity of any of these enzymes, classic galactosemia is known to be caused by several polymorphisms in the GALT gene (5, 6). Among the missense polymorphisms that may alter GALT stability is the N314D variant of the Duarte allele, an A6G transition at nucleotide 940 of the GALT gene that results in a substitution of aspartate for asparagine at the amino acid 314 position of the GALT protein. Uncertainty still exists regarding the influence of diet and of other metabolic genes on the enzyme expression of N314D variants (5, 7). A recent case-control study conducted by Cramer et al. (7) failed to confirm the positive association of GALT levels with ovarian cancer risk, but homozygosity for the Asp314 variant allele was positively related to the odds ratio for disease, especially for endometrioid and clear cell ovarian cancer.

The objective of this case-control study was to examine the hypothesis that reduced GALT activity, an increased ratio of lactose intake to GALT activity, and the inheritance of the N314D polymorphism are positively associated with the risk of epithelial ovarian cancer.

MATERIALS AND METHODS

Eligible cases for this population-based, case-control study in Hawaii and Los Angeles, California, included all patients with histologically confirmed, primary, epithelial ovarian cancer diagnosed between July 1, 1993, and June 30, 1999, on Oahu, Hawaii, or in Los Angeles (8). By using the case-ascertainment systems of population-based cancer registries in the two locations (9), we identified ovarian cancer patients and obtained histologic information from the pathology logs and admission records of the participating hospitals. Eligible women were 18–84 years of age, were residents of the two geographic areas, and belonged to one of the following ethnic groups: Caucasian, Asian (Japanese, Chinese, Filipino, and Korean), and “other” (predominantly Native Hawaiian and Samoan). Native Hawaiian was defined as any part-Hawaiian ethnicity, whereas being of the other ethnicities was defined as having three of four grandparents of that ethnicity. Interview information was obtained from 558 (60 percent) of the ovarian cancer cases eligible for participation in the study. Reasons for nonparticipation included physician refusal (8 percent), patient refusal or death (24 percent), and inability to locate patients (8 percent). Of the 558 ovarian cancer cases, 441 (79 percent) agreed to donate a blood specimen.

Population controls were frequency matched to cases on the basis of ethnicity (e.g., Japanese), 5-year age group, and study site. Eligible controls had no history of ovarian cancer and at least one intact ovary. In Hawaii, the pool of controls was identified from lists of female Oahu residents who were interviewed by the Health Surveillance Program of the Hawaii Department of Health. Annually, the Department of Health identifies a 2 percent representative sample of all households in the state by using a sampling procedure modeled after that of the National Health Survey (10). The refusal rate for this survey is extremely low (<5 percent) because it is conducted under statutory provision. This source was supplemented by selecting women aged 65 years or older who were Health Care Financing Administration participants on Oahu; this second source represented approximately 2 percent of selected controls. In Los Angeles, more than 95 percent of the controls were selected on the basis of a neighborhood walk procedure, in which a control was sought by use of a systematic algorithm based on the address of the case (11). Lists obtained through the Health Care Financing Administration were used to supplement selection of older controls (aged 65 years or older), representing about 1 percent of selected controls. Interview information was obtained from 607 controls (67 percent of eligible women), 430 (71 percent) of whom supplied a blood specimen for analysis.

In initiating this study, we recognized the high costs of the proposed biologic assays and decided, a priori, to examine a subset of approximately 50 percent of study participants in each geographic area, stratified on ethnicity (Caucasian vs. Asian). We did not stratify on lactose intake or lactase persistence because of the reported lack of correlation with GALT activity (4). This analysis included a subset of 239 cases (47.7 percent Caucasian, 35.1 percent Asian, and 17.1 percent “other”) and 244 controls (45.5 percent Caucasian, 40.2 percent Asian, and 14.3 percent “other”) who were interviewed during the first 3.5 years of the investigation.

Interviews were conducted in subjects’ homes by trained interviewers according to a standard protocol, and each interview required about 2.5 hours to complete. On average, cases were interviewed within 4 months of diagnosis. The questionnaire covered reproductive and gynecologic history; use of oral contraceptives and other hormones; contraceptive history, including tubal ligation; medical history; anthropometric measurements; and other lifestyle practices such as smoking and diet. A food frequency questionnaire, modeled after instruments used in other studies (12), included a minimal set of foods that contribute at least 85 percent of the dietary components of interest for each ethnic group. Intake of alcoholic beverages and use of dietary supplements were also assessed. The nutrient content of foods was determined from a customized food composition database developed and maintained at the Cancer Research Center of Hawaii (12). The food composition data were compiled largely from US Department of Agriculture Handbook 8 (13, 14), with supplementation by laboratory analyses of foods, and other commercial publications (15–17). In addition to values for energy and macronutrients, the database includes values for more than 90 other nutrients, including lactose, calcium, and vitamin D. Intake from supplements was quantified by using a database compiled from supplement labels and manufacturers’ information. Total
nutrient intake was calculated as the sum of the nutrients obtained from foods and supplements.

All blood samples were processed within 1–2 hours of collection. The plasma was separated from the cells by centrifugation (4°C for 15 minutes, 1,800 × g). The red cells were washed three times with equal volumes of 0.9 percent sodium chloride before freezing (−70°C). GALT activity was determined in hemolysates by a carbon 14 labeling method, which uses chromatography on O-diethylaminoethyl-cellulose paper, as described by Lee and Ng (18). DNA was purified from peripheral blood leukocytes by sodium dodecyl sulfate/proteinase K treatment and phenol/chloroform extraction. In this study, we examined a single GALT polymorphism: an A6G transition at nucleotide 940, which replaces Asp314 with aspartate. Genotyping for the N314D polymorphism was performed by polymerase chain reaction and enzyme restriction assays, as described previously (6). The average coefficient of variation for the GALT analysis was 16.0 percent (range, 1.8–33.8 percent) among duplicate specimens.

The odds ratios associated with different levels of the exposure variables were evaluated by unconditional multiple logistic regression modeling of case-control status (19). The exposures of interest included several dietary variables, GALT activity, the ratio of lactose intake to GALT activity (defined as log(lactose) × 10/GALT), and the N314D genetic polymorphism. All exposures were entered into the models initially as binary indicator variables representing levels of exposures, generally quartiles for continuous measures, on the basis of the distribution for cases and controls. Odds ratios and 95 percent confidence intervals were computed by exponentiating the coefficients (and the 95 percent confidence intervals) representing exposure levels. Adjustment variables included age (continuous), ethnicity (by indicator: Caucasian, Asian, other), study site (Hawai’i vs. Los Angeles), education (continuous), oral contraceptive pill use (ever vs. never), parity (ever vs. never), tubal ligation (yes vs. no), and energy intake (continuous). The associations of the exposure variables with the risk of ovarian cancer were also modeled within various subgroups (e.g., ethnic group) to examine consistency. We performed a test for linear trend in the logit of risk by using the likelihood ratio test, comparing models with and without a trend variable. The trend variable was assigned the median of the quartile for each level of interaction between the pairs of variables; the reference category was subjects whose GALT activity was below the median (≤24.1 µmol per hour/g hemoglobin [Hb]) and who were “unexposed” (e.g., had never used oral contraceptive pills). We compared this model obtained by using the likelihood ratio test with one in which only the main effects were modeled. Exact confidence intervals for odds ratios were computed, conditioned on the number of events (20). Analysis of covariance (21) was used to compare GALT levels across subgroups, controlling for the adjustment variables specified in the previous paragraph. Covariate-adjusted means were computed at the mean covariate level.

The distributions of study subjects by demographic characteristics and important ovarian cancer risk factors were similar among the 558 cases and 607 controls who provided interview information and the 239 cases and 244 controls included in the GALT subset. In the interview-only analysis, we found an inverse association of years of education, number of full-term pregnancies, number of years of oral contraceptive pill use, and history of tubal ligation with risk and a positive association with risk for a family history of breast or ovarian cancer (8). The odds ratios were consistent with the results shown in table 1 for the subset of women included in the present analysis.

RESULTS

We found a significant inverse association of dairy product consumption with the risk of ovarian cancer (table 2). Among specific dairy products, the association was significant for low-fat milk only, although nonsignificant inverse relations were found in association with consumption of other specific dairy products, such as yogurt, cheese, ice cream, and butter. A marginally significant inverse gradient in the odds ratios was observed in relation to intake of lactose (p = 0.05).

Covariate-adjusted mean GALT activity was similar for cases (23.8 µmol per hour/g Hb, 95 percent confidence interval [CI]: 23.2, 24.4) and controls (23.7 µmol per hour/g Hb, 95 percent CI: 23.1, 24.2) (p = 0.83) as well as for the Caucasian (23.4 µmol per hour/g Hb, 95 percent CI: 22.8, 24.0), Asian (24.3 µmol per hour/g Hb, 95 percent CI: 23.6, 24.9), and “other” (23.6 µmol per hour/g Hb, 95 percent CI: 22.6, 24.6) ethnic groups. Covariate-adjusted mean GALT activity in the cases was unrelated to histologic type of ovarian cancer, ranging from 23.6 µmol per hour/g Hb for serous cancers to 24.2 µmol per hour/g Hb for endometrioid/clear cell cancers (data not shown). No evidence was found for a dose-response relation between level of GALT activity and the odds ratios for ovarian cancer (table 3). In addition, there was no suggestion that women who were clinically GALT deficient (13 cases, 14 controls), defined as having values of <17 µmol per hour/g Hb, had an increased risk of ovarian cancer (odds ratio = 1.02, 95 percent CI: 0.44, 2.33). We found an inverse association between the ratio of lactose intake to GALT activity and risk; however, the trend in the odds ratios was neither monotonic nor significant. No heterogeneity in the odds ratios for ovarian cancer associated with GALT activity was found by study site, ethnic group, or histologic type of cancer (data not shown).

We cross-classified subjects by median GALT activity (>24.1 vs. ≤24.1 µmol per hour/g Hb) and by oral contraceptive pill use (never vs. ever use) and median lactose intake (≤9.1 vs. >9.1 g/day) (table 4). We found a significant (p = 0.04) interaction between GALT activity and oral contraceptive pill use. The inverse association of oral contraceptive pill use for women with low GALT activity (odds ratio = 0.70/2.53 = 0.28) was stronger than that for women with high GALT activity (odds ratio = 1/1.58 = 0.63). Oral contraceptive pill users with low GALT activity had a reduced risk of ovarian cancer compared with women with high GALT activity. However, the reverse was true for never users of oral contraceptive pills—women with low GALT activity.

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had an increased risk of ovarian cancer. No significant interaction was found between lactose or low-fat milk intake and GALT activity.

We analyzed the frequency of the N314D allele in a subset of 229 cases and 200 controls (table 5). The N314D allele frequencies were found to be in Hardy-Weinberg equilib-
The Asp314 allele was present in 11.4 percent of the cases and 13.5 percent of the controls. This percentage varied somewhat by ethnic group, with a greater occurrence of the variant Asp314 allele among Caucasian women.

### TABLE 2. Odds ratios* and 95% confidence intervals for the association of quartiles†,‡ of dairy product and nutrient intake with ovarian cancer among 239 cases and 244 controls, Hawaii and Los Angeles, California, 1993–1997

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Q2 vs. Q1 OR†</th>
<th>95% CI†</th>
<th>Q3 vs. Q1 OR</th>
<th>95% CI</th>
<th>Q4 vs. Q1 OR</th>
<th>95% CI</th>
<th>p for trend§</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dairy products</td>
<td>0.83</td>
<td>0.46, 1.48</td>
<td>0.49</td>
<td>0.27, 0.89</td>
<td>0.50</td>
<td>0.26, 0.95</td>
<td>0.01</td>
</tr>
<tr>
<td>Milk</td>
<td>1.03</td>
<td>0.59, 1.80</td>
<td>0.75</td>
<td>0.43, 1.30</td>
<td>0.63</td>
<td>0.35, 1.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Whole milk</td>
<td>0.71</td>
<td>0.40, 1.24</td>
<td>0.83</td>
<td>0.46, 1.50</td>
<td>0.82</td>
<td>0.43, 1.53</td>
<td>0.69</td>
</tr>
<tr>
<td>Low-fat milk</td>
<td>0.72</td>
<td>0.42, 1.26</td>
<td>0.77</td>
<td>0.44, 1.34</td>
<td>0.50</td>
<td>0.28, 0.88</td>
<td>0.03</td>
</tr>
<tr>
<td>Yogurt</td>
<td>0.78</td>
<td>0.46, 1.32</td>
<td>0.92</td>
<td>0.54, 1.59</td>
<td>0.79</td>
<td>0.46, 1.37</td>
<td>0.56</td>
</tr>
<tr>
<td>Cheese</td>
<td>1.09</td>
<td>0.61, 1.93</td>
<td>1.08</td>
<td>0.56, 2.08</td>
<td>0.72</td>
<td>0.34, 1.51</td>
<td>0.51</td>
</tr>
<tr>
<td>Ice cream</td>
<td>1.12</td>
<td>0.59, 2.12</td>
<td>0.73</td>
<td>0.45, 1.19</td>
<td>0.84</td>
<td>0.49, 1.45</td>
<td>0.37</td>
</tr>
<tr>
<td>Butter</td>
<td>0.84</td>
<td>0.48, 1.47</td>
<td>0.79</td>
<td>0.44, 1.42</td>
<td>0.75</td>
<td>0.42, 1.34</td>
<td>0.48</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.77</td>
<td>0.43, 1.37</td>
<td>0.61</td>
<td>0.34, 1.10</td>
<td>0.56</td>
<td>0.30, 1.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Galactose</td>
<td>0.87</td>
<td>0.49, 1.53</td>
<td>0.85</td>
<td>0.47, 1.53</td>
<td>0.95</td>
<td>0.51, 1.78</td>
<td>0.99</td>
</tr>
</tbody>
</table>

* After adjustment, by unconditional multiple logistic regression, for age, ethnicity, study site, education, oral contraceptive pill use, parity, tubal ligation, and energy intake.
† The following quartile (Q) cutpoints (expressed in grams) were used based on the distribution of the nutrients among cases and controls—all dairy products: 92.3, 222.0, 380.8; milk: 34.5, 128.2, 274.0; whole milk: 3.9, 13.6, 36.6; low-fat milk: 8.1, 60.0, 217.0; yogurt: 0, 9.9, 40.5; cheese: 7.5, 21.5, 47.5; ice cream: 0, 4.4, 11.1; butter: 0.02, 0.16, 1.10; lactose: 3.77, 9.08, 16.34; galactose: 0.28, 0.56, 1.13.
‡ Q1, reference category.
§ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the categories.
¶ OR, odds ratio; CI, confidence interval.

### TABLE 3. Odds ratios and 95% confidence intervals for the association of GALT* activity with ovarian cancer, Hawaii and Los Angeles, California, 1993–1997

<table>
<thead>
<tr>
<th>GALT activity (µmol per hour/g hemoglobin)</th>
<th>Cases (n=239)</th>
<th>Controls (n=244)</th>
<th>Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤21.8</td>
<td>57</td>
<td>23.8</td>
<td>67</td>
</tr>
<tr>
<td>21.9–24.1</td>
<td>66</td>
<td>27.6</td>
<td>54</td>
</tr>
<tr>
<td>24.2–26.5</td>
<td>53</td>
<td>22.2</td>
<td>68</td>
</tr>
<tr>
<td>&gt;26.5</td>
<td>63</td>
<td>26.4</td>
<td>55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lactose:GALT ratio¶</th>
<th>Cases (n=239)</th>
<th>Controls (n=244)</th>
<th>Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.64</td>
<td>61</td>
<td>25.5</td>
<td>59</td>
</tr>
<tr>
<td>0.65–0.94</td>
<td>68</td>
<td>28.5</td>
<td>53</td>
</tr>
<tr>
<td>0.95–1.23</td>
<td>49</td>
<td>20.5</td>
<td>72</td>
</tr>
<tr>
<td>&gt;1.23</td>
<td>61</td>
<td>25.5</td>
<td>60</td>
</tr>
</tbody>
</table>

* GALT, galactose-1-phosphate uridyltransferase; OR, odds ratio; CI, confidence interval.
† After adjustment, by unconditional multiple logistic regression, for age, ethnicity, study site, education, oral contraceptive pill use, parity, tubal ligation, and energy intake.
‡ Based on the likelihood ratio test comparing models with and without a trend variable that was assigned the median for the categories.
§ Reference category.
¶ The ratio of lactose intake to GALT activity, defined as log(lactose) × 10/GALT activity.
women (16.5 percent of cases, 16.1 percent of controls) than Asian women (4.0 percent of cases, 8.1 percent of controls) or women of “other” ethnic groups (10.5 percent of cases, 15.4 percent of controls). The risks associated with the presence of at least one variant Asp314 allele were 0.77 (95 percent CI: 0.42, 1.41) for the entire sample (table 5), 0.91 (95 percent CI: 0.43, 1.89) for Caucasian women, 0.72 (95 percent CI: 0.18, 2.86) for Asian women, and 0.56 (95 percent CI: 0.10, 3.24) for “other” women (data not shown).

Only two cases (0.9 percent) (both Caucasians) and no controls were N314D homozygous for the variant (Asp/Asp), resulting in a direct association with risk but wide confidence limits: the exact lower limit was 0.16.

Covariate-adjusted mean GALT activity in cases and controls varied significantly by N314D genotype (table 6). GALT activity in cases with the homozygous Asn/Asn genotype was significantly higher than in cases with the heterozygous Asn/Asp genotype (p < 0.0001) or in cases with the homozygous Asp/Asp genotype (p = 0.03). GALT activity in controls with homozygous Asn/Asn genotypes was also significantly higher than in controls with heterozygous Asn/Asp genotypes (p < 0.0001).

We observed no significant differences in the odds ratios for the ovarian cancer–N314D genotype association by histologic subtype of cancer (data not shown). Among the 26 cases with at least one Asp314 allele, seven had borderline,
10 serous, three mucinous, three endometrioid/clear cell, and three other histologic types of disease.

**DISCUSSION**

Results of this case-control study do not support the hypothesis that GALT activity or the ratio of lactose intake to GALT activity is associated with the odds ratios for ovarian cancer. In contrast to other dietary studies (4, 22–24), ours showed that intake of dairy products, and perhaps lactose, was inversely related to risk. Cramer et al. (1, 4, 24) were among the first to suspect that dairy-product consumption was a risk factor for ovarian cancer. In a Massachusetts study, this group measured dietary lactose consumption and GALT activity among 145 ovarian cancer cases and 127 controls. In a second study of 563 ovarian cancer cases and 248 controls in southern England, Morland et al. (27) also found that more cases than controls were heterozygous (25.7 percent of cases, 16.9 percent of controls) or homozygous (1.5 percent of cases, 0.4 percent of controls) for the N314D variant allele. However, this association resulted entirely from differences in the frequency of the N314D allele among women with serous and undifferentiated ovarian cancers, not endometrioid and clear cell histologic types, as reported by Cramer et al. (7). The Duarte (N314D) variant of the GALT gene is thought to be prevalent in 6–20 percent of the nongalactosemic population (28), although the frequency of the N314D allele may be as low as 2 percent in Japan (5). The higher prevalence of the N314D polymorphism and lower levels of GALT among Caucasian women than among Asian and Pacific Islander women in our study is consistent with the observed ethnic variation in ovarian cancer incidence in Hawaii. However, we found no differences in the frequency of heterozygosity (10.5 percent of cases, 13.5 percent of controls) or homozygosity (0.9 percent of cases, 0.0 percent of controls) for the N314D polymorphism between all cases and controls combined or within ethnic group, suggesting alternative explanations for the ethnic variation in ovarian cancer risk.

Cramer et al. (7) hypothesized that, on the basis of a relation between the N314D polymorphism and reduced GALT activity, the presence of this polymorphism would lead to an increased risk of ovarian cancer (29). These investigators reported that both cases and controls who had the N314D polymorphism had lower biochemical GALT activity (6). We also observed significantly lower GALT levels in women with the N314D polymorphism. However, it is now

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**TABLE 6. Means* and 95% confidence intervals for GALT† activity by N314D genotype among ovarian cancer cases and controls, Hawaii and Los Angeles, California, 1993–1997**

<table>
<thead>
<tr>
<th>N314D genotype</th>
<th>Cases (n = 229)</th>
<th>Controls (n = 200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>95% CI†</td>
<td>p value‡</td>
</tr>
<tr>
<td>Asn†/Asn</td>
<td>23.9</td>
<td>23.2, 24.7</td>
</tr>
<tr>
<td>Asn/Asp†</td>
<td>20.5</td>
<td>19.1, 22.0</td>
</tr>
<tr>
<td>Asp/Asp</td>
<td>18.5</td>
<td>14.6, 23.2</td>
</tr>
<tr>
<td>Asn/Asp or Asp/Asp</td>
<td>20.3</td>
<td>19.0, 21.8</td>
</tr>
</tbody>
</table>

* Adjusted, by analysis of covariance, for age, ethnicity, study site, education, oral contraceptive pill use, parity, and tubal ligation.
† GALT, galactose-1-phosphate uridyltransferase; CI, confidence interval; Asn, asparagine; Asp, aspartate.
‡ p values comparing GALT levels with those of cases with Asn/Asn genotypes.
§ p value comparing GALT levels with those of controls with Asn/Asn genotypes.
¶ NA, not applicable; no controls had the Asp/Asp genotype.
known that the GALT response to the N314D polymorphism is modified by other genes (28). Laboratory data have demonstrated an association of the N314D polymorphism with normal or increased erythrocyte GALT activity in Duarte 1 carriers but as much as 50 percent reduced GALT activity in Duarte 2 carriers (30, 31). The Duarte 1 and Duarte 2 variants of galactosemia differ regarding other base changes that are in linkage disequilibrium with the N314D polymorphism, such as the L218L polymorphism in exon 7, which coexists with the N314D polymorphism in Duarte 1 variants but not Duarte 2 variants. A recent polymorphism analysis of the GALT gene found a deletion of four nucleotides (-119/-116de/GTCA) in the 5′ promoter region in Duarte 2 alleles but not in Duarte 1 alleles (31). This polymorphism may be functionally related to reduced GALT activity in Duarte 2 carriers. As in other disease processes, such gene-gene interactions on risk are complex and can be addressed only in carefully designed molecular studies with analyses of multiple, related genetic polymorphisms in large samples of women.

Strengths of the present study include a comprehensive, in-person interview; a population-based design; and a multi-ethnic composition of study subjects. This research was entirely hypothesis driven, but we did not commit our entire pool of subjects to the biologic analyses because of the high costs of the assays. Nonetheless, information regarding GALT activity and N314D genotype was available for at least 200 cases and controls, enabling us to test our hypotheses with reasonable study power.

Results of the analysis of the dietary information obtained in this study, including the inverse association of lactose intake with the risk of ovarian cancer, have been described previously (8). Regarding lactose, reasons for findings that were inconsistent with those from previous reports include 1) an inappropriate time frame for the dietary assessment and 2) bias in the exposure assessment or in selection of controls. We focused on recent diet in this study because of the difficulty in evaluating eating patterns in the distant past. It is conceivable that this was not the relevant time period for ovarian carcinogenesis, although our diet reference period was consistent with that of other studies (1, 4, 7, 22, 24–26). It is unlikely that cases or controls would have systematically biased their responses regarding dairy intake, and our dietary assessment methodology was valid and reproducible (32, 33).

The level of participation in blood sample collection by interviewed cases (79 percent) and controls (71 percent) was good, although less so when considered as a percentage of eligible women: 48 percent of eligible cases and 47 percent of eligible controls provided a blood specimen. Low participation rates might have biased our findings if the biologic markers under study were a determinant of participation. We have no reason to think that this was the case. The odds ratios associated with pregnancy, oral contraceptive pill use, and other confounders were similar for subjects participating in the interview only and those participating in blood sample collection.

Misclassification of exposure or disease is an important source of concern, and we spent considerable time validating our assessment methods. Many of the exposures evaluated in our questionnaire, such as pregnancy and oral contraceptive pill use, were probably measured without much error. The possibility of such bias was minimized by using a structured questionnaire with well-defined probing methods and thorough training of the interviewers. To avoid disease misclassification, differentiation of primary ovarian cancer from metastatic colorectal cancer and from primary peritoneal carcinoma was achieved by close interaction of the pathologists with the clinicians and by correlation of the clinical record with pathologic review. Women who did not have definite, primary epithelial ovarian cancer according to clinical or microscopic evaluation were excluded from the study. Loss of cases because of illness or death (6 percent of eligible subjects) was minimized through the rapid-reporting system of the cancer registries in Hawaii and Los Angeles.

In conclusion, we found little evidence to support the hypothesis that either GALT activity or N314D genotype is a risk factor for ovarian cancer. The inverse association of oral contraceptive pill use with the odds ratios for ovarian cancer was strongest among women with low GALT activity, suggesting that gonadotropin levels may modify the beneficial effects of oral contraceptive pills on ovarian carcinogenesis. Long-term cohort studies that can evaluate the joint association of endogenous hormone levels and oral contraceptive pill use with the risk of ovarian cancer are needed to address this interaction more completely.

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