Use of Disulfiram and Risk of Cancer:

A Population-based Case-control Study

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Conflict of interest
The project was funded by the University of Southern Denmark. The authors have no relationships to disclose.

Background
For decades disulfiram has been used to treat alcohol dependence. Experimental studies have demonstrated that disulfiram has growth inhibitory effects in melanoma, 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 disulfiram.

Objectives
To explore the associations between long-term use of disulfiram and risks of melanoma, breast or prostate cancer in a large population-based setting.

Methods
By combining Danish nationwide administrative and health registers, we conducted a population-based case-control study nested within ever-users (≥one prescription) of disulfiram. Cases were all Danish individuals who had a histologically verified first-time diagnosis of malignant melanoma, breast or prostate cancer between January 1st 2000 and December 31st 2009 and who had redeemed at least one disulfiram prescription one year prior to the cancer diagnosis. For each case, we selected four cancer-free controls among ever-users of disulfiram matched by gender, birth year and year of first recorded disulfiram 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 disulfiram, using logistic regression adjusting for general and site-specific confounders.
To assess potential unmeasured confounding, we also analysed the effect on disulfiram use with regard to other cancer sites known to be associated with heavy drinking and/or smoking. Furthermore, we obtained survey data on alcohol consumption, smoking status and weight among users of disulfiram.

Table 1
Characteristics of cancer cases and matched controls

	Cases (n=1,271)	Controls (n=5,046)
Men	588 (46.3%)	2,335 (46.3%)
Women	683 (53.7%)	2,711 (53.7%)
Age, median (IQR, years)	61 (54 - 67)	60 (54 - 67)
Follow-up, median (IQR, years)	6.9 (4.4 – 9.7)	7.0 (4.4 – 9.6)
Cancer site		
Melanoma	166 (13.1%)	NA
Breast	642 (50.5%)	NA
Prostate gland	463 (36.4%)	NA
Use of disulfiram ≥ 1 year prior to index-date		
One-time use (1-100 DDD)	543 (42.7%)	2,031 (40.2%)
Intermediate use (101-499 DDD)	425 (33.4%)	1,798 (35.6%)
Long-term use (≥500 DDD)	303 (23.8%)	1,217 (24.1%)
Charlson Comorbidity Index (CCI)		
CCI Score = 0	769 (60.5%)	3,062 (60.7%)
CCI Score = 1	300 (23.6%)	1,154 (22.9%)
CCI Score ≥ 2	202 (15.9%)	830 (16.4%)
Highest completed education		
Elementary school	476 (37.5%)	2,126 (42.1%)
High school or short training	423 (33.3%)	1,654 (32.8%)
Medium / long training	304 (23.9%)	1,008 (20.0%)
Missing or unknown	68 (5.4%)	258 (5.1%)
Diagnoses		
Conditions related to alcohol	365 (28.7%)	1,471 (29.2%)
Diabetes	93 (7.3%)	434 (8.6%)
COPD	95 (7.5%)	424 (8.4%)
Drugs *)		
5-α-reductase inhibitors	1 (0.1%)	13 (0.3%)
Hormone replacement	232 (18.3%)	808 (16.0%)
Thiazides	168 (13.2%)	691 (13.7%)

IQR = InterQuartile Range
DDD = Defined daily doses
NA = Not applicable
**) Exposure defined by a cumulative use of at least 500 DDD prior to the index date*

Results
Among 53,856 eligible disulfiram users during 2000-2009, we identified 166, 644 and 464 cases, respectively, with first-time melanoma, breast or prostate cancer. Adjusted ORs for the associations between long-term disulfiram 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 revealed generally larger risk reductions with higher cumulative doses of disulfiram. However, the statistical precision of these analyses was limited and tests for trend did not reach statistical significance.

In the analysis of other cancer sites, only cancers of the buccal cavity and pharynx showed a strong association with long-term disulfiram use with an OR of 0.75 (0.58-0.99). Survey data showed similar smoking status and weight among one-time users and long-term users of disulfiram, but higher alcohol consumption among one-time users.

Conclusions
We found a slight reduction in risk of breast and prostate cancer with long-term use of disulfiram. Although we were able to include cancer diagnoses for the entire population of Denmark for a ten-year period, our study had limited statistical precision. Future studies are therefore warranted.

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

Cancer type	Cases Exposed /unexposed	Controls Exposed /unexposed	Crude OR	Adjusted OR *
Use ≥500 DDD				
Melanoma	39 / 79	149 / 280	0.99 (0.60-1.66)	1.04 (0.60-1.78)
Breast	159 / 269	603 / 1,038	0.93 (0.71-1.22)	0.92 (0.70-1.22)
Prostate	105 / 195	465 / 713	0.77 (0·56-1.05)	0.77 (0.56-1.06)
Cumulative dose-response analysis				
Melanoma				
101 - 499 DDD	48 / 79	234 / 280	0.71 (0.46-1.08)	0.72 (0·46-1.13)
500 - 999 DDD	32 / 79	100 / 280	1.25 (0.71-2.21)	1.29 (0.71-2.36)
≥ 1000 DDD	7 / 79	49 / 280	0.59 (0.21-1.60)	0.64 (0·20-2.04)
Breast				
101 - 499 DDD	214 / 269	906 / 1,038	0.93 (0.75-1.14)	0.91 (0.74-1.13)
500 - 999 DDD	106 / 269	384 / 1,038	1.02 (0.75-1.40)	1.02 (0.74-1.41)
≥ 1000 DDD	53 / 269	219 / 1,038	0.80 (0.50-1.29)	0.73 (0·44-1.20)
Prostate				
101 - 499 DDD	163 / 195	658 / 713	0.91 (0.71-1.16)	0.90 (0.70-1.16)
500 - 999 DDD	67 / 195	295 / 713	0.74 (0.51-1.07)	0.76 (0.52-1.10)
≥ 1000 DDD	38 / 195	170 / 713	0.84 (0.51-1.38)	0.86 (0.52-1.45)

** Adjusted for chronic obstructive pulmonary disease (COPD); any registered condition related to heavy alcohol abuse; Diabetes, Charlson Comorbidity Index and highest completed education. Furthermore, adjusted for use of 5-α-reductase inhibitors in analyses for prostate cancer, hormone supplements in analyses for breast cancer and melanoma and thiazides in analyses for melanoma.*