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DIABETES AND OTHER DISEASES-EMERGING ASSOCIATIONS (JJ NOLAN, SECTION EDITOR)

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.

Keywords Diabetes and cancer · Epidemiology · Demography · Lifetime risk of diabetes and cancer · Absolute risk of diabetes

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B. Carstensen (✉) · M. E. Jørgensen
Clinical Epidemiology, Steno Diabetes Center, Gentofte, Denmark
e-mail: bxc@steno.dk
URL: http://BendixCarstensen.com

M. E. Jørgensen
e-mail: maej@steno.dk

B. Carstensen
Department of Biostatistics, University of Copenhagen, København, Denmark

S. Friis
Research Center, Danish Cancer Society, København, Denmark
e-mail: friis@cancer.dk

S. Friis
Department of Public Health, University of Copenhagen, København, Denmark

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 various forms of oral antidiabetic agents (OADs), was associated with a markedly elevated rate ratio (RR) for cancer shortly after initiation of the drug, which subsequently declined to a value close to one.

To our knowledge, the study by Andersson et al. is the only study published so far that followed the entire population of diabetes patients, avoiding selection of subgroups of patients, and thus appear to be the most credible study because of minimized selection bias. We have previously reported that newly diagnosed diabetes patients experience a strongly elevated excess cancer incidence shortly after the diagnosis which levels off 2–3 years following the diagnosis [9•], and a similar pattern has also been observed in other studies [1, 10•, 8••]. Hence, based on the available studies, any potential long-term effects of antidiabetic drugs are likely to be small and difficult to ascribe to a particular cause-effect relationship, if any.

As any potential long-term effects of diabetes drugs are likely to be small in terms of modification of cancer occurrence, we have chosen to ignore these in the present broader discussion of the relationship between diabetes and cancer occurrence. In this paper, we have chosen to focus on the general population impact of diabetes and cancer rather than

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any comprehensive discussion of the potential relationship between diabetes and cancer occurrence. Specifically, we will evaluate the high mortality among cancer patients with pre-existing diabetes, as demonstrated in a few previous studies [11, 12], and quantify the effects of this at the population level.

Incidence of Cancer

Cancer incidence studies have shown cancer incidence rate ratios of similar magnitude in comparisons to diabetes patients and persons without diabetes. Figure 1 compares the RR of different types of cancer between people with and without diabetes from the major population-based studies of diabetes occurrence, which is studies with more than 1,000 cancer cases among persons with diabetes. Key characteristics of these studies are presented in Table 1.

The general picture from the major cancer incidence studies are strongly elevated incidence rates of liver and pancreatic cancer, and somewhat elevated rates of cancer of the endometrium, kidney, and to a smaller extent of cancers of the digestive system (Fig. 1). Single-site studies have generally reported colon cancer as a cancer type occurring in clear excess among persons with diabetes. However, this is likely because colon cancer is a fairly frequent disease and hence exhibits clearly detectable rate elevations as opposed to rarer cancers which could have similarly elevated rates without formally significant elevation due to limited number of events in the study populations.

However, little attention has been paid to differences between people with and without diabetes in relation to the actual size and shape of age-specific cancer incidence rates. Using Danish data, we found that the average increase in cancer incidence rates from age 40 to 70 years was 10.6 % per year for men and 7.2 % per year for women, corresponding to increases of 35 and 23 %, respectively, over 3 years of

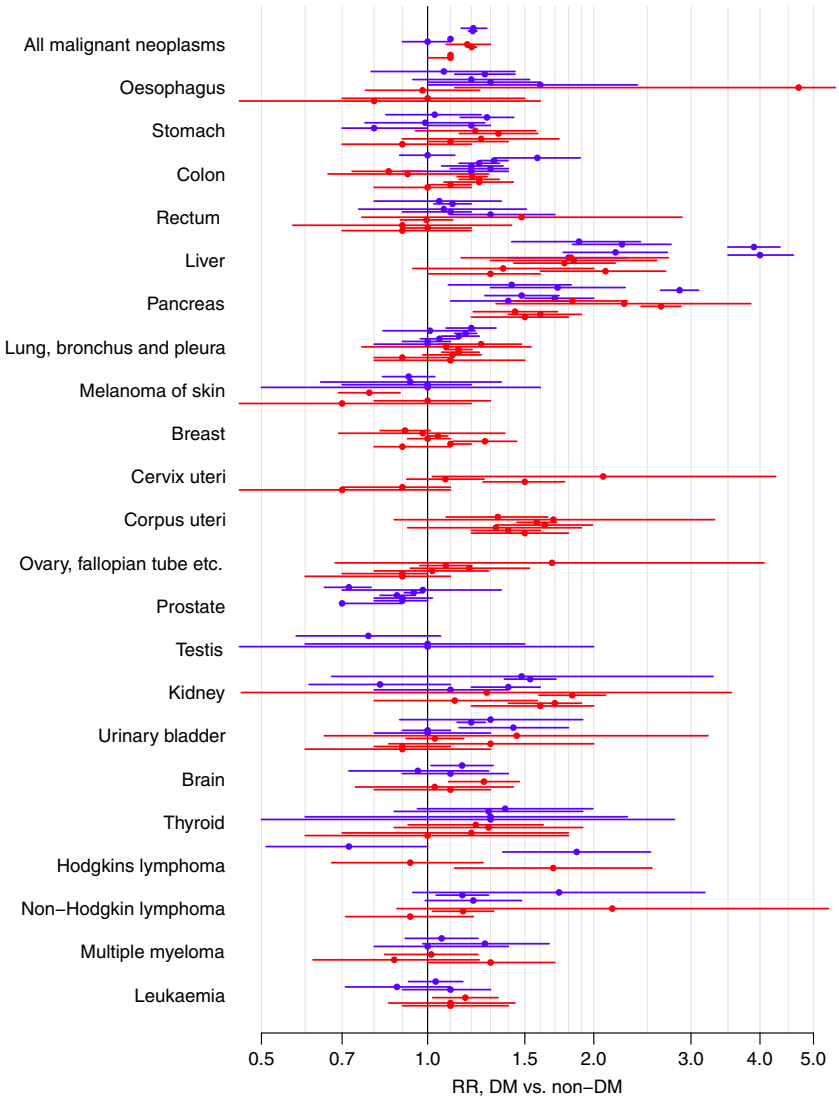

Fig. 1 Estimated RRs from different studies. *Blue lines* are for men, *red lines* for women. Within each cancer site, estimates are from the studies mentioned in Table 1, in the same order as in Table 1

Table 1 Population-based studies of incidence of several major cancer sites in DM patients compared to non-patients, with more than 1,000 cancers among DM patients

Study	Country	No. of sites	No. of cancers in DM ptt.
Adami et al. [1]	Sweden	21	2,417
Wideroff[a] et al. [2]	Denmark	29	8,831
Coughlin[b] et al. [3]	USA	16	2,183
Johnson et al. [10•]	Canada	10	12,438
Carstensen[a] et al. [9•]	Denmark	24	22,826
Sasazuki et al. [13]	Japan	16	2,388
Kajüter et al. [14]	Germany	8	3,664

[a] These two Danish studies are non-overlapping

[b] Cancer mortality study

age. This means that the observed elevation of cancer risk in persons with diabetes by a factor of 1.1–1.2 is of a magnitude that is smaller than that conveyed by an aging of 3 years.

Mortality After Cancer Diagnosis

It is also well known that cancer patients with pre-existing diabetes have a higher mortality than cancer patients without diabetes at diagnosis; however, it is difficult to discern whether this is due solely to the impaired survival associated with the two diseases or if there is interaction between diabetes and cancer which worsen the cancer prognosis. In a systematic review, Barone et al. [15] estimated that the overall mortality rate ratio between cancer patients with and without cancer was 1.41. In a recent nationwide study in Denmark [11], we observed a similar excess mortality among cancer patients with diabetes at diagnosis and with increasing mortality rates by increasing severity of diabetes.

The Broader Picture

The above-mentioned studies are all aimed at describing differences in patterns of cancer incidence rates or mortality rates of cancer patients between persons with and without diabetes. These types of comparisons are illustrated in context in Fig. 2 in which cancer incidence rates are shown in red and mortality rates among cancer patients in black. Studies of diabetes and cancer incidence and mortality have traditionally focused only on pairwise comparison of the thick and thin transition rates in Fig. 2. It is commendable to describe variations between these rates that may give clues to mechanisms underlying the different (typically higher) rates among persons with diabetes compared with those without diabetes. For most of the rates in Fig. 2, however, the major determinant is age, so by only comparing the rates (controlling for age), the impact of the aging in the population is lost.

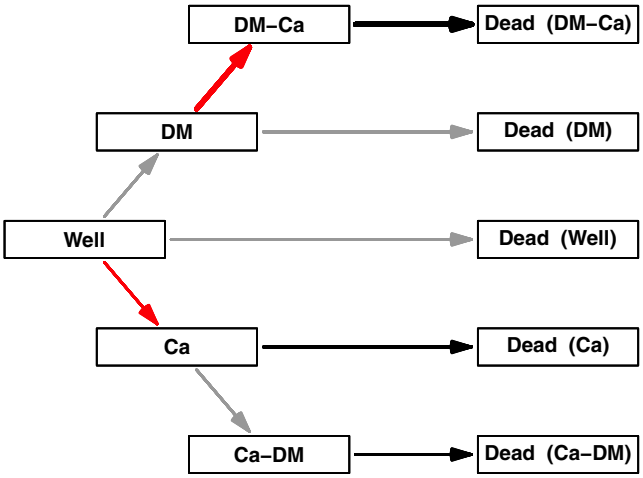

Fig. 2 Transition rates in a population exposed to occurrence of diabetes and cancer. The *red transitions* represent cancer incidence rates and the *black ones* death after a cancer diagnosis

As an example of how to incorporate the impact of the age-dependence of the incidence of cancer and mortality in the general population, we will use nationwide Danish data to estimate all nine sets of rates shown in Fig. 2 by sex, age, and calendar time. This will enable us to illustrate what fraction of persons in a given age that will eventually contract cancer, depending on whether they suffer from diabetes at the given time. It will also provide the possibility to quantify the fraction of persons in a birth cohort who will end in each of the five "death" states.

Duration Dependence

While it is known that both mortality and cancer incidence depends strongly on diabetes duration, in that it is elevated during the initial period after diagnosis (surveillance bias), the period is for most types of events quite short, so ignoring the duration effects will have only minor influence on the summary measures.

Methods

We merged the Danish National Diabetes Register [16, 17] with the Danish Cancer Register [18] and classified all follow-up time after 1995 and after any of the two diagnoses by sex, age, calendar time, and date of birth in 1-year classes (Lexis triangles). We classified deaths and diagnoses of diabetes and cancer similarly. We also extracted the total population size and number of deaths from the Human Mortality Data Base [19]. By subtracting the total number of person-years and deaths in the diabetes and/or cancer population, we obtained the risk time and person-years in the part of the population not diagnosed with any of the two diseases (the "Well" state in Fig. 2).

We then modeled all nine transition rates shown in Fig. 2 using age-period models with natural splines [20]. We assumed that the mortality rates for cancer patients with and without diabetes were proportional, meaning that the rates only differed only by a multiplicative constant for any combination of age and calendar time.

We used the estimated age-specific rates from these models to calculate the burden of disease in a hypothetical population under the scenario of age-specific rates equal to the estimated cross-sectional age-specific rates as of 1 January 2005. The practical calculations were done by multiplying a vector of initial state distribution (with all persons starting at age 0 in state "Well") successively by the age-specific transition matrices derived from the rates for every 1/10 of a year of age. A complete account of the data acquisition, rate-estimation, and state-probability calculations and graphical displays is available as http://BendixCarstensen.com/DMCa/EpiDMCa/Report.pdf.

We computed the following quantities:

- The fraction of a population in each of the nine different states at any age.
- The fraction of a 50/60/70-year-old non-diseased population that are in each of the states at any subsequent age.
- The fraction of a 50/60/70-year-old population with diabetes but not cancer that are in each of the states at any subsequent age.

This approach yields insight into what fraction of the population that is likely to be affected by the two diseases and in particular how the relationship of cancer incidence rates between people with and without diabetes translates into population experience when the mortality rates are taken into account.

Results

Figure 3 shows the estimated rates by age and calendar time. It is seen that both the cancer incidence and, notably, diabetes rates are increasing, whereas the mortality rates are decreasing by calendar time and more rapidly among persons with diabetes. Moreover, it is seen that mortality rates for persons with diabetes and/or cancer are converging by age so that there are

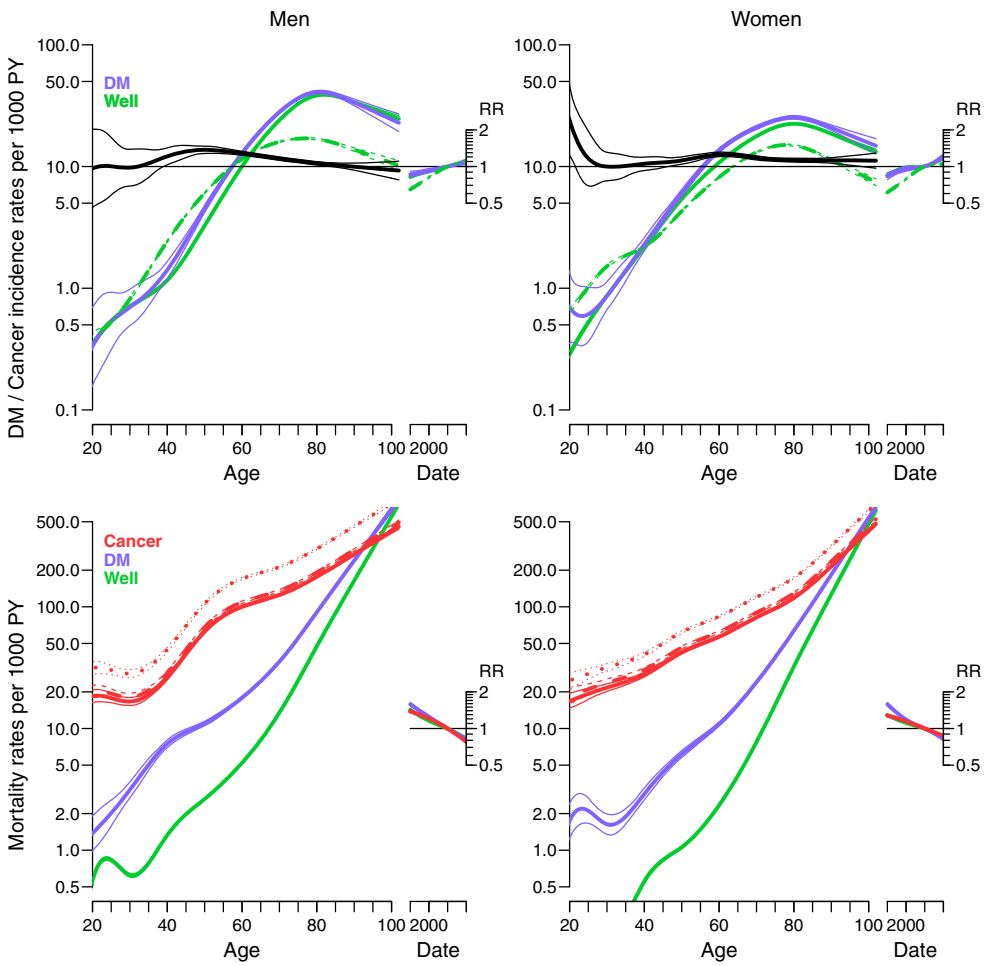

Fig. 3 Estimated age-specific incidence and mortality rates in the Danish population 2005 and trends 1995–2010. The *coloring of the lines* refer to the state from which the rates are. The *full lines* in the *upper panels* are cancer incidence rates, the *broken line* diabetes incidence rates and the *black lines* are the cancer incidence rate ratios between persons with and without diabetes. In the lower panels, the *broken red lines* are for cancer patients developing diabetes after cancer, and the *dotted red lines* are for cancer patients with pre-existing diabetes at time of diagnosis

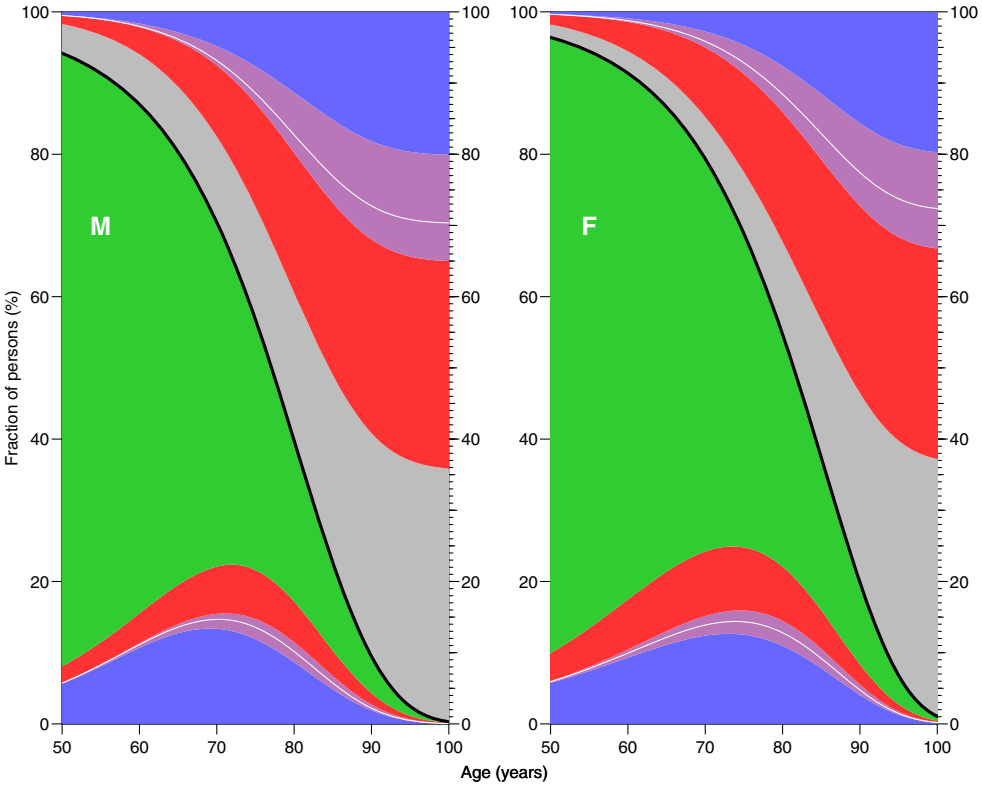

Fig. 4 Fraction of a birth cohort in each state at a given age, based on Danish rates as of 2005. The *black line* is the overall survival *curve*, the *green* part represents those alive without diabetes or cancer, the *gray* those who died without any of the diseases. *Blue areas* are those with diabetes, *red* those with cancer, and the *purple* areas those with both diseases. The *white line* in the *purple area* separates those that had diabetes before cancer (closest to the diabetes part) from those who had cancer before diabetes

only minor differences between the three groups of persons after age 80. This is presumably reflecting the fact that persons without both diabetes and cancer in high ages most likely suffer from other severe diseases.

When using these rates to obtain probabilities of being in one of the nine states at any age (Fig. 4) and derive the probability of having a diagnosis of cancer, respectively, diabetes before a given age (Fig. 5), we found a lifetime risk of cancer of 44 % for both men and women and corresponding lifetime risk of diabetes of 35 % for men and 33 % for women. The lifetime risk of both diseases was 15 % for men and 13 % for women (Fig. 5). Of all persons who contracted diabetes in their lifetime, 43 % of men and 41 % of women had a diagnosis of cancer too, only slightly less than the figures for the entire population.

Examining the conditional distribution given that a person was alive and free of both diabetes and cancer at age 50, 60, or 70 years (Fig. 6, columns 1 and 3), we found that the lifetime risk of cancer were 45, 44, and 38 % among men and 41, 37, and 29 % among women. Comparing to persons who were alive and diagnosed with diabetes only at the same ages (Fig. 6, columns 2 and 4), the lifetime risk of cancer were 37, 36, and 32 % among men and 37, 34, and 27 % among women. So the lifetime risk of cancer for a person with diabetes at a given age

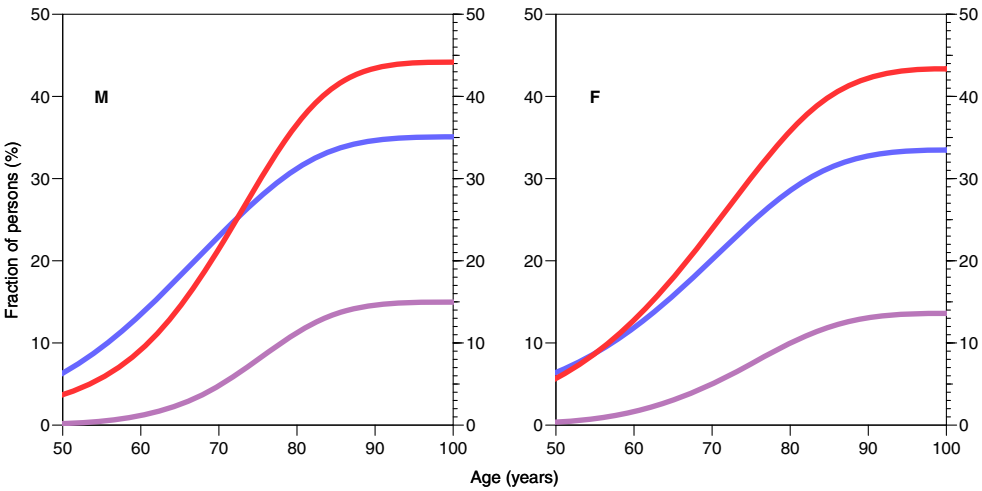

Fig. 5 Fraction of a birth cohort that gets diabetes (*blue*) or cancer (*red*) before a given age. These two events are not exclusive; the fraction suffering both is given in *purple*. Hence, the difference between the *red* and *purple curves* is the fraction of a birth cohort that before a given age gets cancer alone, and the difference between the *blue* and the *purple curve* is the fraction of a birth cohort that gets diabetes alone

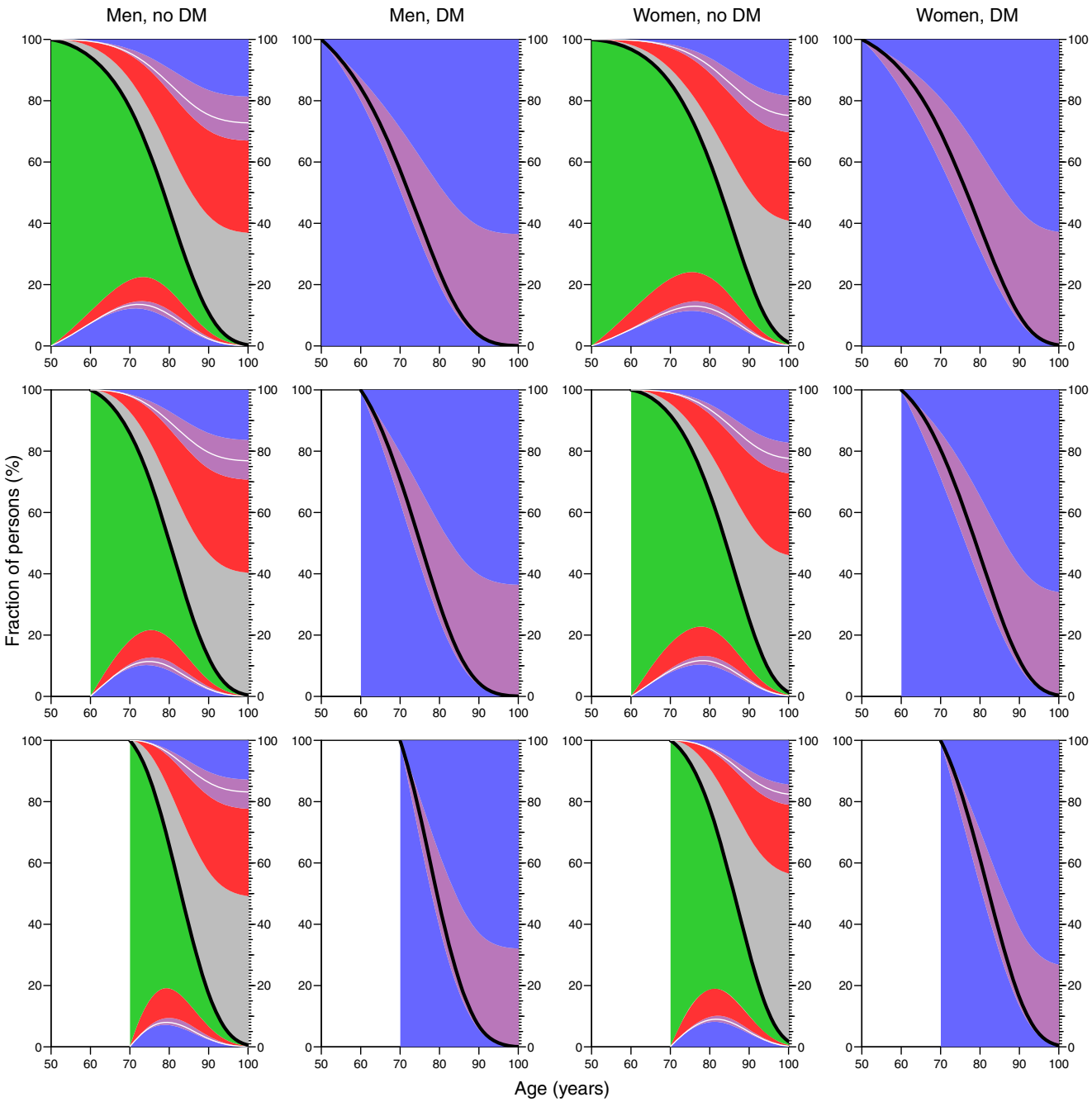

Fig. 6 Fraction of a birth cohort in each state at a given age, based on Danish data. Coloring as in Fig. 4. The *three rows* of graphs give the conditional probabilities given that a person is alive at age 50, 60, and 70, respectively. The 1st and 3rd columns are conditional on having neither diabetes nor cancer; the 2nd and 4th columns are conditional on having diabetes only

is smaller than for a person without diabetes at the same age, and this risk decreases by the age considered.

Discussion

The risk of cancer increases among persons with diabetes with increasing severity of the diabetic disease process. It is not clear (let alone discernible) whether this a result of the disease processes associated with diabetes or if latent cancers contribute to the deterioration of the diabetic status of patients. With the exception of liver and pancreatic cancer, it is also clear that the excess risk among persons with diabetes is moderate, in the order of maximum 20–50 % higher for those cancers for which an increased cancer incidence has been observed and other cancer types there is no excess risk. When incorporating death as a competing risk to cancer incidence, the excess mortality among persons with diabetes is of quantitatively

much larger concern than the excess of cancers [12, 21•]. Our Danish study demonstrated that the lifetime cumulative risk of cancer is smaller among persons with diabetes than among persons not suffering from diabetes. This is due to the higher mortality rates among people with diabetes compared with those without diabetes. In general terms, persons with diabetes die earlier and thus escape development of some cancers.

One limitation of our register-based estimates is that the calculations were based on cross-sectional rates applied longitudinally. Nevertheless, this approach is in complete parallel to classical calculations of life expectancy, and essentially the only practicable approach since the time period covered by the diabetes register (1995–2012) is too short to give reliable cohort specific rates over the entire age range.

Another limitation is that the rates were only modeled by age and calendar time not taking duration of diabetes or cancer into account, as it is known that both incidence rates and mortality rates are higher shortly after a diagnosis of either diabetes or cancer. However, since our focus was on cumulative measures, the impact of ignoring duration of diabetes and cancer is likely small.

Conclusions

- Overall cancer incidence among persons with diabetes patients is 10–20 % higher than among those without diabetes.
- The most elevated incidence rates among persons with diabetes are found for cancers of the liver or pancreas, and incidence rates of cancers of the endometrium, kidney, and colon also seem to be consistently elevated among patients with diabetes across studies.
- In the general population, the lifetime risk of cancer is about 44 %, and the lifetime risk of diabetes about 35 %, and the lifetime risk of both diagnoses about 15 %. For both diseases, these proportions are slightly less for women than for men.
- Persons with diabetes at a given age have a smaller lifetime risk of cancer than persons without diabetes at the same age. This is attributable to the higher mortality rates among persons with diabetes.
- Differences in cancer occurrence between persons with diabetes and those without diabetes are a quantitatively smaller problem than the difference in mortality rates between the two groups.
- A further decrease in mortality among diabetes patients would be expected to increase the fraction of diabetes patients contracting cancer.

Compliance with Ethics Guidelines

Conflict of Interest Bendix Carstensen and Marit Eika Jørgensen are employees of Steno Diabetes Center, a research Hospital owned by Novo Nordisk and operating as part of the Danish National Health Service. Bendix Carstensen and Marit Eika Jørgensen own shares in Novo Nordisk.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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