Cancer occurrence in Danish diabetic patients: Duration and insulin effects

Register details and Supplementary figures

Diabetologia, 2011
Electronic Supplementary Material

Compiled Thursday 17th November, 2011, 13:04
from: C:/Bendix/Steno/DM-register/NDR/projects/Cancer/ESM.tex

Bendix Carstensen — Steno Diabetes Center, Gentofte, Denmark
& Department of Biostatistics, University of Copenhagen
bxc@steno.dk
http://BendixCarstensen.com
Conflict of interest: Stockholder of NovoNordisk

Danel R Witte — Steno Diabetes Center, Gentofte, Denmark
drw@steno.dk
Conflict of interest: Stockholder of NovoNordisk

Søren Friis — Institute of Cancer Epidemiology
Danish Cancer Society, Copenhagen Denmark
& Institute of Public Health, University of Copenhagen
friis@cancer.dk

Contents

List of Figures

Chapter 1

Register content

A complete documentation of data acquisition and statistical analyses is available at the first author's website as:
http://BendixCarstensen.com/DMCa/Diabetologia/Analyses.pdf

1.1 Registers

1.1.1 The National Diabetes Register (NDR)

This register was established in 2006, and currently contains records of all prevalent cases of diabetes as of 1.1.1995 and all incident cases of diabetes until 31.12.2009 [2, 1].

The register contains the CPR-number, sex and dates of birth, inclusion ("diagnosis"), death, and dates for meeting each inclusion criterion, among which are second purchase of insulin and second purchase of oral anti-diabetic medicine (OAD). The reason that the inclusion criterion for the NDR is based on second purchase is to avoid inclusion of persons with only one prescription ever. Patients who have filled two insulin prescriptions are assumed to have continued insulin treatment. OAD purchase is unfortunately not subdivided by type of drug in the register, and this exposure was not considered further in this study because different OADs have been reported to have opposite effects.

1.1.2 The Danish Cancer Register (DCR)

The Danish Cancer Registry was established in 1943 [**?**], and contains all tumours diagnosed in Denmark in the period 1.1.1943–31.12.2009, a total of 1.25 million cancers among 1.15 million persons. All patients alive after 1.4.1968, when the CPR was established, are identified by the CPR number.

We excluded all prevalent cancer patients as of 1.1.1995 from follow-up. Cancers in this study were defined as the first primary cancer only, in order to avoid diagnostic artifacts and possible effects from treatment of the first cancer. Moreover, non-melanoma skin cancer was *not* counted as a cancer in this study.

The relative timing of diagnosis of cancer and diabetes was so that we discarded the first month of follow-up after diagnosis of diabetes. A detailed account of this can be found in the ESM.

1.2 Accuracy of dates

It is implicit in this study that dates of diagnosis are accurately recorded, and in particular that the order of the dates of diabetes and cancer is correct. However until 2004, the date of cancer was only recorded to the nearest month (in practice coded as the first of each month). Since 1.1.2004 the Cancer register has accurate coding of date of diagnosis, as is the case in the diabetes register throughout the study period. However, it is not biologically meaningful to assign a specific date of diagnosis for either diabetes or cancer since both diseases are subject to considerable uncertainty in the date of onset from a biological point of view; particularly diabetes. Consequently, a very sharp distinction of cancer diagnoses appearing immediately before or after diagnosis of diabetes is probably not meaningful.

The relative position of dates of diagnosis of diabetes and cancer and of the dates of cancer and insulin start are shown in figure **??**. There is a very sharp peak just around 0, i.e. where the two dates are less than a month apart, but when the rounded dates of cancer diagnosis were spread evenly over the month they refer to, this peak became smaller, but the number of cancer cases diagnosed more than a month after diagnosis of diabetes hardly changed. Thus, it seems that the purely administrative coding of dates precludes a sensible assignment of the sequence of cancer and diabetes related events if they are within a month of each other. Consequently, follow-up for cancer occurrence among diabetes patients was performed only from one month after the recorded diagnosis of diabetes (inclusion in the NDR). For the same reason, follow-up in the insulin group was not counted until one month after the recorded date of insulin initiation.

The first graph (figure 1.1) in this section illustrate the data-problems connected with defining a cancer occurrence subsequent to a diabetes diagnosis. There is as distinct aggregation of cancer and diabetes diagnoses that are less than one month apart, even when we try to to blur the picture by compensate for the crude rounding of dates of cancer diagnosis prior to 2005.

1.2.1 Distribution of follow-up

To illustrate how follow-up (time and cancer cases) is distributed over the follow-up time since diagnosis of diabetes and since start of insulin, we have shown this in bar charts in figure 1.2. The widths of the bars correspond to the subdivision of follow-up that was done for the statistical analysis.

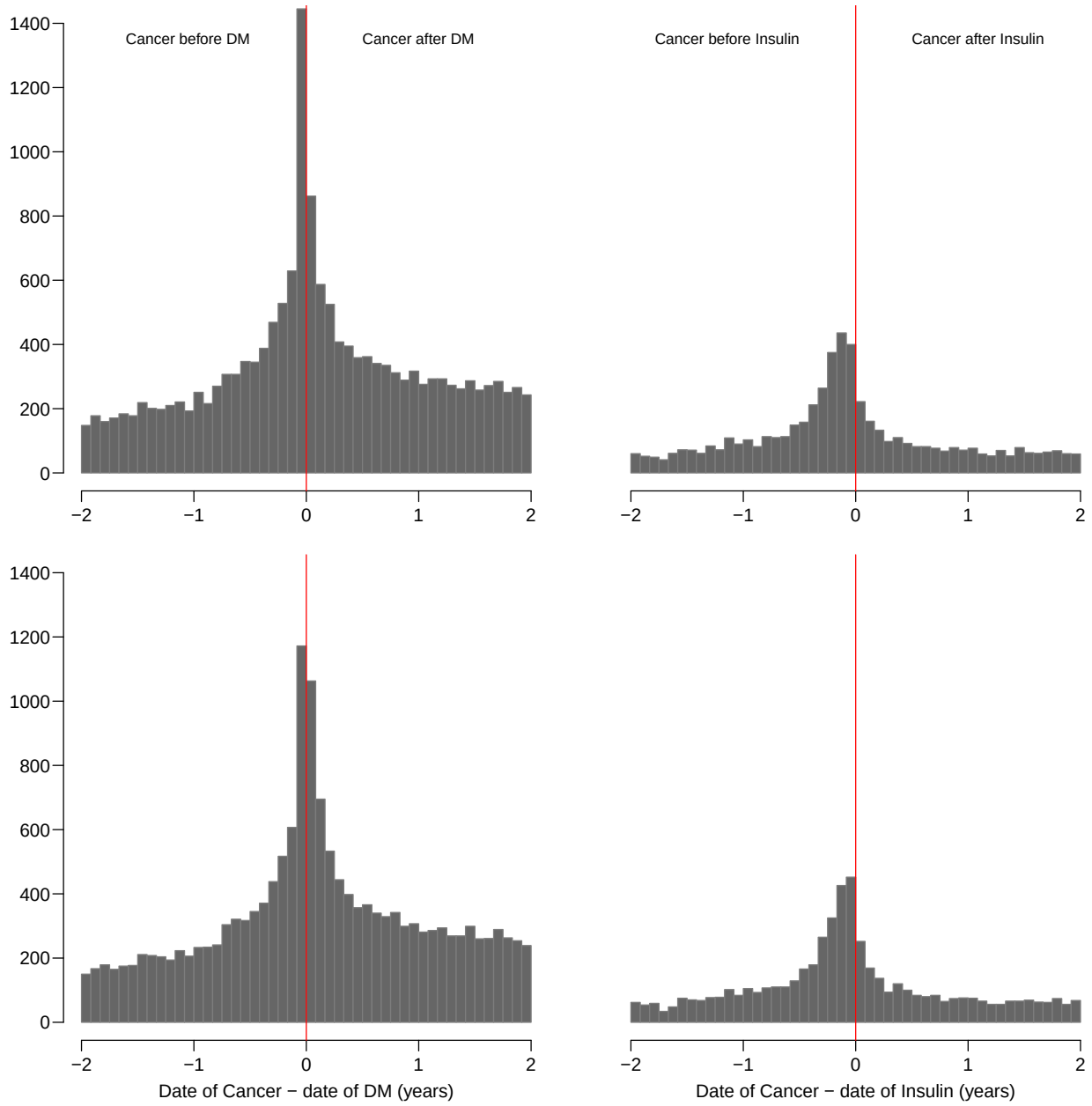

Figure 1.1: *Differences between date of cancer and dates of diabetes and insulin start in 1 month intervals. Top panels: Dates as recorded in the databases. Bottom panels: Rounded dates of cancer (pre-2005) randomly allocated over the recorded month.*

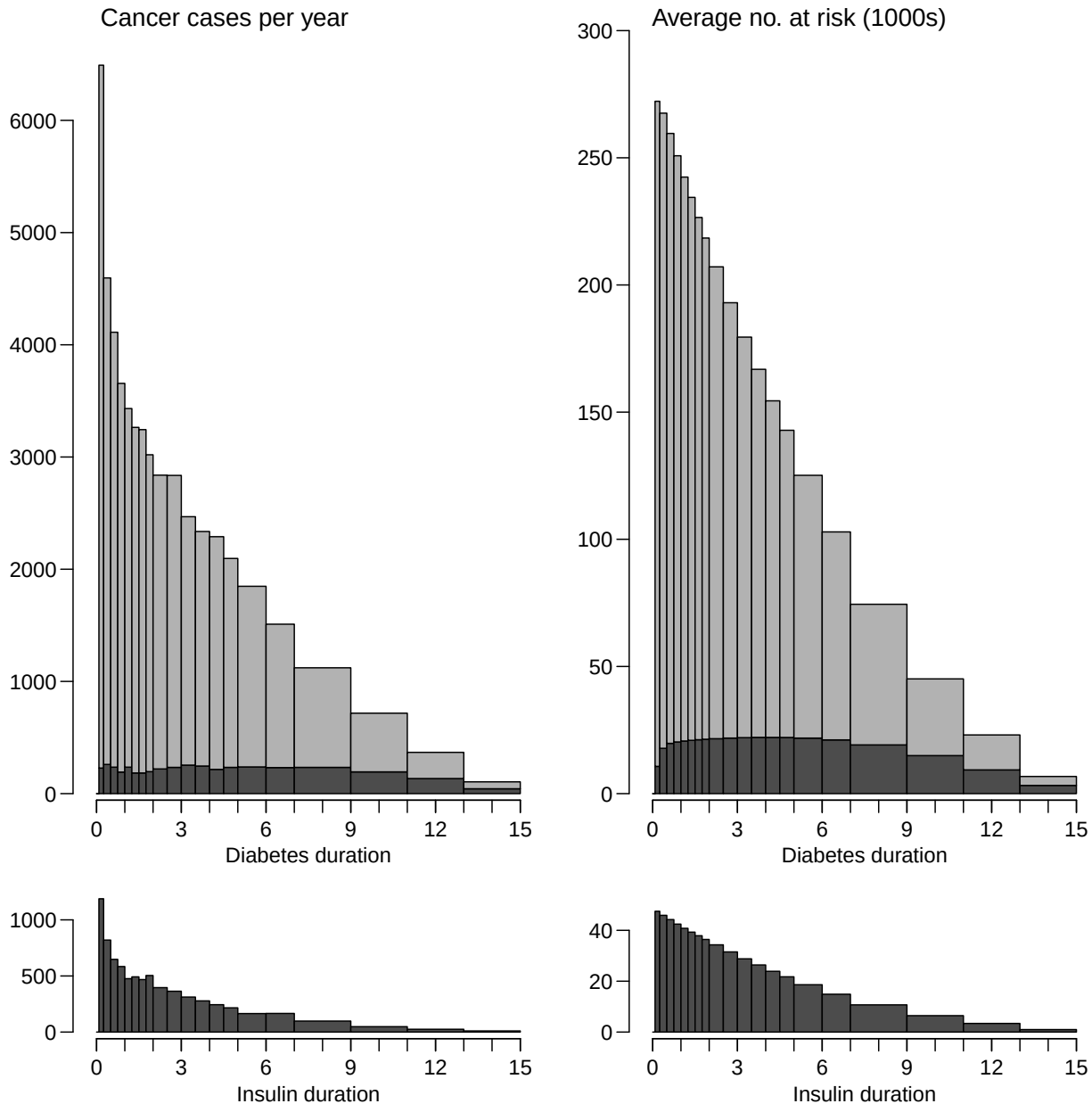

Figure 1.2: *Cases and follow-up time among diabetes patients by duration of diabetes and by duration of insulin. Note that the first month after diagnosis of diabetes and start of insulin is excluded due to measurement inaccuracies, so the first bar is only 2 months wide. The dark gray areas are patients on insulin.*

Chapter 2

Supplementary figures

A complete documentation of data acquisition and statistical analyses is available at the first author's website: http://bxc.dk/DMCa/Diabetologia in the file `Analyses.pdf`

2.1 Constant rate-ratio: ignoring duration

Most previous studies have disregarded duration of diabetes in analyses, and thus lumped together prevalent cases of diabetes (where duration is unknown) and incident cases. Figure 2.1 shows both analyses on the Danish material.

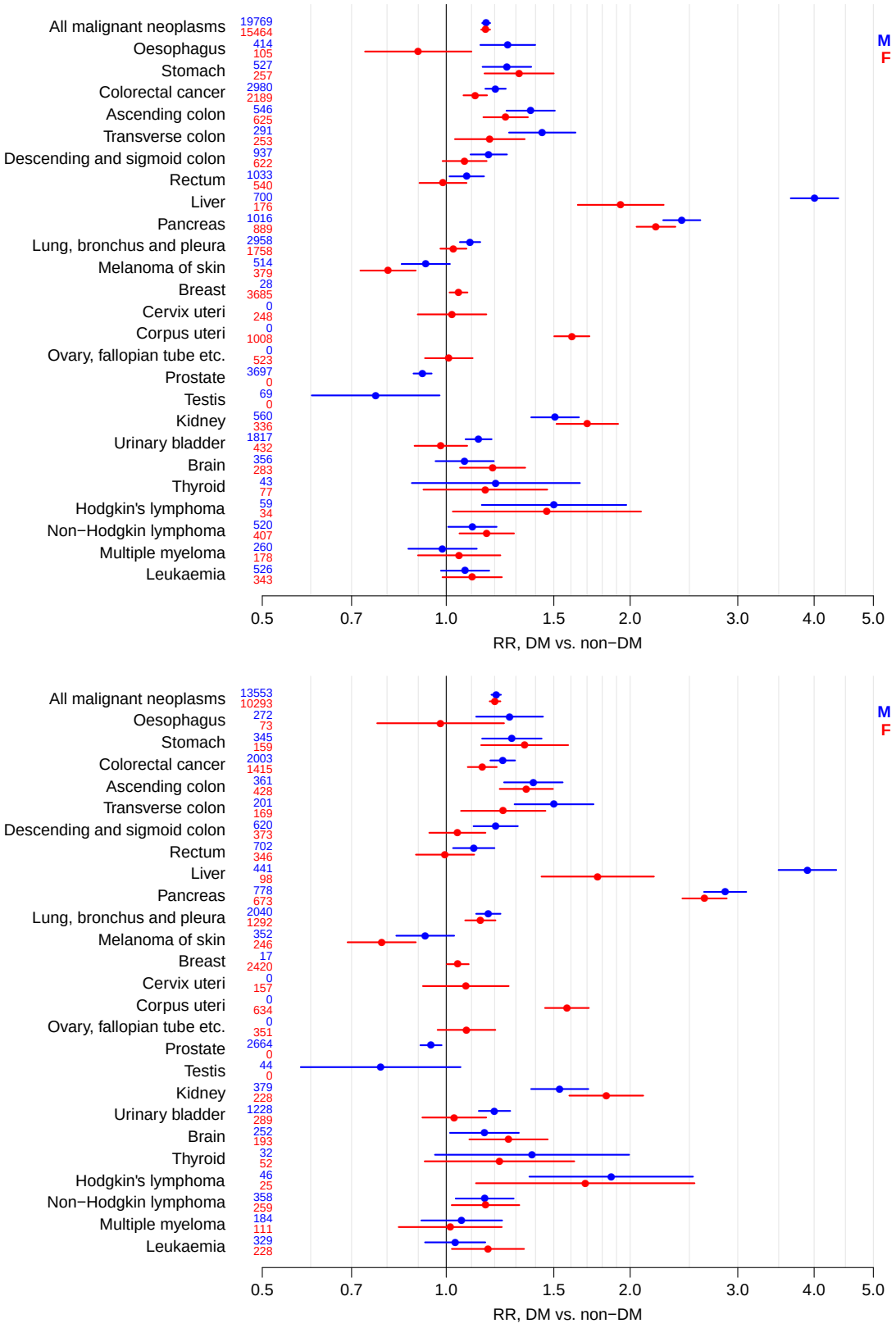

Figure 2.1: *Estimated rate-ratios of cancer occurrence for DM patients (regardless of insulin use and disease duration) versus non-DM-patients. Top panel includes prevalent cases as of 1 January 1995 as well as incident cases after, the bottom panel only incident cases after 1 January 1995. Males: blue; females: red.*

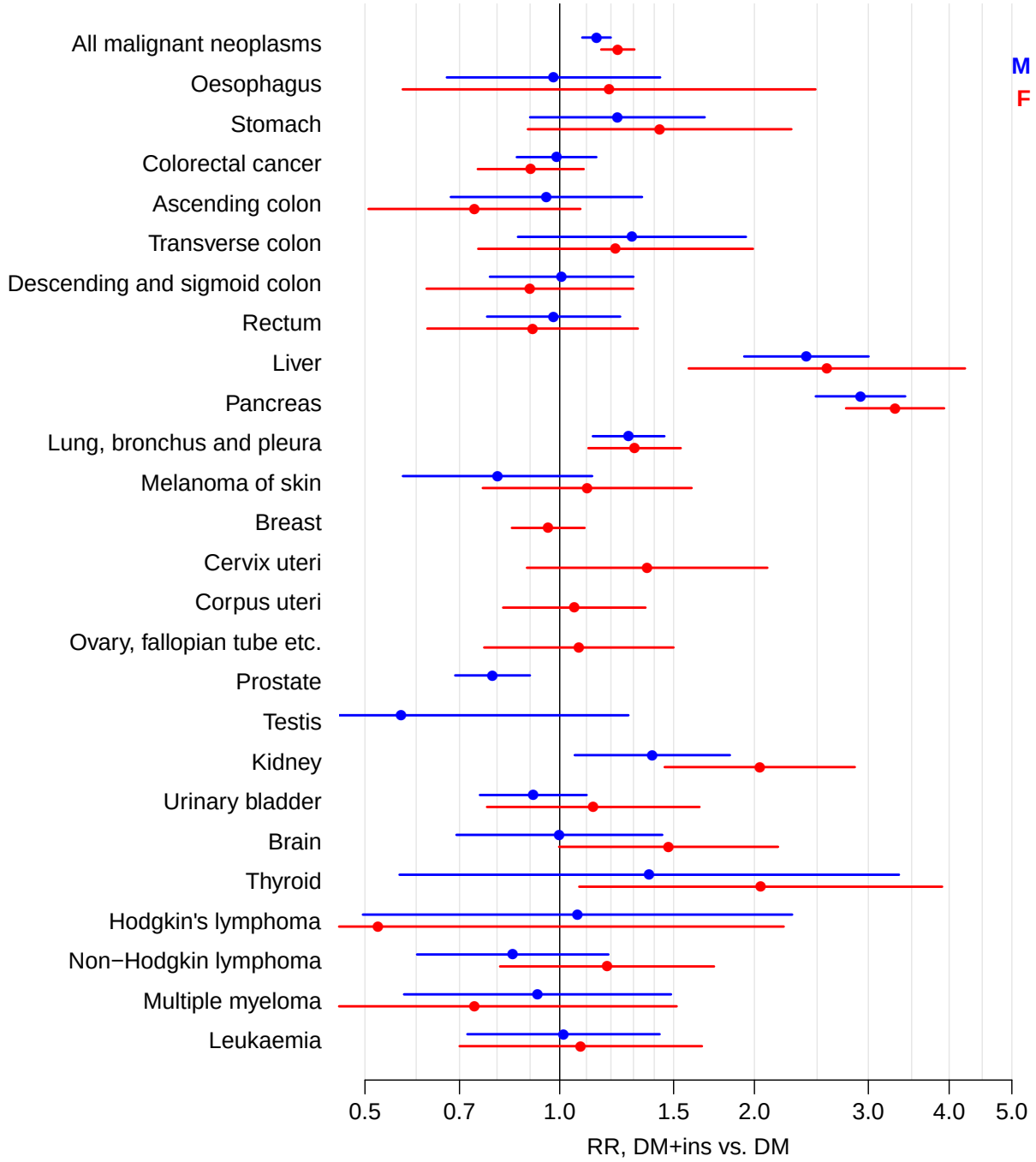

Figure 2.2: *Estimated rate-ratios of cancer occurrence for DM patients on insulin versus DM-patients not on insulin for different cancers. Males: blue; females: red.*

2.2 Duration effects: DM vs. non-DM

The following figures show rate-ratio for analysed cancer sub-sites versus the non-diabetic population, using a spline model with 4 parameters for diabetes duration and 3 parameters for insulin duration.

The full lines are for DM-patients not on insulin, the broken lines are for patients on insulin, starting insulin after 0, 2 and 5 years of DM duration, respectively. Thin lines indicate 95% confidence intervals as derived from the Poisson models.

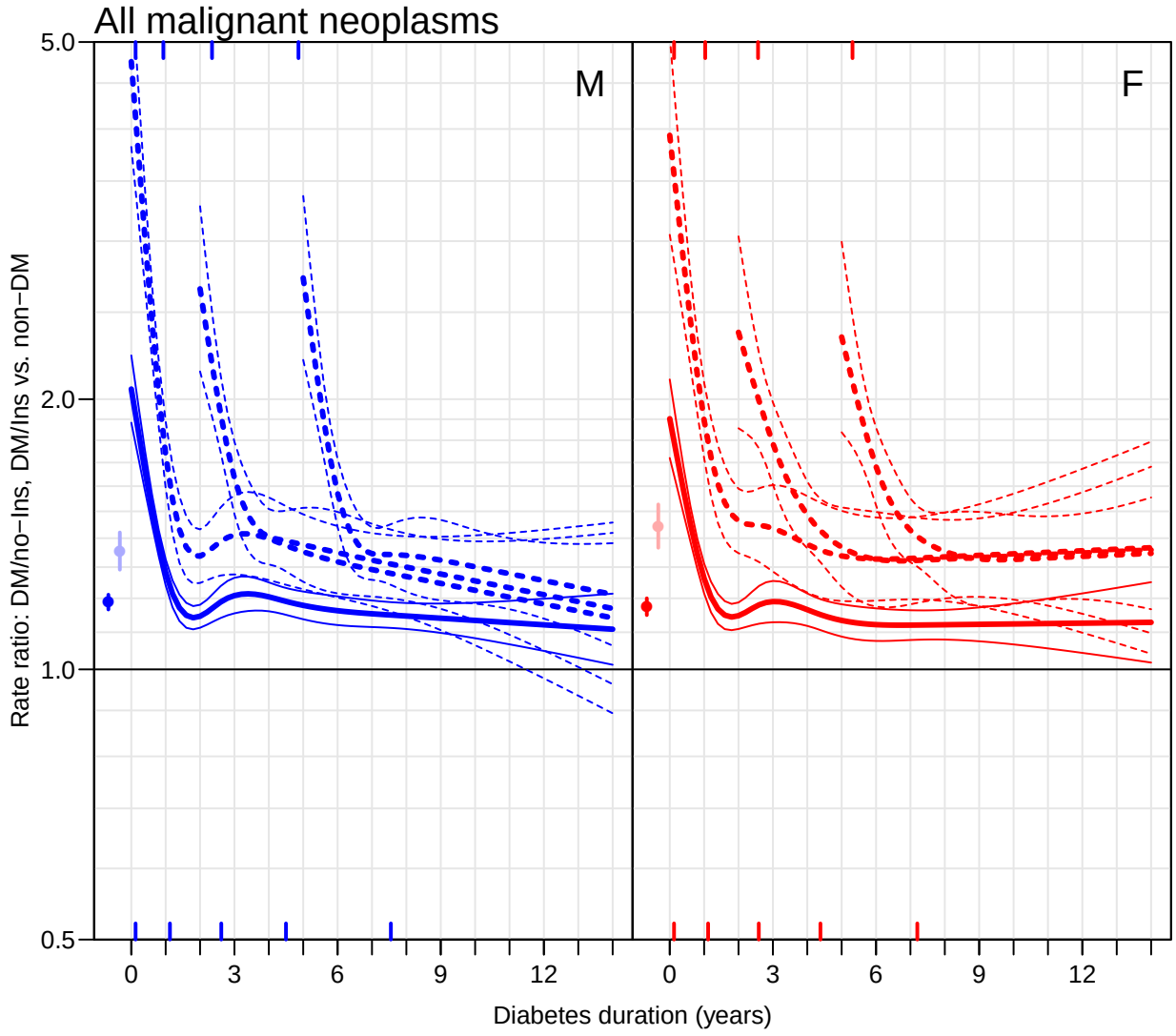

Figure 2.3: *(Also in the paper). Cancer incidence rate-ratio versus the non-diabetic population. Spline models with 5 (DM-duration) and 4 (insulin duration) parameters. The full lines are for DM-patients not on insulin, the broken lines are for patients on insulin, starting insulin after 0, 2 and 5 years of DM duration, respectively. Thin lines indicate 95% confidence intervals. The bars on the left are estimates from the model ignoring duration effects, and the coloured ticks inside indicate the location of the knots for the spline functions—the number of cancers between each pair of knots and to the right of the last are the same.*

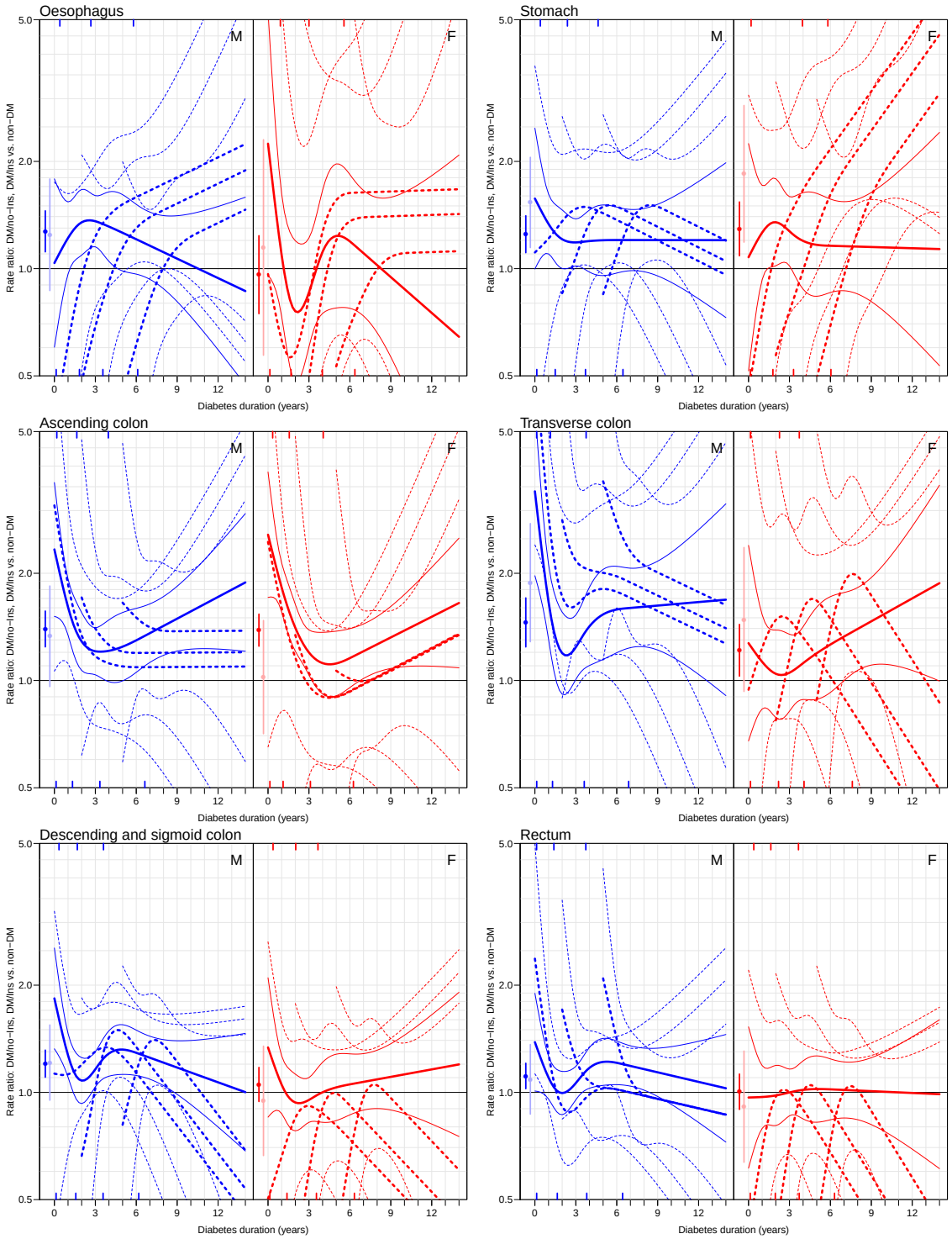

Figure 2.4: *Rate-ratios of specific cancers for diabetes patients non- and users of insulin versus the non-diabetic part of the population: Oesophagus, Stomach, Ascending Colon, Transverse colon, Descending colon, Rectum.*

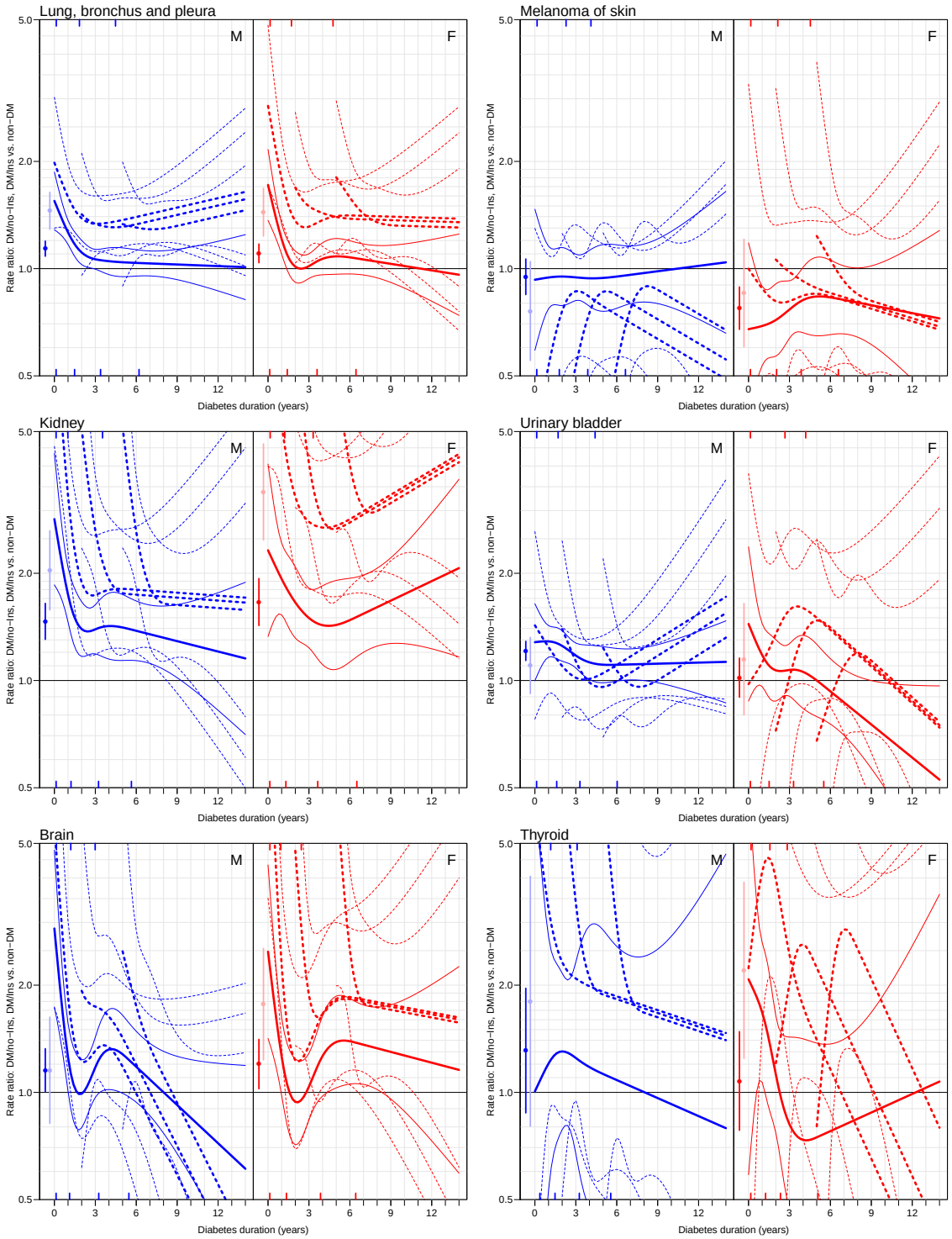

Figure 2.5: *Rate-ratios of specific cancers for diabetes patients non- and users of insulin versus the non-diabetic part of the population: Lung, Melanoma, Kidney, Urinary bladder, Brain, Thyroid.*

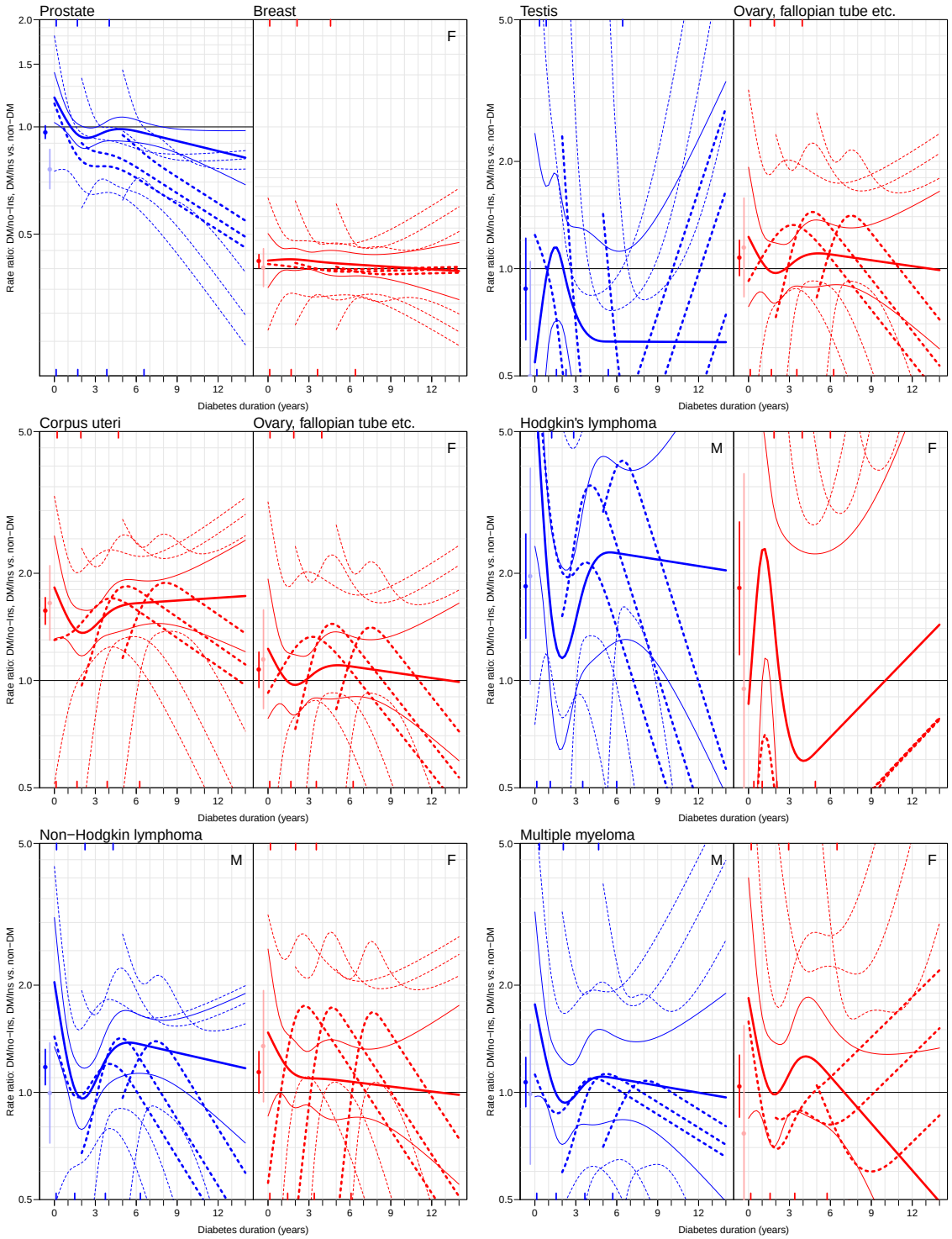

Figure 2.6: *Rate-ratios of specific cancers for diabetes patients non- and users of insulin versus the non-diabetic part of the population: Prostate, Breast, Testis, Ovary, Corpus uteri, Cervix uteri, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Multiple myeloma.*

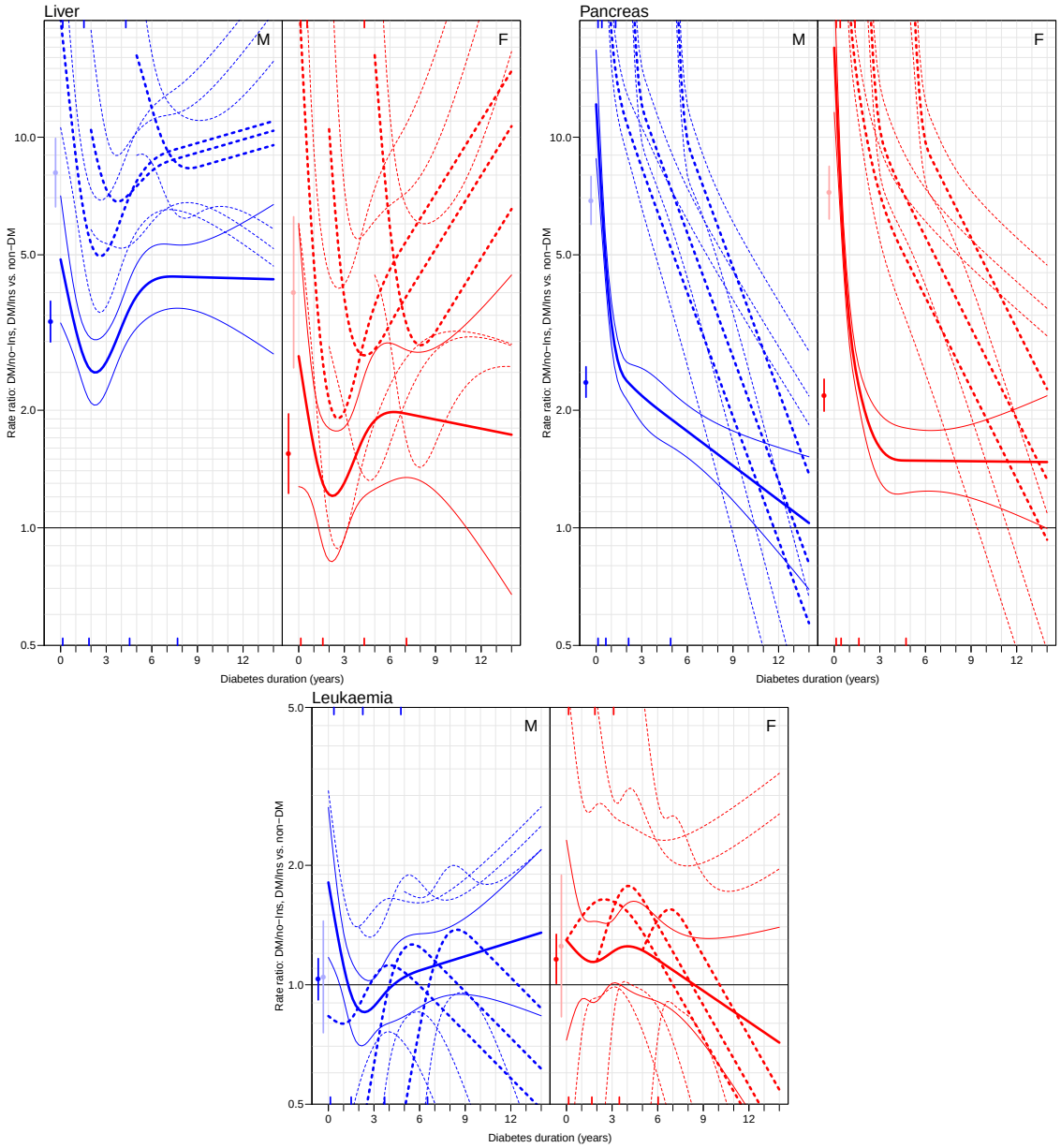

Figure 2.7: *Rate-ratios of specific cancers for diabetes patients non- and users of insulin versus the non-diabetic part of the population: Liver, Pancreas, Leukemia*

2.3 Duration effect: Insulin vs. none

The graphs in this section compares directly diabetes patients on insulin with diabetes patients not on insulin, as a function of time since start of insulin therapy.

Since the model we use has no interaction between the two time-scales (diabetes duration and insulin duration), these effects are independent of duration of diabetes. The curves shown here are derived from those in the previous section by taking the ratio of the leftmost broken line and the full line.

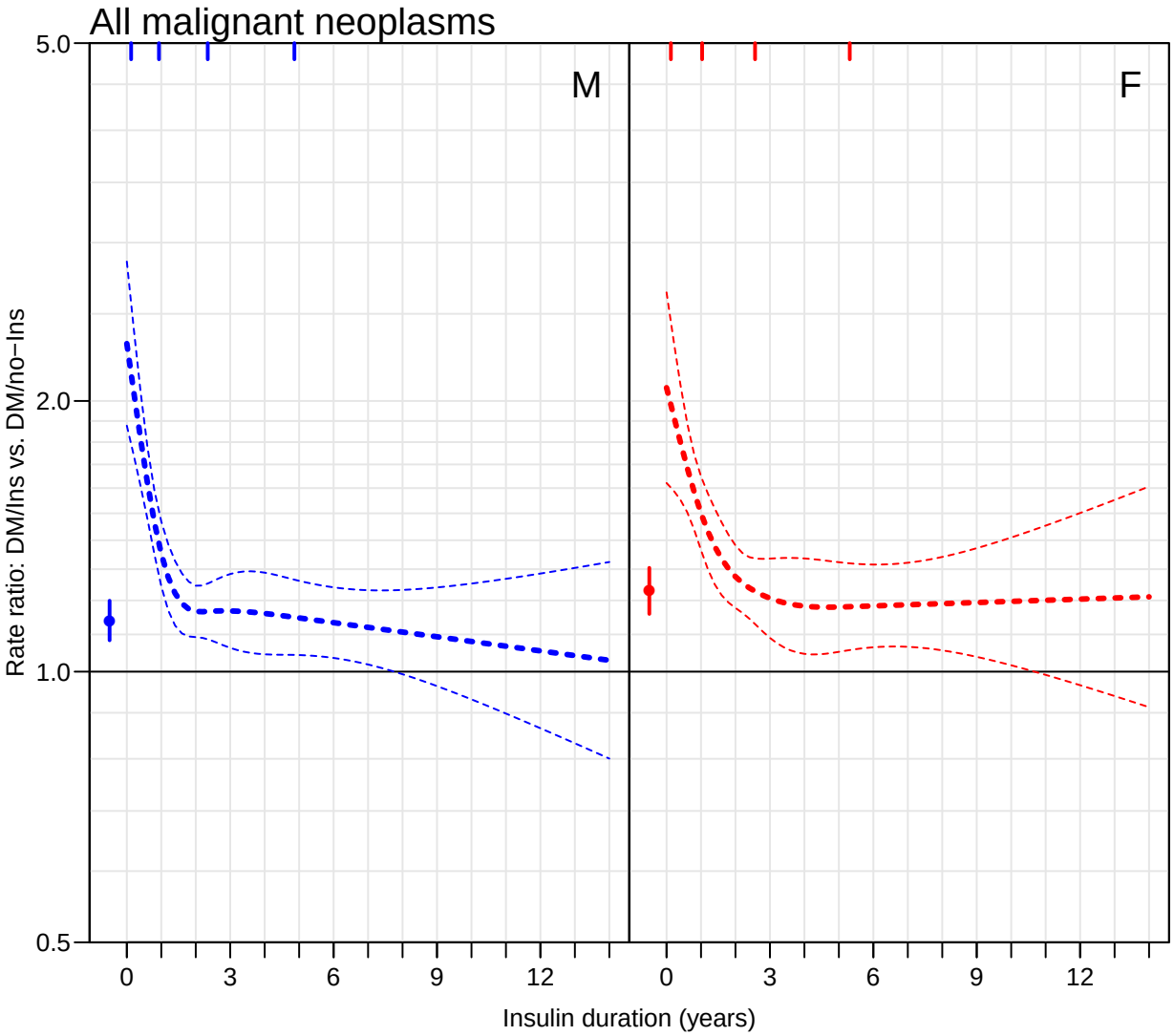

Figure 2.8: *(Also in the paper). Cancer incidence rate-ratio for insulin users versus non users. Spline models with 5 (DM-duration) and 4 (insulin duration) parameters. Thin lines indicate 95% confidence intervals. The bars on the left are estimates from the model ignoring duration effects, and the coloured ticks inside indicate the location of the knots for the spline functions.*

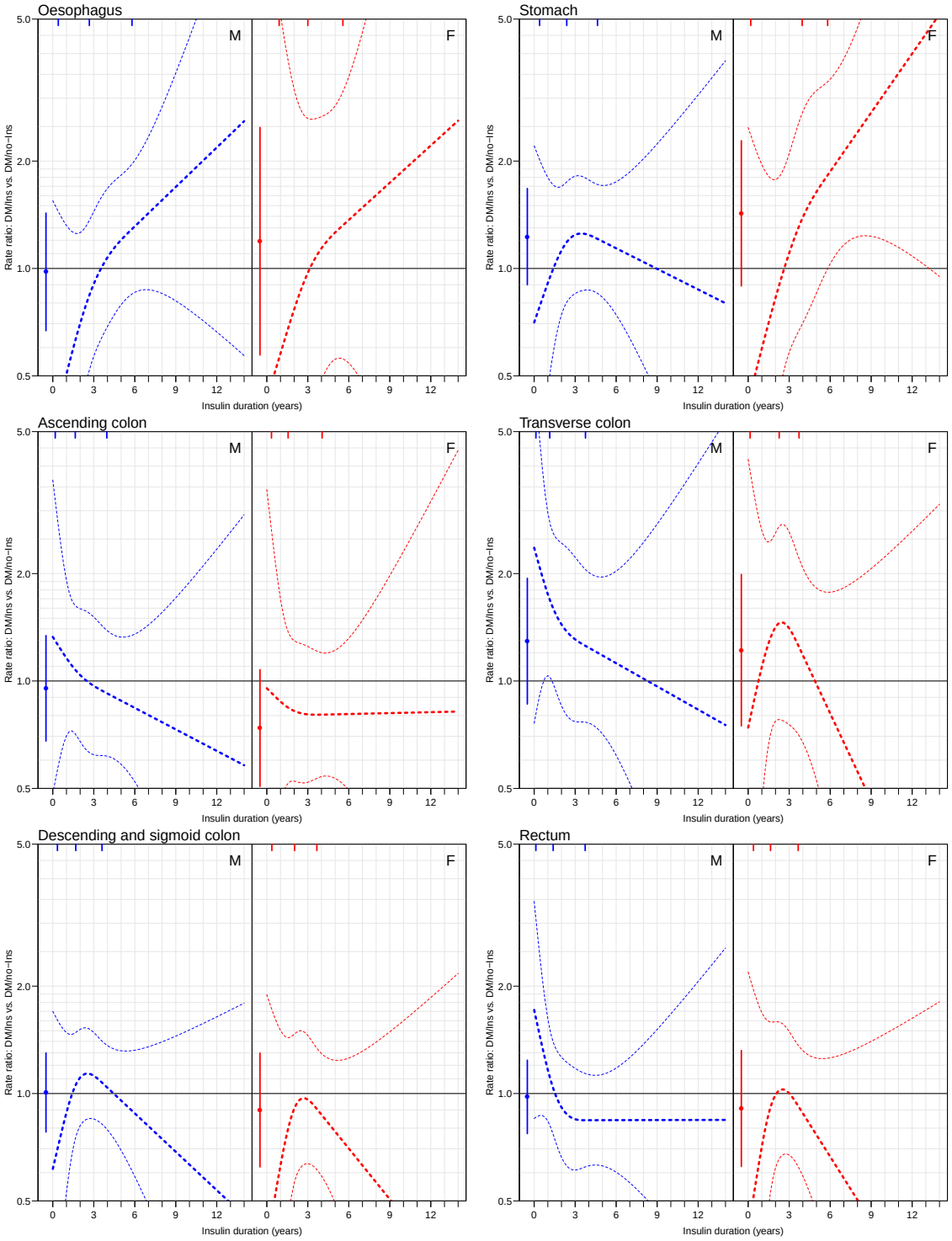

Figure 2.9: *Rate-ratio for insulin users versus non-using diabetes patients: Oesophagus, Stomach, Ascending Colon, Transverse colon, Descending colon, Rectum.*

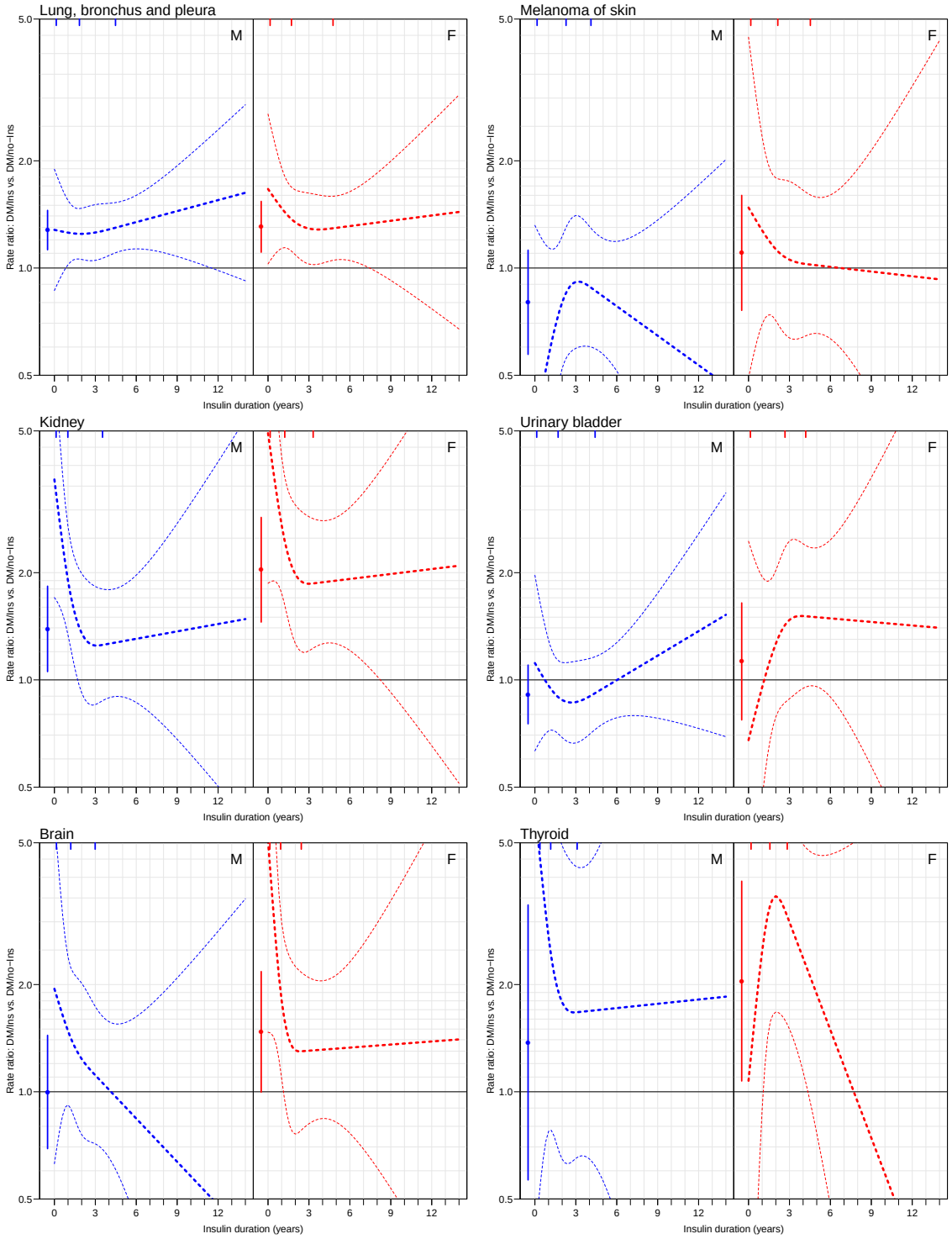

Figure 2.10: *Rate-ratio for insulin users versus non-using diabetes patients: Lung, Melanoma, Kidney, Urinary bladder, Brain, Thyroid.*

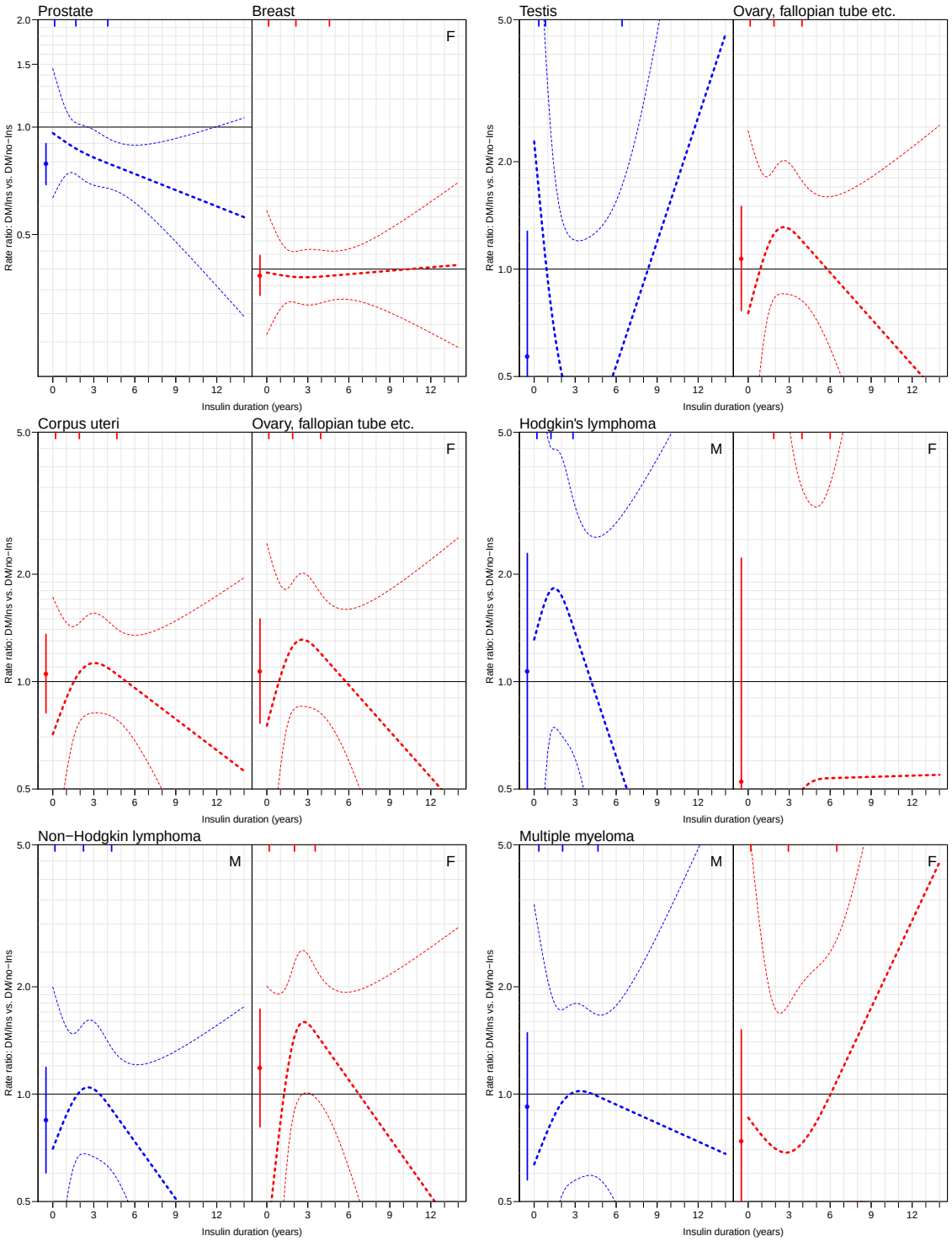

Figure 2.11: *Rate-ratio for insulin users versus non-using diabetes patients: Prostate, Breast, Testis, Ovary, Corpus uteri, Cervix uteri, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Multiple myeloma.*

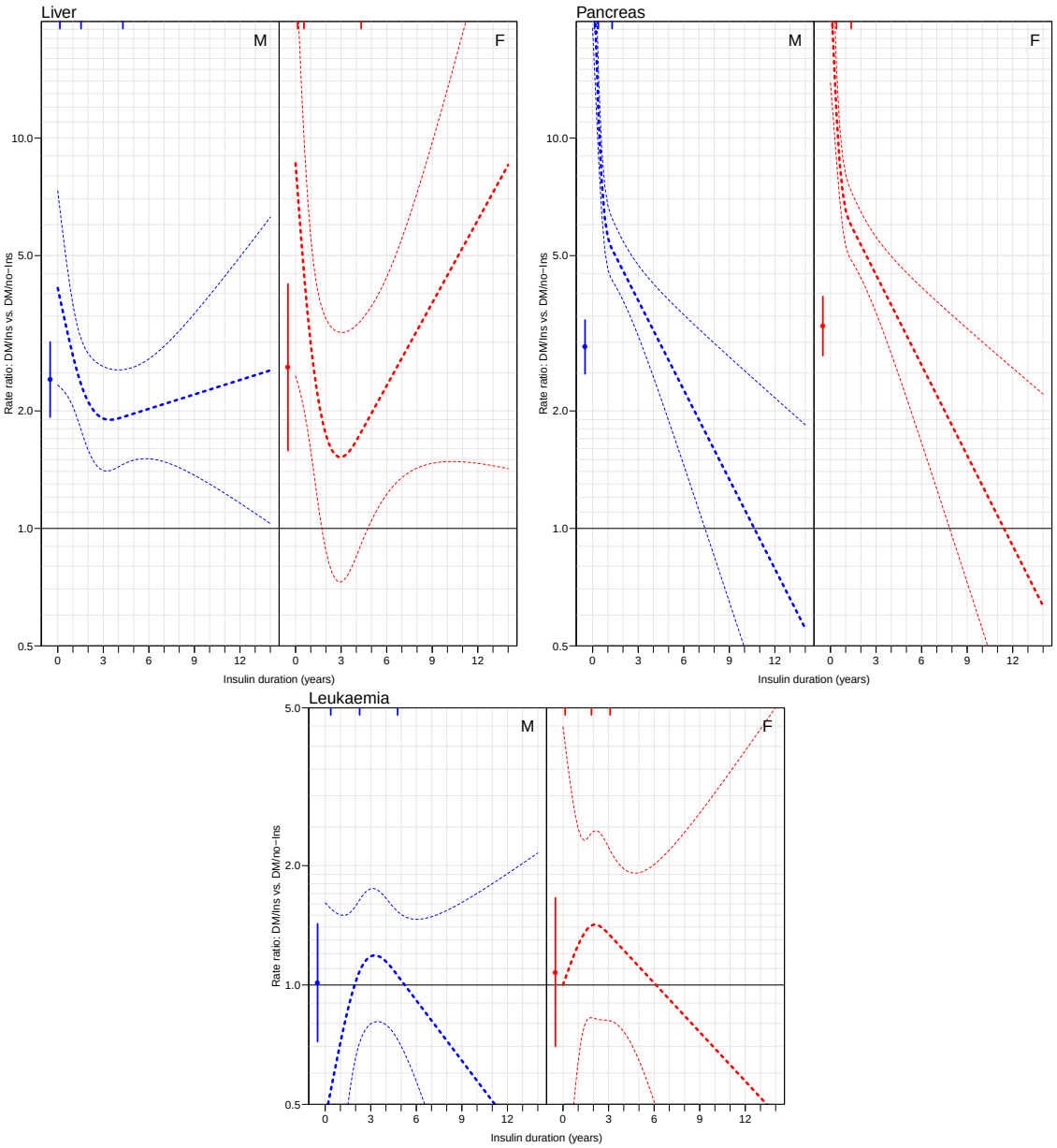

Figure 2.12: *Rate-ratio for insulin users versus non-using diabetes patients: Liver, Pancreas, Leukaemia.*

2.4 Comparison with results from other published studies

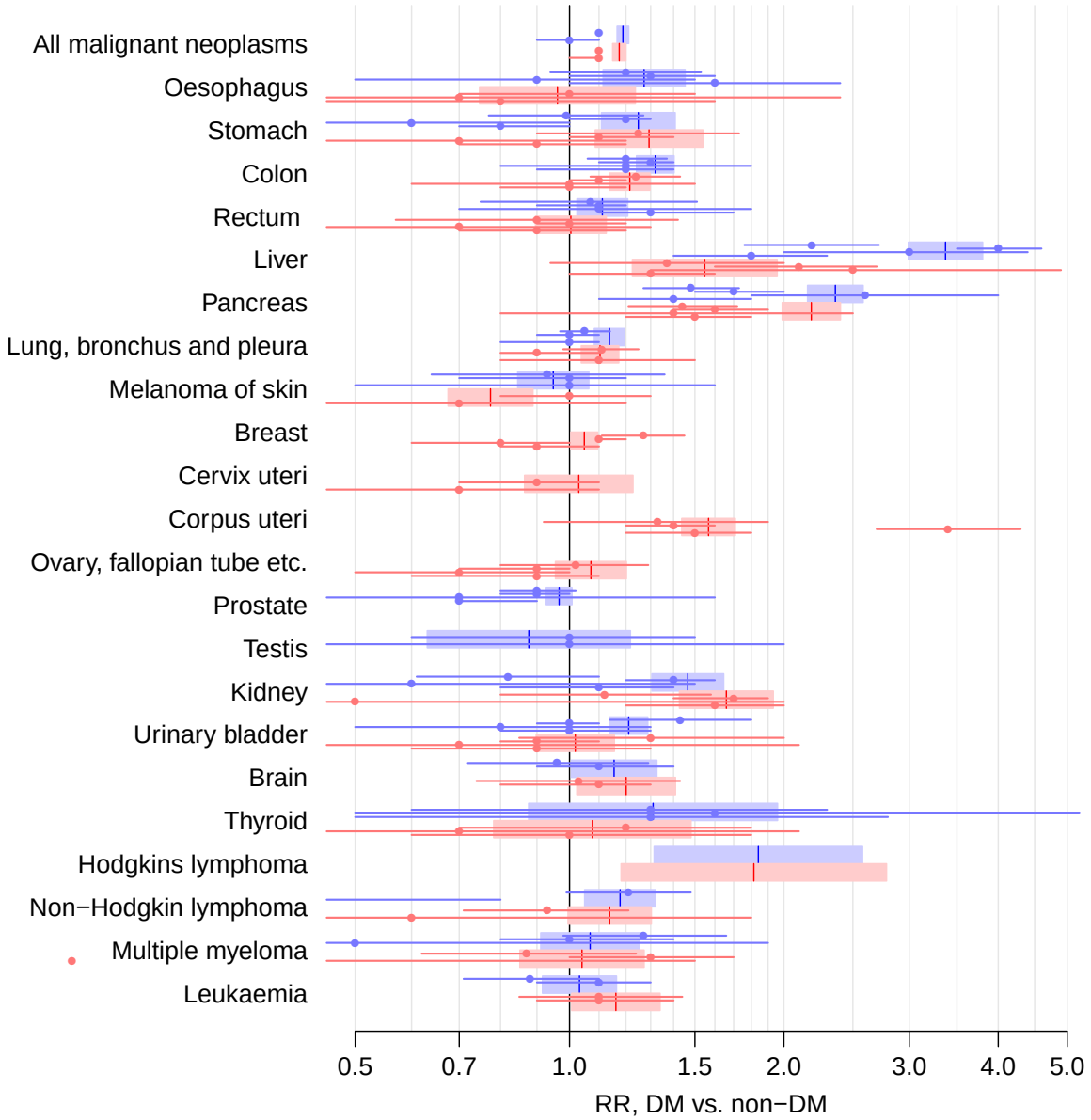

Figure 2.13: *Estimated rate-ratios of cancer occurrence for DM patients versus non-DM-patients for different cancers, ignoring duration and insulin status. The shaded areas with the vertical bars are estimates (95% c.i.) from this study; the dots and bars represent estimates from the studies [?, ?, ?, ?] (in that order from the top).*

Bibliography

[1] B. Carstensen, Christensen J.K., Marcussen M.M., and Borch-Johnsen K. The National Diabetes Register. *Scandinavian Journal of Public Health*, 39(7 suppl):58–61, 2011.

[2] B Carstensen, JK Kristensen, P Ottosen, and K Borch-Johnsen. The Danish National Diabetes Register: Trends in incidence, prevalence and mortality. *Diabetologia*, 51:2187–2196, 2008.