To determine whether lactase persistence might be related to ovarian cancer risk, in 1994–1995 the authors assessed the capacity to digest lactose by measuring breath hydrogen production after oral administration of lactose in 50 women with ovarian cancer and 100 healthy controls. All of the women came from Sassari (Sardinia), Italy, an area where the population has a high frequency of lactose malabsorption. Thirty percent of cases were lactose absorbers, as compared with 15% of controls. The odds ratio for ovarian cancer among lactose absorbers was 2.51 (95% confidence interval 1.10–5.68). These results provide some support for a role of lactose ingestion and galactose cytotoxicity in the pathogenesis of ovarian cancer.


dairy products; galactose; lactose; milk; ovarian neoplasms

Animal models have suggested that ovarian cancer may be the consequence of hypergonadotropic hypogonadism induced by toxic effects on oocytes (1). Experimental and clinical data have shown that galactose may be toxic to ovarian germ cells (2, 3). This has been attributed to the generalized cytotoxicity of galactose due to the accumulation of galactose-1-phosphate or galactitol in tissues.

The possible role of galactose and its disaccharide form (lactose) in the pathogenesis of ovarian cancer has been explored (4–7). A case-control study has suggested that ovarian cancer risk is enhanced in women with higher galactose consumption and lower galactose metabolism assessed by erythrocyte transferase activity (4). However, another case-control study involving women with stage I ovarian cancer did not support these conclusions (7).

Besides the ability to metabolize galactose, persistence of lactase activity, which is responsible for the capacity to split lactose into its component sugars (glucose and galactose) after infancy, has also been included among possible risk factors for ovarian cancer. The activity of lactase, a β-galactosidase located in the brush-border of intestinal epithelial cells, is high during infancy, declines in most humans after weaning, and remains at a low level throughout life (primary adult lactase deficiency phenotype) (8). However, in humans with a long history of milk drinking (such as people from northwestern Europe and Afro-Arabian nomads), lactase activity is maintained at a level similar to that found in infants (lactase persistence phenotype) (9). An autosomal gene is believed to be responsible for the two phenotypes, with a dominant lactase persistence allele and a recessive lactase restriction allele.

Lower rates of ovarian cancer have been shown in populations with higher levels of hypolactasia, and even within countries or regions, variations in ovarian cancer incidence seem to correlate with lactase persistence (5). In Italy, for example, considerable geographic differences in ovarian cancer mortality have been reported, with higher rates found in northern as compared with southern regions (10, 11). This is consistent with the lower prevalence of hypolactasia in northern Italy (12–14).

To obtain further information on the issue, we considered lactose absorption by means of the hydrogen breath test after oral administration of lactose in ovarian cancer cases and healthy controls. The women studied were from a well-defined population on the island of Sardinia, Italy, an area characterized by a low prevalence of lactase persistence.

MATERIALS AND METHODS

In 1994 and 1995, we studied women with ovarian cancer and age-matched controls from Sassari and the...
surrounding areas in Sardinia. All were at least third generation residents of the province. Cases comprised 50 out of 62 patients with incident, histologically confirmed epithelial ovarian cancer who had been admitted to the Department of Obstetrics and Gynecology at the University of Sassari Hospital. The control group comprised 100 healthy women recruited among hospital workers.

The participation rate was 81 percent for cases and 100 percent for controls. Of the 12 cases who did not participate, four were excluded for clinical reasons (severity of the disease) and eight refused. The mean age at diagnosis of patients with ovarian cancer was 54 years (range, 16–77 years). Patients were staged according to 1988 FIGO stage (15): 25 were in early stages (IA, IB, and IC), one was in stage IIA, 18 were in stage III, and six were in stage IV.

The major characteristics of cases and controls are reported in Table 1. There was no significant difference between cases and controls in terms of marital status, parity, previous use of oral contraceptives, and family history of ovarian cancer. Regular milk consumption was defined as consumption of milk and/or dairy products at least once per day.

The hydrogen breath test was carried out to evaluate lactase activity. This test measures the concentration of hydrogen in expired air after oral administration of lactose. Hydrogen in expired air comes almost exclusively from colonic fermentation of nonhydrolized lactose. Lactose malabsorption was diagnosed if the maximum increase in hydrogen in the expired air was greater than 20 parts per million, as previously indicated (17).

We derived odds ratios for ovarian cancer (with corresponding 95 percent confidence intervals) according to lactose absorption using a multiple logistic regression model that included terms for age, parity, and ever use of oral contraceptives, to allow for major potentially confounding factors (18). Further inclusion of terms for social class and marital status did not modify the estimates.

RESULTS

Compared with controls, a higher proportion of women with ovarian cancer reported regular consumption of milk and dairy products (86 percent vs. 66 percent (p < 0.01)). Table 2 shows the maximum hydrogen concentrations in expired air after oral lactose administration in patients with ovarian cancer and healthy women: 30 percent of patients with ovarian cancer were lactose absorbers, as compared with 15 percent of the control group. The multivariate odds ratio for ovarian cancer among lactose absorbers was 2.51 (95 percent confidence interval 1.10–5.68).

DISCUSSION

Findings from several epidemiologic studies have supported the role of galactose as an oocyte toxin; in fact, populations with a higher prevalence of hypolactasia seem to have higher fertility rates (6), as well as lower rates of ovarian cancer (5). In addition, an association between ovarian cancer, increased galactose consumption, and decreased galactose-1-phosphate uridyl transferase activity has been suggested by a US case-control study (4). Lactose consumption, evaluated by means of a self-administered semiquantitative food frequency questionnaire, was higher in women with ovarian cancer than in controls; the use of dairy products with a higher content of prehydrolyzed lactose was higher in women with ovarian cancer, who also showed lower concentrations of a key enzyme that converts galactose to glucose. Although the issue of gastrointestinal absorption of lactose had not been addressed by that study, the authors suggested that lactose consumption may be a dietary risk factor and reduced red blood cell transferase a genetic risk factor for ovarian cancer (4). Those findings, however, were not confirmed by a more recent case-control study that included only

TABLE 1. Distribution of 50 cases with epithelial ovarian cancer and 100 controls according to age and related covariates, Sassari, Italy, 1994–1995

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>54.0 (15.7)*</td>
<td>53.4 (14.2)</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>16–77</td>
<td>16–77</td>
</tr>
<tr>
<td>Parity (no. of women)</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>0</td>
<td>28</td>
<td>53</td>
</tr>
<tr>
<td>≥1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever use of oral contraceptives</td>
<td>(no. of women)</td>
<td>12</td>
</tr>
<tr>
<td>I or II (highest)</td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td>III or IV (lowest)</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>Regular milk consumption (%)</td>
<td>86</td>
<td>66</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, standard deviation.
† Based on the occupation of the head of the household.
‡ More than one time per day.
untreated patients with stage I ovarian cancer (7). Another case-control study from New York State also suggested that milk drinking is not a risk factor for ovarian cancer independently of its fat content (19).

In this study, cases and controls were at least third generation residents of the Sassari province; the participation rate was satisfactory, making selection bias unlikely. Among the limitations of our study were the relatively low number of subjects, which limited the precision of the estimates, and the use of hospital workers as controls. However, cases and controls were comparable with regard to age, parity, and social status. Although the number of cases in our study was inadequate for subgroup analyses, the findings were similar for stage I disease and more advanced disease. The hydrogen breath test was used because it is simple and noninvasive and has proven to be valuable in assessing the incidence of hypolactasia in basically fit population groups (16, 17).

The results of our study confirm that the prevalence of persistent lactase activity in Sardinia is relatively low, with a frequency of lactose absorbers in our control population (15 percent) comparable to that observed in the adult population of Naples (16 percent) (12). The prevalence of lactose absorbers in northern Italy has been reported to be 44–49 percent (13, 14). Therefore, a positive correlation seems to exist in the Italian population between the prevalence of lactase persistence and mortality rates for ovarian cancer (10, 11).

Dietary consumption of milk and dairy products was higher in our patients than in controls. These data differ from those obtained in a US case-control study (7). In that study, however, only 50 percent of cases underwent lactose challenge. In addition, the prevalence of lactose malabsorption in the US study was much lower (12.4 percent in cases and 11.2 percent in controls) than that in our Sardinian population.

In conclusion, the present data, based on an original and isolated population with a high prevalence of lactose malabsorption, provide some support for the hypothesis that lactose ingestion and lactase persistence may play a role in the pathogenesis of ovarian cancer.

REFERENCES