Diabetes and Incidence and Prognosis of Surgical Malignancies

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Diabetes and Incidence and Prognosis of Surgical Malignancies

Diabetes en de incidentie en prognose van chirurgische maligniteiten

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K.M.J. De Bruijn and C.H.J. van Eijck

Chapter 1 General introduction

It is well known that around 15% of the patients with pancreatic cancer develop diabetes mellitus (DM) prior to the detection of their malignancy. In our population of diabetic patients at the ErasmusMC we investigated whether we could identify patients with pancreatic cancer. In this relatively small population of around 2500 patients, we could not find enough patients who were diagnosed with pancreatic cancer, but a high proportion of patients had other forms of cancer. Therefore we started to inquire the relation between DM and cancer incidence and cancer mortality.
Over the past decades, wealth has increased and this has had its impact on the general health of the worldwide population and on health care as well. Below the major issues with regard to the changes in population health will be discussed in the light of this thesis.

Obesity
Worldwide, the population has become increasingly obese; since 1980 obesity has nearly doubled up to 1.4 billion people of 20 years and older who were overweight in 2008 (1). Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Overweight is further defined as a body mass index (BMI) equal or more than 25 and a BMI equal to or more than 30 is called obesity (1). Forecasts predict an ongoing increase in obesity prevalence over the next decades (figure 1), with serious implications regarding worldwide health and healthcare costs (2).

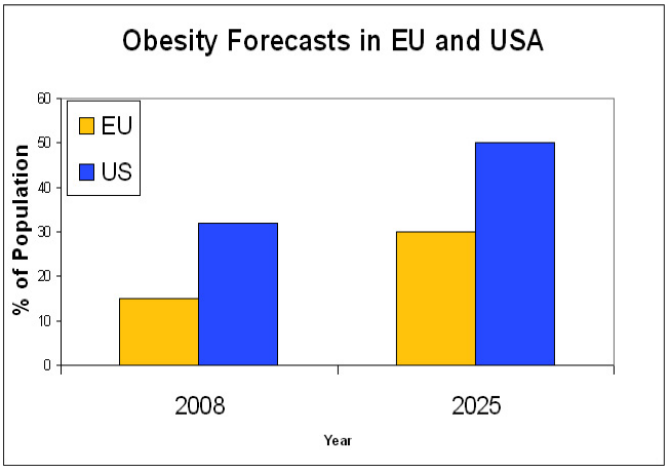

Figure 1. Obesity forecasts. WHO and OECD Health data 2008.

Metabolic syndrome

Following the abovementioned increase in obesity, the metabolic syndrome (MetS) has become a common clinical condition. MetS is a cluster of metabolic disorders with major risk factors being physical inactivity and high-fat diet. The main clinical features are central (or abdominal) obesity, insulin resistance, hypertension and dyslipidemia (3, 4). However, the exact definition of MetS is still debated. Nevertheless it is thought that 20% of adults in the Western world have MetS and that people with MetS have a five times higher risk of developing type 2 diabetes mellitus (T2DM) (3). With the predicted increase of obesity prevalence rates of MetS are expected to rise as well, which will be accompanied by major socioeconomic problems.

Diabetes mellitus

The prevalence of T2DM has increased due to the rise in obesity and MetS since these conditions are related (5). Nowadays, 382 million people worldwide have diabetes mellitus (6). DM was given its name by the Greek physicians Apollonius Memphites and Aretaeus of Cappadocia in 250 before Christ. Diabetes comes from the Greek words 'dia', which means 'through' and from 'baino', which means 'to go'. 'Mellitus' is a Latin word and means 'honey' or 'sweet' and was later added to the name of this disease. So literally, diabetes mellitus means 'sweet flow', referring to the sweet taste of the urine of diabetic patients, which was usually tasted by the physicians in order to obtain the diagnosis.
DM exists of two major forms. Type 1 diabetes (T1DM) is an autoimmune condition characterized by an absolute insulin deficiency and requires daily insulin administration (7). The abovementioned T2DM accounts for 90% of diabetic cases worldwide and results from insulin resistance, which is present in obesity. Patients with T2DM may be treated with diet, exercise, oral glucose-lowering drugs (OGLD, like metformin or SU-derivatives) or insulin (7). Pancreatogenic diabetes or new-onset diabetes (NODM) is another form of T2DM and occurs in case of pancreatic disease or after pancreatic surgery (8).
Forecasts, recently presented by the World Health Organisation, predict that DM will be the 7th leading cause of death in 2030 (9). The latter two types of T2DM (insuline resistance and pancreatogenic diabetes) will be the focus of this thesis.

Obesity, metabolic syndrome, T2DM and cancer

It might be clear that obesity, MetS and T2DM are highly related. These three conditions share common factors; for instance hyperinsulinemia, hyperglycemia, altered adipocytokine levels and an increased state of inflammation (10). It is thought that these factors contribute – individually or collectively – to cancer development.

Hyperinsulinemia develops following insulin resistance which is present in obesity in an attempt to maintain euglycemia when tissues have reduced sensitivity to insulin (11). Insulin promotes cell proliferation and inhibits apoptosis by its receptor and insulin-like growth factors (IGF-I and -II) through the phosphoinositide 3-kinase/Akt, mitogen-activated protein kinase and mTOR pathways (12, 13). In **chapter 4** we assess the expression of the IGF-1 receptor in esophageal adenocarcinoma tissue and relate this to prognostic parameters.

Glucose is known to be an important nutrient for proliferating cells and it is known that cancer cells take up more glucose (Warburg effect) (10, 13). The possibility that *hyperglycemia* facilitates cell proliferation therefore deserves consideration. However, most patients with T2DM suffer from hyperglycemia as well as hyperinsulinemia, and thus, separate effects of glucose and insulin are difficult to distinguish. Studies that indicate hyperglycemia as an independent risk factor are scarce and it is therefore thought that hyperglycemia mainly serves as a surrogate for other causative factors like hyperinsulinemia (14).

Adipose tissue has an active endocrine function; it secretes the *adipokines* leptin and adiponectin (10, 15). Leptin levels are increased in obesity and this stimulates tumor cell growth, migration, invasion and angiogenesis (10, 13, 16). In contrast, adiponectin levels are decreased in obesity and normally have protective effects with regard to carcinogenesis; adiponectin decreases cell proliferation and increases apoptosis (10, 13, 16). The *pro-inflammatory cytokines* tumor necrosis factor-α (TNF-α) and interleukine-6 (IL-6) are also secreted by adipose tissue (10, 15). Both cytokines are increased in obesity and stimulate angiogenesis, cell proliferation and inhibit apoptosis (16). Furthermore, TNF-α and IL-6 contribute to insulin resistance (15, 16) and are suppressed by adiponectin (10). This points out the intertwined relationship between the common factors of obesity, Met S and T2DM (figure 2).

Numerous studies have pointed out the increased risk of cancer and cancer mortality among patients with obesity and MetS with higher risks for e.g. esophageal adenocarcinoma, endometrial, pancreatic, postmenopausal breast and colorectal cancer (17-20). It has even been estimated that 20% of all cancer cases are caused by overweight and obesity (21).

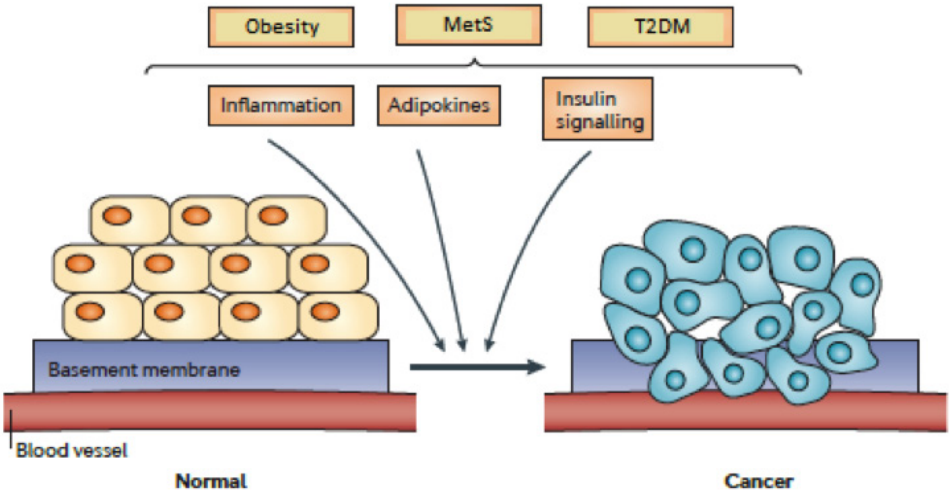

Figure 2. Carcinogenic effects of inflammation, adipokines and insulin resulting from obesity, metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM). Figure adapted and adjusted from Khandekar, et al. Nat Rev Cancer 2011;11:886-95.

With regard to T2DM, many studies have indicated T2DM as a risk factor - independent of obesity - for different types of cancer and mortality (14, 22-24). Breast, endometrial, colorectal, bladder, liver and pancreatic cancer have been consistently linked to T2DM, and interestingly, prostate cancer has been found to have an inverse relation with T2DM. In liver, pancreatic and endometrial cancer a twofold - or higher - risk has been described and for breast, colorectal, bladder a 1.2 to 1.5 fold increased risk has been seen. In liver and pancreatic cancer however, the association with T2DM can be discussed because reverse causality plays an important role with the cancer itself probably leading to the onset of the diabetes (14).

This thesis will mainly focus on T2DM and its influence on the incidence and prognosis of common surgical malignancies, that is, breast, colorectal and esophageal cancer. In initial studies cancer-specific mortality was not extensively studied. Therefore we studied this more accurately in a meta-analysis; **chapter 2** discusses cancer incidence and cancer-specific mortality of the two most common surgical malignancies: breast and colorectal cancer.

Despite the evidence regarding the association between T2DM and cancer seems convincing, important factors that need to be addressed are *detection bias* and diabetes duration. Detection bias occurs when there is increased surveillance of newly diagnosed diabetic patients which accounts for enhanced cancer detection (25). The fact that some studies found different cancer risks with varying durations of diabetes reflects the issue of

detection bias (26-28). In a cohort of the Rotterdam Study we further assessed detection bias and diabetes duration with regard to cancer incidence (**chapter 3**).
Furthermore, DM treatment is thought to be of additional influence on cancer risk and mortality. Metformin has been said to decrease cancer risk and insulin is said to further increase cancer risk (29, 30). However, controversy on this topic exists and future studies should take into account epidemiological biases that can occur while performing studies on medication use (30, 31). The association of glucose-lowering drugs with cancer will not be further discussed in this thesis.
Lastly, studies have shown that diabetic patients receive less optimal treatment in case of cancer (32-34), indicating cancer treatment selection. This might partially explain the diminished prognosis of diabetic patients with cancer compared to non-diabetics.
In **chapter 5** we assess the effect of DM on chances to undergo surgery and prognosis in patients with esophageal adenocarcinoma.

New-onset diabetes mellitus after pancreatic surgery
Another aspect of improved health care is that different imaging modalities are increasingly used in screening or routine examinations. This results in an enhanced detection of asymptomatic lesions ('incidentalomas') in different kind of organs that sometimes require surgical treatment (35, 36). This also concerns asymptomatic lesions of the pancreas which are detected with increased frequency (35). Because these lesions are relatively often situated in the pancreatic body or tail, distal pancreatectomy (37) is a procedure that is increasingly performed (38-40). DP is considered a safe procedure with low mortality rates (41, 42). However, morbidity is substantial, mainly consisting of postoperative pancreatic fistula and NODM (41-43).
After pancreatic head resection, 20-40% of the patients will develop DM, depending on the underlying disease (43-45). Since exact percentages of NODM after DP were not known, we performed a systematic review to obtain exact percentages of NODM after DP (**chapter 6**). In **chapter 7** the incidentaloma-rate among Dutch patients undergoing DP for various indications is assessed. By studying postoperative endo- and exocrine pancreatic function and quality of life the impact of DP and its complications in preoperative asymptomatic patients becomes clearer.

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Chapter 2 A systematic review and meta-analysis on the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer

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Abstract

Background

Increasing evidence suggests that diabetes mellitus (DM) is associated with increased cancer incidence and mortality. Several mechanisms involved in diabetes, such as promotion of cell proliferation and decreased apoptosis, may foster carcinogenesis. This study investigated the association between DM and cancer incidence and cancer-specific mortality in patients with breast and colorectal carcinoma.

Methods

A meta-analysis of controlled trials, prospective cohort studies and pooled cohort studies published after 2007 was conducted. Embase, PubMed and the Cochrane Library were searched. Summary hazard ratios (HRs) were calculated using a random-effects model. Sensitivity and subgroup analyses were performed to adjust for confounders, mode of DM assessment and follow-up time.

Results

Twenty studies were included to investigate the association between DM and breast and colorectal cancer incidence and cancer-specific mortality. The studies predominantly comprised patients with type II DM. The overall HR for breast cancer incidence was 1.23 (95 per cent confidence interval 1.12 to 1.34) and that for colorectal cancer was 1.26 (1.14 to 1.40) in patients with DM compared with those without diabetes. The overall HR was 1.38 (1.20 to 1.58) for breast cancer- and 1.30 (1.15 to 1.47) for colorectal cancer-specific mortality in patients with DM compared with those without diabetes.

Conclusions

This meta-analysis indicated that DM is a risk factor for breast and colorectal cancer, and cancer-specific mortality.

Introduction

Type II diabetes mellitus (DM) develops in obese people owing to insulin resistance, which is a compensatory mechanism for raised blood glucose levels (1). As the incidence of obesity is increasing (2), the incidence of DM is also rising. In surgical patients, obesity and diabetes are risk factors for perioperative and postoperative morbidity and mortality (3,4).
There is also increasing evidence for an association between diabetes and cancer (5). Recent studies have shown that the incidence of breast, colorectal, pancreatic and oesophageal cancer is higher in people with diabetes, and these patients have a poorer prognosis (6–8). Several mechanisms involved in obesity and diabetes have been held responsible for the increased cancer incidence and worse prognosis (9).
The adipokines in adipose tissue (leptin and adiponectin) exert effects on carcinogenesis (10,11). Insulin promotes cell proliferation and inhibits apoptosis by its receptor and insulin-like growth factors (IGF-I and -II) through the phosphoinositide 3-kinase/Akt, mitogen-activated protein kinase and mTORpathways (9,12).
The impact of DM on cancer-specific mortality has rarely been studied. Therefore, the present meta-analysis of published studies focuses on the association between DM and cancer incidence as well as cancer-specific mortality in patients with breast cancer and colorectal carcinoma, two of the most common surgical malignancies.

Methods

This meta-analysis was guided by the procedure proposed by Mahid and colleagues (13).

Study selection criteria and search strategy

Inclusion and exclusion criteria were defined in a review protocol. Eligible studies were those that compared breast and/or colorectal cancer incidence and/or cancer-specific death between patients with and without DM, in which the hazard ratio (HR) was a primary outcome measure. Studies that included patients with type I DM only were excluded. Studies investigating patients without known DM, but that assessed DM by diagnostic blood tests (such as insulin, glucose or homeostatic model assessment score) were included in the analysis.
In August 2012, Embase, PubMed and the Cochrane Library were searched using the search terms 'cancer incidence', 'cancer mortality', 'diabetes mellitus', 'insulin resistance', 'hyperinsulinemia', 'oncogenesis', 'carcinogenesis', 'neoplasmogenesis', 'breast tumor', 'colon tumor', 'oesophageal tumor', without year or language restrictions. Studies published between January 2007 and August 2012 with level I or II evidence according to the Oxford 2011 Levels of Evidence (14) (randomized clinical trials (RCTs), prospective cohort studies, pooled cohort studies), were included in the study. The methodological

quality of the included studies was assessed by means of the Jadad criteria for RCTs and the Newcastle–Ottawa scale for cohort studies (15,16).
Studies that seemed to fulfil the eligibility criteria and those for which information in the abstract was insufficient for exclusion were read in full. Bibliographies of included publications were searched for other studies and authors were contacted when additional unpublished data were needed for analysis.

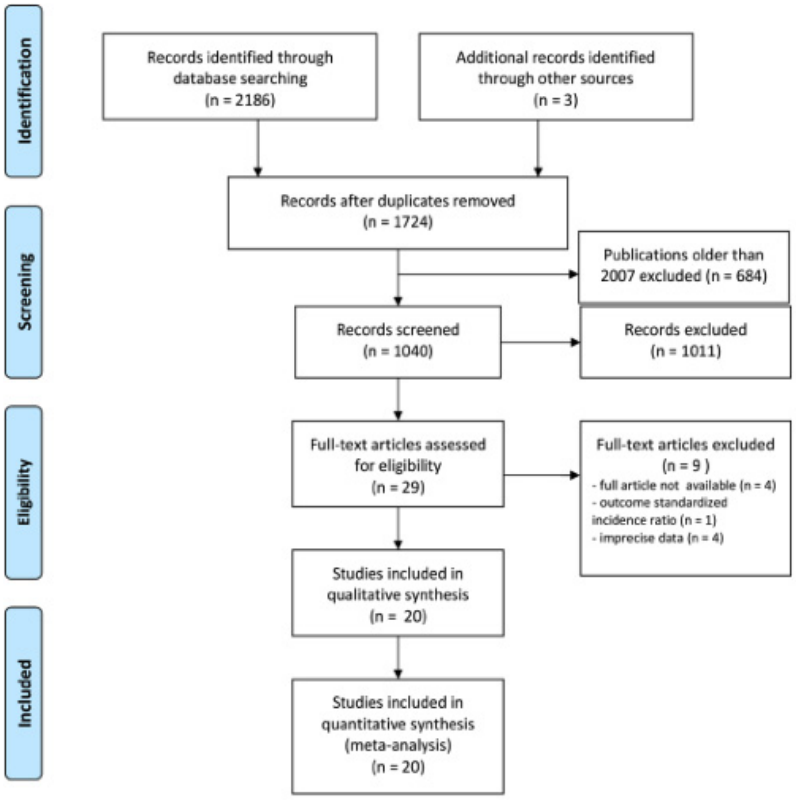
Data extraction
Two independent reviewers screened titles and abstracts, and full articles if necessary, of all citations retrieved from the searches and checked them for eligibility. Any disagreement was resolved until consensus was achieved.
The following data were extracted: HRs for breast and colorectal cancer incidence, and for breast and colorectal cancer-specific mortality, in patients with DM compared with those without. If available, the unadjusted HRs were selected for analysis. If unadjusted HRs were not available, the least adjusted HR was used. Multivariable adjusted HRs were pooled in additional analyses to compare them with the pooled unadjusted HRs. DM was defined by the criteria for the specific study.

Statistical analysis
Analyses were performed with Comprehensive Meta-analysis® software version 2 (Biostat, Englewood, New Jersey, USA) and RevMan 5.1 (http://ims.cochrane.org/revman/download). The pooled estimates for dichotomous variables are reported as HR with 95 per cent confidence interval (c.i.). Meta-analyses were conducted using a random-effects model. If a study contained subgroups of DM (such as quartiles) and consequently multiple HRs, one pooled HR was calculated from these subgroups and used in the final meta-analysis. If no HR was available, HRs and 95 per cent c.i. were calculated from the raw data and the mean follow-up of the study.
Between-study heterogeneity was assessed by means of the I^2 value, with 25, 50 and 75 per cent representing low, moderate and high heterogeneity respectively (17). Publication bias was assessed from funnel plots in which the log HR for each study was plotted against its standard error. Funnel plot symmetry was assessed both visually and formally with Egger's test.
Sensitivity analyses were carried out to investigate the influence of each study on the overall outcome of the meta-analysis. In addition, several subgroup analyses were conducted; the first compared the unadjusted and adjusted HRs, the second examined the effect of mode of assessing DM, and the third explored the impact of the mean follow-up time on the overall HR.

Results

A total of 20 studies published after 2007 were included in the meta-analysis, comprising 1 930 309 individuals with predominantly type II DM (*Fig. 1*).

Figure 1. PRISMA diagram showing selection of articles for review



Characteristics of the included studies are summarized in *Table 1*(18–37). There were 17 prospective cohort studies (18–24,27,29–37), one randomized trial (25), and two articles that described pooled analyses of cohort studies (26,28). It appeared that there was overlap between the latter two studies and one of the cohort studies (23). Nevertheless, these two studies used random and different samples from the total cohort. The total number of overlapping cancer cases and deaths may therefore be expected to be minimal and to have little influence on overall outcome. Thus, the potentially overlapping study (23) was not excluded from the analysis.

Six studies analysed the incidence of breast cancer, and six the incidence of colorectal cancer, in patients with DM. Eight studies examined the association between DM and breast cancer-specific mortality, and nine the association with colorectal cancer-specific mortality.

Table 1. Summary of included trials

Study	Country	Study quality*	Mean FU (years)	No. of patients	Diagnosis DM	Outcome	Hazard ratio
Redaniel et al.[18] (2012)	UK	8/9	9.88	82 867	Diagnosis in database or prescriptions of anti-DM drugs	Breast cancer risk	Unadjusted
Yeh et al.[19] (2012)	USA	9/9	17	18 280	Self-reported	- Breast and CR cancer incidence - Cancer case fatality	Multivariable adjusted
van de Poll et al.[20] (2012)	The Netherlands	8/9	NS	10 862	Hospital medical records	CRC-specific mortality	Unadjusted
Miao et al.[21] (2012)	Sweden	8/9	NS	25 476	HbA1C-level (>58mmol/mol)	Breast cancer incidence	Unadjusted
Dehal et al.[22] (2012)	USA	7/9	6.8	2278	Self-reported	CRC-specific mortality	Calculated
Dankner et al.[23] (2012)	Israel	8/9	21.9	1695	Insulin levels	Breast and CR cancer incidence	Adjusted for age and ethnicity
Liu et al.[24] (2011)	Sweden	7/9	7	16 123	Hospitalization for T2DM	Cause-specific mortality	Multivariable adjusted
Stefansdottir et al.[25] (2011)	The Netherlands	3 (Jadad)	5.0	11 140	HbA1C-level > 6.5%	Breast cancer incidence	Unadjusted
Seshasai et al.[26] (2011)	UK	-	13.6	820 900	Self-reported, medication use, fasting glucose level	Breast and CR cancer death	Multivariable adjusted
Morrison et al.[27] (2011)	UK	7/9	26.3	17 949	Self-reported, blood glucose levels, IGT	CRC death	Age adjusted
Lam et al.[28] (2011)	Asian Pacific Region	-	4.0	367 361	Self-reported, (fasting) blood glucose levels	Site specific cancer mortality	Age adjusted
Irwin et al.[29] (2011)	USA	8/9	6.0	604	C-peptide levels > 1.7nl/mL	Death from breast cancer	Age adjusted
Erickson et al.[30] (2011)	USA	9/9	10.3	3088	HbA1C-levels >6.5%	Breast cancer mortality	Calculated
Duggan et al.[31] (2011)	USA	7/9	6.4	527	HOMA-score > 1.04	Breast cancer mortality	Unadjusted

Zhou et al.[32] (2010)	Finland	6/9	15.8	44 655	Glucose tolerance status	Death from breast and CR cancer	Calculated
He et al.[33] (2010)	USA	6/9	NS	199 142	Self-reported	CRC incidence	Age adjusted
Campbell et al.[34] (2010)	USA	7/9	12.06	184 194	Self-reported	CRC incidence	Calculated
Flood et al.[35] (2010)	USA	6/9	8.4	45 516	Self-reported	CRC incidence	Age-adjusted
Ogunleye et al.[36] (2009)	Scotland	5/9	Diabetics: 3.9	19 154	Medical records	Breast and CR cancer incidence	Calculated
			Non-diabetics: 4.04				
van de Poll et al.[37] (2007)	The Netherlands	8/9	NS	58 498	Medical records	CRC death	Calculated

**Studies scored according to the Newcastle-Ottawa scale and Jadad-criteria. (FU = follow up, DM = diabetes mellitus, CR = colorectal, CRC = colorectal cancer, T2DM = type 2 diabetes mellitus, IGT = impaired glucose tolerance, HOMA = homeostatic model assessment, NS = not stated)*

Effect estimates

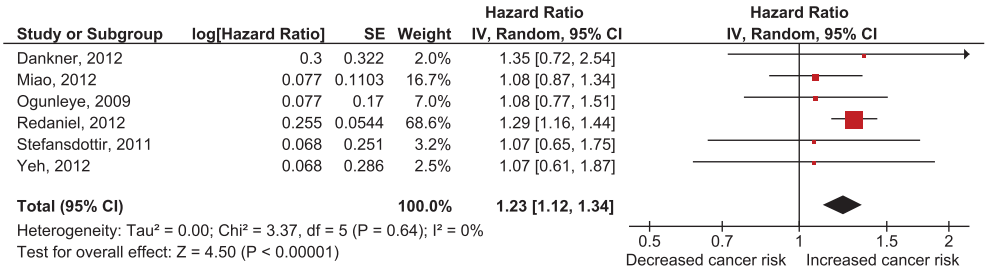
There was no heterogeneity among the 12 studies that reported the incidence of DM in patients with breast (I^2 = 0 per cent, P = 0.640) and colorectal (I^2 =13 per cent, P = 0.330) cancer. The studies that reported on breast cancer-specific mortality showed low heterogeneity (I^2 = 30 per cent, P = 0.190). Those reporting colorectal cancer-specific mortality showed moderate to high heterogeneity (I^2 =59 per cent, P = 0.010).

Primary outcomes

Incidence of breast cancer

Fig. 2 shows the result of meta-analysis of the six studies that reported on the incidence of breast cancer in patients with DM (18,19,21,23,25,36). The random-effects model showed an association between the incidence of breast cancer and DM (HR 1.23, 95 per cent c.i. 1.12 to 1.34; P < 0.001).

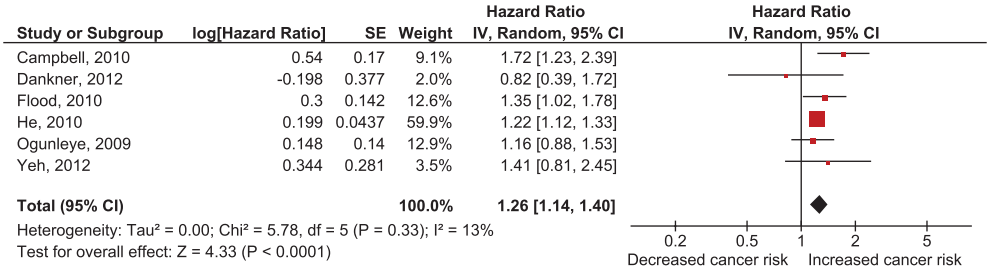
Figure 2. Meta-analysis of breast cancer incidence for patients with versus those without diabetes mellitus (DM). An inverse variance random-effects model was used. Hazard ratios (HRs) are shown with 95 per cent confidence intervals. s.e., Standard error.



Incidence of colorectal cancer

The result of meta-analysis of the six studies that reported on the incidence of colorectal cancer in patients with DM is shown in *Fig. 3* (19,23,33–36). The random-effects model demonstrated an association between colorectal cancer incidence and DM (HR 1.26, 1.14 to 1.40; $P < 0.001$).

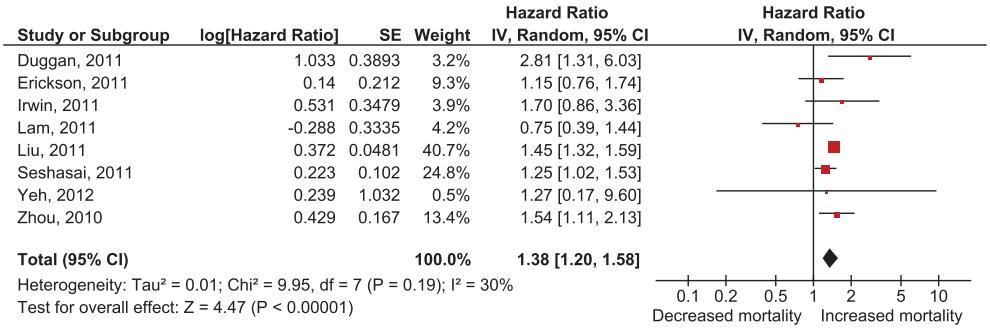
Figure 3. Meta-analysis of colorectal cancer incidence for patients with versus those without diabetes mellitus (DM). An inverse variance random-effects model was used. Hazard ratios (HRs) are shown with 95 per cent confidence intervals. s.e., Standard error.



Breast cancer-specific mortality

Fig. 4 shows the result of meta-analysis of the eight studies on breast cancer-specific mortality (19,24,26,28–32). The random-effects model showed that patients with DM had an increased breast cancer-specific mortality (HR 1.38, 1.20 to 1.58; $P < 0.001$).

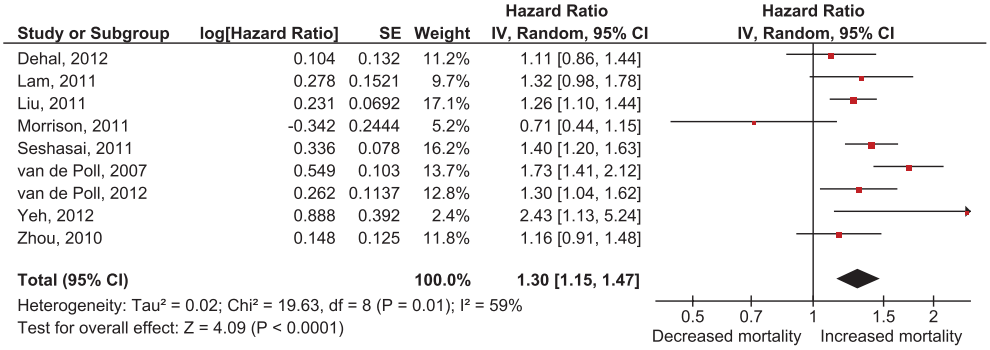
Figure 4. Meta-analysis of breast cancer-specific mortality for patients with versus those without diabetes mellitus (DM). An inverse variance random-effects model was used. Hazard ratios (HRs) are shown with 95 per cent confidence intervals. s.e., Standard error



Colorectal cancer-specific mortality

Meta-analysis of the nine studies that reported on colorectal cancer-specific mortality, using a random-effects model, demonstrated an increased risk of death due to colorectal cancer in patients with DM (HR 1.30, 1.15 to 1.47; $P < 0.001$) (*Fig. 5*) (19,20,22,24,26–28,32,37).

Figure 5. Meta-analysis of colorectal cancer-specific mortality for patients with versus those without diabetes mellitus (DM). An inverse variance random-effects model was used. Hazard ratios (HRs) are shown with 95 per cent confidence intervals. s.e., Standard error



Adjusted HRs

Additional analyses in which multivariable adjusted HRs were pooled did not change the results significantly (data not shown), except for a slightly attenuated overall HR for breast cancer incidence (HR 1.11, 1.00 to 1.23; $P = 0.050$).

Publication bias

For each study, the risk of publication bias was estimated by plotting the log HR against the corresponding standard error. In none of the meta-analyses did visual inspection of the funnel plots or application of Egger's test reveal asymmetry or a statistically significant regression intercept, indicating absence of publication bias (*Figs S1–S4*, supplemental material).

Sensitivity and subgroup analyses

Sensitivity analysis

To assess the influence of individual studies on overall outcome they were removed one by one. Removing the study of Redaniel and colleagues (18) decreased the HR for the incidence of breast cancer in the meta-analysis to 1.09 (0.93 to 1.28; $P = 0.268$). In meta-analyses of the incidence of colorectal cancer, breast cancer-specific mortality and colorectal cancer mortality the I^2 value decreased (to 0, 5 and 40 per cent respectively), albeit not significantly, by removing the studies reported by Campbell and colleagues (34), Lam and co-workers (28) and van de Poll-Franse *et al.* (37) respectively. Removing these studies did not have a significant impact on the overall HRs (data not shown).

Subgroup analysis of unadjusted and multivariable adjusted hazard ratios

A subgroup analysis was conducted for unadjusted and multivariable adjusted HRs. The studies that reported unadjusted HRs for the incidence of breast and colorectal cancer had an overall HR of 1.22 (1.11 to 1.34; $P < 0.001$)(18,21,25,36) and 1.28 (1.13 to 1.46; $P < 0.001$)(33–36) respectively for patients with *versus* without DM. Analysing adjusted HRs in the studies that reported on the incidence of breast and colorectal cancer did not alter these results significantly (*Table S1*, supplemental material).

The studies that reported adjusted HRs for breast cancer-specific mortality had an overall HR of 1.38 (1.23 to 1.55; $P < 0.001$)(19,24,26,28,29,32). For colorectal cancer-specific mortality the unadjusted and adjusted overall HRs remained increased: 1.32 (1.07 to 1.32; $P = 0.009$)(20,22,32,37) and 1.28 (1.07 to 1.53; $P = 0.008$)(19,24,26–28) respectively.

Subgroup analysis of mode of assessment of diabetes

A pooled HR was calculated for studies with self-reported or previously diagnosed DM and studies that used blood tests to assess DM. In the four meta-analyses the pooled HR remained increased for studies in which DM was self-reported (data not shown). When the studies that used blood tests to diagnose DM were combined, only the pooled HR for breast cancer mortality remained increased (HR 1.54, 1.14 to 2.07; $P = 0.004$)(29–32).

Subgroup analysis of follow-up time

This subgroup analysis explored the impact of a mean follow-up of 10 years or less, and more than 10 years. The pooled HR for breast cancer incidence and cancer-specific mortality in studies with a mean follow-up of 10 years or less was 1.26 (1.14 to 1.39; $P < 0.001$) and 1.30 (1.30 to 1.52; $P = 0.001$) respectively for patients with *versus* those without DM(18,24,25,28,29,31,36). Studies with follow-up of more than 10 years did not show an increased incidence and cancer-specific mortality for breast cancer among patients with DM.

The pooled HR for colorectal cancer incidence remained significantly increased in studies with a mean follow-up of 10 years or less (HR 1.49, 1.14 to 1.94; $P = 0.003$)(35, 36) and also in studies with follow-up of more than 10 years (HR 1.25, 1.03 to 1.52; $P = 0.030$)(19, 23, 24). For colorectal cancer mortality, the pooled HR remained significant only for patients with follow-up of more than 10 years (HR 1.24, 1.11 to 1.38; $P < 0.001$) (19,26,27,32).

Discussion

This meta-analysis showed that patients with DM have an increased risk for breast and colorectal cancer of 23 and 26 per cent respectively. A 38 per cent higher cancer-specific mortality in patients with diabetes and breast cancer, and a 30 per cent higher cancer-specific mortality in patients with diabetes and colorectal cancer, was demonstrated. The overall HRs for DM and cancer incidence and mortality were consistent for unadjusted and adjusted HRs. Finally, follow-up of more than 10 years confirmed an increased risk of colorectal cancer-specific mortality in patients with DM; for follow-up times of 10 years or less, there was a positive association between DM and breast cancer incidence and mortality, and colorectal cancer incidence.

The results for breast and colorectal cancer incidence in patients with DM are consistent with those of other meta-analyses (38–42). The present meta-analysis showed a higher risk and a stronger association between DM and cancer-specific mortality for breast and colorectal cancer than reported previously (40,43–45).

This meta-analysis had several limitations. First, not all included studies distinguished between type I and type II DM. The two types are associated with an increased risk for different cancers, and the underlying mechanisms promoting carcinogenesis might differ (46,47). The inclusion of individuals with type I DM could have led to an underestimation of the overall effect on cancer incidence and mortality. Second, the use of antidiabetic medication was not taken into account. There is evidence that metformin has a protective effect on breast cancer risk and colorectal cancer mortality, and recent studies have reported that insulin may increase cancer risk (48–51). Additionally, the

risk of cancer varies with the duration of DM and varying use of diabetes medication (52), but the study did not account for detection time bias. In this review multivariable adjusted HRs were pooled and these results did not differ essentially from those of analyses based on unadjusted HRs. The included studies showed no or moderate heterogeneity, and there was no evidence of publication bias. By calculating the overall outcome on the basis of HRs, the risk of selection bias with respect to the endpoints chosen was less than it would have been had relative risks been used (53), because HRs represent the instantaneous event rate.
It is suggested that future cohort studies should adjust for the type of DM (or only include individuals with type II DM), the duration of DM and the use of antidiabetic medication to further analyse the impact of DM on cancer incidence and mortality.

Acknowledgements
The authors thank H.-C. Yeh, X. Zhou and P. T. Campbell for providing additional data; W. Bramer for an extensive literature search; and K. Hagoort for editing.

Supplemental material

Figure S1. Funnel plot of studies reporting breast cancer incidence

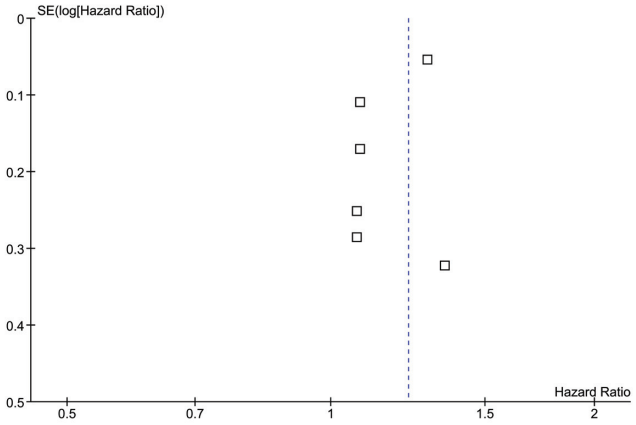


Figure S2. Funnel plot of studies reporting colorectal cancer incidence

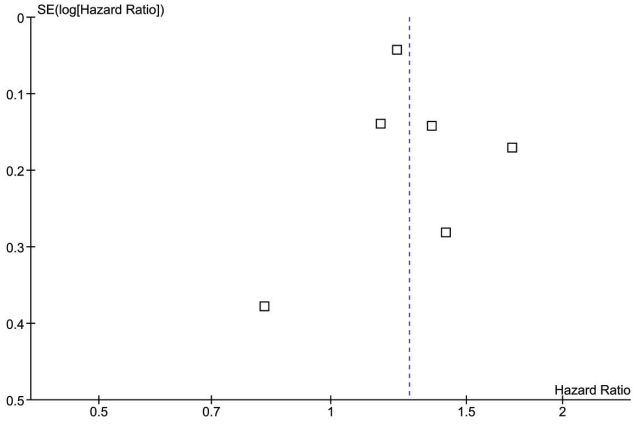


Figure S3. Funnel plot of studies reporting breast cancer-specific mortality

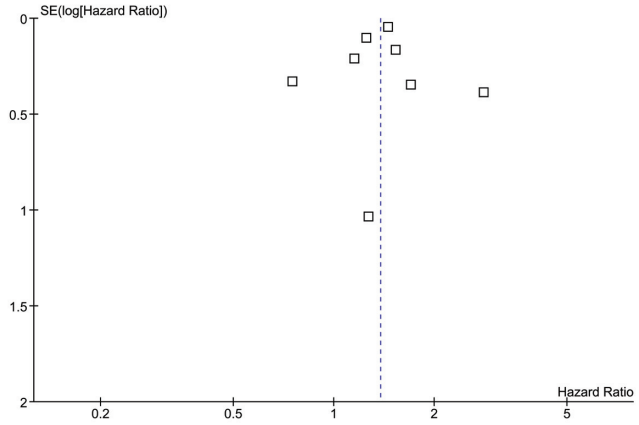


Figure S4. Funnel plot of studies reporting colorectal cancer-specific mortality

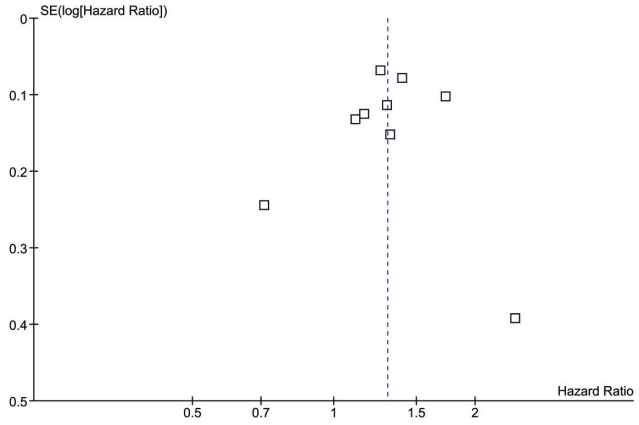


Table S1. Results of subgroup analysis of unadjusted and multivariable adjusted hazard ratios

	Overall HR, unadjusted	**Overall HR, multivariable adjusted**
Breast cancer incidence	HR 1.22 (95 per cent c.i. 1.11-1.34, P <0.001)[18,21,25,36]	HR 1.19 (95 per cent c.i. 0.78-1.80, P = 0.430)[19,23]
CRC incidence	HR 1.28 (95 per cent c.i. 1.13-1.46, P < 0.001)[33-36]	HR 1.14 (95 per cent c.i. 0.68-1.92, P = 0.620)[19,23]
Breast cancer mortality	HR 1.69 (95 per cent c.i. 0.71-4.03, P = 0.230)[30,31]	HR 1.38 (9% per cent c.i. 1.23-1.55, P <0.001)[19,24,26,28,29,32]
CRC mortality	HR 1.32 (95 per cent c.i. 1.07-1.32, P = 0.009)[20,22,32,37]	HR 1.28 (95 per cent c.i. 1.07-1.53, P = 0.008)[19,24,26-28]

CRC; colorectal cancer, HR; hazard ratio, c.i.; confidence interval

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Chapter 3 Detection bias may be the main cause of increased cancer incidence among diabetics: results from the Rotterdam Study

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Abstract

Aim

Type 2 diabetes is associated with an increased cancer risk. Most studies on this topic analyse diabetes as a risk factor without adjusting for diabetes duration before cancer occurrence. This study aimed to investigate the association between diabetes duration and cancer risk in more detail.

Methods

In this prospective cohort study, diabetes diagnosis was based on clinical information and use of glucose lowering medication. Details on incident cancers were obtained via general practitioners and linkage to pathology registers. Cox proportional hazards models were used with onset and duration of diabetes as time-varying determinants.

Results

The study comprised 10,181 individuals. Diabetes was associated with an increased overall risk of incident cancers (hazard ratio (HR) 1.2, 95% confidence interval (CI) 1.07-1.39) and pancreatic cancer (HR 2.9, 95% CI 1.75-4.89). A diagnosis of diabetes less than three months before the diagnosis of cancer was associated with strongly increased risks of all- (HR 3.3, 95%CI 2.50-4.32) and pancreatic cancers (HR 28.7, 95%CI 6.32-130.58).

Conclusions

The magnitude of the association between diabetes and an increased risk of cancer seems to be inflated by detection- or protopathic bias. Future studies investigating this association should adjust for diabetes duration and include a plausible aetiological risk window.

Introduction

There is increasing evidence that type 2 diabetes is associated with an increased risk of cancer (1). However, risk estimates vary per specific cancer site (2-7) and moreover, with regard to prostate cancer, diabetes seems to be a protective factor (8-10). Several possible mechanisms have been proposed as an explanation for the association between type 2 diabetes and the increased cancer risk (11). Obesity is a major acquired risk factor for diabetes as well as for cancer (12). Another possible mechanism is via hyperinsulinaemia - that exists in both diabetic and obese patients and that stimulates the insulin and insulin-like growth factor (IGF) axis (11). Furthermore, evidence suggests that certain oral glucose-lowering drugs (e.g. metformin) have a protective effect on cancer risk but that certain forms of insulin therapy may increase cancer risk (13-16).

Despite the growing body of evidence on the association between type 2 diabetes and an increased risk of cancer, several points should be emphasised. First, the association is complex as, for example, age and obesity are risk factors associated with both outcomes (1). Thus, it is important that studies should adjust for these potential confounders. Second, most observational studies on this topic analyse diabetes as a dichotomous risk factor without taking into account the moment of onset or duration of diabetes before cancer occurrence (1, 17). In this way, detection bias, to which the increased cancer risk has partially been attributed (18-20), cannot be assessed. To account for detection bias, duration of diabetes should be studied in more detail, with duration of diabetes divided into groups of increasing duration. In this way, impact of diabetes per time window can be assessed more accurately.

Finally, carcinogenesis is a slow and multistage process that develops over a period of several years (21). The latency and so-called sojourn periods differ per cancer type – and sometimes amount to a few decades – (22) thus making it difficult to analyse when diabetes has its impact in carcinogenesis.

We tested the hypothesis that the long-term exposure of diabetes in the elderly is associated with an increased risk of some cancers whereas increased risk associated with the peri-diagnosis of diabetes reflects biases like detection bias and protopathic bias. Therefore, the objective of this study was to investigate the association between diabetes duration and cancer risk in detail in order to confirm results with regard to detection bias and possibly resolve problems from earlier studies on this topic.

Patients and methods

Setting

Data were obtained from the Rotterdam Study, a large population-based prospective cohort study. The objectives and design were extensively described elsewhere (23, 24).

In brief, since 1990, inhabitants of the suburb Ommoord, aged 55 years or older were invited to participate. Of all 10,275 invited subjects 7983 entered the study (78%). In 2000, a second cohort with 3011 participants (of 4472 invitees, 67%) was added (Rotterdam Study II). Cancer cases were registered via the general practitioners, on the basis of discharge letters, and by linkage with the academic and regional laboratory for clinical pathology through a nationwide registry of histo- and cytopathology in the Netherlands (PALGA). The Rotterdam Study has been approved by the Medical Ethics Committee and all participants have received written and oral informed consent.

Definition of diabetes duration

Diabetes mellitus was diagnosed on the basis of a fasting plasma glucose level of ≥7.0 mmol/L (≥126 mg/dL), or non-fasting plasma glucose levels of ≥11.1 mmol/L (≥200 mg/dL), or use of blood glucose lowering medication. Date of onset of diabetes was estimated by reference to the date of first prescription of a glucose-lowering drug (Anatomical Therapeutical Chemical code (ATC-code) A10 (25)) based on linkage with pharmacies that serve the Ommoord district. Duration of diabetes was defined as the time interval between the date of onset of diabetes and the date of cancer diagnosis in cases and the same follow-up date in the remainder of the non-censored part of the cohort. Cohort members were censored on the date of first cancer, death or end of the study period, whichever came first.

Regarding the non-diabetic participants the follow-up period started at the moment of inclusion in the study, until the date of first cancer, death or end of the study period, whichever came first.

Outcome

The outcomes of interest were all incident cancers combined, further specified into separate models for the five most frequently occurring cancer types in the Rotterdam Study: breast cancer, prostate cancer, pancreatic cancer, lung cancer and colorectal cancer. With regard to the cancer diagnoses, haematological cancers and non-melanoma skin cancers (NMSC) were excluded. Cancers were classified according to the International Statistical Classification of Diseases and Related Health problems, 10th revision (ICD-10) (26) and the International Classification of Primary Care, 2nd edition (ICPC-2) (27). All cancer cases were confirmed by pathology records.

Covariables

The following baseline patient characteristics, all determined by baseline interview or during the visits to the examination centre, were considered as clinically relevant

confounders: age, sex, baseline body mass index (BMI; kg/m2), smoking status (never/former/current), current alcohol use (yes/no) and year of inclusion in the study. Additionally, educational level, income, prevalence of transient ischaemic attacks (TIA), myocardial infarction (MI), stroke (CVA), peripheral artery disease (PAD), cardiovascular disease (CVD), percutaneous transluminal coronary angioplasty (PTCA, yes/no) and coronary bypass (yes/no) were all individually assessed as potential confounders. If the variables changed the point estimate by more than 10% they were included in the final multivariable model. Ethnicity was not assessed as a confounder since 98% of the cohort was Caucasian.
Furthermore, in additional analyses use of glucose-lowering medication at baseline (metformin, insulin and SU-derivatives) was taken into account.

Statistical analysis
For each cohort participant, follow-up was defined in days starting from inclusion in the study until date of cancer diagnosis, death, or end of the study period (1st January, 2011), whichever came first. For comparison at baseline of normally distributed continuous variables, Student's t-test was used and for categorical variables Chi-square tests were used to assess differences between the diabetic and the non-diabetic population. A Cox regression analysis was carried out to assess the association between diabetes and cancer incidence with onset of diabetes as the time-dependent variable. Subsequently, Cox regression analyses were performed with duration of diabetes as a time-dependent determinant. Hereto, diabetes duration was divided into three mutually exclusive groups on the basis of duration of diabetes on the event date (incident diabetes with duration from 1 to 90 days, 91 days to 5 years, and > 5 years, respectively). Furthermore, separate analyses for the different incident cancers were performed. Multiple imputations (ten times) were used to assess the effect of missing values. *P*-values were considered significant if $p < 0.05$. All analyses were performed using SPSS software (SPSS Inc., version 21.0, Chicago, Illinois, United States of America (USA)).

Results
General characteristics
At baseline, 248 patients had a history of cancer and 565 patients had a diabetes diagnosis before start of the study. They were excluded, leaving 10,181 study participants of whom 4087 men (40%) and 6094 women (60%). Median age was 69 years (SD 9.7). Mean follow-up time was 11 years (SD 5.8 years). The mean BMI of the total cohort was 27 (SD 3.9).
A total of 906 participants were dispensed glucose-lowering drugs and they were considered to have diabetes (9%). In the age category of >65 to <75 years the incidence of incident diabetes was the highest (11%, table 1). There were 2238 patients (22%)

diagnosed with cancer. Table 1 further describes the general characteristics of the diabetic and non-diabetic participants at baseline. Supplementary figure 1 shows the flowchart of how many participants developed diabetes and cancer.

Table 1. General characteristics of the diabetic and non-diabetic participants at baseline.

		Non-diabetics	Diabetics	P-value
Total		9275 (91%)	906 (9%)	
Sex	**Female**	5560 (60%)	534 (59%)	0.56
	Male	3715 (40%)	372 (41%)	
Age		69 (mean)	68 (mean)	**0.00**
		(SD 9.8)	(SD 8.2)	
Age	**=>55 - <65**	4013 (91%)	390 (9%)	
	=>65 - <75	2687 (89%)	343 (11%)	
	=>75 - <85	1816 (93%)	142 (7%)	
	=>85 - <95	709 (96%)	31 (4%)	
	=>95	50 (100%)	0	
Follow-up time (years)		11 (mean)	13 (mean)	**0.00**
		(SD 5.8)	(SD 5.1)	
BMI		26 (mean)	29 (mean)	**0.00**
		(SD 3.8)	(SD 4)	
Smoking	**Never**	3140 (35%)	303 (34%)	0.75
	Former	3804 (43%)	389 (44%)	
	Current	1983 (22%)	194 (22%)	
TIA		94 (1.8%)	11 (1.7%)	0.93
MI		830 (14%)	104 (16%)	0.17
PTCA		52 (0.8%)	2 (0.3%)	0.24
Coronary bypass		134 (2.1%)	25 (3.8%)	**0.01**
PAD		1032 (19%)	88 (15%)	**0.02**
CVD		1899 (29%)	205 (30%)	0.48
CVA		202 (3.1%)	22 (3.2%)	0.87
Educational level	**Low**	5081 (55%)	527 (59%)	0.22
	Middle/ High	3777 (41%)	344 (38%)	
Income	**Low**	3796 (50%)	428 (55%)	**0.02**
	High	3733 (50%)	354 (45%)	
Cancer diagnosis	**Yes**	2086 (22%)	152 (17%)	**0.00**
	No	7189 (78%)	754 (83%)	

SD, standard deviation; BMI, body mass index; TIA, transient ischaemic attacks; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; PAD, peripheral artery disease; CVD, cardiovascular disease; CVA, cerebrovascular accident. Bold values indicate statistically significant results.

Risk of cancer in diabetic participants

The results of the univariable time-dependent Cox regression analyses are shown in table 2. Diabetes was associated with a statistically significantly elevated hazard ratio (HR) for all cancers, as well as for breast- and pancreatic cancer. In contrast, diabetes was associated with a decreased risk of prostate cancer albeit statistically non-significant. The results of the multivariable time-dependent Cox regression are also shown in table 2. No variable proved to be a statistically relevant confounder that changed the point estimate by more than 10%; therefore no additional variables were added to these multivariable models next to clinically relevant confounders as described in the methods section. HRs remained elevated for all cancers and for pancreatic cancer. Further adjustment for use of glucose-lowering medication at baseline (metformin, insulin and SU-derivatives) mainly altered the risks of cancer, especially when adjusted for use of metformin and SU-derivatives (supplementary table 1). However, numbers of cancer cases were small in these analyses, so accuracy of these results can be questioned.

Table 2. Uni- and multivariable time-dependent analysis.

Cancer type	Cases non-DM	Cases DM	Univariable analysis	Multivariable analysis
			HR	**HR**
All cancer	2086	152	**1.3**	**1.2**
			(95%CI 1.01-1.53)	**(95%CI 1.09-1.53)**
Breast cancer	2271	21	**1.7*†**	1.5*†
			(95%CI 1.08-2.65)	(95%CI 0.97-2.44)
Prostate cancer	329	12	0.6†	0.7†
			(95%CI 0.36-1.15)	(95%CI 0.37-1.18)
Pancreatic cancer	69	15	**3.4**	**3.6**
			(95%CI 1.93-6.02)	**(95%CI 1.98-6.41)**
Lung cancer	284	20	1.2	1.3
			(95%CI 0.73-1.82)	(95%CI 0.82-2.08)
Colon cancer	156	10	1.0	1.0
			(95%CI 0.54-1.97)	(95%CI 0.57-2.10)
Rectal cancer	67	7	1.9	2.0
			(95%CI 0.89-4.08)	(95%CI 0.90-4.50)
Rectosigmoid cancer	89	5	1.1	1.1
			(95%CI 0.42-2.61)	(95%CI 0.43-2.72)

Univariable analysis adjusted for age and sex.

Multivariable analysis adjusted for age, sex, BMI, smoking status, alcohol use and year of inclusion in the study.

Bold values indicate statistically significant associations.

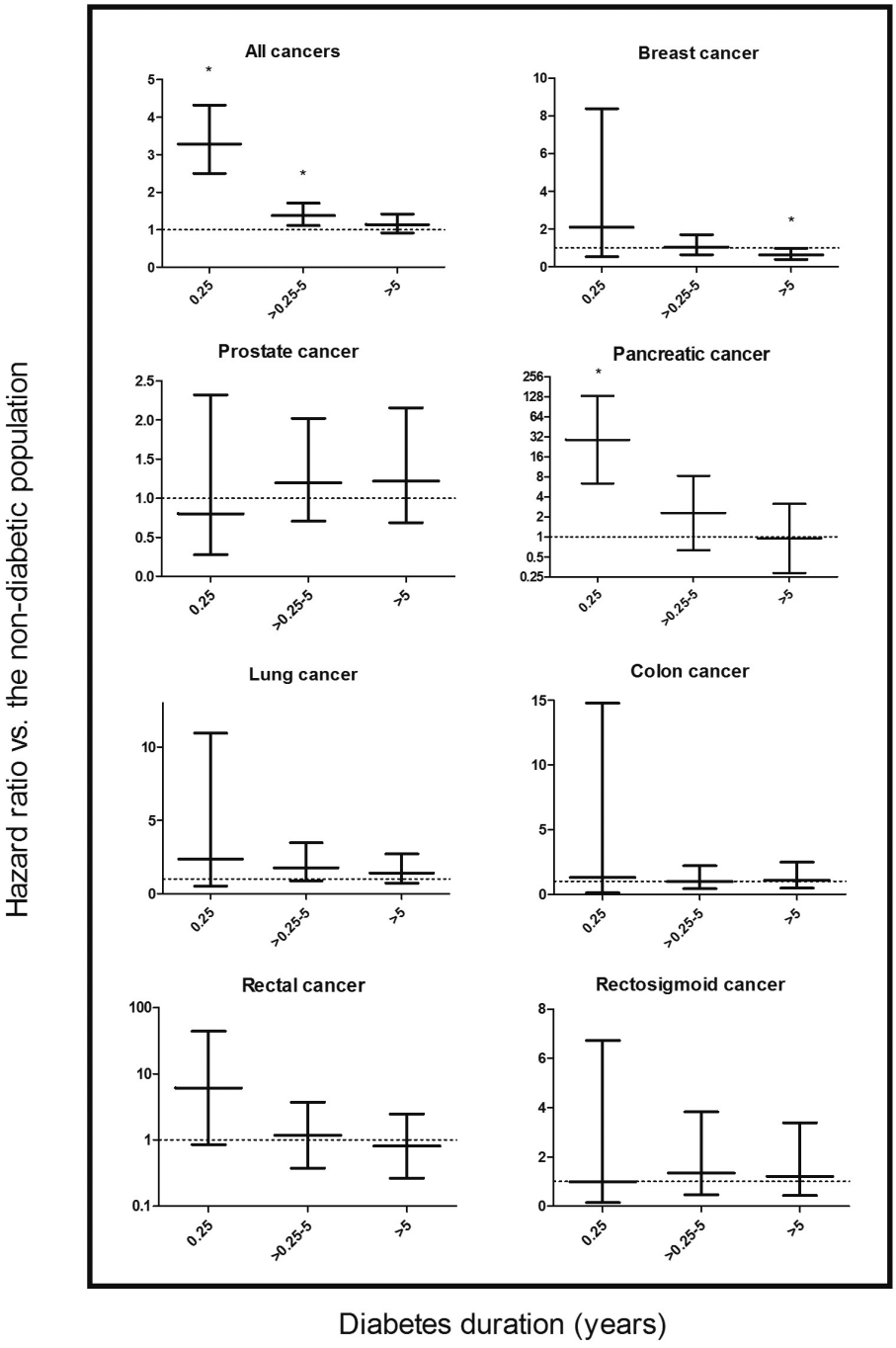
**Analysis in women only,*

† Not adjusted for sex

Analyses accounting for diabetes duration

The results from the additional model in which diabetes duration was divided into three groups are shown in figure 1. Within three months of a diabetes diagnosis the HR for all cancers was 3.3 (95% confidence interval (CI) 2.50-4.32) and for pancreatic cancer 28.7 (95%CI 6.32-130.58). The risk of all cancers remained statistically significantly increased among diabetic patients when diabetes duration was between three months and five years (HR 1.4, 95%CI 1.11-1.71) but not when the diabetes duration was more than five years (HR 1.1, 95%CI 0.92-1.41). Regarding pancreatic cancer the risk remained elevated when diabetes duration was between three months and five years, albeit non-significantly (HR 2.3, 95%CI 0.63-8.30). For a diabetes duration of more than five years no increased risk of pancreatic cancer could be found (HR 1.0, 95%CI 0.29-3.15). The risk of breast cancer was borderline statistically significantly decreased for a duration of diabetes of more than five years (HR 0.6, 95%CI 0.39-0.99) but not for a diabetes duration between three months and five years (HR 1.1, 95%CI 0.64-1.70).

*Figure 1: multivariable model of duration of diabetes exposure. Adjusted for age, sex, BMI, smoking status, alcohol use and year of inclusion in the study. Prostate and breast cancer not adjusted for sex, breast cancer analysis in women only. *Indicates statistically significant result.*



Discussion

In this prospective population-based follow-up study, we hypothesised that there would be an increased risk of cancer among people with diabetes but that this risk would vary by duration of diabetes. The incidence of diabetes was 9%, which is similar to the rate of diabetes in another Dutch study on diabetes and cancer (28). Overall, the risk of cancer was increased by 20% among participants with diabetes. Duration of diabetes of less than three months before a cancer diagnosis was associated with a threefold increased risk of all cancer while a diabetes duration between three months and five years was associated with a much lower increased risk of all cancers of 40%. This high risk shortly after starting glucose-lowering drugs is probably explained by detection bias or protopathic bias. Diabetes was associated with a more than threefold increased risk of pancreatic cancer but this was mainly explained by a peak within 3 months before diagnosis and probably also a result of detection bias because after longer durations of diabetes, the risk of pancreatic cancer declined and rendered statistically not significant.

Earlier literature showed increased overall cancer risks varying from 14% to 56% (19, 29-31). However, not all of these studies investigated diabetes duration extensively. Regarding breast cancer, earlier studies also described conflicting results. A study from 2011 (18) found a non-significant trend towards an increased breast cancer risk within three months of diabetes diagnosis which might be caused by detection or protopathic bias. In another study, no increased risk of breast cancer was found (19). However, both studies did not adjust for BMI which is important as shown earlier (12).

Concerning pancreatic cancer, our results are conflicting with two studies investigating diabetes duration and pancreatic cancer that found significantly elevated risks with longer durations of diabetes (32, 33). Another study also found a decrease towards a protective effect in pancreatic cancer risk by increasing duration of type 2 diabetes (19). However, only one adjusted for BMI (33).

Regarding the protective effect that diabetes appears to have on prostate cancer, our study only showed a trend toward this phenomenon. Other studies on prostate cancer and diabetes reported a decreased risk by increasing duration of diabetes (19, 34), whereas in our study the risk increased (albeit non-significantly).

The protective effect seen in breast cancer after a diabetes diagnosis of more than five years is unexpected. We hypothesise that a possible explanation for this phenomenon might be that some tumors are not sensitive to insulin and thus will not experience IR and IGF-R up regulation. Thus, the PI3K-, MAPK- and mTOR-pathways will not be activated and carcinogenesis will not be stimulated, no matter what period of time.

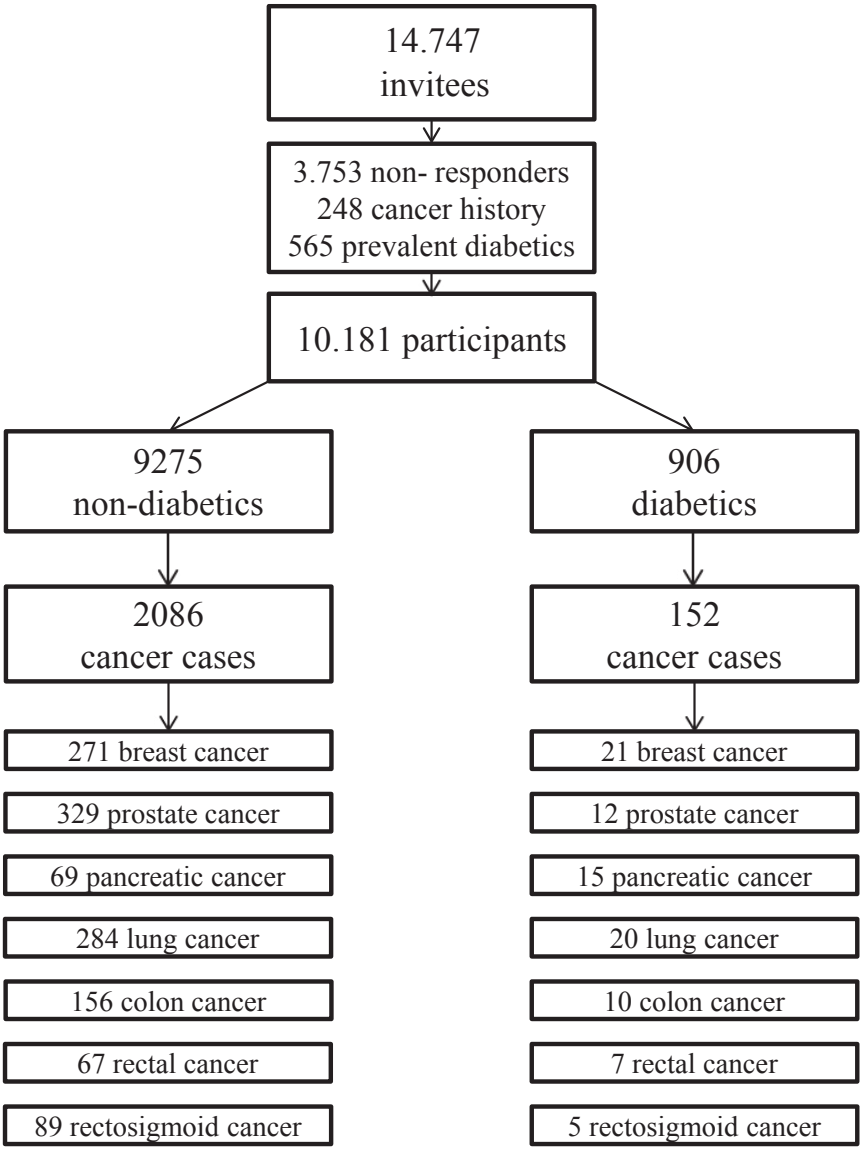
Strengths and limitations

Strengths of this study are the large number of patients, the long follow-up period and its prospective design. Furthermore, this study was able to adjust for the most important confounders and thus aimed to examine diabetes as an independent risk factor for cancer. Also, effects of use of glucose-lowering drugs at baseline were assessed; however results of these analyses need to be interpreted with caution due to small numbers of cancer cases. The time-dependent analyses with adjustment for diabetes duration further increase the strength of the results. A limitation of this study is that no distinction could be made between type 1 and type 2 diabetes. However, only participants aged 55 years or older were included, so it can be assumed that in participants with incident diabetes, everyone was of type 2. Additionally, because of the 70%-response rate in the Rotterdam Study, the possibility exists that diabetes is underreported if the non-responders tend to be diabetic more often. Alas, information about these non-responders is unknown. Furthermore, the time-dependent analysis also revealed potential detection- or protopathic bias because a diagnosis of incident diabetes made during the three-month period before the cancer diagnosis date was associated with an increased hazard ratio for cancer of even 3.3. Lastly, a latency or a so-called sojourn period is important. As mentioned in the introduction, these time periods differ per cancer type, making it difficult to determine a correct aetiological risk window to analyse when diabetes has its possible impact on carcinogenesis.

In conclusion, this study showed that risk of cancer varies with the duration of diabetes. The magnitude of the association between diabetes and increased risk of cancer seems to be inflated by detection- or protopathic bias. Future studies investigating this association should take into account the duration of diabetes and a plausible etiological risk window.

Supplemental material

Supplementary figure 1. Flowchart of how many participants developed diabetes and cancer.



Supplementary table 1. Multivariable time-dependent analysis.

Cancer type	Cancer cases	Adjusted for Metformin (n = 304) HR	Cancer cases	Adjusted for SU (n = 544) HR	Cancer cases	Adjusted for Insulin (n = 45) HR
All cancer	277	**1.5 (95%CI 1.24-1.74)**	116	**2.0 (95%CI 1.64-2.54)**	8	**1.3 (95%CI 1.12-1.57)**
Breast cancer	5	**1.8*† (95%CI 1.12-2.79)**	16	**2.4*† (95%CI 1.35-4.39)**	0	**1.6*† (95%CI 1.02-2.56)**
Prostate cancer	1	0.8† (95%CI 0.42-1.36)	11	1.1† (95%CI 0.54-2.27)	0	0.7† (95%CI 0.39-1.24)
Pancreatic cancer	3	**3.9 (95%CI 2.13-7.16)**	11	**4.3 (95%CI 1.83-10.24)**	1	**3.5 (95%CI 1.93-6.39)**
Lung cancer	3	1.5 (95%CI 0.96-2.45)	13	**2.2 (95%CI 1.24-4.02)**	4	1.2 (95%CI 0.74-1.95)
Colon cancer	0	1.4 (95%CI 0.70-2.59)	10	1.2 (95%CI 0.48-2.85)	0	1.2 (95%CI 0.60-2.22)
Rectal cancer	1	**2.3 (95%CI 1.02-5.21)**	6	2.1 (95%CI 0.68-6.54)	0	2.1 (95%CI 0.93-4.70)
Rectosigmoid cancer	1	1.2 (95%CI 0.48-3.07)	4	1.9 (95%CI 0.58-6.05)	0	1.2 (95%CI 0.46-2.89)

Adjusted for age, sex, BMI, smoking status, alcohol use and year of inclusion in the study. Prostate and breast cancer not adjusted for sex, breast cancer analysis in women only. Further adjusted for baseline use of metformin, SU-derivatives or insulin. Bold values indicate statistically significant associations.

**Analysis in women only*

† Not adjusted for sex

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Chapter 4 Absence or low IGF-1R-expression in esophageal adenocarcinoma is associated with tumor invasiveness and radicality of surgical resection

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Abstract

Background and Objectives

Esophageal adenocarcinoma (EAC) incidence increases, maybe due to increasing prevalences of obesity and diabetes. Concurrent hyperinsulinemia might promote carcinogenesis via the insulin-like growth factor-I –receptor (IGF-1R). Expression of the IGF-1R was studied in correlation with diabetes and prognostic parameters.

Methods

Patients with EAC undergoing esophagectomy were prospectively selected. From resected tumors a tissue microarray was constructed. Immunohistochemistry evaluated IGF-1R-expression. Logistic-, cox regression models and survival analyses assessed if diabetes and IGF-1R-expression were associated with prognostic parameters. IGF-1R-expression in normal and Barrett tissues was studied.

Results

Absence or low IGF-1R-expression was associated with T3-, grade 3 tumors and R1 resections (P= 0.001, P=0.025, P < 0.001, respectively). Logistic regression showed that this was associated with R1 resections (HR 0.24, 95%CI 0.11-0.52). Diabetes was not associated with IGF-1R-expression (P=0.612). Absence or low IGF-1R-expression decreased five-year overall survival (P= 0.023) univariably, but not multivariably. IGF-1R-expression was present in Barrett tissues, but diminished in high-grade dysplasia.

Conclusions

Absence or low expression of IGF-1R was associated with high grade- and advanced tumors and less radical resections. IGF-1R might be a tumor marker in Barrett's esophagus since a change in expression patterns was found in the course from normal esophageal tissue to adenocarcinoma.

Introduction

In 2012, the estimated overall number of new incident esophageal cancer cases was 456.000, thereby being the eight most common cancer worldwide. It was the sixth most common cause of death from cancer with 400.000 deaths annually (1). Over the past decades the incidence of esophageal adenocarcinoma (EAC) has increased in Western countries, while the incidence of esophageal squamous cell carcinoma (ESCC) remains stable or even decreases (2). An explanation for this shift in incidences might be the increasing prevalence of obesity in the Western world (3). Overweight and obesity are strongly associated with an increased risk of EAC (4,5). Additionally, as a result of the increasingly obese population, the prevalence of diabetes mellitus (DM) rises as well (6). In the past years, obesity and DM have been associated with an increased risk of several cancers and higher cancer mortality (3,7-11). Obesity is thought to increase cancer risk because of the endocrine function of adipose tissue and its release of peptide hormones and sex-steroid metabolizing enzymes. The hyperinsulinemia present in obese patients is also held responsible (3). In DM, hyperinsulinemia is also thought to increase cancer risk (12).

Thus, both obesity and DM are associated with increased insulin levels that are thought to promote carcinogenesis via the upregulation of the insulin-like growth factor-I (IGF-1R) and the insulin receptor (IR) (12). Both receptors possess tyrosine kinase activity and exert their effects via the (PI3K)/AKT-, MAPK- and mTOR-pathways which can result in enhanced cell proliferation and reduced apoptosis (12). Overexpression of IGF-1R has been reported in several solid tumors, like breast, bladder and colon cancer, although with conflicting results, so the clinical and prognostic significance of the overexpression remains unclear (13,14).

Regarding EAC less is known about IGF-1R expression and its relation to carcinogenesis and prognosis. Also, the link between DM and esophageal carcinoma is not as clearly established as it is for some other cancers. Studies report conflicting results varying from an increased risk for EAC among diabetics to no increased risk at all (15-18).

Thus, this study assessed the expression of IGF-1R in EAC. Secondly, IGF-1R-expression was correlated with DM, prognostic parameters and survival. Additionally, normal esophageal tissues and (dysplastic) Barrett tissues were studied, hypothesizing that expression patterns change with malignant transformation. In this way IGF-1R was studied as a potential tumor marker and predictive tool for patients with Barrett's esophagus.

Materials and Methods

Patient selection

All patients were treated at the Department of Surgery of the Erasmus MC University Medical Center in Rotterdam, The Netherlands. All patients with EAC who underwent potentially curative resection between January 1995 and December 2005 were identified from a prospectively maintained institutional database. Complete data on tumor grade, clinical- and pathological staging, (neo)adjuvant treatment, patients' demographics and comorbidities were registered. Body mass index (BMI), presence of DM and other comorbidities were retrospectively confirmed via review of medical records since these were not routinely recorded in the database. The TNM and grading classification according to the UICC (*Union Internationale Contre le Cancer, 2009, 7th edition)* was used to assess pathological tumor stage and tumor grade. Radicality was defined as R0- and R1-resections, with an R0-resection having a resection margin >1mm (radical resection) and an R1 resection having a resection margin =< 1mm (no radical resection). In addition, 28 samples from 20 patients (who underwent endoscopic mucosal resection (EMR)) or esophagectomy between January 2008 and January 2014) containing normal esophageal tissue, non-dysplastic or dysplastic Barrett mucosa were studied. Apart from EMR and in some cases esophagectomy, these patients did not receive any other treatment.

Medical ethical approval was obtained for the study.

Tissue microarray

A tissue microarray was constructed. Formalin-fixed, paraffin-embedded tumor blocks were obtained from the Department of Pathology at the Erasmus University Medical Center in Rotterdam, The Netherlands. For each patient, up to six tumor cores (Ø 1 mm each) were taken from the original blocks. Furthermore, an effort was made to include multiple sides of the original tumor, including central parts of the tumor and tumor tissue at the invasive front.

Immunohistochemistry

The TMA slides were deparaffinized, rehydrated and antigen retrieval was carried out by boiling in Tris-EDTA buffer, pH 9.0. After a blocking step with H_2O_2, slides were incubated with a primary mouse monoclonal antibody against IGF-1R. Visualization of the bound antibodies was done with the Dako REAL™ EnVision™ Detection System, Peroxidase/DAB+, Rabbit/Mouse (Dako, Agilent Technologies Inc, Glostrup, Denmark). Slides were counterstained with hematoxylin and coverslipped. Normal human pancreas was used as the positive control and in the negative control the antibody

against IGF-1R was omitted. A photo of the positive control can be found in figure 1. A pathologist specialized on GI pathology (KBI) scored the immunohistochemically stained slides, blinded from the clinical data. Thereby, the staining was scored as 'absent or low expression' or 'high expression'. 'High expression' was defined as intense staining in at least 10% of the cells of interest (dysplastic or carcinoma cells), as used in an earlier study on IGF-1R expression (19). Membranous or cytoplasmatic localization of the IGF-1R was also scored. The normal esophageal tissues, non-dysplastic and the low- and high grade dysplastic Barrett tissues that were used for comparison of IGF-1R expression went through the same staining and scoring process.

Statistical analysis

Only patients with at least 50% useful cores were included in the analyses in order to ensure more reliable measurements. A core was not useful if it did not contain tumor tissue or when large artefacts were present. A mean value of the scores of the used cores was calculated to obtain one overall value per patient for the IGF-1R-expression. These mean values were subdivided into absent or low and high expression (e.g. when 3 out of 5 cores were positive the mean value was expressed as 'high expression' and when 3 out of 5 cores were negative the mean value was expressed as 'absent or low expression').

The student's T-test was used for comparison of continuous baseline variables, while the Chi-square test was used for categorical variables. Fisher's Exact test was used when cells in crosstabulations contained less than 5 observations.

Multilevel logistic regression, in the form of a generalized linear mixed model, was used in order to account for multiple and varying numbers of measurements per patient (20). Thus, in these analyses patients with less than 50% of their cores usable were included. Correlations between repeated measurements were accounted for by including a patient specific random intercept in the models. Variables that were considered as clinically relevant confounders were first analyzed in a univariable analysis. These were age, sex, BMI, DM, neoadjuvant therapy, grading, T-stage, N-stage and insulin use. These predictors were subsequently included in a multivariable model when their P-values were < 0.20. Finally, predictors with a P-value < 0.05 were fitted in a multivariable model. Age and sex were always included regardless of their significance level. With regard to T-stage, T3 and T4 were taken together because of small numbers of T4.

Cox regression was used to assess the influence of DM, IGF-expression on the five-year overall and disease free survival. Independent variables were entered into the equation in one step, according to the Enter method. Finally, Kaplan Meier analyses were performed and by means of the log-rank test possible differences in five-year overall and disease free survival were evaluated. All statistical tests were 2-sided and P-values < 0.05 were

considered statistically significant. Statistical analyses were performed with SPSS version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) and SAS version 9.3, TSM1M1.

Results

Baseline characteristics

The cohort comprised a total of 348 patients. At the time of this analysis, median follow-up was 90.7 months (range 36.3 –199.7 months). Baseline characteristics are shown in table 1.

After exclusion of patients with less than 50% of their tissue cores useful, 270 patients remained for the final analyses. Of these patients, 47% (127 of 270 patients) had a mean high expression of IGF-1R, as described in the methods section. A total of 25 patients had 100% of their cores positive and 23 patients had 100% of their cores negative. Differences between the patients with mean absent or low and high expression of IGF-1R are shown in table 1.

Cytoplasmatic as well as membranous localization of the IGF-1R appeared to occur in all scored cores; therefore no further analyses based on localization were performed.

Information on DM was lacking for two patients. The remaining diabetic and non-diabetic patients in this cohort did not differ in baseline characteristics, except for BMI, which was higher in the diabetic population (mean BMI 26.8 (SD 3.4) vs. 29.6 (SD 3.9), $P < 0.001$), and cardiovascular diseases (CVD), that occurred more frequently in diabetic patients (12.7% vs. 31.6%, $P=0.037$).

Table 1. Baseline characteristics.

		Total population	<50% cores useful	No or low IGF-1R	High IGF-1R	P-value
Total		348	78			
Sex	**male**	302 (87%)	70 (90%)	123 (86%)	112 (88%)	
	female	46 (13%)	8 (10%)	20 (14%)	15 (12%)	0.595
Age (mean)		63.4 (SD 10.3)	62 (SD 9.4)	62.8 (SD 11.0)	64.8 (SD 9.9)	0.121
Dead	**yes**	266 (76%)	46 (59%)	119 (83%)	101 (80%)	
	no	82 (24%)	32 (41%)	24 (17%)	26 (21%)	0.436
BMI (mean)		27.2 (SD 3.6)	27 (SD 3.2)	27.5 (SD 3.7)	27 (SD 3.6)	0.340
DM (2 missing)		38 (11%)	10 (13%)	16 (11%)	12 (9%)	0.612
CVD		51 (15%)	9 (12%)	22 (15%)	20 (16%)	0.565
Pulmonary disease		40 (12%)	8 (10%)	10 (7%)	22 (17%)	**0.032**
CVA/TIA		20 (6%)	3 (4%)	8 (6%)	9 (7%)	0.877
Hypertension		81 (23%)	17 (22%)	35 (25%)	29 (23%)	0.949
Smoking		80 (23%)	21 (27%)	29 (20%)	30 (24%)	0.797

Neoadjuvant therapy		72 (21%)	38 (49%)	21 (15%)	13 (10%)	0.271
Chemotherapy		70 (20%)	37 (47%)	20 (14%)	13 (10%)	0.348
Radiotherapy		33 (10%)	25 (32%)	7 (5%)	1 (1%)	0.070
Adjuvant therapy		5 (1%)	0	3 (2%)	2 (2%)	1.000
Pathological T-stage	**0**	9 (3%)	8 (10%)	0	1 (1%)	
	1	49 (14%)	24 (31%)	10 (7%)	15 (12%)	
	2	61 (18%)	17 (22%)	15 (11%)	29 (23%)	
	3	227 (65%)	29 (37%)	117 (82%)	81 (64%)	
	4	2 (1%)	0	1 (1%)	1 (1%)	**0.017**
N-stage (8 missing)	**0**	146 (42%)	48 (62%)	48 (34%)	50 (41%)	
	1	73 (21%)	17 (22%)	31 (22%)	25 (21%)	
	2	68 (20%)	8 (10%)	33 (24%)	27 (22%)	
	3	53 (15%)	5 (6%)	28 (20%)	20 (16%)	0.709
Tumor location	**upper 1/3**	3 (1%)	1 (1%)	2 (1%)	0	
	middle 1/3	19 (6%)	8 (10%)	5 (4%)	6 (5%)	
	lower 1/3	130 (37%)	29 (37%)	55 (39%)	46 (36%)	
	GEJ	196 (56%)	40 (51%)	81 (57%)	75 (59%)	0.535
IGF-R (mean) (n=270)	**Abs/low**	143 (53%)	-	-	-	
	high	127 (47%)	-	-	-	-
Grading	**1**	20 (6%)	11 (14%)	3 (2%)	6 (5%)	
	2	143 (41%)	34 (44%)	52 (36%)	60 (47%)	
	3	176 (51%)	29 (37%)	87 (61%)	60 (47%)	0.133
Radicality	**RO**	251 (72%)	69 (89%)	81 (57%)	101 (80%)	
	R1	97 (28%)	9 (12%)	62 (43%)	26 (21%)	**0.000**

BMI: body mass index, DM: diabetes mellitus, CVD: cardiovascular disease, CVA: cerebrovascular accident, TIA: transient ischemic attack, GEJ: gastro-esophageal junction. Abs: absent. P-values indicate difference between groups with absent or low or high IGF-1R expression. Bold numbers indicate statistically significant results.

Receptor expression; patient and tumor characteristics

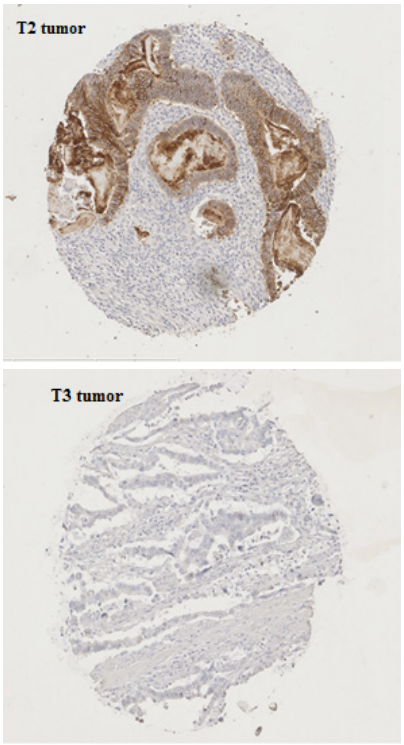
Diabetes

The presence of DM was not significantly associated with T-stage, N-stage, radicality, grading and expression of IGF-1R (data not shown).

IGF-1R-expression

High expression of IGF-1R was associated with T2 tumors (P=0.006) and R0 resections (P < 0.001). Absence or low expression of IGF-1R was associated with T3 tumors, R1 resections and grade 3 tumors (P=0.001, P < 0.001 and P=0.025 respectively). An example of clear and absent expression is shown in figure 1.

Figure 1. Difference in expression pattern in a T2 and T3 tumor. T2-tumor shows clear expression of IGF-1R, whereas in the T3-tumor IGF-1R expression is absent. Hematoxylin staining, magnification 100x. The third photo shows the positive control of normal pancreatic tissue.



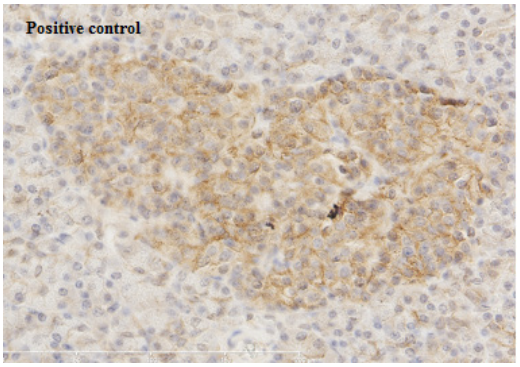


Table 2 shows the results of the generalized linear mixed model (n=338), which showed that radicality was the only significant factor associated with IGF-1R-expression.

Table 2. **Generalized linear mixed model for IGF-1R-expression (n=338).**

		Univariable analysis	First multivariable model	Final multivariable model
		OR (95%CI)	**OR (95%CI)**	**OR (95%CI)**
Age		1.02 (0.98-1.05)	1.02 (0.98-1.05)	1.02 (0.99-1.05)
Sex		1.36 (0.48-3.89)	1.20 (0.43-3.34)	1.09 (0.39-3.05)
BMI		0.95 (0.86-1.06)	*	
DM		0.46 (0.15-1.46)	0.53 (0.18-1.62)	**
Neoadjuvant		0.56 (0.22-1.43)	*	
pT	**1**	Reference category	Reference category	**
	2	1.77 (0.48-6.54)	2.03 (0.06-7.47)	
	3/4	0.38 (0.13-1.15)	0.64 (0.20-2.07)	
pN	**0**	Reference category	*	
	1	0.71 (0.28-1.82)		
	2	0.53 (0.21-1.37)		
	3	0.57 (0.21-1.54)		
Grading	**1**	Reference category	Reference category	**
	2	0.43 (0.10-2.80)	0.63 (0.10-4.02)	
	3	0.20 (0.03-1.30)	0.40 (0.06-2.62)	
Radical resection	**yes**	0.24 (0.11-0.52)	0.41 (0.18-0.96)	**0.24 (0.11-0.52)**
Insulin use		2.21 (0.33-14.89)	*	

*DM = diabetes mellitus, NA = not applicable *P-value not under 0.200 in univariable analysis.*

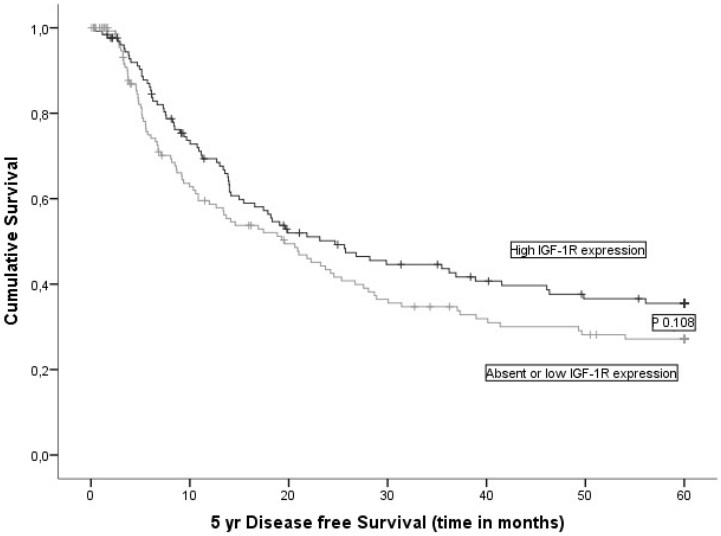
**P-value not under 0.05 in the first multivariable model. Bold numbers indicate statistically significant results.*

Survival

Disease free survival

Survival curves showed that the one-year disease free survival was 59% among the patients with absent or low IGF-1R expression and 69% among the patients with high IGF-1R expression. IGF-1R expression was not significantly associated with five-year disease free survival; only a trend towards a decreased disease free survival among patients with absent or low IGF-1R expression was seen (P=0.108, figure 2). The life table can be found in supplemental table 1.

Figure 2. Survival curves of the five-year disease free survival regarding IGF-1R expression (n=270).

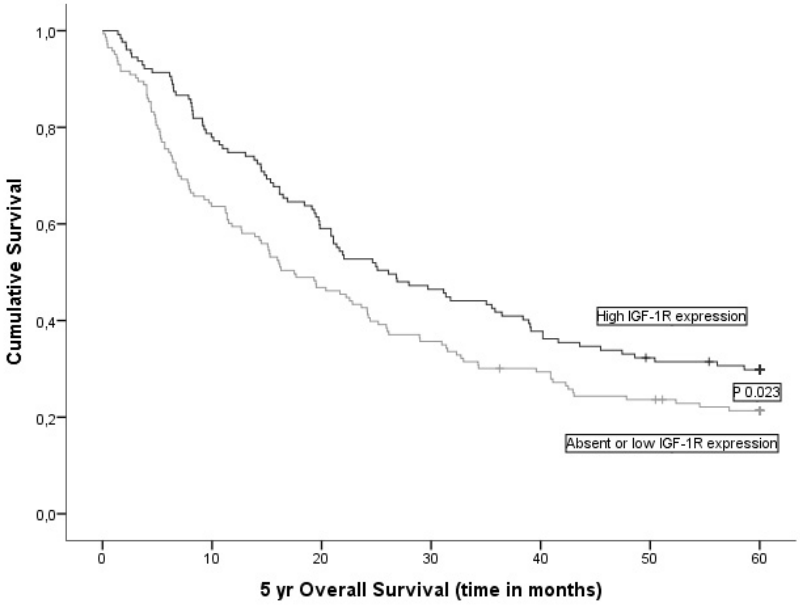


The univariable cox regression model with age, sex and DM showed that DM was not associated with five-year disease free survival (HR 0.89, *P*=0.641, 95%CI 0.56-1.43). The multivariable model showed that DM, adjuvant therapy, pN2 and pN3 were significantly associated with decreased disease free survival (Table 3).

Overall survival

Survival curves showed that the one-year overall survival was 60% for patients with absent or low IGF-1R expression and 75% for patients with high IGF-1R expression. The absence or low expression of IGF-1R was significantly associated with a decreased five-year overall survival (*P*=0.023, figure 3). The life table can be found in supplemental table 2.

Figure 3. Survival curves of the five-year overall survival regarding IGF-1R expression (n=270).



The model with age, sex and DM showed that DM did not have a significant effect on the five-year overall survival (HR 1.01, *P*=0.684, 95%CI 0.73-1.61). In the multivariable model age, pT3/pT4 and pN3 were significantly associated with a decreased five-year overall survival (Table 3).

Table 3. Results of the multivariable cox regression for disease free (DFS) and overall survival (OS).

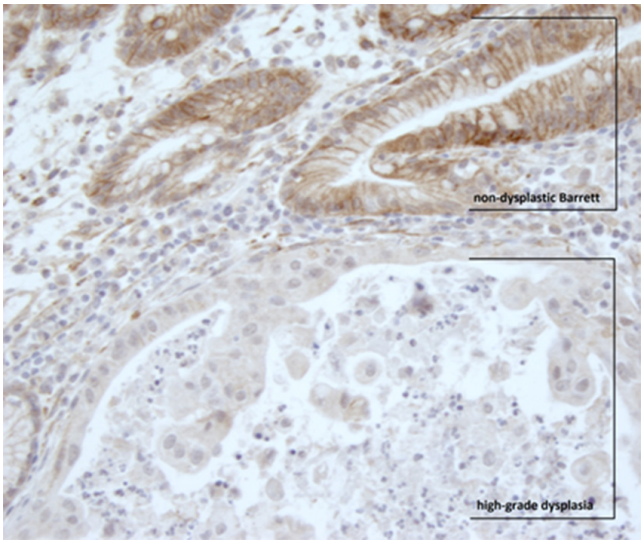
		Five-year DFS	Five-year OS
		HR (95%CI)	**HR (95%CI)**
Sex		1.43 (0.85-2.42)	1.07 (0.65-1.75)
Age		1.02 (1.00-1.04)	**1.03 (1.01-1.05)**
BMI		1.03 (0.98-1.09)	1.01 (0.96-1.06)
DM		**0.51 (0.26-0.99)**	0.65 (0.37-1.16)
CVD		1.15 (0.62-2.14)	1.30 (0.77-2.20)
PD		0.81 (0.55-1.18)	1.04 (0.73-1.47)
Smoking		1.23 (0.84-1.80)	0.96 (0.68-1.36)
Neoadjuvant therapy		0.76 (0.44-1.32)	0.71 (0.43-1.16)
Adjuvant therapy		**3.82 (1.22-11.89)**	2.22 (0.74-6.66)
Grading	**1**	Reference category	Reference category
	2	2.08 (0.47-9.14)	1.26 (0.37-4.27)
	3	3.06 (0.70-13.36)	1.95 (0.58-6.53)
T-stage	**1**	Reference category	Reference category
	2	0.91 (0.31-2.69)	1.28 (0.49-3.38)
	3/4	2.48 (0.94-6.57)	**3.12 (1.29-7.53)**
N-stage	**0**	Reference category	Reference category
	1	1.67 (0.93-3.00)	1.37 (0.82-2.28)
	2	**1.88 (1.07-3.32)**	1.55 (0.95-2.55)
	3	**2.81 (1.54-5.13)**	**2.27 (1.35-3.83)**
Radical resection	**yes**	1.12 (0.72-1.69)	1.19 (0.81-1.74)
IGF-1R expression		0.81 (0.55-1.20)	0.80 (0.56-1.13)

CVD= cardiovascular disease, PD= pulmonary disease. Bold numbers indicate statistically significant results. All variables in the table were included in the model.

Normal esophageal tissue, Barrett and dysplastic tissue

To study a possible change in the expression pattern of IGF-1R from normal esophageal tissue to invasive adenocarcinoma, 28 additional tissue slides containing normal, non-dysplastic and dysplastic Barrett tissue were studied. In the 11 slides that contained normal squamous esophageal epithelium no IGF-1R expression was found. In the 23 slides that contained non-dysplastic Barrett tissue in all a strong expression was seen. In 11 high-grade dysplastic tissues IGF-1R expression became negative (figure 4), where in one high-grade dysplastic sample a mixed expression was seen.

Figure 4. Changing expression pattern of IGF-1R expression in resected esophageal tissue. Evident expression in non-dysplastic Barrett tissue, diminished expression in high-grade dysplasia. Hematoxylin staining, magnification 400x.



Discussion

The present study described that 47% of the EAC tumors had high expression of the IGF-1R. Other studies regarding expression of IGF-1R report percentages varying from 52% - 82% (21-24). However, two of these studies also included ESCC and did not describe EAC separately (22,23).

Furthermore, in the present study high IGF-1R expression was associated with R0 resections and T2 tumors whereas absent or low IGF-1R expression was associated with T3 and grade 3 tumors and R1-resections. In Kaplan Meier analyses, absent or low IGF-1R-expression in EAC tumors was associated with decreased five-year overall survival, but in multivariable analysis this difference could no longer be seen.

These results are partially in conflict with the results from earlier studies. One study found no association between IGF-1R expression in EAC and tumor stage and survival (25). A study from 2011 (21) found no significant differences between IGF-1R expression and invasion, tumor stage and tumor differentiation. Results regarding disease-specific survival remained inconclusive. A third study (22) described that IGF-1R expression was a predictor of poor prognostic outcome in EAC. IGF-1R overexpression showed to be associated with invasion depth and overall survival. The explanation for these conflicting results might be the high proportion (65%) of T3 tumors in the present study. Not all of the studies above described the distribution of T-stage (22) and if T-stage was described, percentages and numbers of T3 tumors were (much) lower (58%, n = 128 and 38%, n = 36, respectively) (21,25). Furthermore, the fact that in the present study IGF-1R-expression was significantly different with respect to overall survival but not with disease-free survival might be explained by the five-year time span that was taken; this might be too long to detect significant differences with regard to disease-free survival since recurrence mostly presents earlier. However, significant results regarding overall survival were no longer present in multivariable cox regression.

Our study is not unique in finding lower expression levels at advanced tumor stages: in breast and colorectal cancer this phenomenon has also been described (19,26,27). Also, the decrease in expression might be due to the dedifferentiation process to which cancer cells are exposed; by becoming more invasive the expression of the IGF-1R gets lost (27). On the other hand, IGF-1 is a differentiation factor. Thus, the loss of IGF-1R may be responsible for the observed appearance of more primitive and invasive tumors. This is in accordance with the decreased prognosis in patients with negative receptor expression found in the present study.

This study found clear expression of IGF-1R in non-dysplastic Barrett tissue, which became negative in high grade dysplastic Barrett tissues. This might indicate that IGF-1R is involved in the malignant transformation of Barrett's esophagus or as discussed above, that loss of the expression of the IGF-1R blocks further differentiation of the Barrett cells. Another study investigating the expression of IGF-1R during the progression of Barrett's associated neoplasia showed contradictory results (24); in the course from Barrett's esophagus to EAC, increasing expression of IGF-1R was found. One explanation could be that in the present study the tumors were not proven to arise in Barrett's esophagus and most tumors were advanced (65% was staged T3). In the study of Iravani et al (24) all tumors developed in Barrett's-associated neoplasia and the percentage of T3 tumors was low (35%). Another explanation for the difference could be that the percentages given in the study of Iravani are based on the intensity of the staining and not on absence or presence of IGF-1R expression. Nevertheless, further studies are

needed to investigate the expression of IGF-1R in the course from Barrett's esophagus to high-grade dysplasia.

Several factors have already been studied as prognostic markers for neoplastic progression in Barrett (28) and for survival in EAC. A meta-analysis found that COX-2, HER-2 and p53 appeared promising markers for the prediction of overall survival in EAC. Overexpression of COX-2 and HER-2 were associated with decreased survival, where expression of p53 was associated with a better prognosis because of its tumor suppressor function (29). Another study provided a biomarker panel consisting of EGFR, TRIM44 and SIRT2 that was correlated with overall survival in patients with EAC (30).

The present study could stimulate further research on the IGF-1R being an additional marker for neoplastic progression in Barrett's esophagus and for survival in EAC. If the IGF-1R could ultimately be established as a marker, patients with expression of IGF-1R might then benefit from IGF-inhibiting therapies.

In this study only EACs and not ESCCs were investigated; it has been described that expression of IGF-1R is different in EAC than in ESCC (31). Probably in ESCC a different molecular pathway may be responsible for carcinogenesis. Furthermore, information on tumor stage, tumor grade and radicality was complete for almost every patient. Limitations of this study should be addressed. First, this study only included patients that were selected for surgery in a tertiairy referral center, thus a selection bias could have been present. Second, patients with esophageal cancer frequently suffer from severe weight loss and might find themselves in a catabolic state pre- and peroperatively. It is known that generalized malnutrition or protein depletion reduces tissue IGF-1 mRNA (32), so this could have influenced our results in a way that findings regarding IGF-1R expression were lower because of possible malnutrition of patients. Third, it has been seen that with increasing age a natural decline in IGF-1 occurs (33). With a mean age of 63.4 years found in this study it is possible that levels of IGF-1R expression were further lowered. However, the mean age of the groups with and without IGF-1R expression was not significantly different from each other and by adjusting for age in the generalized linear mixed model and the cox regression we partially corrected for this effect. Furthermore, interactions with IGF-1R and the abovementioned p53 and HER-2 have been described (34,35). Thus, the possibility exists that changes in expression of IGF-1R were due to changes in p53 and/or HER-2 expression during carcinogenesis.

Lastly, one of the aims of this study was to assess the influence of DM on IGF-1R expression. Because obesity being a risk factor for EAC - with the risk being increased up to three times (3,11) - we could not fully adjust for the fact that obesity itself can contribute to cancer development. Adipose tissue, and especially visceral adipose tissue, is known to cause hyperinsulinemia and higher circulating levels of IGF-1 (3,25). Thus, the

true influence of DM on the expression of IGF-IR levels could not be assessed.

Conclusions

Absence or low IGF-1R expression in EAC tumors was associated with high grade and advanced tumors, less radical resections and decreased five-year overall survival in univariable analyses. IGF-1R might be a possible additional tumor marker for carcinogenesis in Barrett's esophagus since a change in expression patterns was found in the course from normal esophageal tissue to invasive adenocarcinoma. Future studies should further investigate the expression of IGF-1R and its exact role in the development from Barrett tissue to EAC. Ultimately, this receptor could be used as an additional tumor marker for neoplastic progression in Barrett and for survival in EAC and use of IGF-inhibiting therapies might become beneficial.

Supplemental material

Supplemental table 1. Life table showing numbers at risk and events for five-year disease free survival.

Interval start time (months)	Number entering interval	Number withdrawing during interval	Number exposed to risk	Number of terminal events	Proportion terminating	Cumulative proportion surviving at end of interval
Abs/low IGF						
0	143	20	133	52	39%	61%
12	71	3	69.5	18	26%	45%
24	50	2	49	10	20%	36%
36	38	1	37.5	5	13%	31%
48	32	2	31	3	10%	28%
High IGF						
0	127	10	122	37	30%	70%
12	80	3	78.5	22	28%	50%
24	55	3	53.5	7	13%	44%
36	45	2	44	6	14%	38%
48	37	2	36	2	6%	36%

Abs: absent

Supplemental table 2. Life table showing numbers at risk and events for five-year overall survival.

Interval start time (months)	Number entering interval	Number withdrawing during interval	Number exposed to risk	Number of terminal events	Proportion terminating	Cumulative proportion surviving at end of interval
Abs/low IGF						
0	143	0	143	58	14%	59%
12	85	0	85	24	28%	43%
24	61	0	61	18	30%	30%
36	43	1	42.5	9	21%	24%
48	33	2	32	3	9%	21%
High IGF						
0	127	0	127	32	25%	75%
12	95	0	95	28	29%	53%
24	67	0	67	14	21%	42%
36	53	0	53	11	21%	33%
48	42	2	41	4	10%	30%

Abs: absent

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Chapter 5 Diabetes mellitus does not affect chances for surgery and overall survival in patients with esophageal adenocarcinoma

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Submitted

Abstract

Background

The incidence of esophageal adenocarcinoma (EAC) is rising, probably due to a higher prevalence of obesity. EAC still has a dismal prognosis despite improved surgical techniques. As a result of the increase in obesity, there is also an increase in diabetes mellitus (DM). This study therefore investigated the influence of DM on the treatment of patients with EAC and whether DM influences mortality.

Methods

All patients with EAC, newly diagnosed between 1998 and 2012, were selected from the Eindhoven Cancer Registry. Cox proportional hazards models assessed the influence of DM on the treatment of patients with EAC and time dependent cox proportional hazards models determined the influence of DM and surgery on mortality.

Results

A total of 2,729 patients were diagnosed with EAC of whom 426 (16%) were diagnosed with DM. During the study period there was a clear increase of patients with DM. The presence of DM significantly reduced the chance of surgical treatment in univariate analyses (HR 0.81, 95%CI 0.67-0.97), but not in multivariable analyses (HR 0.92, 95%CI 0.76-1.12). DM did not have any influence on overall mortality (HR 1.11, 95%CI 0.99-1.24). Surgery decreased overall mortality; diabetics had an HR of 0.32 (95%CI 0.29-0.36) and non-diabetics and HR of 0.38 (95%CI 0.30-0.49). The difference between these groups was not significant (*P* 0.210).

Conclusions

After adjustment for age, DM did not decrease the number of patients undergoing a surgical treatment for EAC. DM had no effect on overall mortality of these patients. This could probably be explained by the overall dismal prognosis of EAC.

Introduction

The incidence of esophageal cancer has increased over the past decades. This is most likely the result of the increased incidence of esophageal adenocarcinoma (EAC), since the incidence of esophageal squamous cell carcinoma (ESCC) has remained stable or even decreased (1). A reason for this shift in incidence is thought to be the increased prevalence of obesity in the Western world (2) since studies have proven that obesity is associated with an increased risk of EAC (3, 4). Obesity has been associated with Barrett's esophagus and EAC because of increased intra-abdominal pressure, which may promote gastro-esophageal reflux (5, 6). In addition, the prevalence of diabetes (DM) also increases due to this rise of obesity (7). Although DM has been linked to cancer development in several cancers (8-10), for esophageal cancer, studies report conflicting results varying from an increased risk for EAC among diabetics to no increased risk at all (11-14). It is thought that hyperinsulinemia, present in patients with obesity and DM, upregulates the insulin receptor (IR) and the insulin-like growth factor-I receptor (IGF-1R). As a result, carcinogenesis is stimulated and prognosis might be influenced (15). Because of the increasing incidence of EAC and the potential association between DM and EAC – with obesity as a shared risk factor-, it is important to investigate the implications that DM might have on the treatment of EAC and its prognosis.
Esophageal carcinoma still has a dismal prognosis despite improved surgery techniques; the five-year survival rate remains only 30% after curatively intended surgery (16). Only 25% of the patients diagnosed with esophageal carcinoma are eligible and selected for surgery (16). An important reason for exclusion from surgery is not only the presence of metastatic disease but also a poor physical health, often due to comorbidities (17, 18). But because of the improved surgery techniques and postoperative care it is important that physicians carefully evaluate patients with comorbidities, to prevent underuse of esophagectomy (17). Because of the close link with obesity (and subsequent DM), the present study only investigated EAC. The aim of this study was to assess the possible implications that DM might have with regard to surgery and overall mortality in EAC.

Methods

Data sources

Data were obtained from the Eindhoven Cancer Registry (ECR) which is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). The ECR records data on all patients newly diagnosed with cancer in the Southern part of the Netherlands, an area with 2.4 million inhabitants. Six pathology departments, 10 community hospitals, and two radiotherapy departments notify the registry. Trained registration clerks actively collect data on patient characteristics, cancer diagnosis, staging, comorbidity at cancer

diagnosis and initial treatment from hospital medical records. Serious comorbidity that could be of influence on prognosis has been recorded in the ECR for all patients since 1993. Information on initial surgery within nine months after the cancer diagnosis (surgery date and operation type) is also collected. The ECR is recognised as high quality source for epidemiological research in the Netherlands (19).

Patient selection

For the present study only patients with EAC, newly diagnosed between 1998 and 2012, were studied (n=3102). A diagnosis of EAC was coded according to the International Classification of Diseases for Oncology (ICD-O-1, ICD-O-2 and ICD-O-3) (20). The TNM classification according to the UICC (Union Internationale Contre le Cancer, edition 4.2, 5, 6 and 7) was used to assess pathological tumor stage. All comorbidities that were present at the time of cancer diagnosis were recorded according to an adapted version of the Charlson comorbidity index (21). All comorbid conditions were scored as a dichotomous variable (yes/no). Cardiovascular disease (CVD) included myocardial infarction, cardiac insufficiency, angina pectoris, coronary artery bypass graft, peripheral artery disease, cerebrovascular diseases and hypertension. DM comprised both type 1 and type 2. Patients with missing information on DM were excluded (n=373; 12%).

Statistical analysis

Follow-up started from the date of cancer diagnosis until the end of the follow-up (death or end of study period (December 31, 2013), whichever came first). Additionally, time to initial surgery was calculated from the date of the cancer diagnosis until the date of operation.

For comparison at baseline of normally distributed continuous variables, the Student's t-test was used and for categorical variables Chi-square tests were used to assess differences between the diabetic and the non-diabetic patients, and between the operated and the non-operated patients.

The influence of age on the chance of surgery was studied with a fractional polynomial model. Cox proportional hazards models were carried out to assess if DM was of influence on chances to undergo surgery. The effect of a priori established clinically relevant confounders (DM, age, sex, lung disease, CVD and CVA (cerebrovascular accident)/hemiplegia) on chances to undergo surgery was assessed in multivariable models.

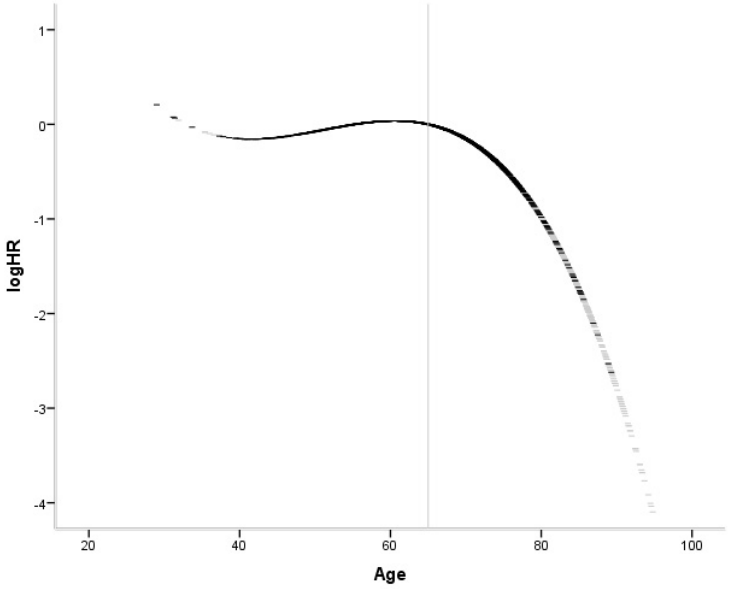
For surgery status survival curves were constructed by using a clock-reset approach, divided into two strata. Stratum one contained patients without surgery who were at risk until time of death or end of follow up. Patients who got operated were in the first

stratum until they got operated; they switched to the second stratum at the time of their surgery and were censored in the first stratum from that time. In the second stratum the time of surgery was then reset as time for the patients' further follow-up in the surgery group, which ended at death or end of follow-up. Both strata were then subdivided into diabetic and non-diabetic groups.
Furthermore, the differences between the survival curves in the no-surgery and surgery groups were assessed with cox proportional hazards regression analyses with time to surgery as the time-dependent variable. Additionally, differences between the diabetic and the non-diabetic patients were analyzed, thereby creating an interaction between DM and the time-dependent variable. By means of likelihood ratio tests survival between the groups was compared. Within the surgery group the effect of a priori established clinically relevant confounders (DM, age, sex, lung disease, CVD and CVA/hemiplegia) on mortality was assessed in multivariable cox proportional hazards models.
All statistical tests were 2-sided and P-values < 0.05 were considered statistically significant. All analyses were performed using SPSS software (SPSS Inc., version 21.0, Chicago, Illinois, USA).

Results

After exclusion of the 373 patients with unknown DM status, the final cohort consisted of 2729 patients. The majority of the patients was male (n=2202, 81%). Mean age was 67.7 (SD 11.6) and mean follow-up was 1.6 years (SD 2.4). A total of 2334 patients (86%) died within the follow-up period. The overall rate of surgical intervention was 34% (n=934). It appeared that the incidence of DM significantly increased over time in the studied cohort. In the group of patients with a cancer diagnosis between 1998 and July 2005 the incidence of DM was 13% (n=140), while in the group of patients with a cancer diagnosis from July 2005 until 2012 the incidence was 18% (n=286) (P=0.001).
A threshold for age and surgery was determined with a fractional polynomial model. Figure 1 shows that patients older than 65 years of age were operated less often.

Figure 1. Scatterplot showing cutoff point for surgery at age 65. After 65 years of age the chance of receiving surgery decreased. – No Surgery, - Surgery.



Diabetes vs. no diabetes

In table 1 the baseline characteristics for the total cohort according to DM status are presented. A percentage of 16% (n=426) was diagnosed with DM. Diabetic patients were significantly older (and more often > 65 years of age), had shorter survival, were operated less often and received less neoadjuvant therapy. Diabetic patients also suffered more from comorbidities and had lower socioeconomic status.

Table 1. Baseline characteristics of the total cohort of esophageal adenocarcinoma patients diagnosed between 1998 and 2012. P-value corresponds with the differences between the diabetic and non-diabetic population.

		DM (n=426)	non-DM (n=2303)	P-value
Sex	**Male**	336 (79%)	1866 (81%)	
	Female	90 (21%)	437 (19%)	0.301
Age (mean)		71.3 (SD 9.9)	67.1 (SD 11.8)	**0.000**
Deceased		374 (88%)	1960 (85%)	0.148
Survival (years, mean)		1.4 (SD 2.0)	1.7 (SD 2.4)	**0.029**
T-stage	**TX**	2 (2%)	44 (5%)	0.209
	Tis	0 (0%)	5 (1%)	
	T0	8 (7%)	50 (6%)	
	T1	26 (22%)	150 (19%)	
	T2	29 (24%)	252 (31%)	
	T3	54 (45%)	292 (36%)	
	T4	2 (2%)	19 (2%)	
N-stage	**NX**	16 (13%)	98 (12%)	0.148
	N0	40 (33%)	291 (36%)	
	N1	46 (38%)	350 (43%)	
	N2	16 (13%)	55 (7%)	
	N3	3 (3%)	18 (2%)	
M-stage	**M0**	77 (77%)	479 (70%)	0.336
	M1	13 (13%)	110 (16%)	
	Unknown (MX)	10 (10%)	96 (14%)	
Surgery		122 (29%)	812 (35%)	**0.008**
Surgery	**TTE**	30 (25%)	217 (27%)	0.836
	THE	35 (29%)	237 (29%)	
	Unknown	57 (47%)	358 (44%)	
Neo-adj	**No**	84 (20%)	510 (22%)	**0.004**
	Rtx	2 (1%)	2 (0%)	
	Ctx-Rtx	25 (6%)	245 (11%)	
	Ctx	11 (3%)	55 (2%)	
Comorbid conditions				
	Lung disease	77 (18%)	307 (13%)	**0.010**
	CVD	209 (49%)	761 (33%)	**0.000**
	CVA/hemiplegia	39 (9%)	105 (5%)	**0.000**
SES	**low**	122 (29%)	539 (24%)	**0.010**
	middle	156 (37%)	901 (40%)	
	high	110 (26%)	686 (31%)	
	institutionalized	32 (8%)	111 (5%)	

TTE: transthoracic esophagectomy, THE: transhiatal esophagectomy, Neo-adj: neo-adjuvant therapy, Rtx: radiotherapy, Ctx: chemotherapy, CVD: cardiovascular disease, HT: hypertension, CVA: cerebrovascular accident, SES: socioeconomic status. TNM-stage was only available for the operated patients. Bold numbers indicate statistically significant differences between both groups.

Diabetes and surgery

The univariate cox proportional hazards model showed that diabetic patients were operated significantly less often compared to non-diabetic patients (HR 0.81, table 2). After adjustment for age the effect of DM on the hazard of receiving surgery disappeared; age under or above 65 years appeared to be the variable with the most effect on the chances of receiving surgery. After age adjustment the effect of DM on the hazard of receiving surgery disappeared. Interactions with DM and age, sex, lung disease, CVD and CVA/hemiplegia were not significant (data not shown).

Table 2. Results of the cox proportional hazards model for the hazard of receiving surgery.

	Univariate analysis	**2nd model**	**3rd model (n=2729)**
	HR (95%CI)	**HR (95%CI)**	**HR (95%CI)**
DM diagnosis yes/no	**0.81 (0.67-0.97)**	0.88 (0.72-1.06)	0.92 (0.76-1.12)
Age 65 yes/no	NA	**0.62 (0.55-0.71)**	**0.67 (0.58-0.76)**
Sex	NA	0.91 (0.77-1.08)	0.88 (0.74-1.04)
Lung disease yes/no	NA	NA	0.87 (0.71-1.07)
CVD yes/no	NA	NA	**0.83 (0.71-0.97)**
CVA/hemiplegia	NA	NA	**0.67 (0.46-0.98)**

DM: diabetes mellitus, CVD: cardiovascular disease, CVA: cerebrovascular accident. Bold numbers indicate statistically significant results.

Diabetes and postoperative overall mortality

To assess the effect of surgery and DM on postoperative overall mortality a time dependent cox proportional hazards model for postoperative overall mortality was performed stratified for DM-status and adjusted for age, sex, lung disease CVD and CVA (table 3). Operated diabetic patients had lower overall mortality compared to non-operated diabetic patients (HR 0.32, 95%CI 0.28-0.35, $P<0.001$, univariate model, HR 0.32, 95%CI 0.29-0.36, $P<0.001$ multivariable model table 3). Similar results were seen for operated non-diabetic patients compared to non-operated non-diabetic patients (HR 0.37, 95%CI 0.29-0.48, $P<0.001$, univariate model, HR 0.38, 95%CI 0.30-0.49, $P<0.001$ multivariable model table 3). The difference between these two operated groups however, was not significant ($P=0.210$) as established via the interaction with DM and the time dependent variable.

Diabetes and overall mortality

Diabetic patients did not have different overall mortality compared to the non-diabetic patients (HR 1.11, $P=0.066$, 95%CI 0.99-1.24, univariate analysis) when surgery was not

taken into account. The crude overall survival for diabetic patients was 39% at 1 year and 11% at 5 year, while for non-diabetic patients this was 44% at 1 year and 13% at 5 year. Non-operated diabetic patients had an HR for overall mortality of 1.01 (95%CI 0.89-1.15, *P*=0.873) for overall mortality in the univariate model compared to non-operated non-diabetic patients (HR 1.04, 95%CI 0.91-1.18, *P*=0.569, multivariable model table 3). Only age was a significantly associated with mortality in the multivariable model (HR1.11, 95%CI 1.01-1.21, *P*=0.027 table 3). Further interactions with the time dependent variable and age, sex, lung disease, CVD and CVA/hemiplegia were not significant.

Table 3. Results of the multivariate time dependent cox proportional hazards model on mortality (n=2729).

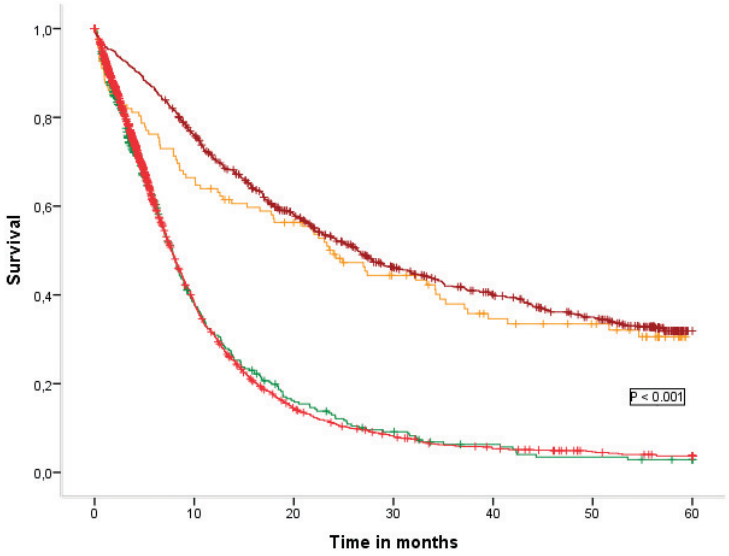
		HR (95%CI)	P-value
Age	**< 65 years**	**1**	**0.027**
	> 65 years	**1.11 (1.01-1.21)**	
Sex	**male**	1	0.090
	female	1.09 (0.99-1.21)	
Lung disease	**no**	1	0.557
	yes	0.97 (0.86-1.09)	
CVD	**no**	1	0.584
	yes	1.03 (0.93-1.13)	
CVA/hemiplegia	**no**	1	0.059
	yes	1.20 (0.99-1.44)	
Within non-DM Surgery*	**no**	**1**	**< 0.001**
	yes	**0.38 (0.30-0.49)†**	
Within DM Surgery*	**no**	**1**	**< 0.001**
	yes	**0.32 (0.29-0.36)†**	
Within non-operated DM	**no**	**1**	0.569
	yes	**1.04 (0.91-1.18)**	
Within operated DM	**no**	1	0.569
	yes	0.96 (0.847-1.095)	

**time-dependent factor.*

† interaction non-significant (P=0.210)

Figure 2 additionally visualizes the survival curves comparing the abovementioned groups, as assessed via the clock-reset approach as described in the methods section. The median overall survival of the operated diabetic group and the operated non-diabetic group was 24 and 26.4 months, respectively. The non-operated diabetic group had a median overall survival of 7.8 months and the non-operated non-diabetic group had a median overall survival of 7.7 months. The difference between the operated and the non-operated groups was significant ($P < 0.001$).

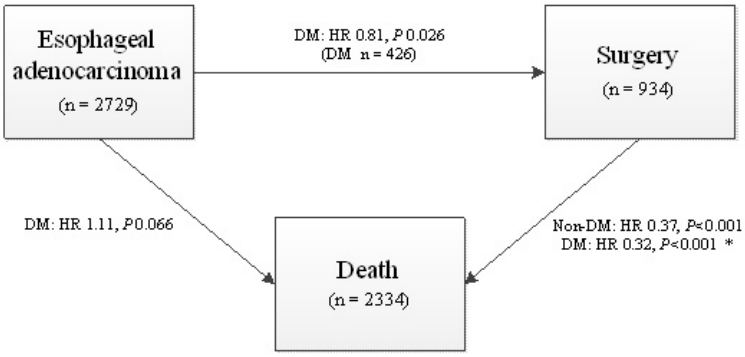
Figure 2. Survival curves comparing the operated and the non-operated patients, with and without diabetes.
-DM+, Surg- (n=426), - DM-, Surg- (n=2303), - DM+, Surg+ (n=122), - DM-, Surg+ (n=789).



Survival curves were constructed using a clock-reset approach. Non-operated patients were in the first stratum until time of death or end of follow up. Patients who got operated were in the first stratum until they got operated; they switched to the second stratum at the time of their surgery and were censored in the first stratum from that time. In the second stratum the time of surgery was then reset as time for the patients' further follow-up in the surgery group. Both strata were subdivided into diabetic and non-diabetic strata.

Figure 3 additionally provides an overview showing numbers of patients at risk and corresponding hazard ratios.

*Figure 3. Overview showing numbers of patients at risk and corresponding hazard ratios (univariable analyses). DM = diabetes mellitus. HR of 0.81 indicates significant lower chances of diabetic patients for surgery. HR of 1.11 indicates that DM has no significant effect on overall survival. HRs of 0.37 and 0.32 indicate the decreased mortality within the operated non-diabetic and diabetic patients, respectively. * Indicates the non-significant difference between the non-diabetic and diabetic group (P 0.210).*



Discussion

The aim of this study was to assess possible implications of DM with regard to surgery and prognosis in patients with EAC. It was shown that DM did not decrease the number of patients undergoing a surgical treatment for EAC. However it was clear that patients above 65 years were less likely to undergo surgery.

An earlier study from the ECR (22) showed that diabetic cancer patients were operated less frequently, but with adjustment for age these results were also non-significant with regard to chances of surgery in case of esophageal cancer. The 16% prevalence rate of DM found in the present study was slightly higher compared to the prevalence rate described in this earlier ECR study. These differences can be explained by the fact that the present study only analyzed EAC and not ESCC as well. Another possibility is that the rising incidence of DM is reflected in this sample that includes more recent EAC diagnoses.

A study from 2004 in 510 patients found a 15% prevalence rate of DM among patients with esophageal or gastroesophageal junction carcinoma (23).

In the present study, DM did not have any impact on overall mortality. The study of van de Poll et al (22) also showed that overall mortality was not different in esophageal cancer patients with DM compared to those without DM. This is probably due to the aggressive behavior of esophageal carcinoma which results in a dismal prognosis; survival is so poor that DM cannot be a 'competing' cause of death. This is strengthened by a study that showed that excess mortality with DM was mostly seen for cancer types with long survival rates (24).

Our study showed that diabetic patients who underwent surgery did not have

significantly different overall mortality rates when compared to the non-diabetic patients who underwent surgery. A study from 2004 (23) reported that DM was a significant predictor of mortality in 510 patients undergoing esophagogastrectomy (HR 1.30, 95%CI 1.09-1.54), however the study does not clearly report whether this concerns direct postoperative mortality or overall mortality. Another study in 609 patients undergoing surgical resection for esophageal or cardia cancer however, showed that DM did not increase postoperative overall mortality (25). Also in our study, we did not find any difference in postoperative mortality between patients with or with out DM. This can probably be explained largely by selection bias. It can be assumed that diabetic patients who are eligible for surgery are in better condition and thus, prognostic differences between them and the non-diabetic patients become smaller.

The overall rate of surgical intervention of 34% found in our study was in accordance with an earlier study among 2386 patients with esophageal cancer (17). This study reports underuse of esophagectomy in patients with comorbidities and points out the need for careful evaluation of patients undergoing esophagectomy since the surgical treatment and postoperative care have improved. Our study did not find differences in overall mortality after surgery in EAC, which is probably explained by the fact that surgeons select the healthiest diabetics for surgery. Possibly, because of improved surgical techniques less healthier diabetics might also be eligible for surgery.

However, investigating DM (and other comorbidities) and its prognostic role regarding surgery and mortality remains a difficult concept. It is shown that DM, together with other concomitant diseases like hypertension and COPD, is one of the most frequently occurring comorbidities in the elderly (26). With increasing age, the number of comorbidities is likely to increase as well and these can all influence performance status and subsequently chances of surgery. Thus, it is difficult to assess the true effect of DM. The fact that age alone (> 65 years) influenced chances to undergo surgery in this study emphasizes this. However, in the present study patients older than 65 years of age were diabetic more often which points out the relationship between increasing age and the presence of comorbidities.

This study only investigated EAC because this tumor type is more closely related to obesity (3, 4) (and possible subsequent DM) than ESCC, which points out the need to distinguish them from each other. Another strength of this study is that we were able to adjust for the effect of age by calculating a threshold. Furthermore, DM and other comorbidities (like lung disease, CVD and CVA), are related. By checking for interactions between diabetes and surgery with these comorbidities, simultaneous influences of comorbidities on diabetes and surgery were ruled out.

However, some limitations of this study should be addressed. This study did not

distinguish between insulin-dependent and non-insulin dependent DM and did not take metformin use into account. Studies have pointed out insulin as an extra risk factor for cancer and metformin as a protective agent in cancer development (27, 28). However, a lot of biases were present in early studies investigating glucose-lowering drugs and thus the potential risks or benefits are debated (29, 30). Furthermore, information on presence of metastasis and tumor stage was not complete for the non-operated patients. This could have influenced the results with regard to surgical treatment. Second, for 44% of the operations the exact type of operation was not known. The possibility exists that these unknown operations included staging operations or aborted operations due to metastatic disease. This could have influenced prognosis of the operated patients in a negative manner and thus the survival difference might be even larger than described. Additionally, this study did not analyze cause-specific mortality. It could have been of value to distinguish between cancer-specific mortality and death from DM or other comorbidities. However, because of the dismal prognosis of esophageal cancer patients might be less likely to die from other causes. Lastly, no information on BMI was available. Thus, we could not assess DM as an independent risk factor. Obesity has additionally been linked to EAC because of increased intra-abdominal pressure, which may promote gastro-esophageal reflux disease (GERD) and the development of Barrett's esophagus (5, 6). Information on reflux disease was not known. It can also be assumed that diabetic patients are more obese and that this could be of influence on chances of surgery and survival. However, studies indicate that obese patients do not have a decreased survival after esophagectomy for cancer (31, 32).

Future research should further study the effect of DM on surgery regarding EAC. Overall- and cause specific mortality should be investigated, so the true effect of DM (and other comorbidities) on mortality can be assessed.

To conclude, this study showed that DM did not influence the number of patients receiving surgical treatment, nor had an effect on overall mortality in patients with EAC. Moreover, the surgeon probably selects only the healthiest diabetic patients for surgery since postoperative overall mortality rates of operated diabetic patients were equal to those of operated non-diabetic patients. In diabetic patients strict regulation of DM is required, in order to keep the patients' chances for surgery optimal in case of EAC. In this way additional comorbidities, that could preclude diabetic patients with EAC from surgical treatment, can be prevented and diabetic patients can be operated safely without a decreased prognosis.

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Diabetes following pancreatic surgery

Chapter 6 New-onset diabetes after distal pancreatectomy: a systematic review

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Abstract

Objective
The true rate of new-onset diabetes (NODM) after distal pancreatectomy (DP) is not known. This systematic review was carried out to obtain exact percentages regarding the incidence of NODM after DP for different indications.

Background
Distal pancreatectomy is the standard procedure for removal of benign or (potentially) malignant lesions from the pancreatic body or tail and increasingly used for removal of often benign lesions. It is associated with low mortality rates, though postoperative diabetes remains a serious problem.

Methods
Embase, PubMed, Medline, Web of Science, the Cochrane Library and Google Scholar were searched for articles reporting incidence of NODM after DP. Methodological quality of the included studies was assessed by means of the Newcastle-Ottawa scale for cohort studies and the Moga-scale for case series. Mean weighted overall percentages of NODM after DP for different indications were calculated with 95% confidence intervals (CI) and corresponding *P* values.

Results
Twenty-six studies were included, comprising 1.731 patients undergoing DP. The average cumulative incidence of NODM after DP performed for chronic pancreatitis was 39% and for benign or (potentially) malignant lesions it was 14%. Comparing the proportions of these 2 groups showed a significant difference (95%CI 0.351-0.434 and 0.110-0.172, respectively, $P < 0.000$). The average percentage of insulin-dependent diabetes among patients with NODM after DP was 77%.

Conclusions
This review is the largest of its kind to assess the cumulative incidence of NODM after DP and shows that NODM is a frequently occurring complication, with incidence depending on the preexisting disease and follow-up time. Because NODM can affect quality of life, patients undergoing DP should be preoperatively provided with this information as specific as possible.

Introduction

Distal pancreatectomy (DP) (also called left-sided pancreatectomy), with or without splenectomy, has been considered the standard procedure for benign or (potentially) malignant lesions located in the pancreatic body or tail (1, 2). Still it was little used because malignant lesions in the pancreatic tail are often metastasized at the time of discovery (3). Today, however, the procedure is increasingly used as the more frequent use of modern imaging studies often reveals asymptomatic - and frequently benign - pancreatic lesions such as intra pancreatic mucinous neoplasms (IPMNs), which are often situated in the pancreatic body or tail (4). As a result of the more benign nature of resected lesions, life expectancy after DP has increased. Furthermore, in chronic pancreatitis (CP) DP is the treatment of choice in patients with small duct disease located in the pancreatic body or tail (5-7).

DP is associated with low mortality rates, but morbidity, especially pancreatic leak, may be high (8, 9). Additionally, postoperative new-onset diabetes (NODM) is a concern, although the true rate of NODM after DP is not known. Rates vary from 5-9% in patients with presumably normal pancreatic parenchyma to 25-50% in patients undergoing distal pancreatectomy for chronic pancreatitis (10). Clearly, the risk of postoperative diabetes depends on the preexisting disease. Furthermore, the extent of the resection logically influences the risk of developing NODM (11).

The aim of this systematic review is to obtain exact percentages regarding the incidence of new-onset diabetes after DP. Preexisting disease, follow-up time and the severity of NODM were assessed. The findings obtained from this review could serve to adequately inform patients who are planned to undergo DP about the possible consequences. This is important especially because diabetes, also in view of the increased life expectancy, can become a lifelong complication.

Methods

Study selection criteria and search strategy

Inclusion and exclusion criteria were defined in a review protocol. Eligible studies were those that reported at least 10 patients undergoing DP. Studies had to report pre- and postoperative numbers of diabetes, or report numbers of NODM postoperatively. Both DPs with and without splenectomy could be included, performed either as an open procedure or laparoscopically.

DPs performed for chronic pancreatitis, benign- or (potentially) malignant lesions were included. Studies that did not report preoperative numbers of diabetes and did not clearly describe numbers of NODM were excluded.

In October 2013, Embase, PubMed, Medline, Web of Science, the Cochrane Library

and Google Scholar were searched using the search terms 'pancreas resection', 'distal pancreatectomy', 'left pancreatectomy', 'diabetes mellitus', 'pancreas insufficiency', 'endocrine dysfunction' and 'pancreatogenic diabetes', without year or language restrictions.
Studies that seemed to fulfil the eligibility criteria and those for which information in the abstract was not sufficient for exclusion were read in full. Bibliographies of included publications were searched for other studies and authors were contacted when additional unpublished data were needed.

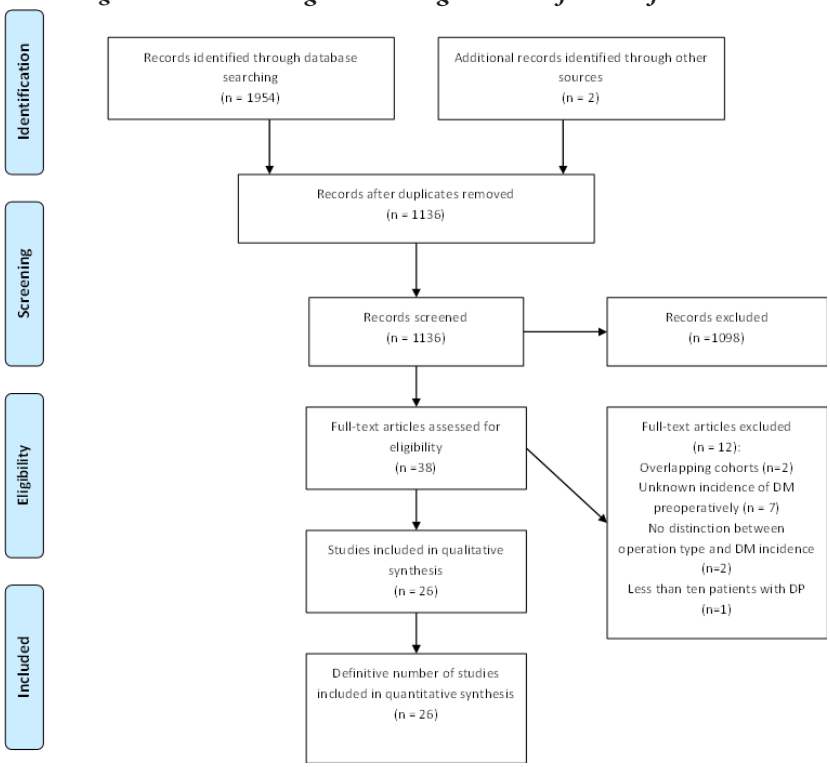
Data extraction
The 2 authors independently screened titles and abstracts, and full articles if necessary, of all citations retrieved from the searches and checked them for eligibility. Any disagreement was resolved until consensus was achieved. Figure 1 shows the flowchart of the selection of articles for review.
The following data were extracted: numbers of pre- and postoperative diabetes (or NODM), duration of follow-up, preexisting disease, whether the operation was performed with or without splenectomy, whether the DP was performed open or laparoscopically and whether patients with NODM were insulin- or non-insulin dependent. Diabetes mellitus (DM) was defined by the criteria for the specific study. If a study reported 'impaired glucose tolerance', 'pathological oral glucose tolerance test' (or anything similar) next to reported 'manifest diabetes', only the numbers of manifest diabetics were used. If a study reported the number of patients available for follow-up, that specific number was taken as the initial number of patients undergoing DP.
Four studies had overlapping cohorts (12-15); only the 2 studies with the largest number of patients were included in this review (12, 14).
The methodological quality of included cohort studies was assessed by means of the Newcastle-Ottawa scale (NOS) (16). An 18-criteria checklist developed by Moga et al (17) served to assess quality of the included case series. Here, a maximum of 18 points could be rewarded to each study.

Statistical analyses
If studies did not report the percentage of NODM, this was calculated by one of the authors (KB). Furthermore, mean weighted overall percentages of NODM were calculated per indication and for NODM being insulin dependent or not. Additionally, by calculating 95% confidence intervals and corresponding *P*-values statistically significant differences between the groups were identified.

Results

A total of 26 studies were included, comprising 1.731 patients undergoing DP (6, 7, 12, 14, 18-39). Details of the included studies are summarized in Tables 1, 2 and 3. Table 1 shows details of the 9 studies reporting CP as the indication for the DP, table 2 shows details of the ten studies reporting benign or (potentially) malignant lesions as the indication for the DP. Table 3 shows details of the 7 studies reporting both indications.

Figure 1. PRISMA diagram showing selection of articles for review.



Preexisting disease - Chronic pancreatitis

NODM onset less than 6 months postoperative

Four studies reported the incidence of NODM within 6 months after surgery (7,29,34,37). Hutchins et al (7) studied 90 patients with chronic pancreatitis who underwent DP; 18 patients had developed NODM directly after surgery (20%). Jalleh et al (29) described that 7 of the 42 patients were rendered diabetic (17%) within 2 months after surgery. The study of Riediger et al (34) described 21 patients undergoing DP; only 1 patient had become diabetic immediately postoperatively (4.8%). Govil et al (37) reported that 7 patients had become diabetic within 6 months after surgery (18%).

NODM onset more than 6 months postoperative

All of the 9 studies reported the incidence of NODM after more than 6 months after surgery. Van der Gaag et al (18) studied a cohort of 37 patients that underwent surgery for painful CP. However, only 22 patients were available for follow-up. Of these patients, 10 (45%) developed NODM. DP had an OR of 1.63, albeit non-significantly, for developing NODM. Longer follow-up after surgery also increased the risk of NODM. A study from Byrne et al (23) contained 41 patients undergoing DP for chronic pancreatitis, of whom 15 (37%) developed NODM. Diabetes developed more frequently in these patients than in patients undergoing Whipple resections. As described earlier, in the study of Hutchins et al (7) 20% of the patients showed NODM at immediate postoperative assessment. In the following 27 months, another 14 patients developed NODM, increasing the total percentage to 36%. Splenectomy was performed in 61 patients and this was associated with an increased incidence of NODM compared to splenic preservation. In the study of Jalleh et al (29) ten patients became diabetic; thus the total percentage of NODM increased to 40%. In 29 cases a splenectomy was performed; unfortunately specific outcomes regarding NODM for these patients were not reported. Sakorafas et al (14) found a total percentage of 48% for NODM after DP. The mean time to onset of diabetes was 3 years in 25 of these patients. The study of Schnelldorfer et al (31) reported the highest incidence of NODM after DP of the studies included in this review (51%). Of the 69 patients who were available for follow-up, 35 developed diabetes. In the study of Riediger et al (34) 7 more patients had become diabetic at last follow-up, bringing the total incidence of NODM to 38%. Uni- and multivariate analyses did not point out any risk factors for the development of NODM. The study of Govil et al (37) showed an incidence of NODM of 32%. In addition to the 7 patients who developed diabetes within 6 months of surgery, another 5 became diabetic. Interestingly, splenectomy was performed in 16 patients and authors reported a higher incidence of NODM after splenectomy compared to the spleen-preserving DPs, however statistically significant numbers were not reported. In a prospective case series studied by Schoenberg et al (6), 74 DPs were performed. Fifteen patients developed diabetes. Time to onset of diabetes was not reported and neither was any influence of splenectomy, which was performed in 45 cases.

In conclusion, cumulative incidences varied from 20% (6) to 51% (31). Within 6 months after surgery, the incidence of NODM was 17%, and this increased to 36% when percentages of NODM after longer follow-up periods of these 4 studies only were combined. Overall, the incidence of NODM was 39% when the numbers of new-onset diabetic patients at the latest follow-up of all 9 studies were combined.

Table 1. Summary of included studies reporting DP for chronic pancreatitis

Reference	Study type	Study quality *†	Mean FUP (yrs)	No. patients	DM diagnosis	Total DM preop	DM < 6 mo	DM > 6 mo	Total DM postop	% NODM (no. patients)	Splenectomy
van der Gaag et al, 2012 [18]	Prospective cross-sectional cohort study	7/9*	5.3	22	FBG, HbA1C, need for Medication	4	NR	10	14	45% (10)	NR
Byrne et al, 1997 [23]	Retrospective cohort study	7/9*	6.8	41	NR	6	NR	15	21 (20 IDDM)	37% (15)	NR
Hutchins et al, 2002 [7]	Retrospective case series	15/18†	2.8	90	OGTT	8	18	14	40	36% (32)	61
Jalleh et al, 1992 [29]	Retrospective cohort study	6/9*	1.7	42	Need for diet or medication, OGTT	1	7	10	18	40% (17)	29
Sakorafas et al, 2000 [14]	Retrospective cohort study	8/9*	7.9	135	NR	12	NR	65	77	48% (65)	11
Schnelldorfer et al, 2007 [31]	Retrospective cohort study	6/9*	5.5	69	NR	NR	NR	35	35	51% (35)	NR
Riediger et al, 2007 [34]	Prospective cohort study	9/9*	4.7	21	WHO-criteria, OGTT	4	1	7	12	38% (8)	NR
Govil et al, 1999 [37]	Retrospective case series	11/18†	4	38	NR	4	7	5	16	32% (12)	16
Schoenberg et al, 1998 [6]	Prospective case series	12/18†	4.8	74	OGTT, WHO-criteria	12	NR	15	27	20% (15)	45
Total	-	-	**4.8**	**532**	-	**51**	**33**	**176**	**260**	**39%(209) (95%CI 0.351-0.434)**	**162**

**NOS quality assessment.*

†Moga quality assessment.

FBG indicates fasting blood glucose level; FUP, follow-up; NR, not reported; OGTT, oral glucose tolerance test

Preexisting disease – Benign or (potentially) malignant lesions

NODM onset less than 6 months postoperative

Two studies reported incidences of NODM within 30 days after surgery (32, 33). Lebedyev et al (32) performed a consecutive series of laparoscopic DPs. The incidence of NODM was 17%. Splenectomy was performed in 5 patients, however the incidence of NODM for this group was not reported. Mori et al (33) described a group of 14 patients undergoing DP; only 1 patient developed NODM (7%).

NODM onset more than 6 months postoperative

Regarding longer durations of follow-up, 8 studies reported benign or (potentially) malignant lesions as the indication for surgery (12, 21, 24-27, 35, 36). Balzano et al (21) reported that 3 patients became diabetic after DP (14%). Eleven patients underwent splenectomy, but the study did not assess the effect on the development of NODM.
A retrospective cohort study performed by Dumitrascu et al (24) analyzed spleen-preserving DPs. Three patients (12%) developed NODM and this was not significantly different from central pancreatectomy to which the DPs were compared with. What this study did show was that the length of the resected pancreas was significantly greater in the DP group than in the central pancreatectomy group (8.5cm vs. 5 cm). DiNorcia et al (25) compared DP with central pancreatectomy as well. Incidence of NODM was 28% in the DP-group, and this was not significantly different from the group undergoing central pancreatectomy. Another study comparing central pancreatectomy with DP (26) found an overall incidence of 23% for NODM. The incidence was significantly higher for patients who underwent DP compared to patients who underwent central pancreatectomy. Falconi et al (27) described 7 patients (14%) with NODM after DP. In this study, a significant hazard ratio of 12 for developing pancreatic insufficiency was found. However, the analysis did not distinguish between exocrine and endocrine dysfunction. The study of Lee et al (12) investigated 188 patients undergoing DP. Twenty of them developed diabetes (11%). No significant differences in incidence of NODM between DP with splenectomy, spleen-preserving DP and central pancreatectomy were found. A study that compared DP to central pancreatectomy found and incidence of 17% for NODM after DP (35). The incidence of NODM in patients who underwent DP was significantly higher than in the patients who underwent central pancreatectomy. Xiang et al (36) investigated 55 patients undergoing DP, 5 of whom developed NODM (9%). The incidence of NODM after central pancreatectomy was zero.
Summarized, cumulative incidences varied from 7% (33) to 28% (25). The 2 studies reporting incidence of NODM within 6 months after surgery had an overall percentage of 12%. A possible increase in incidence of NODM over time could not be assessed since

these studies did not report numbers of NODM after longer periods of time. When the percentages of NODM of the studies reporting after 6 months of follow-up were combined, the overall percentage was 14%.

Table 2. Summary of included studies reporting DP for benign or (potentially) malignant lesions

Reference	Study type	Study quality *†	Mean FUP (yrs)	No. patients	DM diagnosis	Total DM preop	DM < 6 mo	DM > 6 mo	Total DM postop	% NODM (no. of patients)	Splenectomy
Balzano et al, 2003 [21]	Retrospective cohort study	7/9*	5.5	21	Telephone interview	2	NR	3	5	14% (3)	11
Dumitrascu et al, 2012 [24]	Retrospective cohort study	8/9*	3.9	25	FBG	1	NR	3	4	12% (3)	No
DiNorcia et al, 2010 [25]	Retrospective cohort study	7/9*	2.6	50	Dietary restriction, need for medication	11	NR	14	25	28% (14)	NR
Hirono et al, 2009 [26]	Prospective cohort study	6/9*	2.2	26	FBG, HbA1C. OGTT. Need for diet or medication	3	NR	6	9	23% (6)	26
Falconi et al, 2006 [27]	Prospective cohort study	8/9*	NR	50	FBG, OGTT	12	NR	7	19	14% (7)	NR
Lee et al, 2010 [12]	Retrospective cohort study	8/9*	2.9	188	NR	20	NR	20	40	11% (20)	143
Lebedyev et al, 2004 [32]	Retrospective case series	7/18†	NR	12	NR	NR	2	NR	2	17% (2)	5
Mori et al, 2012 [33]	Prospective cohort study	7/9*	NR	14	FBG, OGTT	8	1	NR	6 (some became non-DM)	7% (1)	NR
Shikano et al, 2010 [35]	Retrospective cohort study	9/9*	5.9	35	HbA1C, FBG	NR	NR	6	6	17% (6)	NR

Xiang et al, 2012 [36]	Retro spective cohort study	7/9*	1.4	55	(F)BG	1	NR	5	6	9% (5)	NR
Total	-	-	**3.5**	**476**	-	**58**	**3**	**64**	**122**	**14% (67) (95%CI 0.110-0.172)**	**185**

**NOS quality assessment.*

†Moga quality assessment.

FBG indicates fasting blood glucose level; FUP, follow-up; NR, not reported; OGTT, oral glucose tolerance test

Preexisting disease – CP and benign or (potentially) malignant lesions

NODM onset less than 6 months postoperative

Three studies reported the incidence of NODM directly postoperative (20, 38, 39). Belyaev et al (20) studied 25 patients who underwent DP and 7 of them developed diabetes (28%). CP was the indication for surgery in 10 patients. Patients with exo- or endocrine insufficiency after DP suffered more losses in quality of life scores. Irani et al (38) studied 171 patients, with 75 patients undergoing DP as part of a multivisceral resection. A total of 13 patients had CP as the preexisting disease. Only 6 patients developed diabetes (4%). The incidence of NODM did not differ significantly between the regular DP-group and to the DP-group undergoing multivisceral resection. In the study of Lillemoe et al (39) CP was the preexisting disease in 56 patients. The incidence of NODM was 6%. In 198 patients a splenectomy was performed and these patients did not have more postoperative complications than patients in whom the spleen was preserved. However, incidence of NODM was not reported.

NODM onset more than 6 months postoperative

Four studies reported the incidence of NODM after more than 6 months after surgery (19, 22, 28, 30). Stutchfield et al (19) reported that 17% of patients developed diabetes after DP. In 6 cases of postoperative pancreatic insufficiency the resected specimen showed CP; it was not mentioned however whether these were tissues from patients with endo- or exocrine insufficiency. Furthermore, 50 patients underwent splenectomy, but NODM in these specific patients was not reported. Adam et al (22) found a 5% incidence rate of NODM after DP; 21 of the 41 patients who underwent DP (51%) had preexisting CP. The spleen was removed in 37 patients but NODM was not described for this specific group. King et al (28) reviewed 125 consecutive patients undergoing DP; 11 had preexisting CP. Ten of all patients developed diabetes (8%). The study described a trend towards an increasing risk of NODM in patients with a history of pancreatitis (OR 2.9). A study that assessed pancreatic volume as a predictor for NODM found a 36% incidence of NODM in patients who

underwent DP (30). In comparison with patients who did not develop diabetes, patients with NODM had a significantly higher percentage of resected volume, a lower volume of remnant normal parenchyma and a higher volume of resected normal parenchyma.
To conclude, cumulative incidences varied from 4% (38) to 36% (30). The 3 studies that assessed incidence of NODM directly postoperative had an overall percentage of 6%. A possible increase in incidence of NODM over time could not be assessed since these studies did not report NODM incidences after longer periods of time. The overall percentage of NODM of all 7 studies combined was 10%.

Table 3. Summary of included studies reporting DP for CP and benign or (potentially) malignant lesions

Reference	Study type	Study quality *†	Mean FUP (yrs)	No. patients	DM diagnosis	Total DM preop	DM < 6 mo	DM > 6 mo	Total DM postop	% NODM (no. of patients)	Splenectomy
Stutchfield et al , 2008 [19]	Retrospective case series	12/18†	0.7	65	Need for medication	NR	NR	11	11 (9 IDDM)	17% (11)	50
Belyaev et al, 2013 [20]	Retrospective cohort study	7/9*	NR	25	Need for medication	3	7	NR	10	28% (7)	NR
Adam et al, 2001 [22]	Prospective case series	9/18†	NR	41	NR	7	NR	2	9	5% (2)	37
King et al, 2008 [28]	Retrospective case series	12/18†	1.8	125	Need for medication	14	NR	10	24	8% (10)	105
Shirakawa et al, 2012 [30]	Retrospective case series	13/18†	2.2	61	FBG, OGTT	0	0	22	22	36% (22)	NR
Irani et al, 2008 [38]	Retrospective case series	9/18†	NR	171	NR	NR	6	NR	6	4% (6)	NR
Lillemoe et al, 1998 [39]	Retrospective case series	9/18†	NR	235	NR	6	13	NR	19	6% (13)	198
Total	-	-	**1.6**	**723**	-	**30**	**26**	**45**	**101**	**10% (71) (95%CI 0.077-0.120)**	**390**

**NOS quality assessment.*

†Moga quality assessment.

FBG indicates fasting blood glucose level; FUP, follow-up; NR, not reported; OGTT, oral glucose tolerance test

Insulin vs. non-insulin dependent NODM

Nine studies reported insulin-dependent DM (IDDM) among NODM-patients and thus described its severity (19, 22, 23, 25, 27, 29, 35, 38, 39). Indications for surgery were CP, as well as benign, low grade or (potentially) malignant lesions.

Stutchfield et al (19) reported that 9 of the 11 patients who developed NODM were insulin-dependent (82%). The study of Adam et al (22) described that both patients who developed NODM after DP had become insulin-dependent. Byrne et al (23) described that 20 of the 21 patients with postoperative DM were insulin-dependent. However, information is lacking on whether this 1 patient who was not insulin-dependent had NODM or was diabetic preoperatively. Nevertheless, incidence of IDDM among the new-onset diabetes group would be between 93% and 100%. The retrospective study performed by DiNorcia et al (25) reported that 5 of the 14 patients with NODM had IDDM (36%). Falconi et al (27) described 7 patients who had become diabetic postoperatively; 3 of them were insulin-dependent (43%). In the study of Jalleh et al (29), 17 patients developed NODM and 14 of them became insulin-dependent diabetics (82%). Shikano et al (35) reported that 6 patients who underwent DP developed NODM. Three of them were dependent on insulin at the last follow-up. The study of Irani et al (38) described 6 patients who developed NODM, all of them being insulin-dependent diabetics. Lillemoe et al (39) also reported that all 13 patients with NODM needed insulin for glucose control.

In conclusion, the incidence of IDDM among patients with NODM varied from 36% to 100%. The overall percentage of IDDM among these new-onset diabetics was at least 77%.

Comparison of overall percentages

To determine whether the overall percentages between the groups were significantly different from each other 95% confidence intervals and P-values were calculated. When the overall percentage of the CP-group (39%) was compared with the overall percentage of the group with benign or (potentially) malignant lesions (14%), nonoverlapping confidence intervals were found (0.351-0.434 and 0.110-0.172 for the CP-group and the lesion-group, respectively), indicating a statistically significant difference (P<0.001). When the overall percentage of the CP-group (39%) was compared to the overall percentage of the group with CP and benign or malignant lesions (10%), these also seemed to be statistically significant (95%CI 0.351-0.434 and 0.077-0.120 respectively, P<0.001). When the overall percentage of the group with benign or malignant lesions (14%) was compared with the overall percentage of the group with CP and benign or malignant lesions (10%), another significant difference was found (95%CI 0.110-

0.172 and 0.077-0.120, respectively, *P*=0.024). Furthermore, when the subgroups with information regarding NODM within or after 6 months of follow-up were compared, either within each main group or in between the 3 groups, this all rendered statistically significant differences (data not shown).

Discussion

This systematic review aimed to obtain exact percentages for NODM after DP for different indications. When the DP was performed for chronic pancreatitis the overall cumulative incidence of NODM at latest follow-up was 39%. When the DP was performed for benign or (potentially) malignant lesions the overall cumulative incidence was 14%, significantly lower than when the DP was performed for CP. The overall percentage of NODM in studies that reported both chronic pancreatitis and benign or malignant lesions as the indication for surgery was 10%. In order to get an impression of the severity of the NODM, insulin dependency was reviewed. On average, 77% of the patients with NODM were dependent on insulin.

A possible explanation for the higher occurrence of NODM in patients undergoing DP for chronic pancreatitis is probably the ongoing destruction of pancreatic parenchyma in these patients (40). In patients with benign or malignant lesions, the remaining pancreatic parenchyma is healthy, and these patients have lower risk for developing NODM. Nevertheless, it is hard to distinguish whether postoperative changes are completely due to surgery or also due to the preexisting disease. In most cases it is likely to be a combination of both (41). Furthermore, a long follow-up period is necessary in these patients to make sure a diabetes diagnosis is not missed. This because this review showed an increase in incidence of NODM after DP for chronic pancreatitis with longer durations of follow-up.

Pancreatogenic diabetes, as the new-onset diabetes following pancreatic disease and/or pancreatic resection has been named, is seen in approximately 9% of the general diabetic population; 2-3% of whom have undergone pancreatectomy (42). In a study on pancreatoduodenectomy, incidences for NODM varied between 20 and 50% (43), reasonably in line with the findings from this review.

There is reason for concern, since in general, the patients who undergo DP are relatively young. First, diabetes impacts quality of life. As described by Belyaev et al (20), patients who postoperatively developed endo- or exocrine insufficiency, or both, suffered more losses in their physical quality of life. A study comparing quality of life after total pancreatectomy and partial pancreatic resection found that postoperative diabetes after both procedures had the largest negative impact on leisure and physical activities (44). Second, 77% of the patients with NODM studied in this review had IDDM, which

has more impact on quality of life than only dietary restrictions or use of OGLD (45). Furthermore, pancreatogenic diabetes seems to be similar to type 2 diabetes with regard to glucose tolerance and insulin resistance. However, glucose control is more difficult due to severe fluctuations in glucose-levels associated with treatment of exogenous insulin (46) and deficiency of pancreatic polypeptide (47). Lethal episodes of hypoglycemia – due to the absence of glucagon in combination with an ongoing need for exogenous insulin - have been described in patients who underwent pancreatoduodenectomy (48). Because the glucagon-producing alpha-cells are located mainly in the pancreatic body and tail, patients undergoing DP can be especially at risk for severe hypoglycemia. Third, there is increasing evidence that diabetes is associated with an increased risk of developing several cancers and cancer mortality (49-51). Insulin therapy is thought to increase cancer risk even more, whereas metformin use is thought to decrease cancer risk (51,52). A review of Cui et al (46) addressed concern over the increased cancer risk associated with insulin use among patients with pancreatogenic diabetes. In conclusion, the young age of the patients undergoing DP, together with their increasing life expectancy, may cause problems in the future. Patients might not only live the rest of their lives in poorer health, with 'brittle' diabetes, but they also might be at risk of developing cancer because they have become dependent on insulin.

Strengths and limitations

This review included the largest number of patients so far compared with other reviews assessing cumulative incidence of NODM after DP. By calculating mean weighted overall percentages for NODM, more clarity on its incidence regarding the indication for DP and the severity of the NODM was given. However, some limitations should be addressed. For one, in some cases more parenchyma than the usual 40-60% was resected and not all studies included in this review reported the resected percentage of pancreatic parenchyma. Byrne et al23 described that in 80% of the patients 40-50% of the pancreatic parenchyma was excised. However, in some cases the DP included a 30-70% resection. Hutchins et al (7) reported that the median volume of resection was 50%, but with a range of 10-90% and that the size of the pancreatic remnant unsurprisingly was significantly associated with the development of NODM. In the study of Jalleh et al (29) DPs with 40-70% resection were described. Govil et al (37) reported that the resection usually included 40% of the volume of the pancreas. In the study of Schoenberg et al (6) 4 patients underwent subtotal pancreatectomy and in the study of Lillemoe et al (39) 85% of the pancreas was resected in 10 patients. Thus, not all patients underwent an equal resection and this could have influenced the outcome in terms of NODM.
Second, not all studies used the same criteria for establishing diabetes diagnosis and

some studies did not report how diabetes diagnosis was assessed. With 1 study having more stringent criteria for diabetes than the other, numbers of patients with NODM might be even higher than reported. Third, some studies report substantial dropout rates in follow-up or do not have a sufficient follow-up period, which increases the risk that numbers of NODM are underreported. Fourth, only few studies reported whether the DP was performed laparoscopically (19, 24, 32, 38). Most studies that did not report this were older, and it is likely that the DPs in these studies were performed via laparotomy. Still, this would not seem to affect the results as a meta-analysis proved that laparoscopic DP is a safe procedure and is comparable to the open procedure (53). Lastly, not all studies reported whether the DP was performed with or without splenectomy. Three studies assessed whether splenectomy increased the risk of NODM (7,12,37). In 1 study, splenectomy was not associated with an increased risk of NODM (12) and in 2 studies, splenectomy was (7,37). Furthermore, analyzing studies that report CP as well as benign or malignant lesions as the indication for the DP might not be correct since they are associated with very different outcomes regarding NODM, as seems from this review. This review emphasizes the need to avoid NODM. We recommend more studies comparing DP to other procedures that are more parenchyma sparing, like central pancreatectomy. This procedure seems to carry lower risk of NODM; however, it is associated with an increased incidence of postoperative pancreatic fistula when compared to DP (54,55). Furthermore, risk of a nonradical resection is present since in some cases resected lesions - which preoperatively appeared benign - postoperatively appeared to be an invasive malignancy (28). Thus, a solution for NODM is not expected in the near future.

Conclusions

This systematic review assessed different modalities regarding NODM after DP and revealed a 39% incidence of NODM when the DP was performed for CP. For benign or (potentially) malignant lesions the incidence was 14%. Until other procedures have definitively proven to be safer, DP cannot be avoided and the risk of NODM has to be taken for granted. Patients must be clearly informed about this before they undergo DP.

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Chapter 7 Risk of endo- and exocrine insufficiency after distal pancreatectomy for asymptomatic pancreatic lesions

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Submitted

Abstract

Background

Distal pancreatectomy (DP) is an increasingly performed procedure because of increased detection of asymptomatic, potentially malignant pancreatic lesions. DP is considered a safe procedure however morbidity may be high. This case series studied endo- and exocrine pancreatic function and quality of life after DP in patients with and without an asymptomatic pancreatic lesion.

Methods

A total of 143 patients who underwent distal pancreatectomy in a tertiary referral hospital in the Netherlands were retrospectively analyzed. Asymptomatic lesions were defined as lesion found by imaging techniques performed for other indications than pancreatic disease. From 44 eligible patients information on pancreatic function and quality of life was obtained in the outpatient clinic. New-onset diabetes (NODM), exocrine insufficiency and quality of life were statistically analyzed in (a)symptomatic patients.

Results

In 30% the DP was performed for an asymptomatic lesion and intraductal papillary mucinous neoplasm (IPMN) was the most frequent diagnosis within this group (39%). Asymptomatic patients were older (P=0.006). The overall rate of NODM was 43%, with IPMN being associated with NODM (P<0.001). New exocrine insufficiency developed in 43% of the patients and additional splenectomy was associated with new exocrine insufficiency (P=0.024). Asymptomatic patients reported better mental health (P=0.023) compared to symptomatic patients.

Conclusions

This case series found that 30% of the patients underwent DP for an asymptomatic lesion and IPMN was the main diagnosis in this group. IPMN was associated with NODM, however this had no effect on quality of life. Larger studies should further assess the harm that might be done to patients who undergo resection because of an asymptomatic pancreatic lesion.

Introduction

Distal pancreatectomy (DP) is increasingly being performed due to the increased detection of asymptomatic, potentially premalignant or malignant pancreatic lesions, which are related to the growing use of cross-sectional imaging for other indications (1-3).

Such 'incidentalomas', as these lesions are called, are defined as an asymptomatic mass incidentally detected by a diagnostic test, usually an imaging study (4, 5). Intraductal papillary mucinous neoplasm (IPMN) seems to be the most common asymptomatic lesion leading to surgical resection (6). However, only a few studies on this topic have been published and most of them are small. The need for surgery in case of an asymptomatic lesion depends on the (suspected) diagnosis. For solid lesions, suspicion of malignancy is usually high and surgery is the only potentially curative treatment. In cystic lesions, however, chances for malignancy differ by demographic, radiographic and clinical findings and surgery is often not indicated (7).

The amount of pancreatic tissue resected during DP concerns the portion of the pancreas that extends to the left of the midline and the resection follows - in most patients - the course of the superior mesenteric vein although on indication less pancreas parenchyma may be resected. DP is considered a safe procedure because of 0-2% mortality rates (8, 9). Postoperative morbidity however, can be substantial with rates of clinically relevant complications up to 47% (8). Postoperative pancreatic fistula (POPF) after DP remains a very common (30%) problem (8-10), as well as new-onset diabetes mellitus (NODM), with incidences of NODM varying per underlying disease (11).

Higher postoperative morbidity (mainly POPF) among patients who underwent surgery for an asymptomatic lesion compared to patients who underwent surgery for a symptomatic lesion has been reported (6). It can be hypothesized that postoperative complications in asymptomatic patients have greater impact on physical and mental health compared to patients who were already symptomatic before surgery.

Therefore, this study analyzed a series of DPs performed for various indications in a tertiary referral hospital in the Netherlands. The rate of asymptomatic lesions was studied, as well as the rate of postoperative complications with focus on pancreatic endo- and exocrine insufficiency. This study also aimed to provide more insight in postoperative morbidity and quality of life after DP, thereby studying patients with and without an asymptomatic lesion.

Methods

This study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (12). A number of 143 patients who

underwent distal pancreatectomy from January 2001 until December 2012 at the Erasmus University Medical Center in Rotterdam were retrospectively analyzed. Surviving patients were contacted by telephone and asked whether they were willing to participate in the study or not. Patients who underwent distal pancreatectomy with or without splenectomy either via laparoscopic or open approach were included. Patients with a history of previous pancreatic surgery were excluded.

Data collection

Data on whether the pancreatic lesion was incidentally identified, body mass index (BMI), surgery, postoperative complications and pathological outcome were retrospectively reviewed using medical records. Patients were asked to visit the outpatient clinic where additional information on diabetic status, information on physical health and quality of life was obtained using a validated questionnaire. Additionally, blood and stool samples were drawn to assess pancreatic function. The medical ethics committee approved the study and all patients signed informed consent.

Definition of complications

Postoperative complications were subdivided into POPF, intra-abdominal abscess, post pancreatectomy hemorrhage (PPH), wound infection or other. POPF and PPH were scored using the recommended definitions of the International Study Group of Pancreatic Surgery (ISGPS) (13, 14). Complications were additionally scored according to the Clavien-Dindo classification of surgical complications (15). Only clinically relevant complications (> grade 2) were studied.

Definition of asymptomatic pancreatic lesions

A pancreatic lesion was defined asymptomatic if the lesion was encountered during the workup for atypical abdominal signs or for symptoms not associated with pancreatic disease (acute or chronic pancreatitis, jaundice, steatorrhea etc.), or as a lesion that was discovered during regular follow-up of other diseases or routine (radiologic) examinations.

Definitions of new-onset diabetes mellitus and new exocrine dysfunction

Pancreatic endocrine function was assessed using the non-fasting plasma glucose concentration and glycated hemoglobin (HbA1c). NODM was defined as a non-fasting glucose level above 11.0 mmol/l (200 mg/dl) or a glycated hemoglobin above 42 mmol/mol or a need for use of glucose lowering drugs after surgery in patients who were reported to be non-diabetic before surgery. Furthermore, the type of the glucose-lowering

drug used (metformin, SU-derivatives, insulin, or other) was obtained. The start date of the glucose-lowering drug was also obtained if available. The duration from surgery to onset of NODM was calculated in months using the date of operation and the date of the first use of any glucose-lowering drug. In patients with NODM but without the need for medication the date the blood sample was drawn was used. A subdivision was made into early (< 6 months after surgery) and late onset (> 6 months after surgery) of NODM. Pancreatic exocrine function was analyzed by measuring elastase-1 levels in stool samples. A patient was considered to have new exocrine dysfunction when the elastase-1 level was less than 200 μg/gr or the patient needed to use enzyme supplements after surgery.

Quality of life

Quality of life was assessed by using the Short Form-36 (SF-36) Health Survey questionnaire, a well-known and validated self-report inventory with eight domains focusing on physical and mental health (16). These eight domains are grouped into a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The quality of life of patients included in this study was age-matched and compared to the quality of life of the average Dutch population. Information about this cohort can be found elsewhere (17).

Statistical analyses

Follow-up was defined in years starting from the day of surgery until the date of latest follow-up.

For comparison at baseline of normally distributed continuous variables, the independent student's t-test was used and for categorical variables the Chi-square test was used. The Fisher's exact test was used when cells in cross tabulations contained less than 5 observations. With regard to quality of life confidence intervals were calculated using the mean (mean +/-1.96*SD). By checking for overlap between the confidence intervals statistical significance was assessed. All statistical tests were 2-sided and P-values < 0.05 were considered statistically significant. All analyses were performed using SPSS software (SPSS Inc., version 21.0, Chicago, Illinois, USA).

Results

As mentioned above, 143 patients underwent distal pancreatectomy of whom 36% (n=51) had been diagnosed with an asymptomatic pancreatic lesion. In eight patients it was unknown whether the pancreatic lesion was an incidental finding thus these patients were excluded. In total, a percentage of 55% was female (n=74) and the mean age of the total cohort was 53.5 (SD 15.3) years. Asymptomatic patients were older than

symptomatic patients (59.4 years (SD 12.6) vs. 50 years (SD 15.8), $P < 0.001$), and the most frequent diagnosis among asymptomatic patients was cancer (30%), followed by IPMN and MCN (14% for both).

Of all potentially eligible patients, a total of 19 patients had died (four postoperatively, four of disease specific causes, five from other causes unrelated to disease or surgery and in six patients the cause of death was unknown). Three surviving patients had previous pancreatic surgery and were excluded. A number of 77 patients were not willing or able to participate in the study. Finally, 44 patients were included. Further analyses were performed in these patients only.

Mean age at time of surgery was 54.6 (SD 13.7), 57% was female (n=25) and mean follow-up was 4.3 years (SD 2.7). Other baseline characteristics are shown in table 1. Pathology revealed neuro-endocrine tumors (NET) (n=16, 36%), intraductal papillary mucinous neoplasms (IPMN) (n=8, 18%) and chronic pancreatitis (n=8, 18%) as most common diagnoses. Of the eight patients with IPMN two were thought to have a main duct IPMN (25%), two a side branch IPMN (25%), two a mixed type IPMN (25%) and from two patients the type of IPMN was unknown. Other diagnoses concerned metastasis of an ovary tumor and two concerned traumatic pancreatic rupture.

The overall rate of clinically relevant (Clavien Dindo > grade 2) postoperative complications was 14% (n=6, table 1).

Table 1. Baseline characteristics describing the cohort of 44 patients.

	Total	Symptomatic (n=31)	Asymptomatic (n=13)	P-value
Female	25 (57%)	20 (65%)	5 (38%)	0.111
Age (mean)	54.6 (SD 13.7)	51.6 (SD 4.45)	61.8 (SD 8.7)	**0.006**
Body mass index (mean)*	25.4 (SD 3.4)	25 (SD 3.3)	26.3 (SD 3.6)	0.267
Follow up (mean, years)	4.3 (SD 2.7)	4.8 (SD 3.1)	3 (SD 1.04)	**0.004**
Diagnosis				
Chronic pancreatitis	8 (18%)	7 (23%)	1 (8%)	
Neuroendocrine tumor	16 (36%)	14 (45%)	2 (15%)	
Pseudocyst, cystadenoma	3 (7%)	2 (7%)	1 (8%)	
IPMN	8 (18%)	3 (10%)	5 (39%)	
Mucinous cystic neoplasm	5 (11%)	2 (7%)	3 (23%)	
Carcinoma	1 (2%)	1 (3%)	0	
Other	3 (7%)	2 (7%)	1 (8%)	0.074
Operation type body-tail	14 (32%)	9 (29%)	5 (39%)	0.540
tail	30 (68%)	22 (71%)	8 (62%)	
Splenectomy	15 (34%)	10 (32%)	5 (39%)	0.692
Laparoscopy	8 (18%)	7 (23%)	1 (8%)	0.402

Complications	**none**	30 (68%)	21 (68%)	9 (69%)	0.913
	POPF	5 (11%) (all gr. B)	3 (10%)	2 (15%)	
	Intra-abdominal abscess	1 (2%)	1 (3%)	0	
	PPH	2 (5%)	2 (7%)	0	
	wound infection	1 (2%)	1 (3%)	0	
	other	5 (11%)	3 (10%)	2 (15%)	
Clavien-Dindo	**3A**	4 (9%)	2 (7%)	2 (15%)	0.458
	3B	1 (2%)	1 (3%)	0	
	4A	1 (2%)	0	1 (8%)	
Reoperation		1 (2%)	1 (3%)	0	1.000
Preoperative diabetes		6 (14%)	5 (16%)	1 (8%)	0.652
New-onset diabetes		19 (43%)	11 (36%)	8 (62%)	0.111
Preoperative enzyme supplement		3 (7%)	3 (10%)	0	0.544
Postoperative exocrine insufficient		19 (43%)	15 (48%)	4 (31%)	0.335
MCS (mean)		79.1 (SD 16.5)	75.5 (SD 16.9)	87.7 (SD 11.9)	**0.023**
PCS (mean)		79.3 (SD 21.1)	76.8 (SD 21.7)	85.3 (SD 19.3)	0.226

*BMI: body mass index, IPMN: intraductal papillary mucinous neoplasm, POPF: postoperative pancreatic fistula, PPH: post pancreatectomy hemorrhage, MCS: mental component summary, PCS: physical component summary. P-value indicates differences between the incidentaloma en non-incidentaloma group. Bold values indicate statistically significant results. * Four missings in body mass index.*

Asymptomatic pancreatic lesions

The rate of asymptomatic lesions amongst patients undergoing distal pancreatectomy was 30%. All these lesions were discovered by imaging (abdominal ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI)). Patients with an asymptomatic lesion were significantly older and had shorter follow-up (table 1). IPMN appeared to be the final postoperative diagnosis in 39% of the patients with an asymptomatic lesion. One patient appeared to have signs of chronic pancreatitis in the pathology report, but the lesion was discovered during follow-up after lung cancer and thus this lesion was pointed out as asymptomatic.

New-onset diabetes mellitus

Table 2 shows the differences between patients with and without NODM. Six patients were diabetic preoperatively. Nineteen patients developed NODM after DP (43%). It appeared that IPMN was associated with the onset of NODM and that patients with NODM suffered from complications more often. Asymptomatic lesions were not significantly associated with the onset of NODM.

Of the 19 patients with NODM, 12 started to use glucose-lowering drugs (63%). Six patients used metformin, three used insulin, two used metformin as well as insulin,

one used metformin as well as a SU-derivative. The mean duration from DP to onset of NODM was 25.9 months (SD 33.6). Eight patients developed early NODM, of whom three patients developed NODM directly postoperative during hospital admission. Eleven patients developed NODM more than 6 months postoperatively. The latest case of NODM developed after almost twelve years.

Table 2. Differences between the patients with and without new-onset diabetes (NODM).

		No NODM (n=25)	NODM (n=19)	P-value
Sex	**male**	8 (32%)	11 (58%)	0.086
	female	17 (68%)	8 (42%)	
Age		51.9 (SD 12.2)	58.2 (SD 15)	0.129
Body mass index*		24.9 (SD 3.4)	26.2 (SD 3.3)	0.225
Diagnosis				
	Chronic pancreatitis	4 (16%)	4 (21%)	
	Neuroendocrine tumor	11 (44%)	5 (26%)	
	Pseudocyst, cystadenoma	3 (12%)	0	
	IPMN	0	8 (42%)	
	Mucinous cystic neoplasm	4 (16%)	1 (5%)	
	Carcinoma	1 (4%)	0	
	Other	2 (8%)	1 (5%)	**0.004**
Asymptomatic lesion		5 (20%)	8 (42%)	0.111
IPMN	**no**	25 (100%)	11 (58%)	**0.000**
	yes	0	8 (42%)	
Operation type	**body-tail**	10 (40%)	4 (21%)	0.211
	tail	15 (60%)	15 (79%)	
Splenectomy		9 (36%)	6 (32%)	0.759
Laparoscopy		6 (24%)	2 (11%)	0.433
Complication		3 (12%)	11 (58%)	**0.003**
Non-fasting glucose (mean)		7 (SD 3.3)	8 (SD 2.8)	0.265
HbA1Cmmol/mol (mean)		43.7 (SD 12.1)	54 (SD 10.2)	**0.005**
MCS (mean)		77.1 (SD 16.8)	81.8 (SD 16)	0.357
PCS (mean)		75.8 (SD 24)	84 (SD 16.2)	0.188

*IPMN: intraductal papillary mucinous neoplasm, MCS: mental component summary, PCS: physical component summary. Bold values indicate statistically significant results. Preoperative diabetic patients (n=6) are in the analyses as 'no NODM'. *Four missings in body mass index.*

New exocrine insufficiency

In one patient the postoperative elastase-1 level was lacking. The mean elastase-1 level of the remaining patients was 314 µg/gr (SD 0.18). Table 3 shows the differences between the patients with and without new exocrine insufficiency. Three patients used enzyme supplements before surgery. Nineteen patients were considered to have exocrine insufficiency (43%), of whom eleven patients used supplements (58%). Asymptomatic

lesions were not significantly associated with the onset of exocrine insufficiency. Splenectomy was associated with the onset of new exocrine insufficiency (P=0.024). Eleven patients with exocrine insufficiency had concomitant NODM. NODM and exocrine insufficiency were not significantly correlated (P=0.086).

Table 3. Differences between the patients with and without exocrine insufficiency.

		No new exocrine insufficiency (n=25)	New exocrine insufficiency (n=19)	P-value
Sex	**male**	10 (40%)	9 (47%)	0.625
	female	15 (60%)	10 (53%)	
Age		55.5 (SD 12.8)	53.5 (SD 15.1)	0.645
Body mass index*		25.4 (SD 3.1)	25.5 (SD 3.7)	0.973
Diagnosis				
	Chronic pancreatitis	3 (12%)	5 (26%)	
	Neuroendocrine tumor	8 (32%)	8 (42%)	
	Pseudocyst, cystadenoma	0	3 (16%)	
	IPMN	6 (24%)	2 (11%)	
	Mucinous cystic neoplasm	4 (16%)	1 (5%)	
	Carcinoma	1 (4%)	0	
	Other	3 (12%)	0	0.102
Asymptomatic lesion		9 (36%)	4 (21%)	0.335
IPMN	**no**	19 (76%)	17 (90%)	0.433
	yes	6 (24%)	2 (11%)	
Operation type	**body-tail**	8 (32%)	6 (32%)	0.976
	tail	17 (68%)	13 (68%)	
Splenectomy		5 (20%)	10 (53%)	**0.024**
Laparoscopy		5 (20%)	3 (16%)	1.000
Complication		5 (20%)	9 (47%)	0.054
Elastase-1 level µg/gr (mean)**		391 (SD 14)	217 (SD 19)	**0.001**
MCS (mean)		80.5 (SD 15.1)	77.3 (SD 18.4)	0.527
PCS (mean)		77.1 (SD 23)	82.4 (SD 18.5)	0.416

*IPMN: intraductal papillary mucinous neoplasm. Bold values indicate statistically significant results. Patients using enzyme suppletion preoperatively (n=3) are in the analyses as 'no new exocrine insufficiency'. *Four missings in body mass index. **One missing in elastase-1 levels.*

Quality of life

The mean value of the physical component summary was 79.3 (SD 21.1) and the mental component summary was 79.1 (SD 16.5).

Patients with an asymptomatic lesion reported higher scores with regard to their mental health compared to symptomatic patients (P=0.023, table 1). The differences in quality of life in patients with and without NODM and new exocrine insufficiency were not significant (table 2 and 3). Lastly, the mean physical and mental component

summary were compared to those of the national Dutch population (17), matched on age. The mean age of the asymptomatic patients was 61.8, thus the quality of life of these patients was compared with the age group of 61-70 years. For patients with NODM and exocrine insufficiency the mean age was 58.2 and 53.5 respectively, thus these patients were compared with the age group of 41-60 years. All confidence intervals overlapped, indicating non-significant differences between the groups (table 4).

Table 4. Differences in physical and mental component summary (PCS and MCS) in asymptomatic patients, patients with NODM and new exocrine insufficiency, compared to the Dutch population (17).

	Dutch population 61-70yr (mean (SD), 95%CI)	**Asymptomatic 61-70yr (mean (SD), 95%CI)**	**Dutch population 41-60yr (mean (SD), 95%CI)**	**NODM 41-60yr (mean (SD), 95%CI)**	**New exocrine insufficiency 41-60yr (mean (SD), 95%CI)**
PCS	67.8 (27.8) (13.3-122.3)	85.3 (19.3.6) (73.7-97)	75 (25.3) (25.4-124.6)	83.9 (16.2) (76.1-91.7)	82.4 (18.5) (73.5-91.3)
MCS	76.9 (24.3) (29.3-124.5)	87.7 (11.9) (80.5-94.9)	77.3 (23.5) (31.2-123.4)	81.8 (16) (74-89.5)	77.3 (18.4) (68.4-86.2)

NODM: new onset diabetes mellitus, PCS: physical component summary, MCS: mental component summary.

Discussion

This case series assessed the rate of asymptomatic pancreatic lesions in a cohort of patients undergoing DP for various indications and studied postoperative NODM, exocrine insufficiency and quality of life. The overall rate of asymptomatic lesions amongst patients undergoing DP in this study was 30%. IPMN was most frequently diagnosed within this group (39%). Furthermore, asymptomatic patients were older.

Other studies investigating asymptomatic pancreatic lesions and surgery reported incidence rates varying from 6% to 37% (6, 18-20). Three of these studies also found IPMN to be the most frequent diagnosis (3, 6, 19). However, one study only investigated pancreaticoduodenectomies and not DPs (6). One study also found higher age among asymptomatic patients (19), while two other studies found no differences in age (3, 6). Our study did not find differences with regard to complications in the group with an asymptomatic lesion. Previous studies are conflicting: one reports higher incidences of POPF (6) and another reports lower incidences of POPF (3) among asymptomatic patients.

Regarding NODM, the overall rate in our study was 43%. This was largely explained by the 42% NODM rate in patients with IPMN, which was significantly associated with NODM. This high percentage of NODM is remarkable, since the number of patients with chronic pancreatitis (CP) was small in our study. It is seen that the onset of NODM is associated with the underlying disease and that NODM occurs most frequently in

patients with CP (39%) (11). In our recently published review, the rate of NODM among patients with benign or premalignant lesions was found to be much lower (14%) (11). Therefore the high percentage of patients with NODM in the IPMN group in this study is surprising. However, in our review the numbers of IPMN patients were small and were not studied separately. Thus, the present study may have found IPMN, next to CP, as a risk factor for NODM after DP.

Regarding new exocrine insufficiency, the overall rate was 43%, without differences between groups. Patients undergoing additional splenectomy however, developed new exocrine insufficiency more often. Percentages known from existing literature report incidences of exocrine dysfunction varying from 18% (21) to 27% (22), and even 59% (23). The latter study described other procedures next to DP, which could have accounted for the higher incidence of exocrine insufficiency as it is known that the type of procedure and the extent of the resection correlates with the onset of exocrine insufficiency (24). However, information on exocrine insufficiency in patients with an asymptomatic pancreatic lesion is scarce, thus this might be an important topic for further research. Information on the influence of splenectomy on exocrine insufficiency is also limited. One study from 2002 (25) compared DPs with and without splenectomy and postoperatively described severe diarrhea in two patients, however the study does not tell if this concerned patients in the splenectomy group or not. Most reviews comparing (laparoscopic) DPs with or without splenectomy report direct in-hospital complications and not exocrine (in)sufficiency (26, 27).

Regarding quality of life, the present study found that patients with an asymptomatic lesion reported better mental health. An explanation might be that asymptomatic patients suffer from less physical complaints which possibly has a positive influence on mental wellbeing. To our knowledge, no studies that specify quality of life in patients with asymptomatic pancreatic lesions exist. With regard to quality of life after pancreatic resection and pancreatic dysfunction our study did not find any significant differences and quality of life was comparable to that of the average Dutch population. A study from 2013 (28) reported that patients who developed pancreatic dysfunction had a worse physical, but not mental component summary . This study also showed that the quality of life of patients with pancreatic disease was – and postoperatively remained – lower than the quality of life of the normal population. However, a study from 2014 found that iatrogenic exocrine insufficiency did not impair quality of life (23).

An important but difficult aspect of surgery for asymptomatic pancreatic lesions is the fact that some harbor malignant potential and some do not. In this series 85% (11 out of 13) of the asymptomatic lesions had malignant potential. Earlier studies found that 25%-30% of asymptomatic pancreatic lesions was malignant and almost 50% was a malignant

precursor lesion (3, 6). For solid lesions, suspicion of malignancy is high and surgery is the preferred treatment. In cystic lesions however, chances for malignancy differ by demographic, radiographic and clinical findings and in some patients follow-up would be sufficient (7). With IPMN being the most frequent diagnosis among asymptomatic lesions, it is important that preoperative distinction between the two main types is made. In our study, 25% of the IPMNs was of the main duct type and 25% was of a side-branch type. With the main duct type harboring 70% and the side-branch approximately 25% malignancy the necessity to surgery differs greatly (7, 29). Patients' age and tumor size should be carefully considered in case of a side-branch IPMN to avoid unnecessary operations (29), especially in patients who have an asymptomatic lesion.

Limitations

Some limitations of this study should be addressed. At first, baseline differences with regard to age and follow-up between patients with and without an asymptomatic lesion were found. Thus, these groups might not be ideally comparable. With regard to quality of life it would have been of more value if a pre- and postoperative comparison could have been made, especially in patients with an asymptomatic lesion. Due to the partially retrospective aspect of this study preoperative information on quality of life was not available. However, by comparing quality of life from this study with that of the average Dutch population some conclusions could be drawn. Furthermore, the study population was relatively small and thus no further associations with regard to onset of NODM or exocrine insufficiency could be statistically assessed. Nevertheless, this study provided detailed information on patients with an asymptomatic pancreatic lesion and linked this to the onset of NODM and exocrine insufficiency and assessed quality of life, which no studies on asymptomatic pancreatic lesions have done before.

To conclude, because of future innovations in diagnostic imaging the incidence of asymptomatic pancreatic lesions is likely to increase. Larger studies in patients with an asymptomatic pancreatic lesion are needed to assess onset of NODM, exocrine insufficiency and quality of life. This, in order to adequately inform patients who are planned to undergo DP - especially for asymptomatic lesions - about the possible consequences. This is important because diabetes, also in view of the increased life expectancy, can become a lifelong complication.

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Chapter 8 Summary
Nederlandse samenvatting

Summary

Chapter 1 provides the reader with an overview of the major changes in disease prevalence that have occurred over the past decades. The population has become increasingly obese and forecasts predict an ongoing increase in the future. Together with the rise of obesity the prevalence of the metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) have increased as well, since these three conditions are highly related. Common factors of obesity, MetS and T2DM are hyperinsulinemia, altered adipocytokine levels and a state of increased inflammation. These factors are thought to stimulate carcinogenesis because they have effects on - for instance - cell proliferation, apoptosis and angiogenesis. As a result, T2DM has been linked to an increased cancer incidence and mortality. This thesis studies the incidence and mortality of breast and colorectal cancer among diabetic patients in a meta-analysis. Additionally, detection bias and duration of diabetes (DM) were investigated with regard to cancer incidence. In esophageal adenocarcinoma the expression of the insulin-like growth factor-1 receptor (IGF-1R) and its influence on prognostic parameters was assessed. Also the influence of diabetes on the chance of undergoing surgery for esophageal adenocarcinoma was studied.
Moreover, diabetes can also occur after distal pancreatectomy (DP). DP is an increasingly performed procedure due to enhanced detection of asymptomatic pancreatic lesions. In a systematic review we obtained exact percentages of new-onset diabetes (NODM) after DP and in a case series we assessed the rate of asymptomatic pancreatic lesions and studied the effect of DP on endo-, exocrine pancreatic function and quality of life.

Chapter 2 describes the results of a meta-analysis investigating the association between DM and breast and colorectal cancer incidence and cancer-specific mortality. A total of twenty studies, consisting of controlled trials, prospective or pooled cohort studies, were included. The studies predominantly comprised patients with type II DM. It was seen that patients with diabetes had significantly increased incidences of breast, as well as colorectal cancer compared to non-diabetic patients. Also with regard to breast and colorectal cancer mortality the diabetic patients experienced higher mortality rates. This meta-analysis indicated that DM is a risk factor for breast and colorectal cancer incidence and mortality. However, future studies should adjust for diabetes duration and use of glucose-lowering drugs.

In **chapter 3** detection bias and duration of DM and the association with cancer incidence were studied in more detail in a large cohort of the Rotterdam Study. The

total cohort consisted of 10.181 individuals. Incident diabetes was associated with an increased overall risk of incident cancers and pancreatic cancer. A diagnosis of diabetes less than three months before the diagnosis of cancer was associated with strongly increased risks of all- and pancreatic cancers. We concluded that the magnitude of the association between diabetes and an increased risk of cancer seemed to be inflated by detection- or protopathic bias. However, future studies investigating this association should include a plausible aetiological risk window to assess when exactly diabetes has its impact in carcinogenesis.

In **Chapter 4** the expression of the insulin-like growth factor-1 receptor (IGF-1R) in esophageal adenocarcinoma (EAC) is investigated. The incidence of EAC increases, maybe due to the increasing prevalence of obesity and diabetes. Because hyperinsulinemia might promote carcinogenesis via the IGF-1R its expression was studied in correlation with diabetes and prognostic parameters in patients with EAC. Absence of IGF-1R appeared to be associated with T3-, grade 3 tumors and R1 resections. Diabetes was not associated with IGF-1R-expression. Furthermore, IGF-1R was present in Barrett tissues, but diminished in high-grade dysplasia. Absence of IGF-1R might be a result of tumor dedifferentiation. Also, IGF-1R might be an additional tumor marker in Barrett's esophagus, since a change in expression patterns was found in the course from normal esophageal tissue to adenocarcinoma.

In **Chapter 5** the influence of diabetes on the chance to undergo surgery for EAC and mortality is discussed. EAC still has a dismal prognosis and many patients are - often because of comorbidities – not eligible for surgery, despite improved surgery techniques. Patients were selected from the Eindhoven Cancer Registry; a total of 2729 with EAC were included in the study. DM significantly reduced chances of surgery in univariable analyses but after adjustment for age this effect disappeared. DM did not have any influence on overall mortality. Surgery – unsurprisingly – decreased overall mortality and diabetes was not of significant influence on mortality after surgery. The fact that diabetes did not have any influence on mortality could be explained by the dismal prognosis of EAC. Moreover, the surgeon probably selects the healthiest diabetic patients for surgery.

In **Chapter 6** the results of a systematic review investigating the incidence of new onset-diabetes after distal pancreatectomy are presented. Postoperative diabetes is a common problem after DP, but so far, exact rates were not known. In this review, a total of twenty-six studies were included, comprising 1731 patients undergoing DP. The average rate of NODM after DP performed for chronic pancreatitis was 39% and for benign or

(potentially) malignant lesions it was 14%. The average percentage of insulin-dependent diabetes among patients with NODM was 77%. This review showed that NODM is a frequently occurring complication, with the incidence depending on the preexisting disease. Because NODM can affect quality of life, patients undergoing DP should be preoperatively provided with this information as specific as possible.

Distal pancreatectomy is an increasingly performed procedure because of increased detection of asymptomatic, potentially (pre)malignant pancreatic lesions. In **chapter 7** the rate of asymptomatic pancreatic lesions is studied in a case series of 44 patients who underwent DP. Postoperative endo- and exocrine pancreatic function and quality of life was assessed. In 30% the DP was performed for an asymptomatic lesion and 39% of asymptomatic lesions were intraductal papillary mucinous neoplasms (IPMN). The overall rate of NODM was 43%, with IPMN being significantly associated with NODM. New exocrine insufficiency developed in 43% of the patients and asymptomatic patients reported better mental health compared to symptomatic patients. Larger studies should further assess the harm that might be done to patients who undergo DP because of an asymptomatic pancreatic lesion.

Nederlandse samenvatting

Hoofdstuk 1 geeft een overzicht van de grote veranderingen op het gebied van ziekte prevalentie die zich de afgelopen decennia hebben voorgedaan. De populatie is in toenemende mate obees geworden en de voorspelling is dat dit in de toekomst alleen maar zal toenemen. Samen met de gestegen prevalentie van obesitas zijn ook de prevalentie van het Metabool Syndroom (MetS) en diabetes mellitus type 2 (T2DM) toegenomen aangezien deze drie aandoeningen direct aan elkaar verwant zijn. Gezamenlijke factoren behorend bij obesitas, MetS en T2DM zijn hyperinsulinemie, verhoogde adipocytokine levels en een verhoogde staat van inflammatie. Van deze factoren wordt gedacht dat zij de carcinogenese stimuleren, omdat zij allen effect hebben op bijvoorbeeld celproliferatie, apoptose en angiogenese. Dit heeft als gevolg dat T2DM wordt geassocieerd met een verhoogde kanker incidentie en mortaliteit. In dit proefschrift wordt de incidentie en mortaliteit van mamma- en colorectaalcarcinoom onder diabeten bestudeerd in een meta-analyse. Aanvullend worden detection bias en de duur van diabetes (DM) en hun invloed op kanker incidentie onderzocht. De expressie van de insulin-like growth-factor-I receptor (IGF-1R) in het adenocarcinoom van de oesophagus wordt bekeken en gecorreleerd aan prognostische parameters. Verder wordt nog de invloed van DM op de kans om chirurgie bij een oesophagus adenocarcinoom (OAC) te ondergaan onderzocht.
Daarnaast kan DM ook voorkomen na een distale pancreatectomie (DP). Deze operatie wordt in toenemende mate uitgevoerd vanwege een verhoogde detectie van asymptomatische laesies in het pancreas. Door middel van een systematisch review hebben we exacte percentages van new-onset diabetes (NODM) na DP verkregen en in een case serie hebben we gekeken naar het aantal asymptomatische pancreas laesies en hebben we het effect van een DP op de endo- en exocriene pancreasfunctie en kwaliteit van leven onderzocht.

Hoofdstuk 2 beschrijft de resultaten van een meta-analyse die de associatie tussen DM en de incidentie en mortaliteit van mamma- en colorectaal carcinoom onderzoekt. Twintig studies, bestaande uit controlled trials, prospectieve of gepoolde cohort studies, werden geïncludeerd. Deze studies bevatten met name patiënten met T2DM. Wat werd gezien is dat patiënten met DM een significant verhoogde incidentie van mamma- alsmede van colorectaal carcinoom hadden ten opzichte van patiënten zonder DM. Ook de mortaliteit van deze twee carcinomen was hoger onder patiënten met DM. Deze meta-analyse laat zien dat DM een risicofactor is voor het ontstaan van en sterven aan mamma- en colorectaal carcinoom. Toekomstige studies moeten

echter nog corrigeren voor de duur van de DM en het gebruik van glucose verlagende middelen.

In **hoofdstuk 3** worden detection bias en de duur van DM en de relatie met kanker incidentie nader onderzocht in een groot cohort van de Rotterdam Studie. Het totale cohort behelst 10.181 patiënten. Incidente DM was geassocieerd met een verhoogd overall risico op incidente kankers en pancreas carcinoom. Een DM diagnose minder dan drie maanden voor de kanker diagnose was geassocieerd met een sterk verhoogd risico op alle en pancreas carcinomen. We concluderen dat een groot deel van de associatie tussen DM en het verhoogde kankerrisico wordt veroorzaakt door detection- of protopathic bias. Toekomstige studies die deze associatie onderzoeken dienen echter wel een etiologisch risico window op te nemen zodat onderzocht kan worden wanneer DM precies zijn impact heeft in de carcinogenese.

In **hoofdstuk 4** wordt de expressie van de insulin-like growth factor-1 receptor (IGF-1R) in oesophagus adenocarcinoom (OAC) onderzocht. De incidentie van het OAC stijgt, mogelijk door de toegenomen prevalentie van obesitas en DM. Omdat hyperinsulinemie misschien de carcinogenese stimuleert via de IGF-1R werd de expressie hiervan onderzocht en gecorreleerd aan DM en prognostische parameters in patiënten met een OAC. Afwezigheid van expressie van IGF-1R was geassocieerd met T3 en graad 3 tumoren en R1 resecties, met als gevolg een verlaagde vijfjaars overall survival. DM was niet geassocieerd met IGF-1R-expressie. Daarnaast was IGF-1R aanwezig in Barrett weefsel, maar de expressie nam af in weefsels met hooggradige dysplasie. Afwezigheid van IGF-1R is mogelijk een gevolg van tumor dedifferentiatie. IGF-1R kan misschien ook gebruikt worden als een tumor marker in Barrett oesophagus, omdat een verschil in expressiepatronen werd gevonden in het beloop van normaal oesophagus weefsel tot aan een adenocarcinoom.

In **hoofdstuk 5** wordt de invloed van DM op de kans om chirurgie voor OAC te ondergaan bestudeerd, evenals de invloed van DM op de mortaliteit. OAC heeft, ondanks verbeterde chirurgische technieken, nog steeds een slechte prognose en veel patiënten komen niet in aanmerking voor een operatie, vaak vanwege comorbiditeit. Vanuit de Eindhoven Cancer Registry (ECR) werden 2729 patiënten met een OAC geïncludeerd in de studie. DM reduceerde de kans op chirurgie significant in univariabele analyses, maar na correctie voor leeftijd verdween dit effect. DM bleek geen invloed te hebben op de overall mortaliteit. Chirurgie verlaagde – niet onverwacht- de overall mortaliteit en DM had geen significante invloed op de mortaliteit na chirurgie. Het feit

dat DM geen invloed had op de mortaliteit wordt misschien verklaard door de slechte prognose van OAC. Daarnaast selecteren chirurgen waarschijnlijk de gezondste diabeten om chirurgie te ondergaan.

Hoofdstuk 6 beschrijft de resultaten van een systematisch review welke de incidentie van new-onset diabetes na distale pancreatectomie (DP) onderzoekt. Postoperatieve diabetes na DP is een veelvoorkomend probleem, maar desondanks waren tot op heden exacte percentages niet bekend. In dit review werden 26 studies geïncludeerd met totaal 1731 patiënten die een DP ondergingen. Het gemiddelde percentage van NODM na DP die voor chronische pancreatitis werd uitgevoerd bedroeg 39%, waar het percentage voor benigne of mogelijk (pre)maligne laesies 14% was. Het gemiddelde percentage van insuline-afhankelijke diabetes onder de patiënten met NODM bedroeg 77%. Dit review liet zien dat NODM een veel voorkomende complicatie is, waarbij de incidentie afhangt van de onderliggende ziekte. Omdat NODM de kwaliteit van leven kan aantasten moeten patiënten die een DP ondergaan preoperatief zo goed mogelijk geïnformeerd worden over deze complicatie.

Een DP wordt in toenemende mate uitgevoerd vanwege de verhoogde detectie van asymptomatische, mogelijk (pre)maligne laesies in het pancreas. **Hoofdstuk 7** bestudeert asymptomatische pancreas laesies in een case serie van 44 patiënten die een DP ondergingen. De postoperatieve endo- en exocriene pancreasfunctie en de kwaliteit van leven werd in deze groep onderzocht. In 30% van de gevallen was de DP uitgevoerd voor een asymptomatische laesie en 39% hiervan betrof een intraductale papillaire mucineuze neoplasie (IPMN). Het totale percentage patiënten met NODM bedroeg 43%, waarbij IPMN significant geassocieerd was met NODM. Een percentage van 43% van de patiënten ontwikkelde nieuwe exocriene insufficiëntie. Daarnaast rapporteerden asymptomatische patiënten een betere mentale gezondheid vergeleken met symptomatische patiënten. In de toekomst dienen grotere studies de mogelijke schade die patiënten kunnen ondervinden van een DP die uitgevoerd is voor een asymptomatische pancreaslaesie nader te onderzoeken.

Chapter 9 General discussion and future perspectives

K.M.J. De Bruijn and C.H.J. van Eijck

General discussion and future perspectives

With the tremendous increase of obesity in the worldwide population and a subsequent increase of type 2 diabetes mellitus (T2DM) (1, 2) attention has gone out the possible association between T2DM and cancer incidence and cancer mortality. The numerous studies that have been published on this topic initially caused some panic among physicians. However, later on it appeared that most of the studies did not account for some important biases that can be present in studying the diabetes-cancer link (3-5).
In this thesis we aimed to investigate aspects that had not yet been sufficiently investigated with regard to diabetes and incidence and prognosis of surgical malignancies. Additionally, the influence of pancreatic surgery on pancreatic function and new-onset diabetes (NODM) was studied in more detail.

T2DM and cancer incidence, prognosis and future perspectives

During the past few years, a large body of evidence has indicated a strong association with T2DM and cancer incidence. All cancers combined, pancreas, liver, colorectal, (postmenopausal) breast, kidney, bladder and endometrial cancer have been consistently associated with T2DM (3, 5, 6). However, a large part of the association is influenced by detection bias as shown in this thesis. The risk is particularly increased in the period just after the diabetes (DM) diagnosis, which can indicate increased medical surveillance, as described in this thesis and other studies (7-9). However after this first period, risks for cancer among DM patients remain increased - yet somewhat declined (3, 9). Regarding liver and pancreatic cancer the association is largely due to reversed causality with the cancer initiating DM (3, 6). What needs to be investigated in more detail is the so-called latency or sojourn period that is present in carcinogenesis (10, 11). Because this period differs per cancer type it is difficult to determine a correct aetiological risk window and to analyse when diabetes has its possible impact on carcinogenesis.
With regard to cancer mortality, it is important to distinguish all-cause and cancer-specific mortality. Our meta-analysis proved that DM increased breast and colorectal cancer-specific mortality. It has been seen that cancer incidence and cancer-related mortality are not interchangeable (4). For colorectal, liver, pancreas and bladder positive associations with regard to cancer mortality have been found (12-15). However, for breast and endometrial cancer results are somewhat inconsistent (12, 14).
When studying the link between T2DM and cancer mortality, one should account for several biases that can occur, for example the possible diminished use of cancer screening among diabetics (16-18), more advanced tumour stage at diagnosis (19, 20) and selection bias for cancer treatment (21, 22). This thesis assessed the chance of undergoing surgery

for esophageal adenocarcinoma and found that probably only the healthiest diabetic patients are selected for surgery. With regard to mortality DM had no influence in patients with esophageal adenocarcinoma. This is probably because of the grim prognosis of esophageal adenocarcinoma and thus DM cannot be a competing cause of death. This reflects in the fact that other studies proved that excess mortality with DM was mostly seen in cancer types with long survival rates (23, 24).

With regard to the insulin-like growth factor receptor-1 (IGF-1R) its expression has been described in a majority of solid tumours (25). Concerning the influence of IGF-1R expression on cancer progression and prognosis, results are not completely consistent among the different cancer types. Some studies find that an increased expression of IGF-1R correlates with worse prognosis (26-28), while other studies consider IGF-1R as a good prognostic marker (29, 30). It is important to investigate whether IGF-1R could function as a prognostic marker in tumour tissue, which might be the case as shown in this thesis where we describe a high expression of IGF-1R in Barrett's esophagus. This is also important in the light of IGF-1R inhibiting therapies, which have been more closely investigated during the past years. Several studied approaches include monoclonal antibodies and tyrosine kinase inhibitors ligand binding antibodies (31, 32). Patients with tumours that express 1GF-1R might benefit from these kinds of therapies, however more studies are needed to find suitable biomarkers and to study adverse effects and interactions with normal cancer treatment regimens in more detail (31, 32, 33).

An important issue that has not been addressed in this thesis is the influence of glucose-lowering drugs (like metformin) and cancer risk and cancer mortality. Initially, metformin was found to decrease cancer risk (34-36). However, most of these studies did not take into account important biases with the result that the protective effect of metformin was probably exaggerated. Thus, true treatment and duration effects of metformin are not clear yet and more, well-conducted epidemiological studies are needed before metformin will be associated with a decreased cancer incidence (37-39).

To conclude, the link between T2DM and cancer incidence and mortality has been established, however some aspects still need more careful investigation. Despite this established link cancer screening among all diabetics might be too premature. Only in case of pancreatic or liver cancer, where the cancer is associated with the onset of DM it might be beneficial to screen patients. For instance, patients who do not carry normal risk factors for diabetes but do develop this disease might be candidates for pancreas or liver cancer screening. With regard to other cancers screening of all diabetic patients might not yet provide enough benefits and is probably too costly. A first improvement however, could be the reassurance of screening of diabetic patients whom belong to an eligible screening population (e.g. breast or cervical cancer screening due to a certain age). As

described above, diabetic patients undergo less screening and finding out which factors contribute to this phenomenon might lead to a first improvement.
Nevertheless, we think that the problem of obesity and subsequent T2DM must be dealt with from its origin. This thesis emphasizes once more the need for a globally increased awareness with regard to prevention of obesity and T2DM. Especially since it has been seen that not only adults, but also children have become increasingly obese with 42 million children under the age of 5 being overweight or obese in 2013 (40). Furthermore, overweight and obesity were first considered problems of high-income countries, but are now becoming increasingly prevalent in low- and middle income countries, thereby additionally contributing to the increase in childhood overweight and obesity (40).
The World-Health Organization (WHO) has identified priorities for population-based strategies to prevent childhood obesity. Interventions with regard to dietary patterns and physical activity must take place at national, sub-national and local levels in order to achieve desired effects (41). Especially in low- and middle-income countries where health care is less developed more possibilities with regard to prevention should be created. Otherwise the increase of obesity and T2DM will have ongoing and detrimental effects on health care, accompanying costs and the health of the global population. By preventing obesity and subsequent T2DM an increase in cancer occurrence and cancer mortality might be prevented.
In the case of existing diabetes, treatment should be as strict as possible, to reassure well-controlled diabetes. In this way physicians should reduce the chance of complications due to diabetes and maybe prevent the onset of cancer.

Diabetes following pancreatic surgery

Enhanced detection of asymptomatic pancreatic lesions leads to increased rates of pancreatic resections, mainly distal pancreatectomies (DPs) (42). Since a large amount of these incidentally discovered lesions harbor malignant potential (42, 43), surgery can be of great importance. However, in case of lesions that might not require surgery, like side-branch intraductal papillary mucinous neoplasms (SB-IPMN), it is important to perform careful preoperative examinations. In this way unnecessarily performed surgery can be prevented. Especially since we showed in this thesis that the incidence of new-onset diabetes (NODM) can be very high after DP and that IPMN might be associated with the onset of NODM.
With an expected ongoing increased detection of asymptomatic pancreatic lesions, for example due to the use of total-body scans, enhanced screening and future innovations, other procedures next to DP should be investigated. For instance central pancreatectomy (CP). Rates of NODM after CP are reported to be lower compared to DP however, rates

of pancreatic fistula are higher (44, 45). Furthermore, the risk of a nonradical resection is present in CP when resected lesions postoperatively appear to be malignant.
DP cannot be avoided yet and thus NODM will remain a common complication after DP. Surgeons should be aware of the harm they might inflict on patients and they should clearly inform patients about this diabetes risk before they undergo surgery. With the results of our meta-analysis, patients can now be more accurately informed. However, it is unknown whether the relative high percentage of NODM in the literature after DP is due to obesity and preoperative hyperinsulinemia of most patients. Again, an increased awareness with regard to prevention of obesity might prevent this harmful complication in these patients.
With regard to **future perspectives** on this topic diabetes after pancreatic surgery might be prevented with the help of islet autotransplantation (IAT). IAT has been performed in cases after partial or total pancreatectomy in patients with chronic pancreatitis (46, 47). Possibly, by extending the indications for IAT, the problem of brittle NODM after surgery in patients who undergo extensive pancreatectomy for benign or (potentially) malignant pancreatic disease might be postponed or even prevented (46, 48). However, more data on this topic should be gained before implementing this into daily surgical practice.

To conclude, the diabetes-cancer links does exist, but detection bias accounts for the largest part of the increased cancer incidence. Diabetes increases the mortality of breast and colorectal cancer, but more studies are needed to definitively establish mortality rates per cancer type among patients with diabetes. The IGF-1R, which is activated by insulin, might serve as a prognostic marker in Barrett's esophagus and esophageal adenocarcinoma and should further be studied, also in other cancers. Diabetic patients are thought to receive less or less aggressive treatment for cancer, however in this thesis diabetes did not decrease chances for surgery in esophageal adenocarcinoma.
With regard to pancreatic surgery and diabetes, this thesis describes exact numbers of NODM after distal pancreatectomy. This aids physicians in carefully informing their patients before surgery, especially when it comes to patients with an asymptomatic pancreatic lesion. In the light of diabetes and cancer, ways to prevent NODM after DP should be found.
Most important of all, great attention should go out to the prevention of obesity and subsequent diabetes in a world where these diseases have become - and account for - major health issues.

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Appendices

List of publications

Acknowledgments

PhD-portfolio

Curriculum Vitae

List of publications

De Bruijn K.M.J, Arends L.R, Hansen B.E, Leeflang S, Ruiter R, van Eijck C.H.J. 'A systematic review and meta-analysis on the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer.' *Br J Surg. 2013 Oct;100(11):1421-9*

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Other publications

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BMJ Case Rep. 2013 Sep 16;2013.

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Z-flat bewoners, oud en nieuw, wat was het soms lachen, gieren, brullen in de Hunkerbunker... Van Flügels in de koelkast tot (extreem) slechte kantoorhumor... Dat er nog letters op papier kwamen was soms een klein wonder. Zonder jullie was het promoveren een stuk minder aangenaam geweest. Voor de achterblijvers: het ga jullie goed daar!

Alle assistenten uit het EMC en uit de regio, zowel op de vele borrels, maar ook op de racefiets buiten werktijd is het altijd weer leuk, wat is de Rotterdamse regio toch gezellig! Één ding; er moet wel weer meer gefietst gaan worden! Ik heb in ieder geval nu weer wat meer tijd...

Voutje bedankt! Zonder jouw hulp was de kaft denk ik jammerlijk mislukt.

Lioor, Mar, Juul en Em; het begon met het studiegroepje in ons eerste jaar (ok, Mar schoof later aan) en het is nog steeds gezellig! Hoe mooi is het dat we inmiddels allemaal in opleiding zijn! Ik ben er heilig van overtuigd dat jullie allen een glansrijke carriére te wachten staat.

EJD 2007! Maaike, Janneke, Eline, Jiska, Geeske, Sam (en Chloe). Wat zijn wij een uniek stel apart! Iedereen zo anders, maar toch een mooi geheel. Dat iedereen nog steeds door één deur kan verbaast me eigenlijk nog steeds ;) Supermooi dat we elkaar nog steeds zien, waarbij iedereen op zijn gebied nog steeds de meest fantastische dingen bereikt: Olympische Spelen, moeder worden, kookboeken schrijven, carriéretijgers; nog steeds topsport! Dat wij nog maar lang lol mogen hebben!

Meisjes van 6B, mijn dierbaarste vriendinnetjes! An, wat kennen wij elkaar al lang. Van de peuterschool tot de turnzaal en de opzettelijk slapeloze nachten vol met kattenkwaad... Ik hoop écht écht écht dat als we oud en grijs zijn nog steeds kunnen lachen en kletsen zoals nu! Suus, jij getrouwd, ik gepromoveerd; serious business... Desalniettemin hoop ik dat wij nog heel vaak onze avondjes kletsen met wijntjes zullen gaan hebben. Mees, de globetrottert naar Nijmegen! Superknap dat je die stap hebt durven nemen. Ik kijk nu al uit naar jouw promotie!

Mijn paranimfen, Eelke en Kirsten. Eel, van huisgenootje tot paranimf, hoe leuk!! Ik ben heel blij dat wij gezellig samen bij de chirurgie zitten, misschien over niet al te lange tijd wel samen in het Ikazia....! Met jou gaat het helemaal goed komen, dat weet ik zeker. Ik ben heel blij met jou als vriendinnetje en collega! Als jij over niet al te lange tijd jouw dankwoord geschreven hebt gaat nog een keer het dak eraf!

Kir, dank dat je mijn paranimf wilt zijn ondanks jouw drukke leven! Werk, verhuizen/verbouwen en nog wat meer... Ik heb bewondering voor alles wat jij altijd zó enorm goed doet, al vanaf dat ik je leerde kennen in de eerste klas. Ik wens je veel liefde en gezondheid samen met jouw Olaf!

Gerard en Marja, ik prijs me gelukkig met zo'n fijne schoonfamilie!

Anke en Anouk, lieve schatzies! Ik ben trots op jullie! Aak, hoe jij het allemaal voor elkaar bokst, ik vind het heel erg knap...! Met de twee boykes erbij, ik zou het je niet nadoen. Nouk, de beste OK-assistente uit het SFG, jij geniet van het leven en maakt lol, blijf dat doen! Ik hou van jullie!
Knook, jij bent inmiddels ook part of the family, ik ben blij dat je erbij bent gekomen! O wee als je vertrekt...

Lieve pap en mam, dank jullie wel voor jullie altijd aanwezige steun, vertrouwen en blijk van trots. Ik heb geluk met zulke lieve, zorgzame ouders. Ook al is de situatie nu anders, ik zal er altijd voor jullie zijn, wat er ook gebeurt. Ik hou van jullie.

Lieve Bernard, wat ben jij een lucky shot (of moet ik zeggen swipe? ;))! Ik kan me geen liever persoon wensen. Jouw energie, humor en positieve kijk op het leven zijn heerlijk. Dankjewel voor je luisterend oor wanneer nodig. Nu samen in de Tabor is het begin van hopelijk nog veel meer leuks! Ik hou van je!

PhD-portfolio

Name PhD-student:	Kirstin Marie Jeanne De Bruijn, MD
ErasmusMC Department:	Surgery
PhD-period:	01-07-2012 – 24-06-2015
Research group:	ErasmusMC, Department of Surgery, division of pancreatic surgery
Promotor(s):	prof. dr. C.H.J. van Eijck prof. dr. B.H. C. Stricker

1. PhD-training

	Year	Workload (ECTS)
General courses		
Nihes-Introduction to Data-analysis (ESP03)	2012	1.0
MolMed Basic Introduction Course on SPSS	2012	0.8
BROK-course	2012	1.0
MolMed Biomedical English Writing Course	2012	2.0
Endnote course	2012	1.0
CPO mini-course	2013	0.5
Basic literature search course	2013	0.5
Presentations conferences		
ECCO-congress (international)	2013	2.0
NVvH Najaarsdag (national)	2013	2.0
DCRC meeting (international)	2014	2.0
EASD (international)	2014	2.0
AUGIS (international, poster presentation)	2014	1.0
ADIT (international, invited speaker)	2015	2.0

2.Teaching	Year	Workload (ECTS)
Examination BLS medical students	2013-14	0.5
Tutor medical students	2013	0.5
MDL-minor teaching	2013-14	0.5
Supervising medical students	2013-14	0.5

Curriculum Vitae

Kirstin Marie Jeanne De Bruijn werd geboren op 15 juni 1986 te Rotterdam als jongste van drie dochters. Ze groeide op in Capelle aan den IJssel en later Rotterdam. Tijdens haar middelbare schooltijd turnde ze fanatiek en werd ze Nederlands Kampioene. Ze behaalde haar eindexamen gymnasium in 2004. Datzelfde jaar startte ze met haar studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Tijdens haar studententijd deed ze aan wedstrijdroeien bij de Rotterdamsche Studenten Roeivereniging Skadi. Haar oudste co-schap vond plaats op de afdeling chirurgie in het Maasstad Ziekenhuis. In maart 2011 behaalde ze haar artsexamen. Daarna werkte zij ruim een jaar als ANIOS chirurgie in het ErasmusMC. Vanaf juli 2012 werkte ze als arts-onderzoeker in het ErasmusMC waarin de basis voor dit proefschrift werd gelegd. Vanaf 1 januari 2015 is Kirstin gestart met de opleiding tot chirurg in het ErasmusMC (opleider: dr. B.P.L. Wijnhoven), welke zij zal gaan continueren in het Ikazia Ziekenhuis (opleider: dr. P.T. den Hoed). Ter ontspanning en vermaak houdt Kirstin van sporten (wielrennen (al dan niet met collega's), hardlopen en bikram yoga), lezen, koken en muziek.