Nitrate in drinking water and colorectal cancer

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Endogenous Nitrosation

Drinking water standard: 50 mg/L protects infants from methemoglobinemia

Chronic effects?
• NOCs are animal/human carcinogens

IARC group 2A
probably carcinogenic to humans under conditions that result in endogenous nitrosation

Ward et al. (2005), IARC (2010,2016), Mirvish et al. (1998), Møller et al. (1989)
Colorectal Cancer

Established risk factors

- red/processed meat intake
- smoking
- alcohol intake
- physical inactivity
- obesity

Epidemiologic Studies Nitrate & CRC

Ecologic studies

Gulis et al. (2002): increased risk CRC >20 mg/L

Case-control studies

De Roos et al. (2003): susceptible groups (low vitamin C/high red meat intake):
  ≈ 2-fold increased risk for colon cancer at >22 mg/L for >10 years
McElroy et al. (2008): increased risk for proximal colon cancer, no overall association
Espejo-Herrera et al. (2016): ≈ 1.5-fold increased risk for colon cancer >4.3 mg/L,
  rectum cancer >8.6 mg/L

Cohort studies

Weyer et al. (2001): no clear association with colon cancer, inverse association with
  rectum cancer
METHODS
Register-based Cohort Study

Exposure
*Jupiter*-database
Nitrate concentrations

Residence
*Civil Registration System*
Address history

Effect
*National Cancer Register*
Diagnoses and dates:
Colon/rectum/others

Covariates
*Health- & administrative registers*
Age, sex, education
smoking, diet
Nitrate in Public Water Supply Areas

For every person:
Residence between 1978 – 2012 → known exposure to nitrate level

Schullehner et al. (2017b)
Study Population

All residents of Denmark

Exposure
average nitrate concentration between age 20-35

Covariates
age, sex, calendar year, other cancer diagnosis, socio-economic status

Follow-up
from age 35 until cancer diagnosis / death / end of study

Cox-PH model
1.7 million individuals, 5944 colorectal cancer cases
RESULTS
Nitrate in Drinking Water and Colorectal Cancer

Drinking water nitrate more than 9.25 mg/l 15% (7%-24%) increased risk of colorectal cancer compared to < 1.27 mg/l

Preliminary results – under review
DISCUSSION
Nitrate in Drinking Water and colorectal cancer

One of few epidemiological studies

**Positive association** between nitrate in drinking water and colorectal cancer, colon cancer, and rectal cancer

Observed effect far below the current drinking water standard of 50 mg/l

Consistent with results from Spanish-Italian study from 2016

Sensitivity analyses show robust results
Strengths

• Population-based
• Largest study population/ number of cases
• High validity and completeness of register data
• Prospective data collection

• Exposure assessment
  • Based on longitudinal data from water sample analysis by certified labs
  • maximal physical boundaries of a waterworks
  • Inclusion of private wells
  • High spatial and temporal resolution
  → Most detailed dataset available on nitrate exposure from drinking water
Limitations

Lack of individual-level data of
• Other sources of nitrate/nitrite/NOCs
• Diet, smoking, BMI, physical activity...
• Modulators of endogenous nitrosation

Private wells: nitrate ↑  knowledge ↓
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