Conflict of interest
The project was funded by the University of Southern Denmark.

Background
For decades diosulfam has been used to treat alcohol dependence. Experimental studies have demonstrated that diosulfam has growth inhibitory effects in melano-

anoma, breast and prostate cancer cell lines. While the few available human studies on the matter have shown conflicting results, there are several on-going clinical trials investigating the potential antineoplastic effects of diosulfam.

Objectives
To explore the associations between long-term use of diosulfam and risks of melanoma, breast or pro-

states in a large population-based setting.

Table 1
Characteristics of cancer cases and matched controls

<table>
<thead>
<tr>
<th>Case (n=270)</th>
<th>Control (n=600)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>580 (43.5%)</td>
</tr>
<tr>
<td>Black</td>
<td>65 (9.5%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>20 (2.9%)</td>
</tr>
<tr>
<td>Other</td>
<td>25 (3.6%)</td>
</tr>
<tr>
<td>Follow-up, median GFR, years</td>
<td></td>
</tr>
<tr>
<td>Cancer site</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>186 (13.1%)</td>
</tr>
<tr>
<td>Breast</td>
<td>186 (13.1%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>186 (13.1%)</td>
</tr>
</tbody>
</table>

Methods
By combining Danish nationwide administrative and health registers, we conducted a population-based case-control study nested within ever-users (some prescription) of diosulfam. Cases were all Danish indi-

viduals who had a histologically verified first-time diag-

nosis of malignant melanoma, breast or prostate cancer between January 1st 2000 and December 31st 2009 and who had redeemed at least one diosul-

fram prescription one year prior to the cancer diagnos-

sis. For each case, we selected four cancer-free con-

trols among ever-users of diosulfam matched by gender, birth year and year of first recorded diosulfam prescription. We estimated odds ratios (ORs) and 95% confidence intervals (CI) for cancer associated with long-term (≥500 daily defined doses) versus one-time (one prescription) use of diosulfam, using log-

istic regression adjusting for general and site-specific confounders.

To assess potential unmeasured confounding, we also analysed the effect on diosulfam use with regard to other cancer sites known to be associated with heavy drinking and/or smoking. Furthermore, we ob-

tained survey data on alcohol consumption, smoking status and weight among users of diosulfam.

Results
Among 53,866 eligible diosulfam users during 2000-

2009, we identified 166, 644 and 464 cases, respec-


tively, with first-time melanoma, breast or prostate cancer. Adjusted ORs for the associations between long-term diosulfam use and risks of melanoma, breast or prostate cancer were 1.04 (95% CI: 0.60-

1.78), 0.92 (95% CI: 0.70-1.22) and 0.77 (95% CI 0.56-1.06), respectively. Dose-response analyses re-

vealed generally larger risk reductions with higher cum-

ulative doses of diosulfam. However, the statistical precision of these analyses was limited and tests for trend did not reach statistical significance.

Conclusions
We found a slight reduction in risk of breast and prostate cancer in long-term use of diosulfam. Although we were able to include cancer diagno-

ses for the entire population of Denmark for a ten-

year period, our study had limited statistical preci-

sion. Future studies are therefore warranted.

Table 2
Association between diosulfam use and cancer risk, specified by cumulative use and cancer site

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Cases exposed</th>
<th>Cases unexposed</th>
<th>Cases exposed</th>
<th>Cases unexposed</th>
<th>Case OR</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>186 (13.1%)</td>
<td>186 (13.1%)</td>
<td>N.A.</td>
<td>N.A.</td>
<td>1.04(1.00-1.09)</td>
<td>1.04(1.00-1.09)</td>
</tr>
<tr>
<td>Prostate</td>
<td>186 (13.1%)</td>
<td>186 (13.1%)</td>
<td>N.A.</td>
<td>N.A.</td>
<td>0.92(0.70-1.22)</td>
<td>0.92(0.70-1.22)</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate
OSD = defined daily doses
N.A. = not applicable
5. Exposure defined for a cumulative use of at least 500 days prior to the rate data.

In the analysis of other cancer sites, only cancers of the buccal cavity and pharynx showed a strong asso-

ciation with long-term diosulfam use with an OR of 0.75 (0.59-0.99). Survey data showed similar smoking status and weight among one-time users and long-


term users of diosulfam, but higher alcohol consump-

tion among one-time users.