The Danish National Diabetes Register (NDR)

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Data processing in Health Care
Copenhagen, December 2014
Background for the NDR

Population surveillance

Health care surveillance
Background for the NDR

Population surveillance
- Monitor and describe:
  - Prevalence (no. and %)
  - Incidence (no. and rates)
  - Mortality and SMR

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Results up to 31.12.2006 reported in:
Construction of the register

- Based on existing registers in Denmark:
  - National Patient Register — all hospital and outpatient clinic contacts.
  - National Health Insurance Service Registry — all services provided in the NHS.
  - Register of Medicinal Product Statistics — all prescriptions taken out at pharmacies.
  - Linked to mortality and migration data from the Central Person Register.
  - All records are CPR-identified, for linkage purposes.
  - Inclusion start at 1.1.1990.
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- Foot-therapy for diabetics recorded in NHISR.
- 5 blood-glucose measurements within 1 year recorded in NHISR.
- Prescription on insulin or oral antidiabetics in Register of Medicinal Product Statistics.
- Metformin alone in women aged 20–39 excluded (PCOS).
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- Diagnosis of DM in NPR.
- Gestational diabetes excluded. A diagnosis of GDM precludes inclusion for a period of 1 year.
- Foot-therapy for diabetics recorded in NHISR.
- 5 blood-glucose measurements within 1 year recorded in NHISR.
- 2 blood-glucose measurements per year in 5 consecutive years recorded in NHISR.
- Prescription on insulin or oral antidiabetics in Register of Medicinal Product Statistics.
- Metformin alone in women aged 20–39 excluded (PCOS).
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- Foot-therapy for diabetics recorded in NHISR.
- 5 blood-glucose measurements within 1 year recorded in NHISR.
- 2 blood-glucose measurements per year in 5 consecutive years recorded in NHISR.
- Prescription on insulin or oral antidiabetics in Register of Medicinal Product Statistics. Metformin alone in women aged 20–39 excluded (PCOS).
Variables in the NDR

- **D_FODDTO**: date of birth
- **C_SEX**: sex
- **D_INKLDTO**: date of inclusion
- **C_INKLAARSAG**: criterion first met
- **D_DODSDTO**: date of death
- **D_LPR**: first DM diagnosis in LPR
- **D_FODT**: first date of chiropody
- **D_BLOD2I5**: first date of 2 BG / 5y
- **D_BLOD5I1**: first date of 5 BG / 1y
- **D_OAD**: date of 2nd OAD purchase
- **D_INS**: date of 2nd insulin purchase
- **V_PID**: person-id
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Methods: Incidence

- New cases tabulated by age and date of diagnosis (1995-2007) and date of birth, in 1-year classes.

- Corresponding person-years figures from Statistics Denmark — person-years in the diabetes register subtracted.

- Incidence rates analysed by Poisson-regression with smooth parametric terms in age and date of diagnosis, using log-person-years as offset.
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Digression: Lexis diagram

Wilhelm Lexis (1837–1914) German demographer, statistician and economist.
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<td>358,729</td>
<td>497,232</td>
<td>855,961</td>
</tr>
</tbody>
</table>
Incidence summary

- Women with gestational diabetes are closer monitored (?), hence the increased incidence rates in ages 20–35 ($RR \approx 1.5$).
Incidence summary

▶ Women with gestational diabetes are closer monitored (?), hence the increased incidence rates in ages 20–35 ($RR \approx 1.5$).

▶ Incidence rates peak in ages 70–85: 1.2%/year for men, 1.2%/year for women in 2005.
Incidence summary

- Women with gestational diabetes are closer monitored (?), hence the increased incidence rates in ages 20–35 ($\text{RR} \approx 1.5$).
- Incidence rates peak in ages 70–85: 1.2%/year for men, 1.2%/year for women in 2005.
- Annual increase in incidence rates over the period 1995–2004 was 5.6%, after 2004 almost flat.
Glucose criteria

- Women who have a glucose tolerance test triggers typically 6 blood glucose measurements.

- Omitting the glucose criteria:

  - Some are removed from the register
  - Some have a later diagnosis (meeting a different criterion).

- The new diagnostic criteria based on HbA1c makes the blood glucose criteria even more uncertain.

- No consensus on how to proceed.
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Men

Age at inclusion

P(Deletion if BG omitted) (%)

20 40 60 80

Women

P(Later dx if BG omitted) (%)

20 40 60 80

Age at inclusion
Methods: Prevalence

- Prevalent cases by 1 Jan 1995,...,2010 tabulated by sex and 1-year age.

- Corresponding population figures from Statistics Denmark.

- Prevalence analysed by a binomial model with log-link and the population size as denominator. Separate parametric terms used for each sex and date.
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- Corresponding population figures from Statistics Denmark.
- Prevalence analysed by a binomial model with log-link and the population size as denominator. Separate parametric terms used for each sex and date.
## Prevalence of diabetes

<table>
<thead>
<tr>
<th>Year</th>
<th>No. patients</th>
<th>Prevalence (%)</th>
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</thead>
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<td>M</td>
<td>F</td>
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<td>49,126</td>
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<td>1996</td>
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<td>79,895</td>
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<td>2003</td>
<td>89,291</td>
<td>86,364</td>
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<td>2004</td>
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<td>93,199</td>
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<td>100,227</td>
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<td>2006</td>
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<td>112,018</td>
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<td>2008</td>
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<td>2009</td>
<td>132,847</td>
<td>126,295</td>
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<td>2010</td>
<td>140,940</td>
<td>133,318</td>
</tr>
<tr>
<td>2011</td>
<td>149,702</td>
<td>140,507</td>
</tr>
<tr>
<td>2012</td>
<td>160,352</td>
<td>150,309</td>
</tr>
</tbody>
</table>
Prevalence of diabetes — age distribution

1995

Persons in 1 year class (1000s)

Age

6 5 4 3 2 1 0 1 2 3 4 5 6

0
20
40
60
80
100

1995

49,438
N
49,126
Prevalence of diabetes — age distribution

1996

53,443  N  52,631

Persons in 1 year class (1000s)

Age

Persons in 1 year class (1000s)
Prevalence of diabetes — age distribution
Prevalence of diabetes — age distribution

1999

66,746  N  64,974

Persons in 1 year class (1000s)

Age

Persons in 1 year class (1000s)
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

Age

6 5 4 3 2 1 0 1 2 3 4 5 6

0 20 40 60 80 100 2000

N 71,798 69,692

Persons in 1 year class (1000s)
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

Age

6 5 4 3 2 1 0 1 2 3 4 5 6

0

20

40

60

80

100

200

77,120

N

74,570
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

Age
6 5 4 3 2 1 0 1 2 3 4 5 6

2002
100
80
60
40
20
0

82,914 N 79,895
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

Age

6 5 4 3 2 1 0 1 2 3 4 5 6

0
20
40
60
80
100
200
3 89,291 86,364 N

2003
## Prevalence of diabetes — age distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>Persons in 1 year class (1000s)</th>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>96,706</td>
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<tr>
<td>5</td>
<td>93,199</td>
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</table>

![Age distribution chart](image_url)
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

Age

Persons in 1 year class (1000s)

2005

104,149

N

100,227
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

Age

2006

110,581  N  106,028
Prevalence of diabetes — age distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>Persons in 1 year class (1000s)</th>
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</thead>
<tbody>
<tr>
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<td>124,501</td>
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<tr>
<td>1</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>118,726</td>
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</table>
Prevalence of diabetes — age distribution

<table>
<thead>
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<th>Age (6)</th>
<th>Persons in 1 year class (1000s)</th>
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<tbody>
<tr>
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</tbody>
</table>
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

<table>
<thead>
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<th>Age</th>
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<th>5</th>
<th>4</th>
<th>3</th>
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<th>1</th>
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<td>0</td>
<td>20</td>
<td>40</td>
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<td>80</td>
<td>100</td>
<td>2010</td>
<td>140,940</td>
<td>133,318</td>
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</tr>
</tbody>
</table>
Prevalence of diabetes — age distribution

Persons in 1 year class (1000s)

Age

6 5 4 3 2 1 0 1 2 3 4 5 6

0

20

40

60

80

100

2011 149,702 140,507

N

20/ 1
Prevalence of diabetes — age distribution

2012

160,352 N 150,309

Persons in 1 year class (1000s)

Age

Persons in 1 year class (1000s)
Methods: Mortality and SMR

- Deaths and person-years of follow-up among diabetics tabulated by age and period at follow-up in 1-year classes.

- Corresponding mortality figures from Statistics Denmark. Deaths and person-years from the diabetes cohort subtracted.

- Mortality analysed by Poisson-regression of deaths with smooth parametric terms for current age, current date and current disease duration, using log-person-years as offset.

Methods: Mortality and SMR

- Deaths and person-years of follow-up among diabetics tabulated by age and period at follow-up in 1-year classes.
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SMR analysed using dataset amended by mortality among non-DM persons, using interaction between DM / non-DM and age / duration.
Methods: Mortality and SMR

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# Number of deaths — imbalance

<table>
<thead>
<tr>
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<th>New cases</th>
<th>Deaths</th>
<th>Surplus</th>
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<td>1995</td>
<td>14,874</td>
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<td>7,497</td>
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<td>1996</td>
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<td>15,438</td>
<td>7,366</td>
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<tr>
<td>1998</td>
<td>16,842</td>
<td>7,457</td>
<td>9,385</td>
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<tr>
<td>1999</td>
<td>17,853</td>
<td>8,058</td>
<td>9,795</td>
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<tr>
<td>2000</td>
<td>18,480</td>
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<tr>
<td>2001</td>
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<td>11,154</td>
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<tr>
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<td>21,948</td>
<td>9,072</td>
<td>12,876</td>
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<tr>
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<td>23,712</td>
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<td>14,285</td>
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<tr>
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<td>20,592</td>
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<table>
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<td>11,782</td>
<td>20,592</td>
</tr>
</tbody>
</table>
Mortality among DM patients

Mortality in DM patients (per 1000 PY)

Age
SMR relative to persons without DM

Age

SMR in DM patients vs. no DM
Mortality summary

- Mortality in DM patients increases exponentially by age.
- Decreasing by time: 4.0/3.8%/year (non-DM: 2.8/2.4)
- SMR is the same for men and women.
- SMR is 3 at age 45, 1 at 85.
Mortality summary

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Summary: Danish Diabetes Register

Note: a register of “administrative” diabetes:
Summary: Danish Diabetes Register

Note: a register of “administrative” diabetes:
- Population based 1995–2012 (18 years)
- Coverage 100%
Summary: Danish Diabetes Register

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- Imprecise diagnostic criteria
Summary: Danish Diabetes Register

Note: a register of “administrative” diabetes:
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- Imprecise diagnostic criteria
- Incidence rates increasing in general
- Mortality and SMR decrease
- Prevalence increases
Summary: Danish Diabetes Register

**Note:** a register of “administrative” diabetes:
- Population based 1995–2012 (18 years)
- Coverage 100%
- No selection bias at individual level
- Imprecise diagnostic criteria
- Incidence rates increasing in general
- Mortality and SMR decrease
- Prevalence increases
- Discontinued . . .
RUKS — Register for Udvalget Kroniske Sygdomme

- NDR only updated until 2012 — discontinued
- RUKS comprises:
  - Asthma
  - Dementia
  - COPD
  - Arthritis
  - Osteoporosis
  - Schizophrenia
  - Diabetes, type 1
  - Diabetes, type 2
RUKS definition of T2 DM

- Two purchases of OAD (A10B)
- Latest NPR diagnosis is E10 / E11
- Women with PCOS
- Date of T1D debut is the first of:
  - date of first (!) insulin/OAD purchase
  - date of first NPR recording
RUUKS definition of T1 DM

- Two purchases of insulin (A10A)
- NPR diagnosis E10
- Purchase of insulin $\pm 280$ days from GDM diagnosis not counted
- Persons classified as T2D excluded
- Date of T1D debut is the first of:
  - date of first (!) insulin purchase
  - date of first NPR recording
RUUKS definition of T1/T2 DM

- If a person have no recording of insulin/OAD purchase or diagnosis E10 / E11 in NPR, the person is excluded from RUUKS.
- Not specified whether the person is excluded from registrations earlier than the 10 year limit.
- Not clear to what extent the register is available as individual records for research purposes.
Cancer among diabetes patients

- Merge the Diabetes Register with the Danish Cancer Register.
- Compute the RR of cancer between persons with and without diabetes.
- 25 cancer sites, 2 sexes, age-interaction, duration.
Cancer among diabetes patients

- Merge the Diabetes Register with the Danish Cancer Register.
Cancer among diabetes patients

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Cancer among diabetes patients

- Merge the Diabetes Register with the Danish Cancer Register.
- Compute the RR of cancer between persons with and without diabetes.
- 25 cancer sites, 2 sexes, age-interaction, duration.
Aims

- Describe cancer incidence rates among diabetes patients in Denmark.
Aims

- Describe cancer incidence rates among diabetes patients in Denmark.
- and how rates vary relative to the non-DM population with:
Aims

- Describe cancer incidence rates among diabetes patients in Denmark.
- and how rates vary relative to the non-DM population with:
  - duration of diabetes
Aims

▶ Describe cancer incidence rates among diabetes patients in Denmark.
▶ and how rates vary relative to the non-DM population with:
  ▶ duration of diabetes
  ▶ duration of insulin use
Aims

- Describe cancer incidence rates among diabetes patients in Denmark.
- and how rates vary relative to the non-DM population with:
  - duration of diabetes
  - duration of insulin use
- for all types of cancer
Aims

- Describe cancer incidence rates among diabetes patients in Denmark.

- and how rates vary relative to the non-DM population with:
  - duration of diabetes
  - duration of insulin use

- for all types of cancer

- and for specific sites of cancer
Cancer occurrence in Danish diabetic patients: duration and insulin effects

B. Carstensen · D. R. Witte · S. Friis

Received: 5 April 2011 / Accepted: 31 October 2011 / Published online: 27 November 2011
© Springer-Verlag 2012

Abstract

Aims/hypothesis Cancer is more frequent among diabetes patients, but it is unknown how this excess varies with duration of diabetes and insulin use. The aim of this study was to analyse disease data to examine this issue further.

Methods We linked the Danish National Diabetes Register and Cancer Registry and performed a cohort analysis of the entire Danish population by diabetes status, duration of diabetes and insulin use, comparing cancer incidence rates in diabetic patients with the non-diabetic population for the 15 year period 1995–2009, using Poisson regression with natural splines to describe the variation by duration.

Results We found 20,032 cancer cases among patients not using insulin and 2,794 cancer cases among diabetic patients using insulin. The cancer incidence rate ratio among non-insulin users relative to the non-diabetic population decreased from over 2 at diagnosis to 1.15 after 2 years of diabetes duration. The cancer incidence rate ratio was higher among patients using insulin, decreasing from 5 at the start of insulin treatment to about 1.25 after 5 years of insulin use. Among non-insulin users, cancers of the stomach, colorectum, liver, pancreas, lung, corpus uteri, kidney and brain, and lymphomas were elevated. Among insulin users the rate ratio of prostate cancer was decreasing by duration whereas we found higher risk of cancer of the stomach, lung, liver, pancreas and kidney. Breast cancer incidence rates were not affected by either diabetes or insulin use.

Conclusions The observed duration effects suggest that both increased surveillance for cancer in the first years after diagnosis of diabetes, and reverse causation, where undiagnosed cancers increase the likelihood of diabetes diagnosis, play a role. For longer durations, a combination of common causes for diabetes and cancer, as well as the effects of diabetes and insulin exposure per se, may play a role in the association between diabetes and some cancers.
Follow-up of the Danish population

Well
Follow-up of the Danish population
Follow-up of the Danish population
Follow-up of the Danish population
Follow-up of the Danish population

```
Well Ca
DM
DM/Ins
DM + Ca
DM/Ins + Ca
```

Diagram:
- Well → Ca
- Ca → DM
  - DM → DM + Ca
  - DM → DM/Ins
    - DM/Ins → DM/Ins + Ca

Follow-up of the Danish population

Well 75,637,670

Ca

DM 1,279,524

DM + Ca

DM/Ins 239,516

DM/Ins + Ca
Follow-up of the Danish population

- Well: 75,637,670
- Ca: 346,138
- DM: 1,279,524
- DM + Ca: 20,032
- DM/Ins: 239,516
- DM/Ins + Ca: 2,794
Follow-up of the Danish population

Well
75,637,670

Ca

DM
1,279,524

DM + Ca

DM/Ins
239,516

DM/Ins + Ca

346,138

20,032

2,794
Follow-up in the population

Persons are followed 1 Jan 1995 to:
Follow-up in the population

Persons are followed 1 Jan 1995 to:

- **event**: first primary cancer of a given type
Follow-up in the population

Persons are followed 1 Jan 1995 to:

- **event**: first primary cancer of a given type
- **censoring**: diagnosis of any other primary cancer
- 31 Dec 2009
Follow-up in the population

Persons are followed 1 Jan 1995 to:

**event:** first primary cancer of a given type

**censoring:**
- diagnosis of any other primary cancer
- death
Follow-up in the population

Persons are followed 1 Jan 1995 to:

- **event:** first primary cancer of a given type

- **censoring:**
  - diagnosis of any other primary cancer
  - death
  - 31 Dec 2009
Duration model

\[ \text{rate} = f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \]
Duration model

\[ \text{rate} = f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \]
Duration model

rate = \( f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \times t(\text{DM-duration}) \)
Duration model

\[
\text{rate} = f(\text{age}) \times g(\text{date of FU}) \times h(\text{date of birth}) \\
\times t(\text{DM-duration}) \\
\times s(\text{Ins-duration})
\]
All malignant neoplasms

Rate ratio DM, DM+Ins vs No DM

Diabetes duration (years)
Colorectal cancer

Rate ratio DM, DM+Ins vs No DM

Diabetes duration (years)
Lung, bronchus and pleura

Diabetes duration (years)
Rate ratio DM, DM+Ins vs No DM

M

F

Diabetes duration (years)
The Epidemiology of Diabetes and Cancer

Bendix Carstensen · Marit Eika Jørgensen · Søren Friis

Abstract The literature on cancer occurrence in persons with diabetes has almost invariably been concerned with relative measures. In this paper, we briefly review this, but the aim is to quantify the absolute occurrence of diabetes and cancer in the population in order to give a fuller picture, which also includes the competing mortality risk. Overall, we find that some 35% of the population will have a diagnosis of diabetes in their lifetime, 44% a diagnosis of cancer, and about 15% will have both diagnoses. The impact of differing mortality between persons with and without diabetes is illustrated by the fact that a person without diabetes at age 50 has a smaller lifetime risk of cancer than a person aged 50 with diabetes. Thus, the differences in cancer occurrence between persons with and without diabetes are of quantitatively smaller importance than the differences in mortality.

Introduction

The link between diabetes and cancer occurrence is well established, and comprehensive population-based studies have demonstrated that the association relates to both cancer incidence and mortality [1–3]. Recently, an increasing number of studies have examined cancer incidence among patients with diabetes, particularly following the report in 2009 of a potential association between the insulin analog glargine and cancer risk [4–7]. The majority of the studies have focused on comparisons of cancer incidence among diabetes patients using different antidiabetic regimes. However, these studies are prone to bias due to confounding by indication, as illustrated convincingly by Andersson et al. [8••] who reported that the use of any type of antidiabetic drug, whether insulins or...
Demography: Life time risk

- DM
- Ca
- DM−Ca
- Ca−DM

Well
DM
Ca
DM−Ca
Ca−DM

Dead (Well)
Dead (DM)
Dead (Ca)
Dead (DM−Ca)
Dead (Ca−DM)
DM / Cancer incidence rates per 1000 PY
Mortality rates per 1000 PY

Men

Women

DM Well

Cancer DM Well

Age Date
Age Date

Age Date
Age Date

20 40 60 80 100 2000
20 40 60 80 100 2000
20 40 60 80 100 2000
20 40 60 80 100 2000
Demography: Cumulative risk

![Graph showing cumulative risk for males (M) and females (F).](image_url)

- **X-axis**: Age (years)
- **Y-axis**: Fraction of persons (%)

The graph illustrates the cumulative risk for both males and females across different age groups, highlighting the varying risks at different ages.