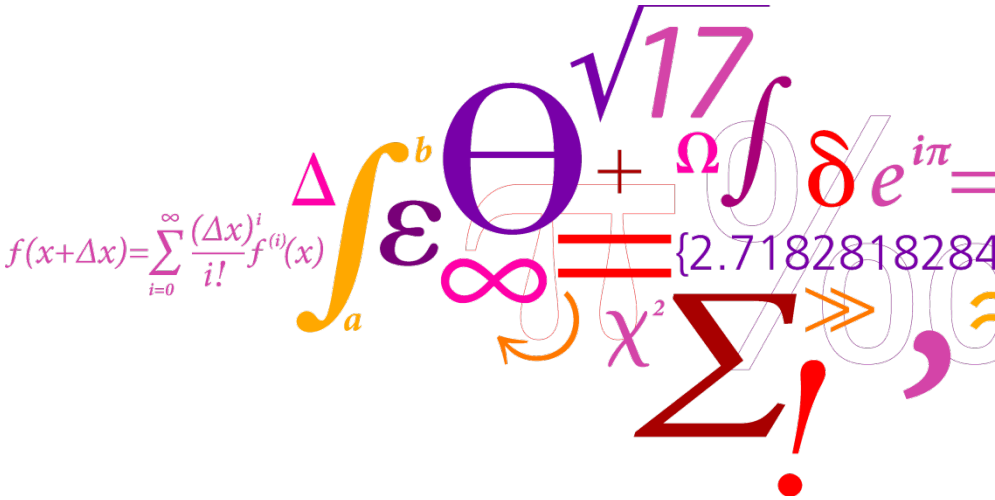
Single Nucleotide Polymorphisms and Alcohol Intake in Relation to Breast Cancer

Two prospective studies nested within the Danish "Diet, Cancer and Health" cohort



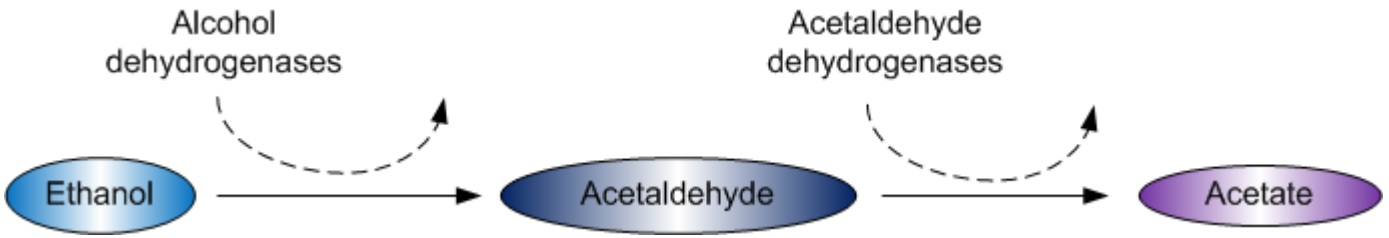
DTU Food
National Food Institute

ADH, Alcohol Intake and Breast Cancer

- Three possible mechanisms behind alcohol related breast cancer:

1. Increased estrogen levels,
2. Disturbing of the folate metabolism, or
3. The primary metabolite acetaldehyde acting as a mutagen

Alcohol metabolism:



SB Larsen et al., 2010: *"Interaction between ADH1C Arg^{272}Gln and alcohol intake in relation to breast cancer risk suggest that alcohol is the causal factor in alcohol related breast cancer"*

- Two functional SNPs in two genes encoding alcohol dehydrogenases – *ADH1B* and *ADH1C* – are analysed in Danish postmenopausal women

  – Carriers of the variant allele of *ADH1B* Arg^{48}His: "very fast metabolisers" of ethanol → ↑ conc. of acetaldehyde

  – Carriers of the variant allele of *ADH1C* Arg^{272}Gln:"slow metabolisers" of ethanol → ↓ conc. of acetaldehyde

SB Larsen et al., 2010: *"Interaction between ADH1C Arg^{272}Gln and alcohol intake in relation to breast cancer risk suggest that alcohol is the causal factor in alcohol related breast cancer"*

Variable	Cases (N = 809)		Controls (N = 809)		OR[a] (95% CI)
	No. (%)	Median (5–95%)	No. (%)	Median (5–95%)	
Frequencies of alcohol intake					
Abstain	21 (3)		21 (3)		1.15 (0.60–2.24)
<0–3 g/day	162 (20)		204 (25)		
3–15 g/day	321 (40)		344 (43)		
15–30 g/day	133 (16)		91 (11)		
>30 g/day	172 (21)		149 (18)		
Alcohol intake (g/day)[b]		11 (1–43)		10 (0.7–42)	1.07 (1.00–1.14)
NSAID[c] use (% ever users)	334 (41)		288 (36)		1.26 (1.03–1.55)
Duration of HRT[d]		2 (0–18)		2 (0–18)	1.00 (0.89–1.13)
School education					
Low	246 (30)		287 (35)		1.00 (Ref.)
Medium	394 (49)		383 (48)		1.23 (0.97–1.56)
High	169(21)		139 (17)		1.41 (1.03–1.93)
Nulliparous	115 (14)		98 (12)		0.87 (0.57–1.33)
Number of births[e]		2 (0–4)		2 (0–4)	0.95 (0.83–1.08)
Age at first birth[f]		23 (18–32)		23 (18–31)	1.11 (0.96–1.29)
BMI[g]	21 (3)		21 (3)		1.02 (0.99–1.04)

[a] IRR are mutually adjusted.
[b] The risk is estimated for the increment of 10 g alcohol/day.
[c] Non-steroid anti-inflammatory drugs.
[d] The risk is estimated per additional year of HRT use.
[e] The risk is estimated per additional birth.
[f] The risk is estimated per additional 5 years.
[g] The risk is estimated per additional 1 kg/m^2.

SB Larsen et al., 2010: *"Interaction between ADH1C Arg^{272}Gln and alcohol intake in relation to breast cancer risk suggest that alcohol is the causal factor in alcohol related breast cancer"*

IRR for breast cancer in relation to the studied polymorphisms.

Genotype	$N_{cases}/N_{controls}$ (809/809)	Cases/controls (%)	OR (95% CI)[a]	OR (95% CI)[b]
ADH1B Arg^{48}His				
GG	778/768	96/95	1.00	1.00
AA + AG	31/41	4/5	0.75 (0.47–1.20)	0.78 (0.48–1.26)
ADH1C Arg^{272}Gln				
CC	291/311	36/38	1.00	1.00
CT	378/376	47/47	1.07 (0.86–1.33)	1.09 (0.87–1.36)
TT	140/122	17/15	1.22 (0.90–1.65)	1.27 (0.94–1.73)
CT + TT	518/498	64/62	1.10 (0.89–1.35)	1.13 (0.91–1.40)
Phenotype[c]				
Very fast	31/41	4/5	0.73 (0.45–1.18)	0.75 (0.46–1.23)
Fast	273/282	34/35	0.94 (0.76–1.17)	0.91 (0.73–1.14)
Slow	505/486	62/60	1.00	1.00

[a] Crude.

[b] Adjusted for parity (parous/nulliparous, number of births, age at first birth) education (low, medium, high), duration of HRT (years), BMI (kg/m^2) and consumption of alcohol (10 g/day).

[c] Phenotypes of ethanol oxidation: all ADH1B variant allele carriers are considered 'very fast'; double homozygous wildtype carriers are considered 'fast', and wildtype ADH1B who are variant allele carriers of ADH1C are considered 'slow'.

SB Larsen et al., 2010: *"Interaction between ADH1C Arg^{272}Gln and alcohol intake in relation to breast cancer risk suggest that alcohol is the causal factor in alcohol related breast cancer"*

IRR for breast cancer in relation to genotypes per 10 g alcohol/day.

Genotype	$N_{cases}/N_{controls}$ (768/768)	IRR (95% CI)[a]	*P*-value[c]	IRR (95% CI)[b]	*P*-value[c]
ADH1B Arg^{48}His					
GG	740/728	1.09 (1.02–1.16)		1.08 (1.01–1.16)	
AA + AG	28/40	1.11 (0.80–1.54)	0.89	1.10 (0.79–1.54)	0.90
ADH1C Arg^{272}Gln					
CC	276/295	1.02 (0.90–1.12)		0.99 (0.89–1.11)	
CT	359/356	1.12 (1.02–1.24)	0.17	1.12 (1.01–1.24)	0.14
TT	133/117	1.19 (1.02–1.40)		1.19 (1.01–1.39)	
CC	276/295	1.01 (0.90–1.12)		0.99 (0.89–1.11)	
CT + TT	492/473	1.14 (1.05–1.25)	0.08	1.14 (1.04–1.24)	0.06

[a] Crude.
[b] Adjusted for parity (parous/nulliparous, number of births, age at first birth) education (low, medium, high), duration of HRT (years) and BMI (kg/m^2).
[c] *P*-value for interaction.

- ⇒ *"ethanol rather than the metabolite acetaldehyde is the carcinogenic substance in relation to alcohol induced breast cancer in postmenopausal Caucasian women"*

PPAR-γ, Alcohol Intake and Breast Cancer

- "Alcohol consumption is associated with a 7-10 % increased risk of breast cancer per 10 g/day" (A Tjonneland, 2008; P Boffetta, 2006)

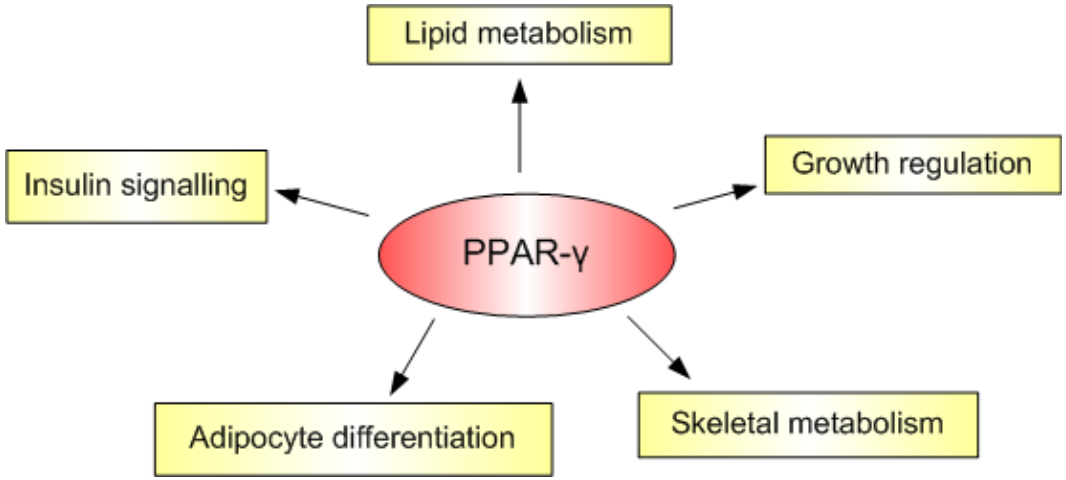
- One unit of alcohol ~ 12 g ethanol (*Source: National Board of Health*)

- The National Board of Health until recently: Women < 14 units/week and men: 21 < units/week

PPAR-γ, Alcohol Intake and Breast Cancer

- PPAR-γ, alcohol and breast cancer:

1. Alcohol intake increases aromatase expression in adipocytes → ↑ sex hormone level
2. PPAR-γ agonists inhibit adipocyte aromatase activity



U Vogel et al., 2006: "*Peroxisome profilerator-activated receptorγ2 Pro^{12}Ala, interaction with alcohol intake and NSAID use, in relation to risk of breast cancer in a prospective study of Danes*"

- The variant allele of the *PPARγ2* Pro^{12}Ala polymorphism changes the transcriptional activation of target genes →
  - ↓ risk of metabolic syndrome and improved insulin sensitivity (A Meirhaeghe et al., 2004) and
  - ↓ risk of colorectal cancer compared to wild type carriers (S Landi et al., 2003)

U Vogel et al., 2006: "*Peroxisome profilerator-activated receptorγ2 Pro[12]Ala, interaction with alcohol intake and NSAID use, in relation to risk of breast cancer in a prospective study of Danes*"

Table I. Baseline characteristics of study participants selected from the Danish 'Diet, Cancer and Health' prospective cohort study

Variable	Cases ($N = 361$)		Controls ($N = 361$)		IRR[a] (95% CI)
	No. (%)	Median (5–95%)	No. (%)	Median (5–95%)	
Abstain	10 (3)		10 (3)		1.23 (0.47–3.21)
Alcohol intake (g/day)[b]		11 (1–44)		10 (0.7–42)	1.08 (0.98–1.20)
NSAID use (% ever users)	157 (43)		134 (37)		1.28 (0.94–1.74)
Present smoking	121 (34)		131 (36)		0.90 (0.62–1.30)
Duration of HRT[c]		6 (0.5–20)		5 (0.5–21)	1.00 (0.84–1.19)
Benign breast disease	70 (19)		47 (13)		1.52 (1.00–2.33)
School education					
Low	102 (28)		123 (34)		1.00
Medium	176 (49)		176 (49)		1.18 (0.81–1.73)
High	83 (23)		62 (17)		1.52 (0.94–2.44)
Parous[d]	47 (13)		43 (12)		0.67 (0.35–1.27)
Number of births		2 (1–4)		2 (1–4)	0.94 (0.77–1.14)
Age at first birth, years[d]		23 (18–32)		23 (17–31)	1.18 (0.94–1.48)
BMI[d]		25 (20–33)		25 (20–34)	1.01 (0.97–1.05)

Observed median values (5–95 percentiles) or fractions of the distribution of alcohol, NSAID, smoking and potential breast cancer confounders among breast cancer cases and controls.

[a]IRR's are mutually adjusted.

[b]Risk estimate per 10 g increment/day for alcohol.

[c]Among HRT users, risk estimate per additional year.

[d]Risk estimate par additional birth, per additional year of age and per 1 kg/m^2.

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Table II. IRR for breast cancer in relation to the studied genotypes

Genotype	N_{cases}/ $N_{controls}$ 361/361	Cases/ controls (%)	IRR (95% CI)[a]	IRR (95% CI)[b]
IL-6 G-174C				
GG	108/98	30/27	1.00	1.00
CG	167/177	46/49	0.84 (0.59–1.18)	0.81 (0.56–1.16)
CC	86/86	24/24	0.91 (0.61–1.36)	0.95 (0.63–1.43)
CG+CC	253/263	70/73	0.86 (0.63–1.19)	0.86 (0.62–1.20)
IL-8 T-251A				
TT	88/78	24/22	1.00	1.00
AT	160/167	44/46	0.81 (0.55–1.21)	0.83 (0.55–1.25)
AA	88/78	24/22	0.85 (0.56–1.28)	0.81 (0.53–1.24)
AT+AA	273/283	76/78	0.83 (0.58–1.19)	0.82 (0.57–1.20)
PPARγ2 Pro^{12}Ala				
CC	283/258	78/71	1.00	1.00
CG	71/93	20/26	0.68 (0.47–0.98)	0.66 (0.45–0.96)
GG	7/10	2/3	0.67 (0.25–1.83)	0.81 (0.29–2.29)
CG+GG	78/103	22/29	0.68 (0.48–0.97)	0.67 (0.46–0.97)
COX2 T8473C				
TT	167/155	46/43	1.00	1.00
CT	150/165	42/46	0.82 (0.59–1.14)	0.82 (0.58–1.15)
CC	44/41	12/11	1.01 (0.64–1.62)	1.04 (0.64–1.70)
CT+CC	194/206	54/57	0.87 (0.64–1.17)	0.87 (0.64–1.19)

[a]Crude.
[b]Adjusted for parity (parous/nulliparous, number of births and age at first birth), education, duration of HRT, BMI and alcohol consumption.

U Vogel et al., 2006: "*Peroxisome profilerator-activated receptorγ2 Pro^{12}Ala, interaction with alcohol intake and NSAID use, in relation to risk of breast cancer in a prospective study of Danes*"

Table III. IRR for breast cancer per 10 g alcohol/day for different genotypes

Genotype	N_{cases}/ $N_{controls}$	IRR (95% CI)[a]	*P*-value[c]	IRR (95% CI)[b]	*P*-value[c]
IL-6 G-174C					
GG	108/98	1.03 (0.85–1.24)		1.02 (0.84–1.24)	
CG	167/177	1.21 (1.05–1.39)	0.27	1.20 (1.04–1.40)	0.25
CC	86/86	1.02 (0.83–1.27)		1.00 (0.80–1.25)	
GG	108/98	1.02 (0.84–1.22)	0.28	1.01 (0.83–1.22)	0.31
CG+GG	253/263	1.15 (1.02–1.29)		1.14 (1.01–1.29)	
IL-8 T-251A					
TT	88/78	1.15 (0.94–1.40)		1.12 (0.90–1.38)	
AT	160/167	1.10 (0.96–1.26)	0.94	1.11 (0.96–1.28)	0.97
AA	88/78	1.11 (0.93–1.32)		1.08 (0.90–1.30)	
TT	88/78	1.15 (0.94–1.34)	0.72	1.11 (0.90–1.37)	0.91
AT+AA	273/283	1.10 (0.99–1.23)		1.10 (0.98–1.23)	
PPAR-γ2 Pro^{12}Ala					
CC	283/258	1.21 (1.08–1.35)		1.20 (1.06–1.35)	
CG	71/93	0.85 (0.68–1.06)	0.01	0.86 (0.68–1.08)	0.02
GG	7/10	0.55 (0.13–2.32)		0.48 (0.10–2.22)	
CC	283/258	1.21 (1.08–1.35)	0.003	1.20 (1.06–1.35)	0.005
CG+GG	78/103	0.83 (0.67–1.03)		0.83 (0.67–1.04)	
COX2 T8473C					
TT	167/155	1.17 (1.02–1.32)		1.16 (1.01–1.33)	
CT	150/165	1.15 (0.95–1.38)	0.32	1.15 (0.94–1.40)	0.18
CC	44/41	0.91 (0.69–1.20)		0.85 (0.64–1.14)	
TT	167/155	1.15 (1.01–1.31)	0.44	1.15 (1.00–1.32)	0.34
CT+TT	194/206	1.07 (0.92–1.23)		1.04 (0.90–1.22)	

[a]Crude IRR for breast cancer per 10 g alcohol/day.
[b]Adjusted for parity (parous/nulliparous, number of births and age at first birth), education, duration of HRT and BMI.
[c]*P*-value for interaction.

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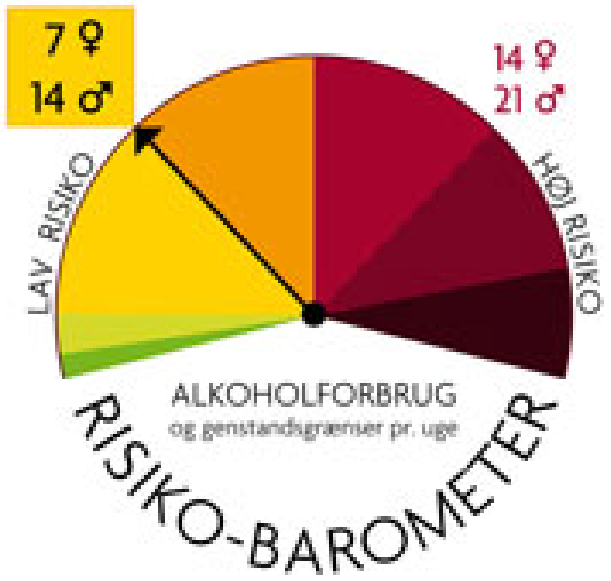
- PPAR-γ, alcohol and breast cancer:

1. Alcohol intake increases aromatase expression in adipocytes → ↑ sex hormone level
2. PPAR-γ Pro^{12}Ala changes the risk of alcohol related breast cancer
3. PPAR-γ agonists inhibit adipocyte aromatase activity

⇒ Alcohol intake may interact with PPAR-γ → increased aromatase activity → increased sex hormone level → increased breast cancer risk

U Vogel et al., 2006: "*Peroxisome profilerator-activated receptorγ2 Pro^{12}Ala, interaction with alcohol intake and NSAID use, in relation to risk of breast cancer in a prospective study of Danes*"

- 30 % of Danish women are not at risk of alcohol related breast cancer, but...
- 70 % of Danish women have an increased risk of alcohol related breast cancer – from 7-10 % (general population – women) to 20 % per 10 g/day
- The "new" recommendations from the National Board of Health:



Discussion

- Should we in the future be more aware of individual differences when recommending for example diet intake or toxicological levels of known carcinogens?

- Which problem(s) could emerge?