The Diet, Cancer and Health study – a prospective cohort study

The importance of record linkage in Cancer Epidemiology

Anne Tjønneland
ENCR ,
September 28th, 2018

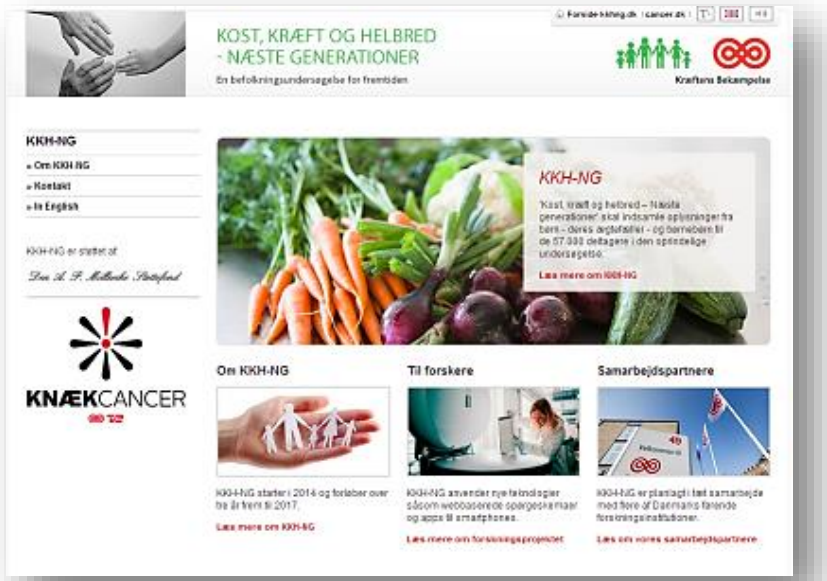
Danish Cancer Society Research Center

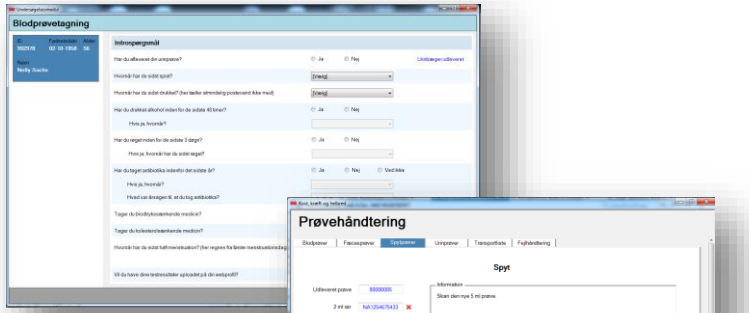
250 researchers and technicians from all parts of the world

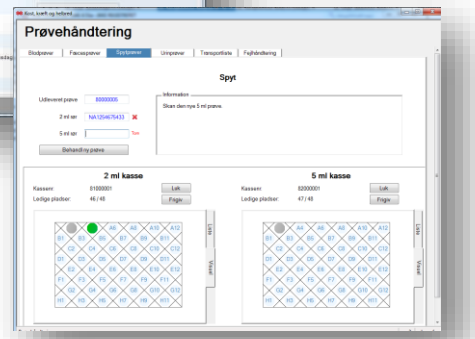
- **Diet, Genes and Environment**
- Virus, Lifestyle and Genes
- Cell Stress and Survival
- Cell Death and Metabolism
- Genome Integrity
- Survivorship
- Translational Cancer Research
- Statistics, Bioinformatics and Registry
- Danish Centre for Translational Breast Cancer Research

Agenda

- Cohort description
- Record linkage examples
- Perspectives







Diet, Cancer and Health cohort

- Baseline data collection 1993–1997
- Follow up questionnaires 1999-2002

57,053 healthy participants, 50–64 y

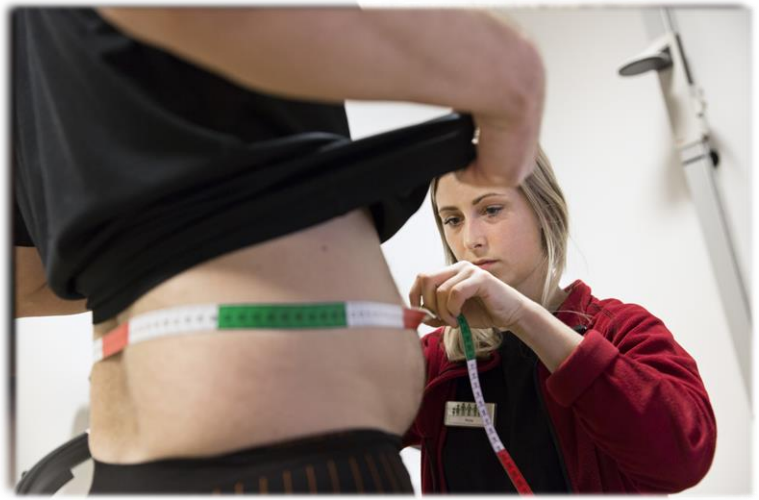
- 27,178 men
- 29,875 women

Follow up for disease events (31/12 2016)

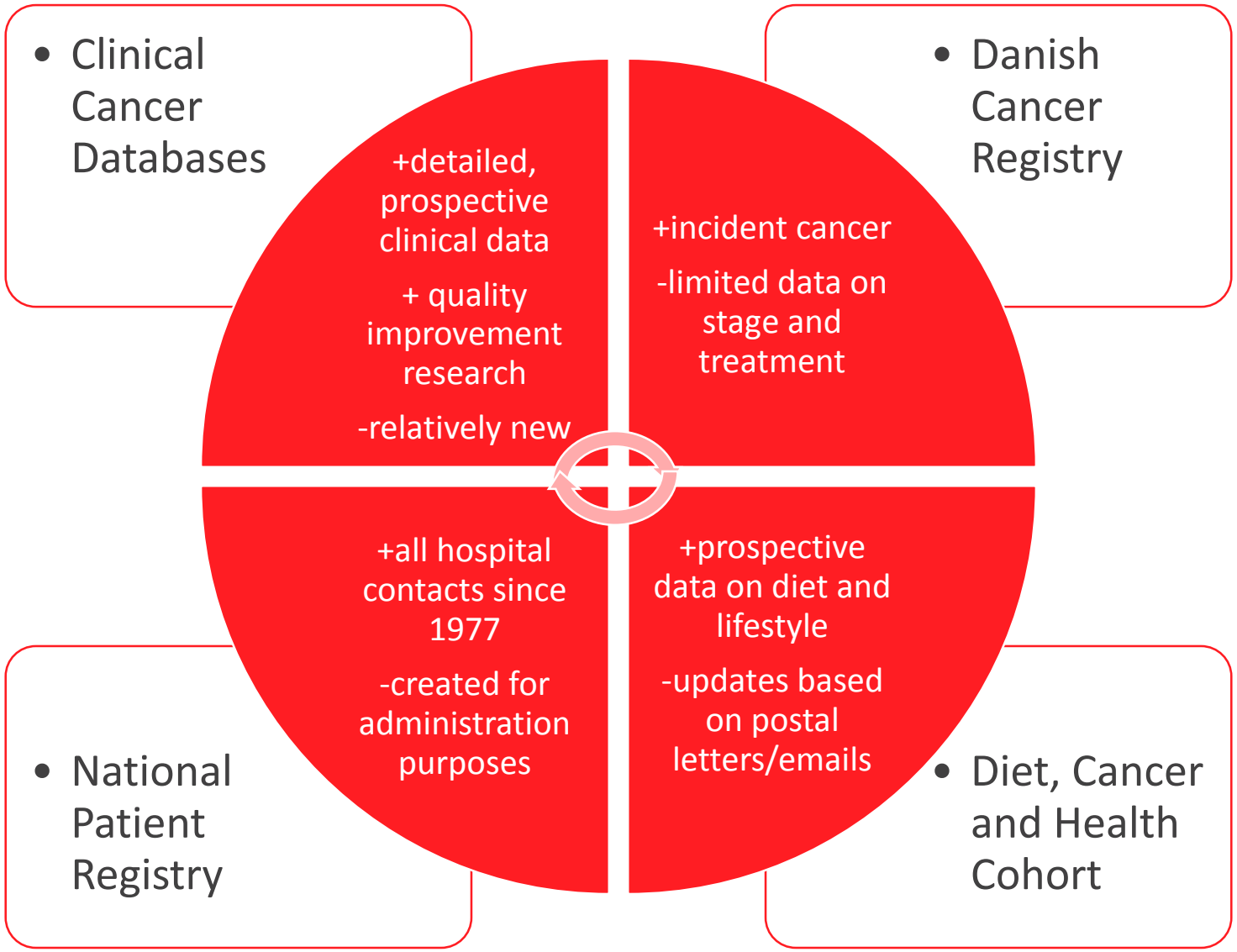
- 14,000 deaths, all causes
- 14,875 incident cancers
- 1,909 diagnosed colorectal cancer
- 2,495 diagnosed prostate cancer
- 2,311 diagnosed breast cancer

Diet, Cancer and Health cohort

- **Baselinedata:**
- Food frequency questionnaires, 24HDR (subset)
- Lifestyle questionnaires
- Biological specimens
  - Blood
  - Urine
  - Adipose tissue
  - Toenail clippings
- Physical measurements
  - Weight, height, standing height, sitting height
  - waist circumference, hip circumference
  - blood pressure



Key data sources for follow up



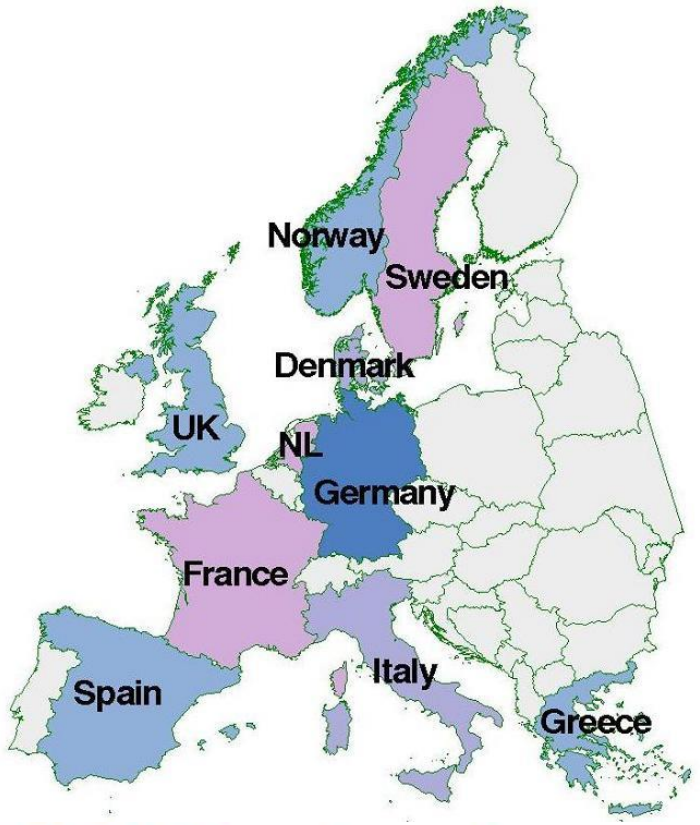
Other registries:

- **The Civil Registration System (from 1968)**
- The National Diabetes Registry (from 2006-11)
- School Health Records Registry
- Birth Records
- The Danish Pension Fund Registry to individual employment history
- CPR and exposure modelling for air pollution, traffic noise etc.
- **Statistics Denmark , incl. Danish Prescription Registry**

Follow-up rate: 99.8 %

EPIC collaboration

- European collaboration, EPIC, 10 countries, 500.000 participants.
- Continuous collaboration for more than 25 years among 25 research institutions in Europe
- Common EPIC database at IARC and Imperial College, London
- Working groups on cancer end points, and other chronic diseases
- Very productive collaboration with app. 100 publications pr. year
- Monthly telephone meetings, and 1-2 yearly face-to-face meetings
- Extended collaboration through i.e. Cohort Consortium



25 years of research

> 1000 scientific papers:

- Hormone therapie during menopause increases the risk of breast cancer, ovarian cancer and endometrial cancer
- Alcohol intake increases the risk of breast cancer
- Whole grain intake protects against colorectal cancer
- High pre diagnostic blood levels of enterolactone improves survival after breast cancer
- Healthy Nordic diet reduce overall mortality
- Air pollution increases the risk of lung cancer

Diet, Cancer and Health – Next Generations

Rationale and objectives

To extend the existing Diet, Cancer and Health (DCH) cohort by recruiting “next generations”

Overall aims:

- Enable trans-generational studies of the pathogenesis of multiple cancers and other diseases
- Valuable in the search for biomarkers and omics technologies for early detection and exposure

DIET, CANCER AND HEALTH
NEXT GENERATIONS

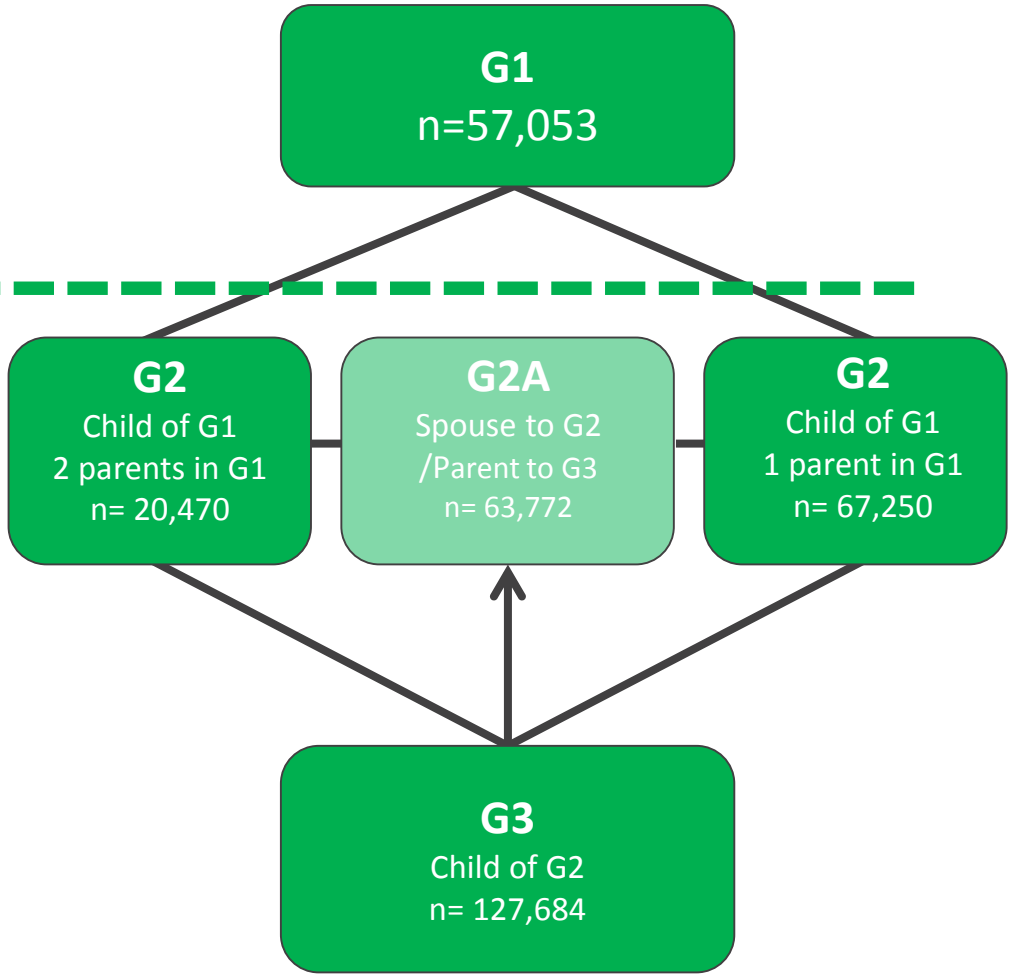
Identification of “next generations”

- using The Danish Civil Registration System

Kost, kræft og helbred

Original Diet, Cancer and Health cohort

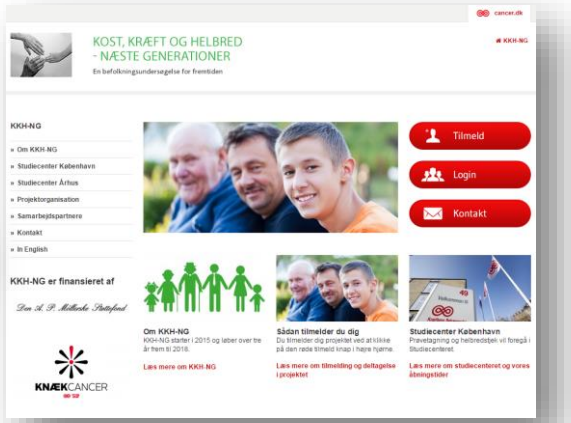
DIET, CANCER AND HEALTH
NEXT GENERATIONS



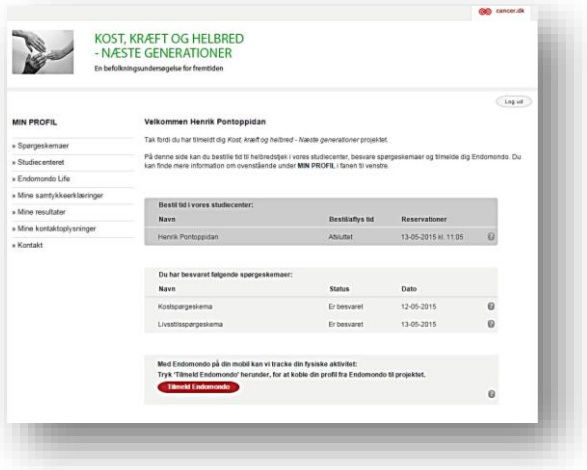
Recruitment process

Invitation letter

DCH-NG homepage



Webprofile (Web)



KOST, KRÆFT OG HELBRED
NÆSTE GENERATIONER

Questionnaires

Food frequency questionnaire

- 366 food items

Background and lifestyle questionnaire

- Socio-demographics
- Work conditions and environment
- Smoking habits and history
- Alcohol habits and history
- Physical activity
- Sleep pattern and quality
- Weight history
- Medication and medical history
- Family history of disease
- Female/male reproductive factors
- Quality of life (SF36)
- Family relations

KOST, KRÆFT OG HELBRED
NÆSTE GENERATIONER

Baseline assessment at the study center

Physical measurements	
Anthropometry	Height, weight, waist, hip
Bioimpedance	Body composition (e.g. fat and muscle mass)
Blood pressure	Pulse rate and blood pressure
App	Physical activity, steps

Biological samples (non-fasting)	
Urine	Spot urine
Saliva	Pure saliva, saliva with added RNAlater
Feacal sample	Imidiately frozen and preserved for DNA extraction
Blood, storage	Plasma, serum, buffy coat, erythrocytes, RNA extraction tube
Blood, up-front	Triglycerides, total, HDL and LDL cholesterol, HbA1c, hs-CRP, creatinine

KOST, KRÆFT OG HELBRED
NÆSTE GENERATIONER

DCH-NG MAX n=500

Data collection

- Height
- Weight
- Bioimpedance
- Blood pressure
- Waist circumference
- Hip circumference

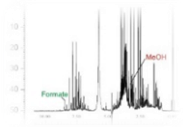
- Blood
- Urine
- Saliva
- Faeces

- Food frequency questionnaire
- Lifestyle questionnaire
- 24-hour dietary recall

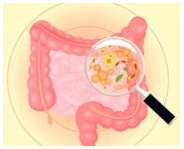
Baseline 6 months 12 months

Analyses

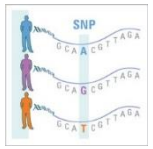
HbA1c, triglyceriders, total cholesterol, LDL cholesterol, HDL cholesterol, creatinin, hs-CRP



Untargeted **metabolomics** using LC-QTOF-MS



Gut microbiota analysed by 16S rRNA and whole genome sequensing



GWAS incl.cardio metabolic traits (lipids, lipoproteins, BMI, waist) and diseases (cardiovascular and Type 2 diabetes)

Diet, Cancer and Health – Next generation status

>51,000 participants have registered (response rate ~26%)

>42,000 participants visited the study center (300-350 visits/week)

Data collection is almost complete: 99.5-100% for all measurements including anthropometry, blood pressure and blood, urine and saliva samples

~24,000 fecal samples will be available for future research

Datacollection to end in 2018

Courses of Death Registry Statistics Denmark

Participation and mortality among 80,996 men and 79,729 women invited to the DCH study.

Eur J Epidemiol (2012) 27:837–845
DOI 10.1007/s10654-012-9739-x

METHODS

Mortality among participants and non-participants in a prospective cohort study

Signe Benzon Larsen · Susanne Oksbjerg Dalton · Joachim Schüz · Jane Christensen · Kim Overvad · Anne Tjønneland · Christoffer Johansen · Anja Olsen

Received: 8 May 2012 / Accepted: 5 October 2012 / Published online: 16 October 2012

Abstract Socioeconomic position and lifestyle often affect participation in scientific studies. The authors investigated differences in overall and cause-specific mortality between participants and non-participants in the prospective Danish cohort study "Diet, Cancer and Health" and the association between non-participation and mortality by socioeconomic position. A total of 80,996 men and 79,729 women aged 50–64 years, were invited. The authors obtained register data on education, income, death and cause-specific mortality for participants and non-participants and used survival curves to examine differences in overall mortality. Poisson regression models were used to estimate the mortality rate ratio (MRR) by socioeconomic group and by cause of death of participants and non-participants. After a median follow-up of 13 years (5–95 percentiles, 5–14 years), the MRRs for overall mortality among non-participants were 2.09 (95 % CI 1.99–2.14) and 2.29 (95 % CI 2.19–2.40) among men and women, respectively compared with participants. After adjusting for socioeconomic position, the MRRs changed to 1.73 (95 % CI 1.66–1.79) and 2.10 (95 % CO 2.01–2.20) among men and women, respectively. The MRRs did not level out after up to 15 years of follow-up. The MRRs were all significantly increased and ranged from 1.51 to 4.28 for men, depending on the cause of death, and from 1.60 to 3.99 for women. Clear differences in mortality from all investigated causes of death were found between participants and non-participants, which persisted after up to 15 years of follow-up. Socioeconomic position had little effect on this result.

Keywords Participation · Cohort study · Overall mortality · Cause-specific mortality · Socioeconomic position · Lifestyle

Introduction

The establishment of population-based cohorts is widely used in modern epidemiology for studying associations between exposure in its broadest sense and health outcomes prospectively [1]. The main advantages of follow-up studies are that they are less prone to the selection and recall bias often observed in case–control studies [1]. A number of studies have shown lower mortality rates among cohort participants than among non-participants [2–13]. In several of these studies, the differences in mortality decreased gradually with prolonged follow-up [3–6]. These findings may primarily reflect that sick people are less likely to participate in such studies. Other studies have, however, shown substantial differences in long-term mortality [7–12], which might indicate that participants have a healthier lifestyle in general, resulting in a lower disease incidence and perhaps better survival from the diseases under study.

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Overall Mortality (log MRR) participants/non-participants in DCH study

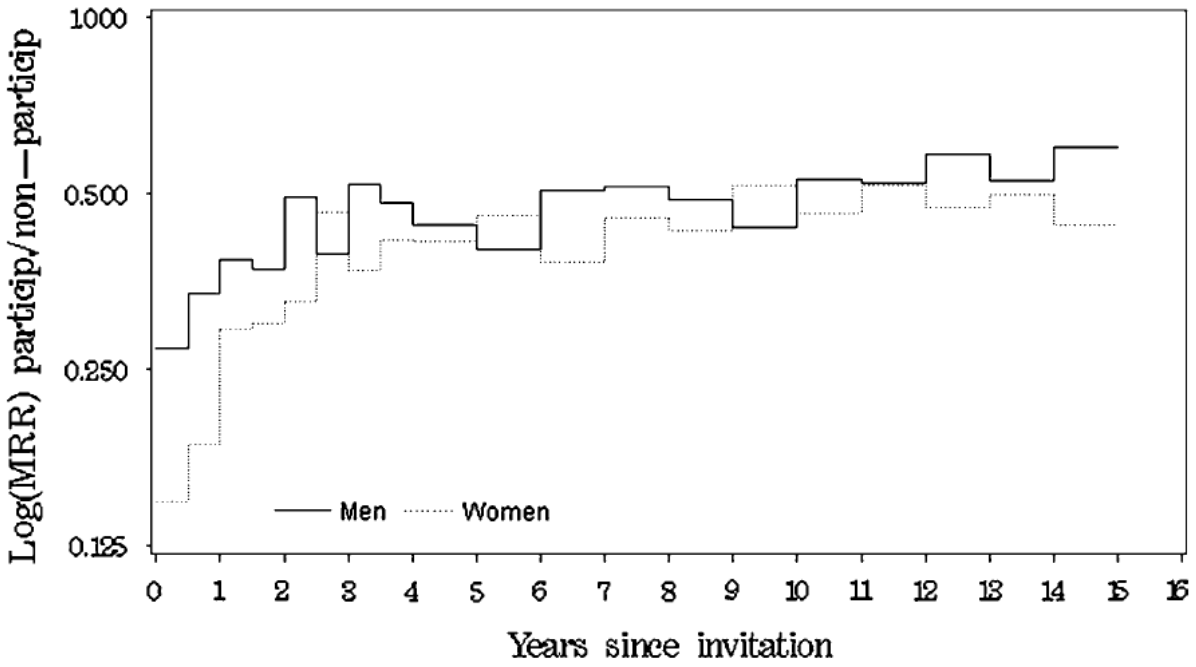


Fig. 2 Log rate ratio of overall mortality (*logMRR*) between participants and non-participants in the prospective Danish "Diet, Cancer and Health" Study stratified by sex

Mortality rate ratios for participants and non participants in DCH study (1993-2008), men

Socioeconomic indicator	Men			
	Participants		Non-participants	
	MRR	95 % CI	MRR	95 % CI
Total	1.00	(Reference)	2.06	(1.99–2.14)
Education				
Basic/high school	1.89	(1.72–2.07)	3.68	(3.41–3.98)
Vocational training	1.40	(1.29–1.53)	2.76	(2.56–2.98)
Higher education	1.00	(Reference)	1.77	(1.63–1.94)
Income (quartile)				
1st	2.94	(2.66–3.24)	5.46	(5.03–5.92)
2nd	1.77	(1.60–1.95)	3.07	(2.82–3.34)
3rd	1.20	(1.08–1.33)	2.12	(1.94–2.32)
4th	1.00	(Reference)	1.61	(1.46–1.76)

Conclusion:

- Mortality differs within social strata
- Self selection is based both on health at enrolement and also on a lifestyle keeping you healthier throughout the course of the study
- Mortality rates differed, even after accounting for differences in SEP between participants and non-participants

DIET, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER SURVIVAL (BY OUTCOME)

	Outcome	ALL CAUSE MORTALITY		BREAST CANCER MORTALITY		SECOND PRIMARY BREAST CANCER	
		DECREASED RISK	INCREASED RISK	DECREASED RISK	INCREASED RISK	DECREASED RISK	INCREASED RISK
STRONG EVIDENCE	Convincing						
	Probable						
LIMITED EVIDENCE	Limited-suggestive	Physical activity: Before diagnosis; ≥12 months after Foods containing fibre: Before diagnosis; ≥12 months after diagnosis Foods containing soy: ≥12 months after diagnosis	Body fatness: Before diagnosis; <12 months after diagnosis; ≥12 months after diagnosis tal fat: Before diagnosis aturated tty acids: Before diagnos	Physical activity: Before diagnosis	Body fatness[1]: Before diagnosis; <12 months after diagnosis		Body fatness: Before diagnosis; <12 months after diagnosis
STRONG EVIDENCE	Substantial effect on risk unlikely						

STRONG: Evidence strong enough to support a judgement of a convincing or probable causal relationship and generally justify making recommendations
LIMITED: Evidence that is too limited to justify making specific recommendations

1 Post menopause only

Lignans – prognosis after breastcancer

Published in final edited form as:
Breast Cancer Res Treat. 2010 July ; 122(1): 229–235. doi:10.1007/s10549-009-0681-x.

Dietary lignan intakes in relation to survival among women with breast cancer: the Western New York Exposures and Breast Cancer (WEB) Study

Susan E. McCann[1], **Lilian U. Thompson**[2], **Jing Nie**[3], **Joan Dorn**[3], **Maurizio Trevisan**[4], **Peter G. Shields**[5], **Christine B. Ambrosone**[1], **Stephen B. Edge**[6], **Hsin-Fang Li**[1], **Christina Kasprzak**[1], and **Jo L. Freudenheim**[3]
Susan E. McCann: susan.mccann@roswellpark.org

Postmenopausal (n = 807)		
All cause mortality		
<155	33	1.00
155–227	33	0.91 (0.55–1.52)
227–318	29	0.78 (0.46–1.33)
>318	21	0.49 (0.26–0.91)
P for trend		0.02
Breast cancer mortality		
<155	18	1.00
155–227	20	0.94 (0.48–1.87)
227–318	11	0.51 (0.23–1.15)
>318	7	0.29 (0.11–0.76)
P for trend		0.01

Cox proportional hazards adjusting for age, race, total energy, stage at diagnosis, body mass index, and education

Lignans is convertet/fermented by the gut microbiota by to enterolactone.

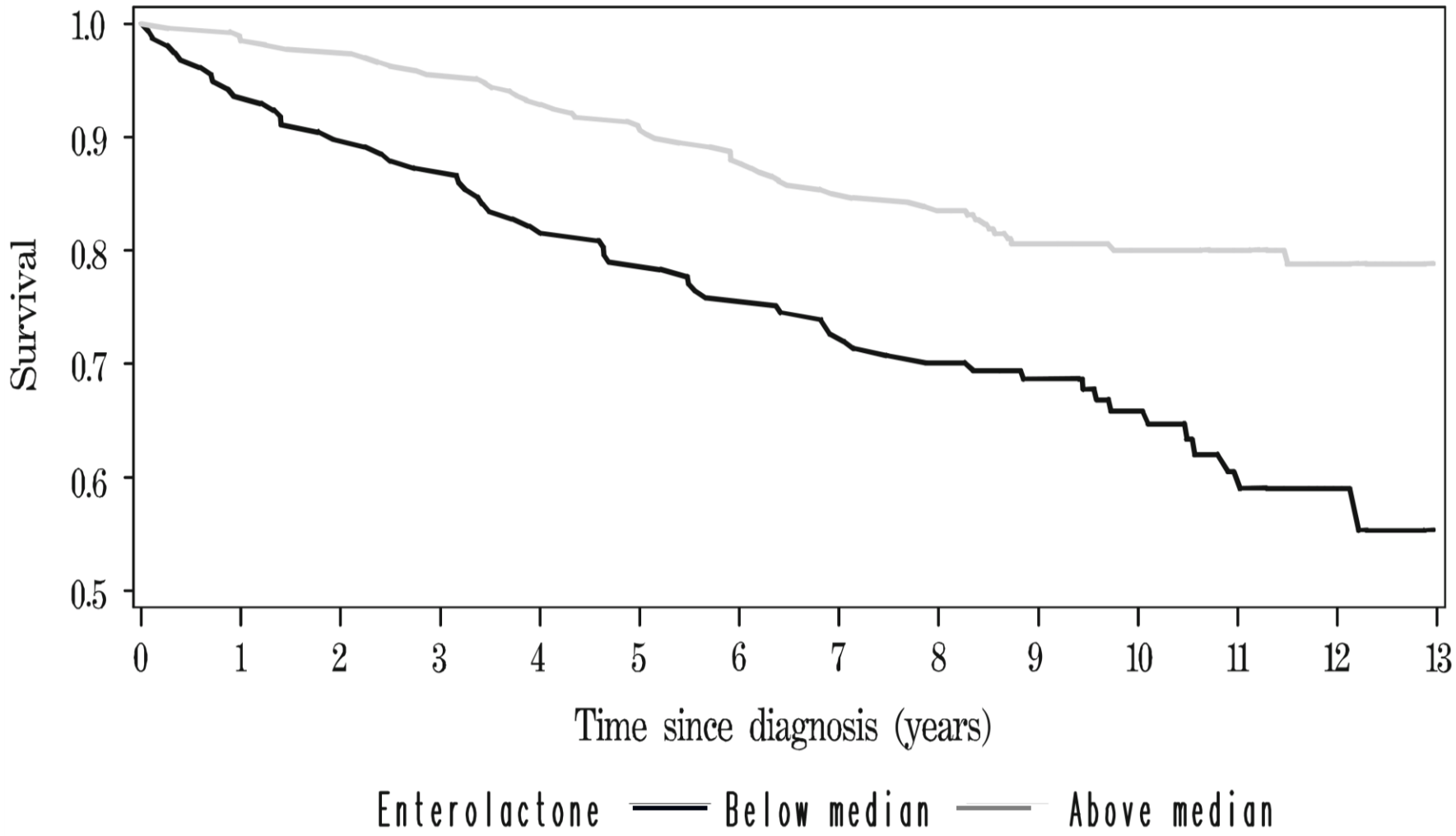
Enterolactone is a weak estrogen.

Estrogen dependent mechanisms include agonist and antagonist effects on the estrogen receptor, depended on the level of estrogen exposures.

In vitro studies have found, enterolactone to inhibit metastasis and reduce cell proliferation.

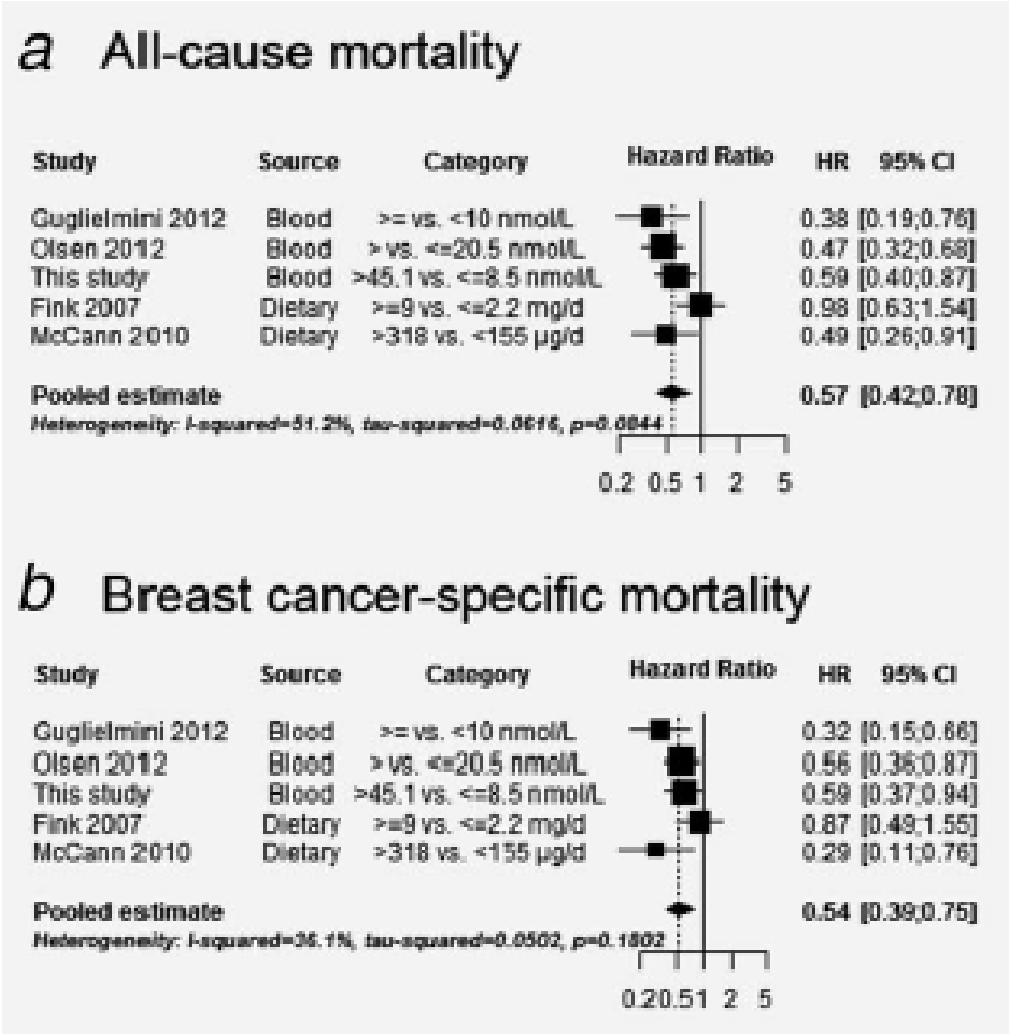
Enterolactone may improve prognosis among post menopausal women with breast cancer.

Mortality and prediagnostic level of enterolactone



Olsen, A., et al. (2011). Breast Cancer Res Treat 128(3): 883-889.

Enterolacton and breast cancer - metaanalyses



Int. J. Cancer: **135**, 923–933 (2014)

Figure 1. Meta-analysis: Association between lignan exposure and breast cancer prognosis in postmenopausal women. Results for all-cause mortality (*a*) and breast cancer-specific mortality (*b*) are pre-

Enterolactone and the Danish Prescription Registry

Flaxseed, whole grains, vegetables, berries etc.	Lignans	Enterolactone og enterodiol

DOI 10.1002/mnfr.201600566 *Mol. Nutr. Food Res.* 2016, *60*, 2712–2721

RESEARCH ARTICLE

Use of antibiotics is associated with lower enterolactone plasma concentration

Anne K. Bolvig[1], Cecilie Kyrø[2], Natalja P. Nørskov[1], Anne K. Eriksen[2], Jane Christensen[2], Anne Tjønneland[2], Knud E. Bach Knudsen[1] and Anja Olsen[2]

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Scope: High enterolactone levels may have health benefits in relation to risk of noncommunicable diseases. Enterolactone is produced by the colonic microbiota after intake of lignans and treatment with antimicrobials may result in altered enterolactone production. This study investigates the association between antibiotic use and enterolactone concentration.

Methods and results: Using LC–MS/MS, enterolactone concentrations were quantified in plasma samples from 2237 participants from the Diet, Cancer and Health cohort. The participants were healthy at enrollment, but were later diagnosed with cancer. At enrollment, participants had blood drawn and completed a food frequency questionnaire and lifestyle questionnaire. Antibiotic use was assessed as reimbursed antibiotic prescriptions up to 12 months before enrollment. Antibiotic use ≤3 months before enrollment was associated with a 41% (Δ_{crude}: −41; 95% CI: −52, −28) lower enterolactone concentration in women and 12% in men (Δ_{crude}: −12; 95% CI: −31, 11), while antibiotic use >3–12 months before enrollment was associated with 26% lower enterolactone in women (Δ_{crude}: −26; 95% CI: −37, −14) and 14% in men (Δ_{crude}: −14; 95% CI: −28, 1).

Conclusion: Use of antibiotics up to 12 months before enrollment was associated with lower plasma enterolactone levels, especially among women.

Keywords:
Antibiotics / Enterolactone / Epidemiology / Lignans / Microbiota

Additional supporting information may be found in the online version of this article at the publisher's web-site

Antibiotic treatment/reimbursed prescription and levels of enterolactone, women

Table 2. Percentage difference in enterolactone plasma concentration and 95% CI by most recent antibiotic use among 2237 participants included in the Diet, Cancer and Health cohort

		Female ($n = 1106$)											
		Crude model				Model-1[a)]				Model-2[b)]			
R^2		0.030				0.075				0.089			
	n	Δ	95% CI		p-Value	Δ	95% CI		p-Vlue	Δ	95% CI		p-Value
No antibiotic treatment	731	Ref.	—	—	—	Ref.	—	—	—	Ref.	—	—	—
Antibiotic use 0–3 months	132	–41	–52	–28	<0.0001	–39	–50	–25	<0.0001	–40	–50	–26	<0.0001
Antibiotic use 3–12 months	243	–26	–37	–14	0.0002	–24	–35	–11	0.0007	–23	–34	–10	0.0011

a) Model-1 is adjusted for smoking, schooling, alcohol consumption, and BMI.
b) Model-2 is adjusted for smoking, schooling, alcohol consumption, BMI, and whole-grain intake.
The percentage estimates were derived from regression with log-transformed values. The results presented are back-transformed log-values
n, number of participants; Ref., reference ($\Delta = 0$); R^2, fitness of model; Δ, estimates reported as percentage change in enterolactone concentration.

Conclusion:

- Level of enterolactone depends on the ‘recent’ intake of antibiotics

- This should be taken into account, when analysing the association between enterolactone and disease endpoints.

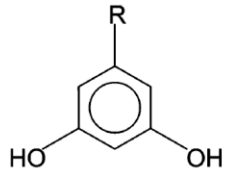
Assessment of whole-grain intake

Assessment of whole-grain intake

- Most cohort studies have no information on whole-grain intake
- In some cohorts, the whole-grain intake is very low
- Dietary assessment of whole-grain intake from questionnaires can especially be difficult
- Biomarkers of intake could overcome some of these problems

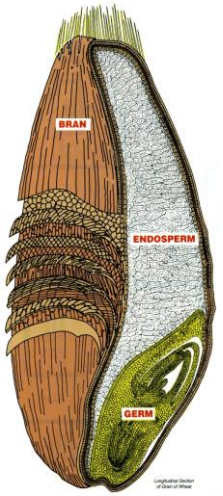
Alkylresorcinols
- *Biomarkers of whole-grain intake*

- Phenolic lipids – found in the bran part of rye and wheat
- Unaffected by food processing
- Validated (measured in plasma) both in intervention studies and in cohort studies
    - Questionnaire vs. biomarker: r=0.25–0.57



Alkylresorcinol	Abbreviation used	R	Molecular weight (g/mole)
5-n-Heptadecylresorcinol	(C17:0)	$C_{17}H_{35}$	348
5-n-Nonadecylresorcinol	(C19:0)	$C_{19}H_{39}$	376
5-n-Heneicosylresorcinol	(C21:0)	$C_{21}H_{43}$	404
5-n-Tricosylresorcinol	(C23:0)	$C_{23}H_{47}$	432
5-n-Pentacosylresorcinol	(C25:0)	$C_{25}H_{51}$	460

Figure 1. Structures of alkylresorcinols (ARs) commonly found in cereals.



Research projects - methods

Questionnaire data/ Record Linkage

- Colorectal cancer (1100 cases)
- Myocardial infarction (2300 cases)
- Diabetes (7000 cases)
- Mortality (7800 deceased)

Biomarker

- Nested case-control design
- 1372 colorectal cases and 1372 matched controls
- The biomarker “Alkylresorcinols” analyzed using GC-MS

Plasma Alkylresorcinols, Biomarkers of Whole-Grain Wheat and Rye Intake, and Incidence of Colorectal Cancer

Cecilie Kyrø, Anja Olsen, Rikard Landberg, Guri Skeie, Steffen Loft, Per Åman, Max Leenders, Vincent K. Dik, Peter D. Siersema, Tobias Pischon, Jane Christensen, Kim Overvad, Marie-Christine Boutron-Ruault, Guy Fagherazzi, Vanessa Cottet, Tilman Kühn, Jenny Chang-Claude, Heiner Boeing, Antonia Trichopoulou, Christina Bamia, Dimitrios Trichopoulos, Domenico Palli, Vittorio Krogh, Rosario Tumino, Paolo Vineis, Salvatore Panico, Petra H. Peeters, Elisabete Weiderpass, Toril Bakken, Lene Angell Åsli, Marcial Argüelles, Paula Jakszyn, María-José Sánchez, Pilar Amiano, José María Huerta, Aurelio Barricarte, Ingrid Ljuslinder, Richard Palmqvist, Kay-Tee Khaw, Nick Wareham, Timothy J. Key, Ruth C. Travis, Pietro Ferrari, Heinz Freisling, Mazda Jenab, Marc J. Gunter, Neil Murphy, Eilo Riboli, Anne Tjønneland, H.B(as). Bueno-de-Mesquita

Manuscript received June 27, 2013; revised October 25, 2013; accepted October 29, 2013.

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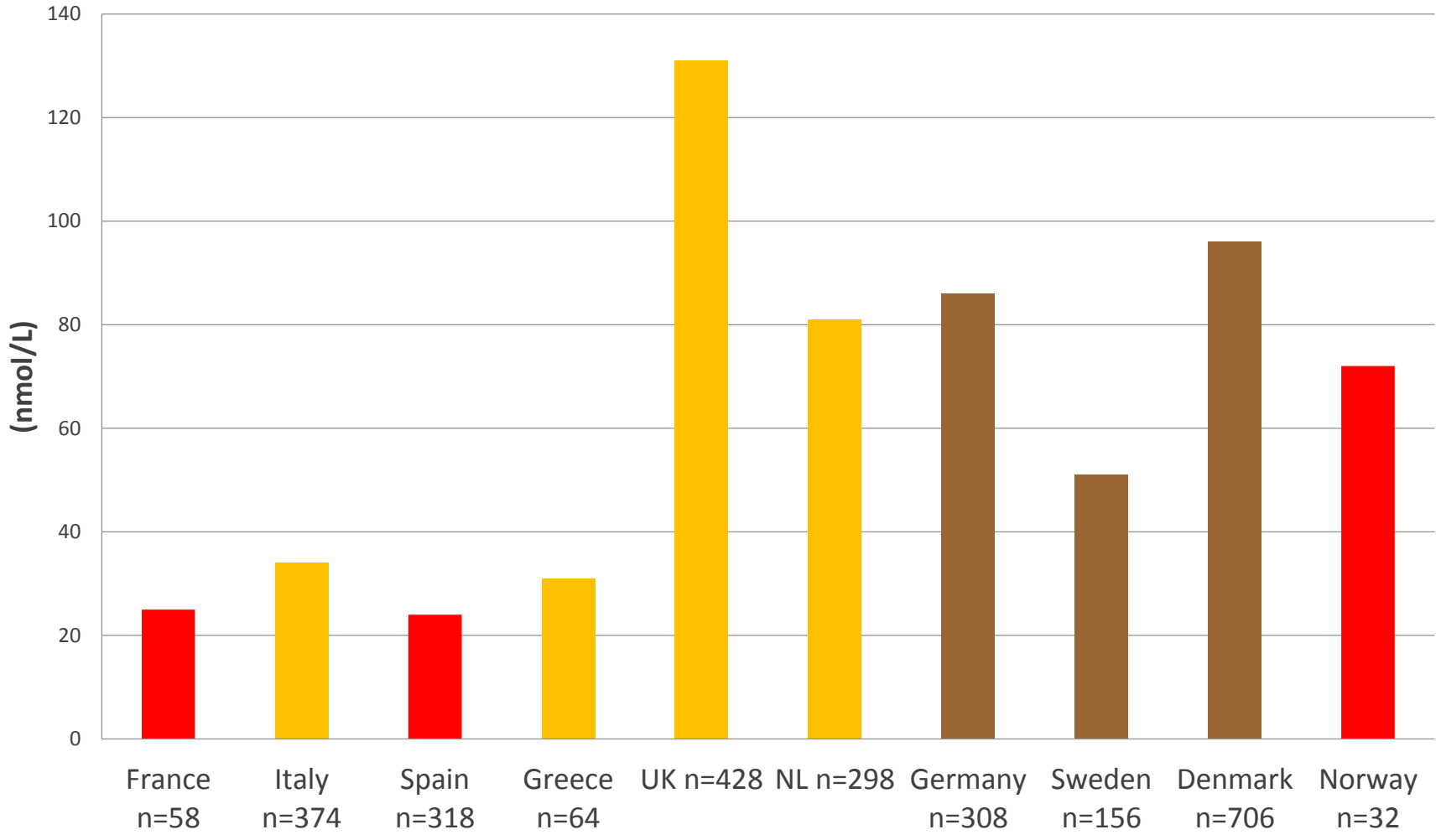
Background Few studies have investigated the association between whole-grain intake and colorectal cancer. Because whole-grain intake estimation might be prone to measurement errors, more objective measures (eg, biomarkers) could assist in investigating such associations.

Methods The association between alkylresorcinols, biomarkers of whole-grain rye and wheat intake, and colorectal cancer incidence were investigated using prediagnostic plasma samples from colorectal cancer case patients and matched control subjects nested within the European Prospective Investigation into Cancer and Nutrition. We included 1372 incident colorectal cancer case patients and 1372 individual matched control subjects and calculated the incidence rate ratios (IRRs) for overall and anatomical subsites of colorectal cancer using conditional logistic regression adjusted for potential confounders. Regional differences (Scandinavia, the Mediterranean, Central Europe) were also explored.

Results High plasma total alkylresorcinol concentration was associated with lower incidence of distal colon cancer; the adjusted incidence rate ratio of distal colon cancer for the highest vs lowest quartile of plasma total alkylresorcinols was 0.48 (95% confidence interval [CI] = 0.28 to 0.83). An inverse association between plasma total alkylresorcinol concentrations and colon cancer was found for Scandinavian participants (IRR per doubling = 0.83; 95% CI = 0.70 to 0.98). However, plasma total alkylresorcinol concentrations were not associated with overall colorectal cancer, proximal colon cancer, or rectal cancer. Plasma alkylresorcinols concentrations were associated with colon and distal colon cancer only in Central Europe and Scandinavia (ie, areas where alkylresorcinol levels were higher).

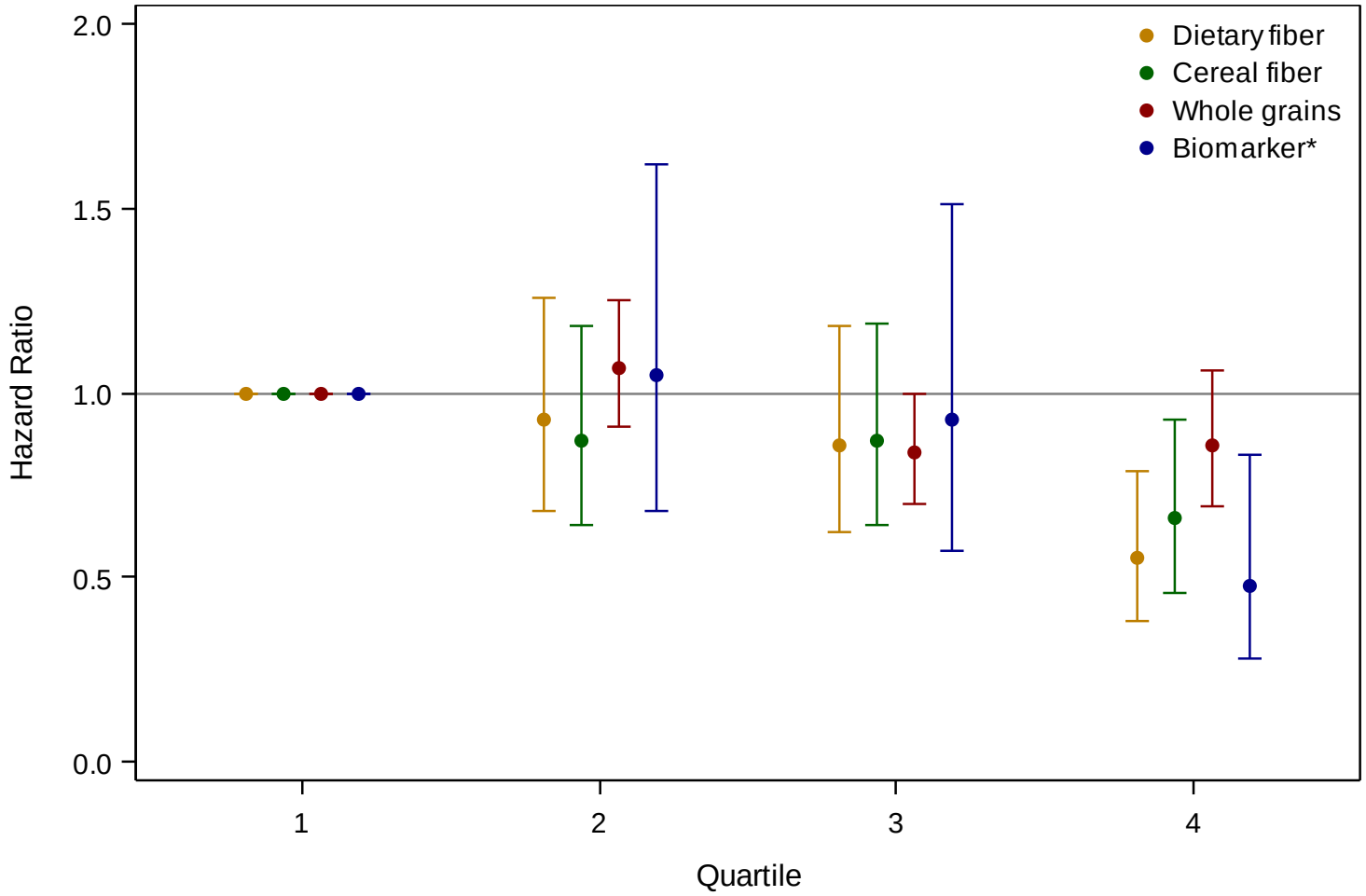
Conclusions High concentrations of plasma alkylresorcinols were associated with a lower incidence of distal colon cancer but not with overall colorectal cancer, proximal colon cancer, and rectal cancer.

Mean plasma levels of alkylresorcinols



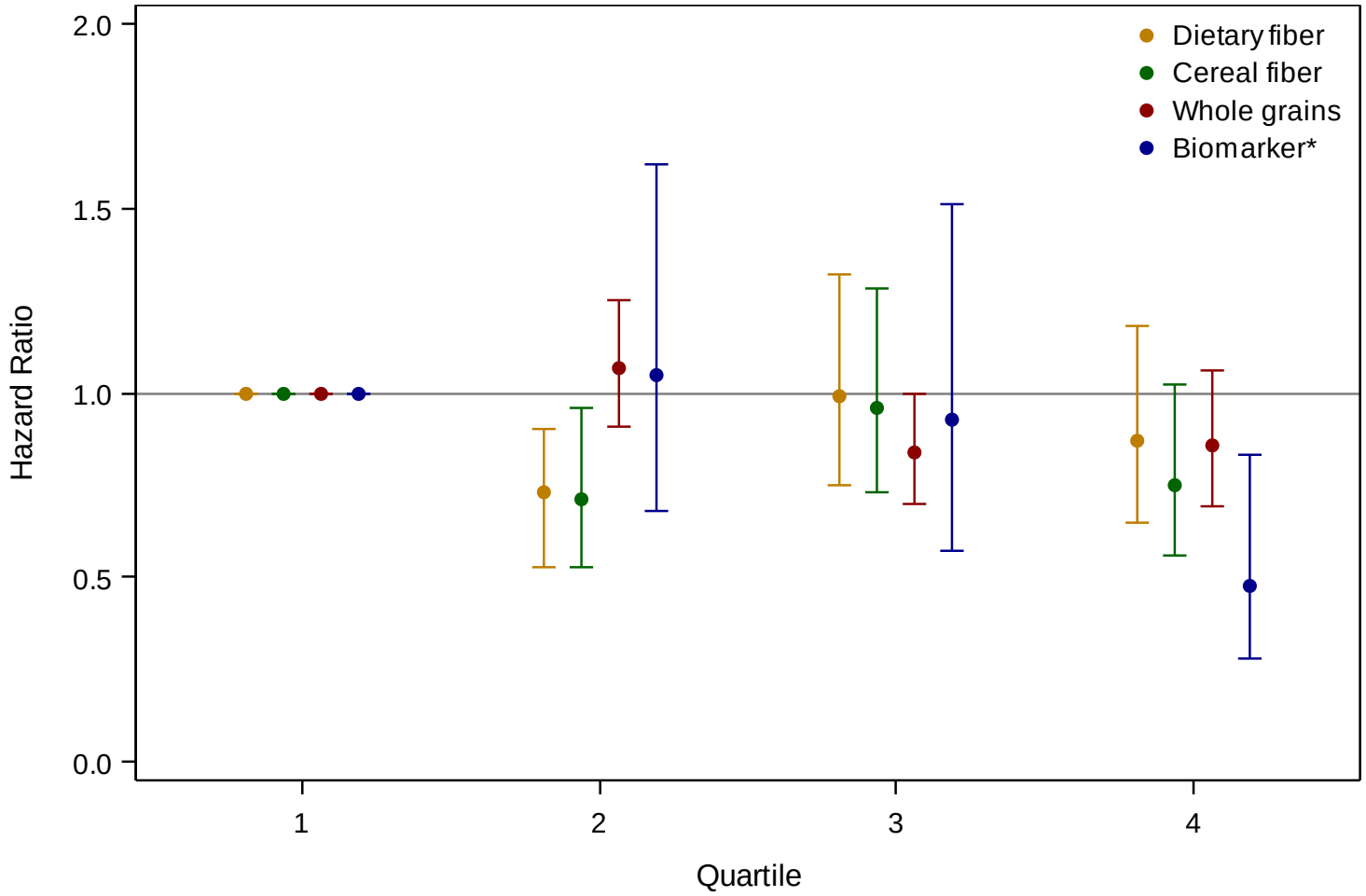
Wheat dominated diet **Rye dominated diet**

Studies on colorectal cancer - MEN



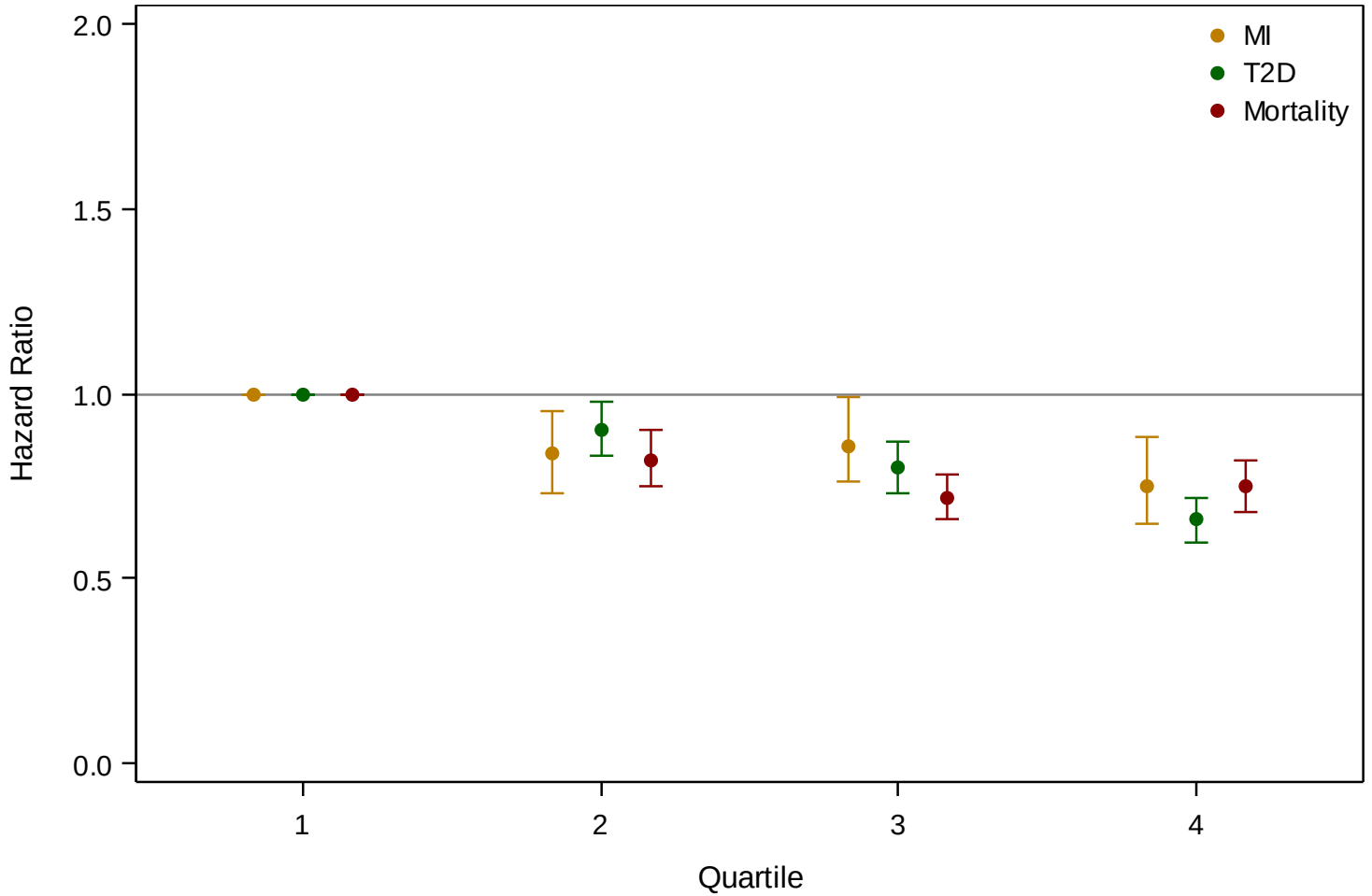
Hansen L *et al*. Int J Cancer 2012 (HELGA cohort)
Kyrø C *et al.* Cancer Causes Control 2013 (HELGA cohort)
Kyrø C *et al.* J Natl Cancer Inst 2014 (EPIC cohort)

Studies on colorectal cancer - WOMEN



Hansen L *et al*. Int J Cancer 2012 (HELGA cohort)
Kyrø C *et al.* Cancer Causes Control 2013 (HELGA cohort)
Kyrø C *et al.* J Natl Cancer Inst 2014 (EPIC cohort)

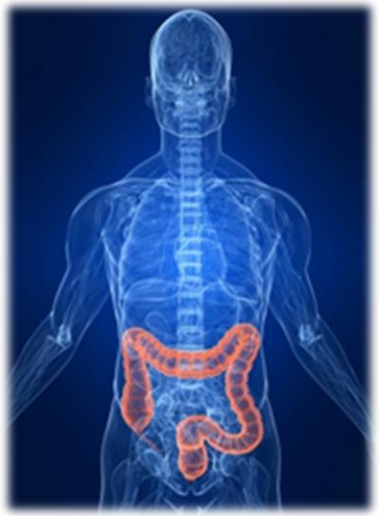
Studies on other diseases - MEN



Johnsen NF *et al.* Br J Nutr 2015 (HELGA cohort)
Helnaes et al., Am J Clin Nutr 2016 (Diet, Cancer and Health cohort)
Whole grains and type 2 diabetes – in preparation! (Diet, Cancer and Health cohort)

Conclusions and perspectives

- Whole grains associated with lower risk of colorectal cancer
- In new update of the WCRF/AICR report – recommendation for whole grains (2017)
- Also beneficial in relation to other non-communicable diseases and overall mortality!



2017 DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER 2017

		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing	**Physical activity[1,2]**	**Processed meat[3]** **Alcoholic drinks[4]** **Body fatness[5]** **Adult attained height[6]**
	Probable	**Wholegrains** **Foods containing dietary fibre[7]** **Dairy products[8]** **Calcium supplements[9]**	**Red meat[10]**
LIMITED EVIDENCE	Limited – suggestive	Foods containing vitamin C[11] Fish Vitamin D[12] Multivitamin supplements[13]	Low intakes of non-starchy vegetables[14] Low intakes of fruits[14] Foods containing haem iron[15]
	Limited – no conclusion	Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern	
STRONG EVIDENCE	Substantial effect on risk unlikely		

Conclusion – Use of Linkage data in cohort studies:

- More efficient data collection and lower participant burden, multiple outcome domains in the same cohort of individuals, at a low cost
- Collection of information that cannot be obtained by participants or biomarkers
- Increased information for correction of participant bias e.g. missing data, objective measures

Overall conclusion:

- Follow up in Cohort studies is not possible without linkage to national registries
- Better identification of high risk groups, and improvement of personal prevention and treatment
- Challenges in relation to data storage and handling
- Ethical aspects, balance protection of participants info vs nature and constraints of the research, GDPR
- Important and necessary contribution to public health research

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KNÆKCANCER
TV2

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HELGA

norden
NordForsk

Thank you for your attention