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Diabetes mellitus and outcomes of colorectal cancer

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Abstract

Background. Patients with diabetes mellitus have an increased risk of colorectal cancer. However, there is limited information on the outcome for diabetic patients diagnosed with this type of cancer. *Methods.* The health records of all 1 194 patients treated for colorectal adenocarcinoma at Levanger Hospital from 1980–2004 were reviewed. Diabetes status and prognostic factors were registered. Primary endpoints were cancer specific survival and overall survival. *Results.* There were no significant differences between diabetic patients and non-diabetic patients concerning stage, grade, treatment, infective or non-infective postoperative complications, hospital stay, or 30 days mortality after laparotomy. After a curative resection, the estimated 5-year cancer specific survival in 97 diabetic patients was 73% (95% CI 60–87) and 79% (95% CI 75–82) in 1097 non-diabetic patients (not significant). The estimated overall 5-year survival in patients treated with curative intent was 46% (95% CI 33–59) in diabetic patients and 65% (95% CI 62–69) in non-diabetic patients ($p < 0.001$). The diabetic patients were significantly older and more frequently had cardiac diseases. *Conclusion.* Diabetes mellitus did not affect the short-term survival or the cancer specific survival. A shorter overall survival was associated with cardiac diseases and higher age.

Several studies have shown an increased incidence of cancer, including colorectal cancer, in diabetic patients [1–7]. There is limited information on the short and long-term outcome for diabetic patients diagnosed with colorectal cancer [8]. In some reports, diabetic patients had a worse cancer related prognosis [9], while other investigators found no such relationship [10,11].

The purpose of this study was to investigate if diabetic patients diagnosed with a colorectal adenocarcinoma presented with more adverse characteristics regarding TNM stage or tumor differentiation, received different treatments, or had a different outcome than patients without a history of diabetes in a non-selected population.

Patients and methods

The health records of all patients treated for colorectal cancer at Levanger Hospital from 1980 – 2004 were reviewed. This hospital serves a well-defined geographical area in central Norway with a population of 87 000. The patients were identified from the hospital patient registry system, and a complete cohort was obtained using data registered at the Cancer Registry of Norway.

The cohort comprised 1 194 patients with histologically confirmed adenocarcinoma of the colon or rectum. Of a total of 97 patients (8.1%) with diabetes mellitus, three patients had diabetes type 1 and 94 had diabetes type 2. The median duration of diabetes was 6 years, range 0 – 56 years. Three patients were treated with metformin, 47 patients were treated with sulfonylurea and 14 patients received both drugs. Diet regulation was the only treatment for 28 patients. Five patients used insulin as monotherapy and insulin was combined with peroral antidiabetic drugs in 23 patients. The prevalence of diabetes mellitus in this region of Norway was 4.8% in men and 5.6% in women during 1984–1986 according to the Nord-Trøndelag diabetes study [12].

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The American Society of Anaesthesiologists score [13] was used to compare preoperative comorbidity. As ASA score is influenced by diabetes it could not be used in a multivariate analysis to determine the independent predictive effect of diabetes on long-term survival. We instead chose to assess important accompanying diseases separately: Any cardiac disease, any pulmonary disease and any other disease were used as three different dichotomous variables.

To assign cancer staging, the TNM classification of malignant tumors, 6th edition was used. A stage T4b tumor was considered not to have perforated. Adjuvant chemotherapy was offered to patients with stage III colon cancer after 1995 in accordance with national guidelines.

Resection of the tumor-bearing segment of colon or rectum was defined as a major resection. If there was no evidence of metastases found in preoperative investigations and no macroscopic evidence of residual tumor after the operation, the procedure was considered a resection with curative intent. The resection was considered curative when there was an additional histological confirmation of microscopically free margin and no bowel perforation. This applied regardless of T stage. A bowel resection without curative intent due to distant metastases or local residual tumor was defined as a palliative resection. Palliative resections, bypass or stomia, as well as no operation at all were defined as treatment with non-curative intent. Recurrent disease was defined as metastases or local recurrence after a resection with curative intent.

Patients younger than 75 years old and who were considered healthy enough for a liver or pulmonary resection in case of later metastases entered a follow-up program of four visits the first year, two visits the next year, and yearly visits thereafter up to 5 years. This schedule was used all 25 years, and was based upon clinical examination, measurement of the carcinoembryonic antigen (CEA) at every visit, and the use of a chest radiograph and endoscopy at intervals. As liver ultrasound examination and CT scans became available, they were used at intervals.

Mortality data were collected from the medical records and the hospital patient registry system. By the end of January 2008, 361 (30.2%) were still alive, 483 (40.5%) were dead as a result of colorectal cancer, 244 (20.4%) were dead from other causes, and 106 (8.9%) were dead from unknown causes and had died outside the hospital.

Postoperative mortality was defined as all deaths within 30 days after laparotomy or during the same hospital stay, regardless of time. Overall survival was defined by inclusion of death from any cause. Cancer specific survival was defined as death due to colorectal cancer [14]. However, as the autopsy rate in Norway is low, calculations using "cancer specific survival" must be assessed with caution. As not all patients in the present study entered a frequent follow-up program, recurrence free survival was considered an unreliable endpoint and was not applied.

Statistical analysis

Groups were compared using Fisher's exact test for dichotomous and nominal data, Cochran-Armitage test for trend for ordinal data and Wilcoxon rank-sum test for continuous data.

Kaplan-Meier survivor functions were plotted and compared using the Log-rank test. A Cox proportional hazards model, using backward stepwise variable selection, was fitted to the data. Estimates ware accompanied by 95% confidence intervals (CI). Two-sided p-values <0.05 were considered significant. The analyses were performed using SPSS 15.0 and LogExact 8.

Results

Baseline characteristics by diabetes mellitus status

Baseline characteristics in relation to diabetes mellitus status are shown in Table I. Diabetic patients were on average 4.8 years older and more frequently had accompanying cardiac diseases than non-diabetic patients. Diabetic patients did not present with more advanced TNM stages nor did they have less differentiated tumors. The type of cancer treatment given to diabetic patients did not differ from non-diabetic patients; this is shown in Table II. Of a total of 88 patients with different types of cancer related perforations, a major resection with curative intent was only possible in 29 patients.

Postoperative complications and hospital stay

After laparotomy, the rates of infective complications were 25% in diabetic patients (21/85) and 25% in non-diabetic patients (253/994). The corresponding rates of non-infective complications were 16% (14/85) and 19% (193/994), $p=0.57$. The respective rates of 30 days postoperative mortality were 6% (5/85) and 5% (50/994), $p=0.61$. After a curative resection, the rates of infective complications were 26% in diabetic patients (16/62) and 23% in non-diabetic patients (165/707), $p=0.64$. The corresponding rates of non-infective complications were 19% (12/62) and 19% (136/707). The median

Table I. Baseline characteristics of colorectal cancer patients by diabetes mellitus status.

Characteristic	Diabetes (N = 97) n (%)	No Diabetes (N = 1097) n (%)	p-value
Age (median)	76.2	71.7	<0.001 *
Gender			
Male	54 (56)	574 (52)	0.60 †
Female	43 (44)	523 (48)	
Cardiac disease			
Yes	57 (59)	347 (32)	<0.001 †
No	40 (41)	750 (68)	
Pulmonary disease			
Yes	13 (13)	110 (10)	0.30 †
No	84 (87)	987 (90)	
American Society of Anaesthesiologists Score (ASA)			<0.001 ‡
1	1 (1)	101 (9)	
2	28 (29)	631 (58)	
3	57 (59)	318 (29)	
4	10 (10)	44 (4)	
5	1 (1)	3 (0.3)	
Bowel obstruction, without perforation, at presentation			
Yes	1 (1)	107 (10)	0.001†
No	96 (99)	990 (90)	
Bowel perforation			
Spontaneous, outside tumor	6 (6)	32 (3)	
Spontaneous, within tumor	1 (1)	12 (1)	
Perforation of tumor by surgeon	2 (2)	35 (3)	
No perforation	88 (91)	1018 (93)	
Location			0.24 *
Coecum-transverse colon	33 (34)	391 (36)	
Left flexure-rectosigmoid	39 (40)	354 (32)	
Rectum	25 (26)	352 (32)	
Stage (TNM)			
I	7 (7)	154 (14)	0.66 ‡
II	42 (43)	377 (34)	
III	22 (23)	257 (23)	
IV	18 (19)	246 (22)	
Unknown	8 (8)	63 (6)	
Poor differentiation			
Yes	15 (15)	200 (18)	0.58 †
No	82 (85)	897 (82)	
Mean percentage positive nodes after resection	15.5	17.2	0.46 *
Adjuvant chemotherapy			
Yes	3 (3)	31 (3)	0.75 †
No	94 (97)	1066 (97)	

- By Wilcoxon rank sum*
- By Fisher exact test†
- By Cochran-Armitage trend test ‡

postoperative stay after a laparotomy was 9 days regardless of the presence of diabetes.

Survival

Overall survival. Estimated overall 5-year survival for all 1 194 patients was 31% (95% CI 21–40) in diabetic patients and 46% (95% CI 42–49) in non-diabetic patients. The corresponding 10-year survival was 21% (95% CI 11–30) and 34% (95% CI 31–37), $p < 0.001$, log rank test. The Kaplan Meier survival curves after a major resection with curative intent and non-curative treatment are shown in Figure 1. A multivariate Cox regression analysis (Table IIIa) showed that diabetes, cardiac disease, pulmonary disease, other diseases, stage, and age were significantly related to overall survival, while gender was not.

After a curative resection the estimated overall 5-year survival was 46% (95% CI 33–59) in diabetic patients and 65% (95% CI 62–69) in non-diabetic

Table II. Treatment of colorectal cancer patients in relation to diabetes mellitus status.

Type of treatment	Diabetes	No diabetes
Best supportive care, no operation	8 (8%)	66 (6%)
Local resection (transanal or endoscopic)	3 (3%)	36 (3%)
Nonresective procedure (stomia or bypass)	6 (6%)	46 (4%)
Palliative resections	15 (15%)	195 (18%)
Major resection, curative intent, microscopic involved circumferential margin	2 (2%)	19 (2%)
Major resection, curative intent, bowel or tumor perforation	1 (1%)	28 (3%)
Curative resection	62 (64%)	707 (64%)
Total	97 (100%)	1097 (100%)

patients. The corresponding 10-year survival was 29% (95% CI 16–42) and 48% (95% CI 44–52), $p < 0.001$, log rank test. In a multivariate cox regression analysis (Table IIIb) of patients treated with a curative resection, diabetes was no longer significantly related to overall survival.

In 336 patients the treatment had non-curative intent. The median overall survival in these patients was 7 months (95% CI 2–13) in diabetic patients and 7 months (95% CI 5–8) in non-diabetic patients ($p = 0.70$, log rank test).

Cancer specific survival. The estimated 5-year cancer specific survival of all 1 194 patients was 52% (95% CI 40–64) in diabetic patients and 57% (95% CI 54–60) in non-diabetic patients. The corresponding 10-year cancer specific survival was 52% (95% CI 40–64) and 54% (95% CI 50–57), $p = 0.56$, log rank test. The corresponding Kaplan Meier survival curves were almost overlapping, see Figure 2. A multivariate Cox regression analysis (Table IVa) showed that stage and age were significantly related to cancer specific survival, while diabetes, cardiac disease, pulmonary disease, other diseases, and gender were not. This was also found In another Cox regression analysis, where the end-point was both death from cancer as well as death from unknown reasons.

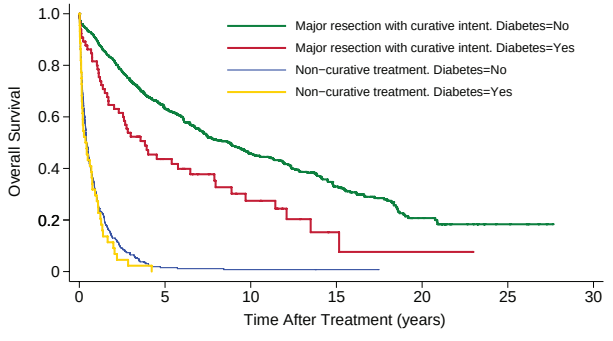

Figure 1. Overall survival after major resection with curative intent and after non-curative treatment, in relation to diabetes status.

After a curative resection the estimated 5-year cancer specific survival in diabetic patients was 73% (95% CI 60–87) and 79% (95% CI 75–82) in non-diabetic patients. The corresponding 10-year cancer specific survival was 73% (95% CI 60–87) and 76% (95% CI 72–79), $p = 0.51$, log rank test. In a multivariate Cox regression analysis (Table IVb) of patients treated with a curative resection, only age and stage were significantly related to cancer specific survival.

Discussion

In the present study there were no differences between diabetic patients and non-diabetic patients concerning stage or tumor differentiation at presentation, type of treatment and follow-up, short-term outcome, or cancer specific survival. However, overall survival was shorter in diabetic patients.

The shorter overall survival in diabetic patients treated with curative intent in this study, as well as in previous studies, may be explained by other diseases than cancer. As shown in the baseline characteristics, diabetic patients were significantly older and more frequently had cardiac disease compared to non-diabetic patients. This view was further supported by a multivariate cox regression analysis of patients treated with a curative resection where diabetes was not significantly related to overall survival. These patients are generally believed to be the healthiest among colorectal cancer patients. As the cancer specific survival was almost the same in the two groups, a direct effect of diabetes upon the cancer recurrence was considered less likely. There were no signs of more aggressive disease in diabetic patients treated with non-curative intent compared to non-diabetic patients as overall survival was the same. A large retrospective trial [10], showed a significantly elevated risk of death from any cause in patients with colorectal cancer and diabetes mellitus compared to colorectal cancer patients without diabetes. In accordance with our findings this elevated risk was due to causes of death other than colorectal cancer.

Table IIIa. Results of multivariate analysis of overall survival of patients with colorectal cancer.

Characteristics	No (%)	Non-adjusted hazard ratio	p-value	Adjusted hazard ratio	p-value
Diabetes mellitus	97 (8.1)	1.55 (1.23 to 1.96)	<0.001	1.36 (1.07 to 1.72)	0.013
Cardiac disease	404 (33.8)	1.55 (1.34 to 1.78)	<0.001	1.27 (1.10 to 1.48)	0.002
Pulmonary disease	123 (10.3)	1.41 (1.14 to 1.74)	0.002	1.28 (1.03 to 1.59)	0.024
Other diseases	502 (42.0)	1.36 (1.19 to 1.56)	<0.001	1.22 (1.06 to 1.41)	0.005
Tumor stage			<0.001		<0.001
I	161 (14)	1	1		
II	419 (35)	1.56 (1.20 to 2.02)		1.43 (1.11 to 1.86)	
III	279 (23)	2.02 (1.55 to 2.65)		1.90 (1.45 to 2.49)	
IV	263 (22)	11.25 (8.56 to14.80)		13.89 (10.5 to 18.3)	
Unknown	72 (6)	4.31 (3.06to 6.05)		3.96 (2.81 to 5.57)	
Age		1.042 (1.035 to1.050)	<0.001	1.045 (1.038 to1.053)	<0.001

When making corrections for known cardiac disease, pulmonary disease, other diseases, stage and age, diabetes still imposed an effect on overall survival in patients treated with curative intent (Table IIIa). Although these patients had no known cardiac disease, this was not excluded as many diabetic patients have incipient cardiovascular disease. In a study by Haffner et al. [15], diabetic patients with no history of cardiac disease had the same risk of myocardial infarction as patients with previous myocardial infarction and no history of diabetes.

In a large, randomized adjuvant chemotherapy trial, Meyerhardt et al. [9] found a significantly worse 5-year survival rate in diabetic patients with high-risk stage II and III colon cancer. Even more important was a 21% increased risk of cancer recurrence. Meyerhardt has been criticized for specifically failing to report deaths from colon cancer, thereby making it difficult to determine the effect of diabetes and its complications on patient survival [8]. It is however reasonable to assume that increased cancer recurrence implies worse survival. Although these are important findings for diabetic patients receiving chemotherapy, general conclusions on the prognostic effect of diabetes for all colorectal cancer patients must be drawn carefully based on subgroup analyzes.

In the present study diabetes was not associated with adverse stage or grade at presentation, in contrast to what has been shown for breast cancer [16]. The rate of curative resection was 64% in both groups, and the types of non-curative treatment were quite similar in patients with and without diabetes.

At Levanger Hospital, there were no indications of less aggressive cancer treatment in diabetic patients per se. This was in contrast to the findings of Poll-Franse et al. [17] where diabetic patients with colorectal cancer presented at a higher stage and seemed to receive radiotherapy and chemotherapy to a lesser extent.

The major strength of this study is that Levanger hospital served a well defined geographical area and a complete cohort of patients treated for adenocarcinoma in the colon or rectum during 1980–2004 was obtained, thereby avoiding selection bias. The surgery has been performed or supervised by a few, and largely the same, surgeons and according to the same surgical principles throughout the period. It seems reasonable to compare the two groups as treatment and follow-up has been similar and offered regardless of a history of diabetes or not.

As a retrospective study, there are several potential limitations. As the main aim of this study was measuring short and long-term mortality, uncertainties concerning cause of death would affect the

Table IIIb. Results of multivariate analysis of overall survival after a curative resection for colorectal cancer.

Characteristics	No (%)	Non-adjusted hazard ratio	p-value	Adjusted hazard ratio	p-value
Diabetes mellitus	62 (8.1)	1.79 (1.31 to 2.44)	<0.001		
Cardiac disease	273 (35.5)	1.96 (1.62 to 2.36)	<0.001	1.39 (1.15 to 1.69)	0.001
Pulmonary disease	72 (9.4)	1.45 (1.08 to 1.95)	0.015	1.41 (1.05 to 1.90)	0.023
Other diseases	335 (43.6)	1.69 (1.40 to 2.04)	<0.001	1.43 (1.19 to 1.73)	<0.001
Tumor stage			0.001		0.006
I	143 (18.6)	1		1	
II	390 (50.7)	1.52 (1.16 to 1.99)		1.39 (1.06 to 1.83)	
III	236 (30.7)	1.75 (1.31 to 2.33)		1.61 (1.21 to 2.15)	
Age		1.069 (1.058 to1.080)	<0.001	1.061 (1.050 to1.073)	<0.001

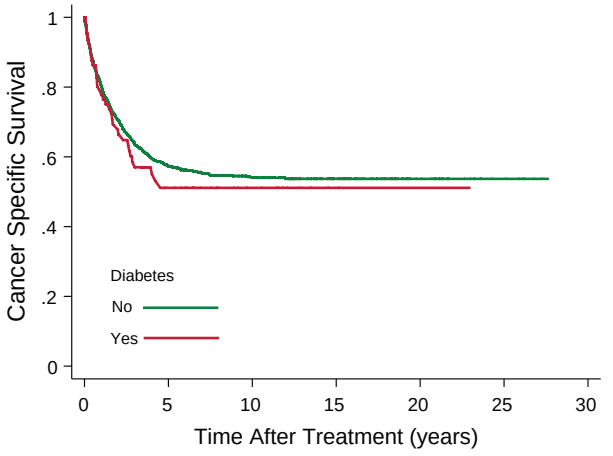

Figure 2. Cancer specific survival of 1 194 patients with colorectal cancer, in relation to diabetes status.

results. Cause of death was established through a thorough evaluation of the patients' medical records, and in most medical journals a copy of the death certificate was available. Despite these efforts, a low and even decreasing autopsy rate during the period made data uncertain. In 2006, the autopsy rate in Norway was only 12% [18]. This could affect the analysis of cancer specific survival, but was assumed to equally affect the results of patients with and without diabetes.

In Norway, national guidelines have secured equal and rigorous follow-up of patients treated for colorectal cancer younger than 75 years old. In this study, the median age of diabetic patients treated for a colorectal adenocarcinoma was 76 years and heart disease was more prevalent. This could explain why fewer diabetic patients entered the routine program, and in turn could leave cancer recurrence undiagnosed. This would also affect cancer specific survival. However, it is reasonable that these patients have been closely monitored by their primary physicians due to the emphasis on diabetes care in Norway, thereby disclosing symptomatic residual disease.

Table IVa. Results of multivariate analysis of cancer specific survival of patients with colorectal cancer.

Characteristics	n (%)	Adjusted hazard ratio (95% CI)	p-value
Tumor stage			
I	161 (14)	1	<0.001
II	419 (35)	2.72 (1.52 to 4.87)	
III	279 (23)	6.45 (3.63 to 11.5)	
IV	263 (22)	54.5 (30.9 to 96.3)	
Unknown	72 (6)	12.6 (6.62 to 23.9)	
Age		1.026 (1.018 to 1.035)	<0.001

Table IVb. Results of multivariate analysis of cancer specific survival after curative resection of colorectal cancer.

Characteristics	n (%)	Adjusted hazard ratio (95% CI)	p-value
Tumor stage			
I	143 (18.6)	1	<0.001
II	390 (50.7)	2.43 (1.28 to 4.60)	
III	236 (30.7)	5.42 (2.88 to 10.2)	
Age		1.027 (1.012 to 1.044)	<0.001

Conclusion

In the present study diabetes mellitus did not seem to affect the TNM stage or tumor differentiation at presentation, type of treatment, or the short-term outcome of patients treated for a colorectal adenocarcinoma. Cancer specific survival was the same in diabetic patients and non-diabetic patients. Overall survival was equal for diabetic patients and non-diabetic patients after treatment with non-curative intent. A worse overall survival after resection with curative intent was most likely due to comorbidity and higher age in diabetic patients.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: Results from a large-scale population-based cohort study in Japan. Arch Intern Med 2006;166:1871–7.

[2] Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: A meta-analysis. J Natl Cancer Inst 2005;97:1679–87.

[3] Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: A meta-analysis. Diabetologia 2006;49:2819–23.

[4] Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: A meta-analysis. Int J Cancer 2007;121:856–62.

[5] Limburg PJ, Vierkant RA, Fredericksen ZS, Leibson CL, Rizza RA, Gupta AK, et al. Clinically confirmed type 2 diabetes mellitus and colorectal cancer risk: A population-based, retrospective cohort study. Am J Gastroenterol 2006;101:1872–9.

[6] Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: Exploring the hyperinsulinaemia hypothesis. Br J Cancer 2001;84:417–22.

[7] Yang YX, Hennessy S, Lewis JD. Type 2 diabetes mellitus and the risk of colorectal cancer. Clin Gastroenterol Hepatol 2005;3:587–94.

[8] Richardson LC, Pollack LA. Therapy insight: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol 2005;2:48–53.

[9] Meyerhardt JA, Catalano PJ, Haller DG, Mayer RJ, Macdonald JS, Benson AB, et al. Impact of diabetes mellitus on

outcomes in patients with colon cancer. J Clin Oncol 2003;21:433–40.

[10] Polednak AP. Comorbid diabetes mellitus and risk of death after diagnosis of colorectal cancer: A population-based study. Cancer Detect Prev 2006;30:466–72.

[11] Shonka NA, Anderson JR, Panwalkar AW, Reed EC, Steen PD, Ganti AK.Effect of diabetes mellitus on the epidemiology and outcomes of colon cancer. Med Oncol 2006;23:515–9.

[12] Midthjell K, Bjørndal A, Holmen J, Kruger Ø, Bjartveit K. Prevalence of known and previously unknown diabetes mellitus and impaired glucose tolerance in an adult Norwegian population. Indications of an increasing diabetes prevalence. The Nord-Trøndelag diabetes study. Scand J Prim Health Care 1995;13:229–35.

[13] ASA Physical Status Classification System. 2006. www.asahq.org/clinical/physicalstatus.htm.

[14] Platell CF, Semmens JB. Review of survival curves for colorectal cancer. Dis Colon Rectum 2004;47:2070–5.

[15] Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.

[16] Wolf I, Sadetzki S, Gluck I, Oberman B, Ben-David M, Papa MZ, et al. Association between diabetes mellitus and adverse characteristics of breast cancer at presentation. Eur J Cancer 2006;42:1077–82.

[17] van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: A large population based analysis. Int J Cancer 2007;120:1986–92.

[18] Soreide K, Ellingsen CL. [Autopsy--quality assurance in the last link]. Tidsskr Nor Laegeforen 2007;127:2799.