Diet, Cancer and Health

Linkage to enhance populationbased cohort data

Anne Tjønneland

Danske Kræftforskningsdage,
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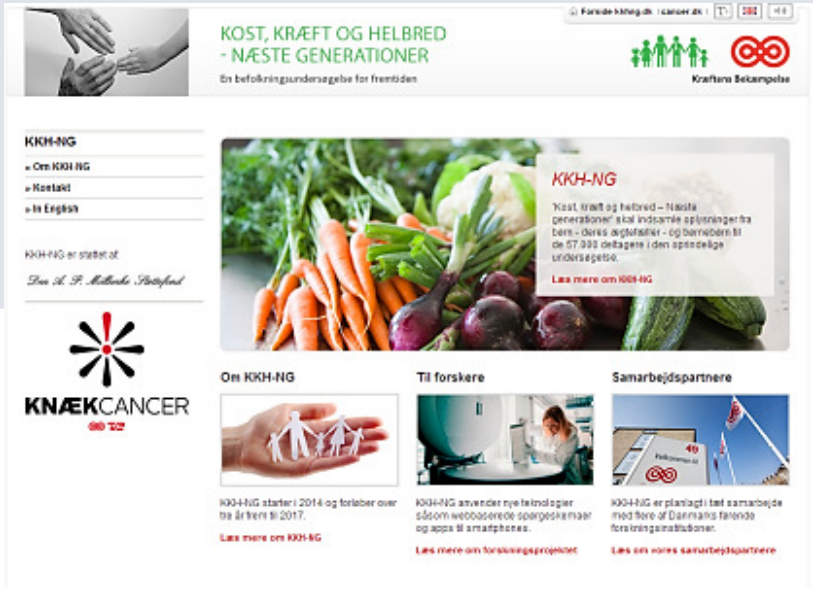
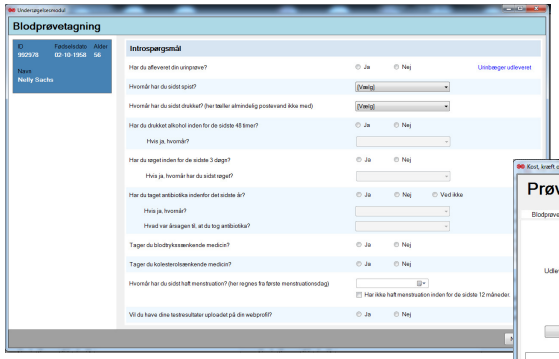
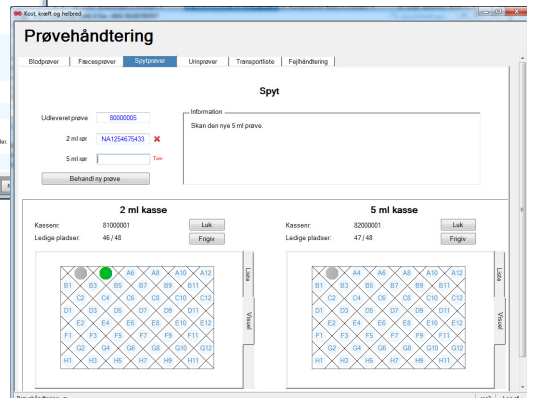
Agenda

- Cohort description
- Record linkage examples
- Perspectives







Diet, Cancer and Health cohort

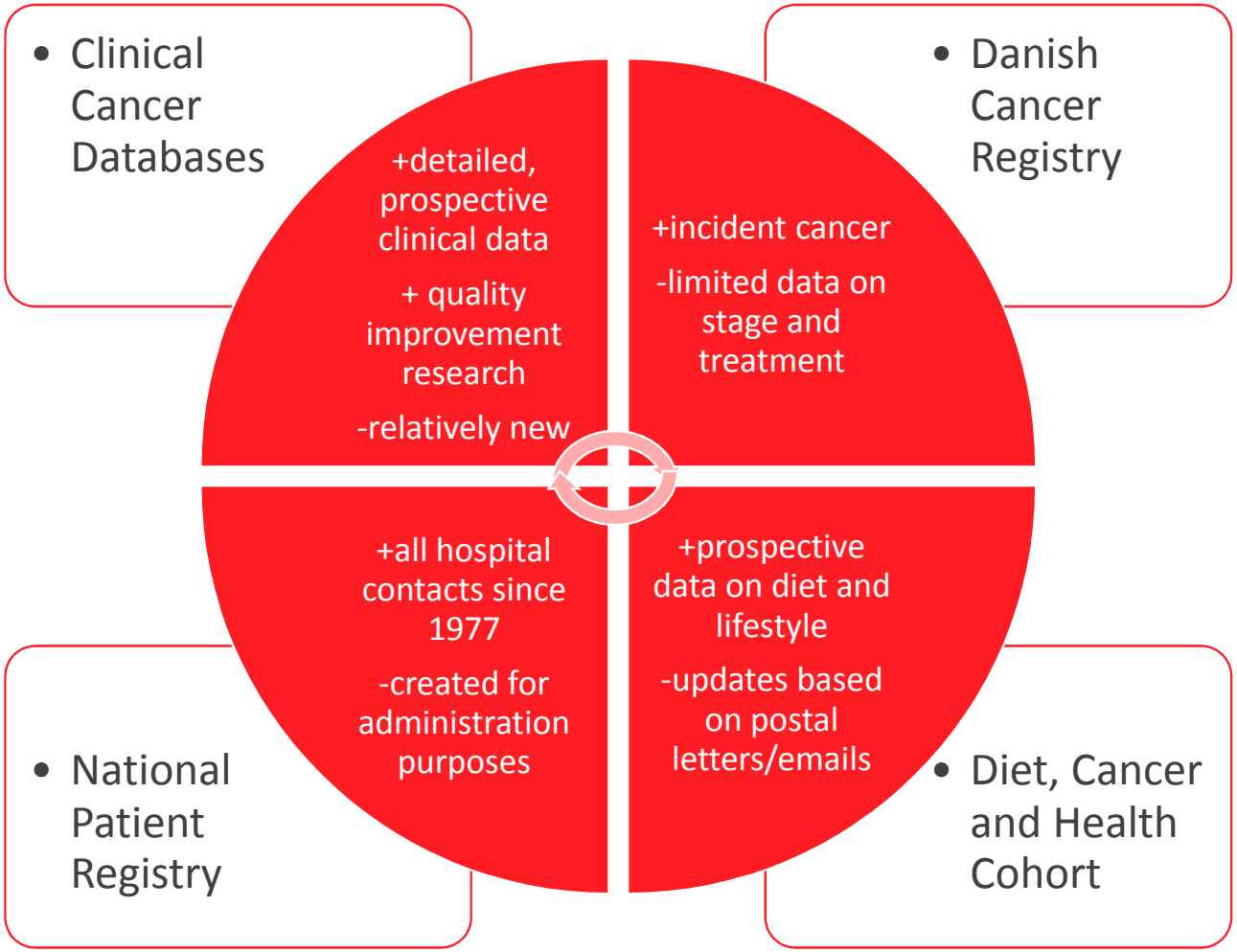
Baseline data collection 1993–1997
Follow up questionnaires 1999-2002

57,053 healthy participants, 50–64 y
27,178 men
29,875 women

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 cancer research



Diet, Cancer and Health cohort – follow up

Registries

- The Civil Registration System (from 1968)
- The Danish Cancer Registry (from 1943)
- Clinical databases, pathology records
- The Causes of Death Registry (from 1993)
- The National Patient Registry (from 1977)

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

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 %

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

Rationale and objectives

DIET, CANCER AND HEALTH
NEXT GENERATIONS

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

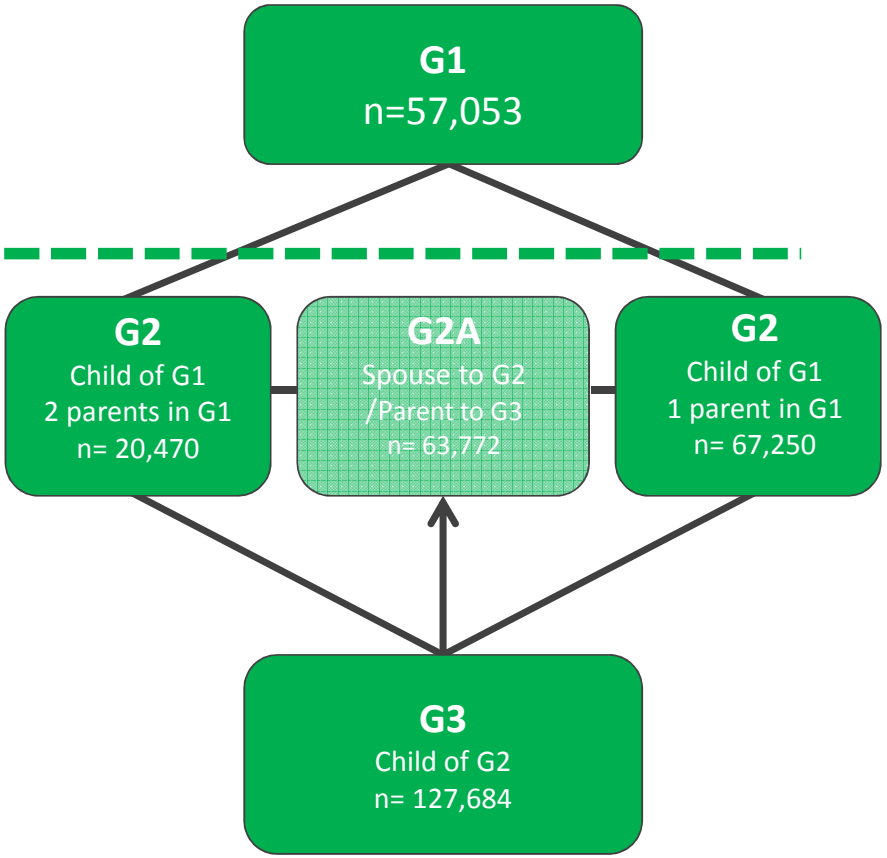
- Valuable in the search for biomarkers and omics technologies for early detection and exposure

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 generation status

>50,000 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

~23,000 fecal samples will be available for future research

Datacollection to end in 2018

Courses of Death Registry

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

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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

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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

S. B. Larsen (✉) · S. O. Dalton · J. Christensen · A. Tjønneland · C. Johansen · A. Olsen
Danish Cancer Society Research Center,
Strandboulevarden 49, 2100 Copenhagen, Denmark
e-mail: benzon@cancer.dk

J. Schüz
Section of Environment and Radiation, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France

K. Overvad
Department of Epidemiology, School of Public Health, Aarhus University, Bartholins Allé 2, 8000 Århus, Denmark

K. Overvad
Department of Cardiology, Aalborg Hospital, Aarhus University Hospital, Sdr. Skovvej 15, 9000 Aalborg, Denmark

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.

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

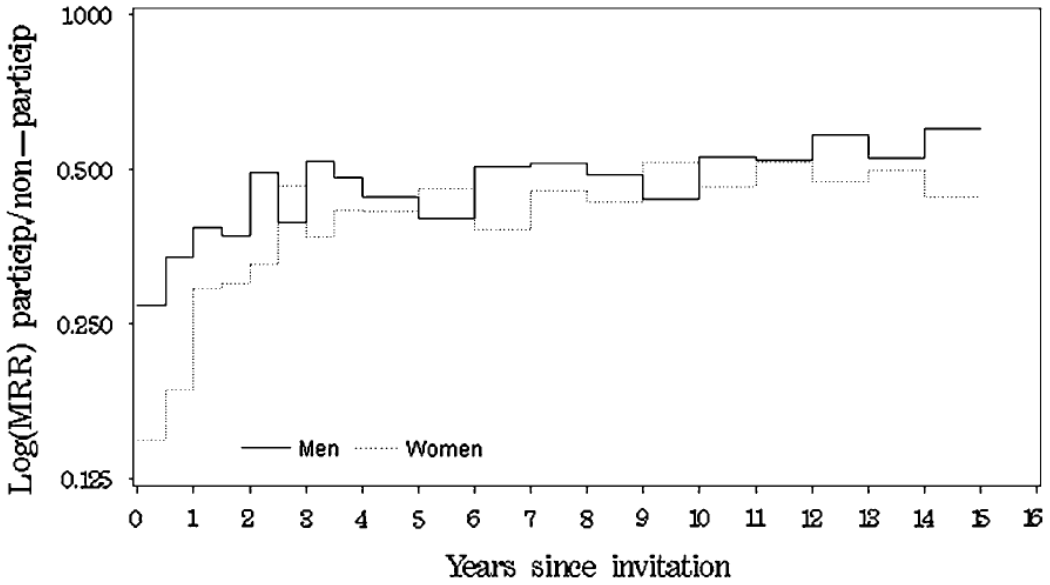

Fig. 2 Log rate ratio of overall mortality (*logMRR*) between participants and non-participants in the prospective Danish "Diet, Cancer and Health" Study stratified by sex

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

Enterolactone and the Danish Prescription Registry

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

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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]

[1] Department of Animal Science, Aarhus University, Tjele, Denmark
[2] Unit of Diet, Genes and Environment, Danish Cancer Society Research Center, Copenhagen, Denmark

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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

Enterolactone is a weak estrogen, and possibly irrelevant in women with high levels of endogenous and/or exogenous estrogens.

Estrogen dependent mechanisms include agonist and antagonist effects on the estrogen receptor depended on 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.

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 – Linkage data:

- More efficient data collection and lower participant burden, multiple outcome domains in the same cohort of individuals, low cost
- Collection of information that cannot be obtained by participants
- Increased information for correction of participant bias e.g. missing data, objective measures
- Necessary for follow up on cohort data, unique foundation for cohort-based research, better life course and transgenerational transmission of health

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
- Important contribution to public health research

VI VIL ET LIV **UDEN KRÆFT**