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METHOD

The Impact of Diabetes Mellitus on Breast Cancer Outcomes: A Single Center Retrospective Study

Swaroopa Yerrabothala · Hamid Shaaban · Gerardo Capo · Michael Maroules · Vincent A. Debari

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Abstract Diabetes mellitus has been implicated to affect the prognostic outcomes of patients with various types of cancer. This study explores the impact of diabetes mellitus on the survival outcomes of patients with all stages of breast cancer. We performed a retrospective analysis of 255 patients with all stages of breast cancer. Survival outcomes were compared for diabetic and non-diabetic patients. A greater percent of patients in the non-diabetic group (54.1 %) presented with early-stage (stage 0 and 1) cancer than diabetics for which 41.2 % presented with stage 0 or 1 breast cancer; however this difference did not achieve statistical significance (p=0.068). Overall, we observed a significant difference in survival between the diabetics and non-diabetic subjects (p=0.001). Even after adjustment for all covariates and after stratification for Body Mass Index (BMI), diabetics were found to have a poorer prognosis in terms of survival time. In patients with breast cancer, diabetes mellitus is an independent predictor of lower overall survival rates, even after adjusting for other comorbidities. Primary caregivers and oncologists alike should aggressively screen breast cancer patients for diabetes mellitus and vice versa.

S. Yerrabothala · G. Capo
Trinitas Regional Medical Center, Seton Hall University School of Health and Medical Sciences, Elizabeth, USA

H. Shaaban (✉)
St Michael's Medical Center, Seton Hall University School of Health and Medical Sciences, St Joseph's Regional Medical Center, 111 central avenue, Newark, NJ 07102, USA
e-mail: hamidshaaban@gmail.com

M. Maroules
St Joseph's Regional Medical Center, Seton Hall University School of Health and Medical Sciences, Paterson, USA

V. A. Debari
Seton Hall University School of Health and Medical Sciences, South Orange, NJ, USA

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Introduction

Diabetes mellitus (DM) and cancer are major causes of morbidity and mortality worldwide. In the United States alone, by 2007, there were approximately 24 million people with DM (approximately 8 % of the adult population) and 2.5 million survivors of breast cancer [1]. In developed countries, Type 2 DM affects about 7 % of adults and about 15 % of people older than 60 years [2]. The main risk factors for type 2 DM are old age, obesity, and genetic predisposition. Similar to type 2 DM, the incidence of breast cancer rises with age, and the cumulative incidence in Western Europe and the USA is about 2.7 % by age 55, about 5.0 % by age 65, and about 7.7 % by age 75 [3]. An association between DM and various types of cancers was first reported more than 100 years ago and DM is now implicated as a risk factor for several types of cancers, including endometrial and pancreatic carcinoma [4]. In recent years, an increasing amount of research, both laboratory and clinical, suggest intricate associations between type 2 diabetes mellitus and breast cancer. The insulin resistance and high levels of insulin seen in type 2 diabetes mellitus are shown to be mitogenic for breast cancer cells [5]. The insulin receptors are also often overexpressed in breast cancer [6].

Breast cancer and DM commonly occur together, and up to 16 % of older breast cancer patients may suffer from DM [7–9]. The potential interactions between DM and breast cancer are not very clear and appear to be very complex. Less intensive care for either DM or breast cancer seems to negatively affect the survival in patients with DM and breast cancer [10–14].

Given the propensity for a higher risk of breast cancer in women with DM, research investigating how pre-existing

DM may influence breast cancer diagnosis, treatment, and survival is of grave importance for the proper care and education of these women. We therefore conducted a retrospective analysis to test the hypothesis that DM has adverse effect on survival in various clinical stages of breast cancer.

Methods

Design and Protocol

This is an observational, cohort-nested, case–control study. We collected medical record numbers of patients who were diagnosed with breast cancer from 2001 to 2010 using the cancer registry at an urban teaching hospital in Elizabeth, New Jersey. All the data collected was retrospective, and all identifying records were omitted from data collection sheets, in full compliance with the Health Insurance Portability and Accountability Act of 1996. This study was approved by the Institutional Review Board of TRMC.

Breast cancer patients with a decreased survival secondary to non-breast cancer-related malignancy, familial breast cancers, and patients who were diagnosed with DM after diagnosis of breast cancer were excluded from our study. After applying the exclusion criteria, we stratified all the remaining patients into two groups, based on whether they have DM type 2 or not at the time of diagnosis of breast cancer; the group of breast cancer patients with DM representing our cases and the group of breast cancer patients without DM as our controls. We matched cases to controls at 1:2 ratio, matching for age (+/− 2 years).

The variables that we collected for both groups (cases and controls) are, age at the time of breast cancer diagnosis, ethnicity, body mass index (BMI), history of alcohol abuse and smoking, whether the patient is on treatment with statins or not, stage of breast cancer as per tumor, node, metastasis (TNM) staging system, at the time of diagnosis, hormonal receptor status (estrogen, progesterone, HER-2/neu), lymph node status for stage 2 breast cancer patients, treatment for breast cancer, recurrence of breast cancer, history of bilateral breast cancer, survival of the patient (in months) since the diagnosis of cancer. For the diabetic cases, we also collected other variables—HgbA1C at the time of diagnosis of cancer, and on treatment with insulin or not.

Statistical Methods

For this study, α was set at 0.05, therefore statistical significance required $p<0.05$ (two-tailed). For analysis of univariate comparisons, interval data were subjected to the *t*-test for independently assorted groups ("unpaired" *t*-test) and nominal data were cross-tabulated in contingency tables and analyzed by Fisher's exact test. Interval data were dichotomized by the use of receiver-operator characteristic (ROC) curves.

Unadjusted hazard ratios (HR) and 95 % confidence intervals (CI) were computed from Kaplan-Meier plots; adjustment for potential confounders was based on a model which included differences in baseline characteristics and computed using Cox regression.

Data were analyzed using Prism® software (v 5.04, GraphPad Corp., San Diego, CA) or SPSS® v.18 (IBM Corp. Armonk, NY).

Results

A breakdown of the number of subjects by group (diabetic and non-diabetic) and by breast cancer stage is provided in Table 1. A greater percent of patients in the non-diabetic group (54.1 %) presented with early-stage (stage 0 and 1) cancer than diabetics for which 41.2 % presented with stage 0 or 1 breast cancer; however this difference did not achieve statistical significance ($p=0.068$). The smallest percentage of patients was seen in stage 4 for both groups; 6/85 (7.1 %) diabetics presented with stage 4 disease compared to 7/170 (4.1 %; $p=0.474$). Stages 2 and 3, combined provided 44/85 (51.8 %) of the subjects with DM and 71/170 (41.8 %) of the patients without DM ($p=0.167$).

The differences in baseline characteristics are given in Table 2. As per our protocol, we included ethnicity, smoking status, alcohol use, status of estrogen, progesterone, and HER2/*neu* receptors, including triple negativity, nodal status, bilateral vs. unilateral breast involvement and statin use in the Cox model for any comparisons for which the HR were significant (or trending toward significant, in the case of stage 2 patients. Also included was BMI; however BMI was further stratified into "overweight", i.e., >25 kg/m^2 and obese (BMI>30 kg/m^2).

For stages 0, 1 and 4 we were unable to detect any significant differences between the DM and non DM groups (Fig. 1). Not unexpectedly, 120 month survival was reasonably good for both groups with either stage 0 (Fig. 1a) and stage 1 (Fig. 1b). In the case of stage 4 breast cancers (Fig. 1c), survival was essentially poor for both groups.

Table 1 Distribution of subjects (with and without DM) in each stage

Stage	Subjects with DM (*N*=85)	Subjects without DM (*N*=170)
Stage 0	9	22
Stage 1	26	70
Stage 2	28	46
Stage 3	16	25
Stage 4	6	7

DM diabetes mellitus

Table 2 Baseline characteristics for the subjects with Diabetes Mellitus and without Diabetes Mellitus

Characteristic	Subjects with DM (*N*=85)	Subjects without DM (*n*=170)	*p* Value
Age at diagnosis of Breast Ca			
Interquartile range	55–71	55–71	0.946
Median	61	62	
BMI			
Interquartile range	25.0–37.2	24.8–32.9	
Median	29.8	28.3	0.105
Ethicity			
Hispanics	37	58	0.172
Non Hispanics	48	112	
Smoking			
Yes	34	50	0.089
No	51	120	
Alcohol			
Yes	19	17	0.009
No	66	153	
ER			
Positive	62	149	0.005
Negative	23	21	
PR			
Positive	43	118	0.004
Negative	42	52	
HER2/neu			
Positive	12	33	0.370
Negative	73	137	
Triple (ER,PR, HER2 neu)			
Negative	19	12	0.003
Not Triple Negative	66	154	
Lymph Node status in Stage II			
Positive	12	27	0.227
Negative	16	18	
Bilateral breast Ca			
Yes	10	5	0.003
No	75	165	
On Statin	54	57	<0.0001
Not on Statin	31	113	<0.0001
Recurrence			
Yes	8	14	0.8016
No	77	156	

DM Diabetes Mellitus; *BMI* body mass index; *ER* estrogen receptor; *PR* progesterone receptor

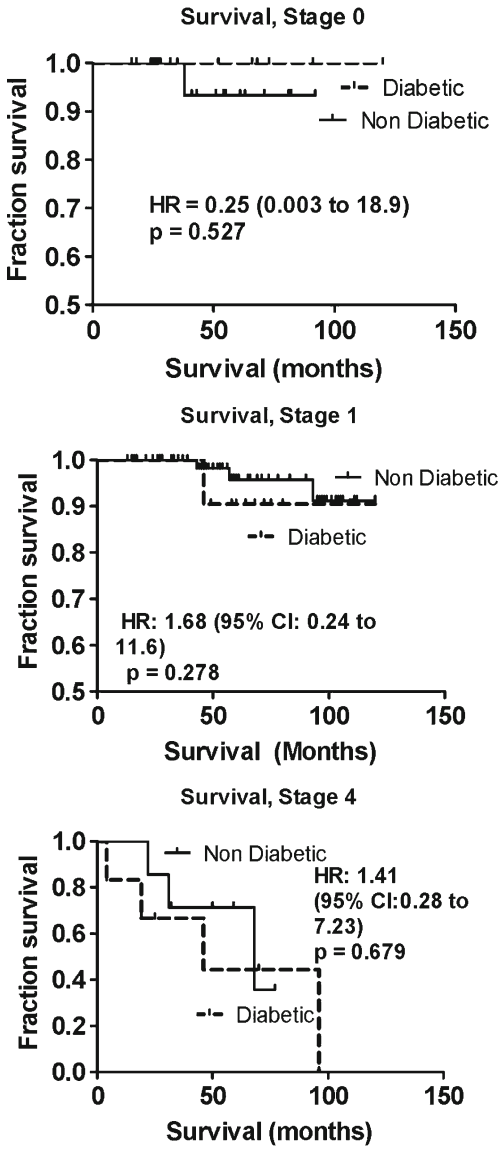

Fig. 1 Kaplan Meier plots for 10 year survival of diabetic subjects (dashed lines on plots) compared to non-diabetic subjects. (**a** *Upper Panel*) Stage 0; (**b** *Center Panel*) Stage 1; (**c** *Lower Panel*) Stage 4

Overall, however, we observed a significant difference in survival between the diabetics and non-diabetic subjects (Fig. 2a). Even after adjustment for all covariates and after stratification for BMI, diabetics were found to have a poorer prognosis in terms of survival time. This difference is based primarily on the larger number of subjects with stage 2 and stage 3 breast cancers, as described in Table 1. The data for stage 2 (Fig. 2b) suggest that, although the difference between the DM and non DM groups approached statistical significance prior to adjustment, after inclusion in the Cox model, no significant difference was detected, notwithstanding an apparent trend toward poorer prognosis in the DM group. Figure 2c shows the differences for stage 3 breast cancer for which there were significant differences in the fully adjusted model after stratification for both overweight and obese subjects.

Discussion

This study demonstrated that diabetes mellitus is associated with poor prognosis in breast cancer patients. In the

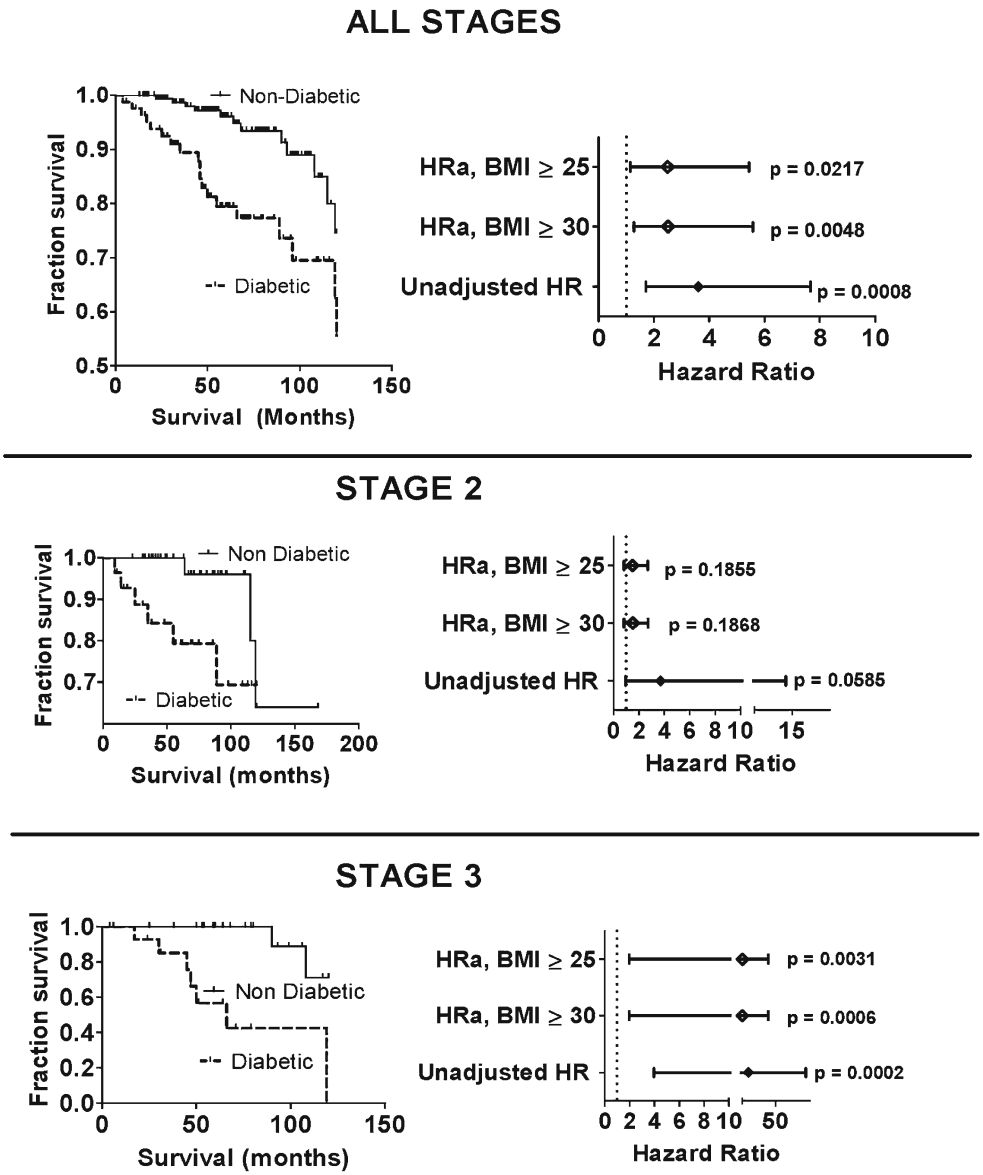

Fig. 2 Results of survival analysis for all stages of breast cancer (**a** *top panel*); stage 2 (**b** *Center panel*); stage 3 (**c** *lower Panel*) comparing diabetic subjects (*dashed lines*) and non diabetics (*solid lines*). Forest plot alongside Kaplan Meier plot shows the unadjected hazards ratio (HR) and 95 % confidence interval (CI) and the adjusted models for Body Mass Index (BMI) of ≥25 kg/m^2 and ≥30 kg/m^2. The same presentation is made for stage 2 (center panel) and stage 3 (bottom panel) breast cancers

literature, meta-analysis demonstrated that DM was associated with worse cancer prognosis compared with non-diabetic cancer patients [7]. Studies have also demonstrated that diabetic breast cancer patients have an increased risk of all-cause mortality [8, 9]. The association between breast cancer-specific mortality and diabetes mellitus is not clear. Fleming et al. concluded that breast cancer-specific mortality was not increased in diabetic patients. Srokowski et al. demonstrated increased breast cancer-specific mortality in diabetic patients receiving chemotherapy [10, 11]. There are five studies in the medical literature that have examined the impact of diabetes mellitus on the stage of breast cancer [10–15]. Four of the five studies demonstrated a correlation between diabetes mellitus and the stage of breast cancer [10, 12–14]. Conflicting results are seen in studies evaluating the relationship between tumor size, lymph node involvement and diabetes mellitus. Although a prospective study showed a strong relationship between tumor size, lymph node involvement and diabetes mellitus [10], an earlier retrospective study failed to show such a relationship [11].

Although we were able to demonstrate that, a greater percent of patients in the non-diabetic group (54.1 %) presented with early-stage (stage 0 and 1) cancer than diabetics for which 41.2 % presented with stage 0 or 1 breast cancer; however this difference did not achieve statistical significance (p=0.068). There were fewer stage 4 cases for both groups; 6/85 (7.1 %) diabetics compared to 7/170 (4.1 %; p=0.474). We also demonstrated that patients with stages 2 and 3 breast cancer combined provided 44/85 (51.8 %) of the subjects with DM and 71/170 (41.8 %) of the patients without DM (p=0.167). Therefore, in our study, we did not see a strong relationship between stage of breast cancer and DM.

The present study demonstrated that DM is an independent predictor of survival outcomes in patients with all stages of breast cancer. Furthermore, the prognostic influence of DM was consistent across multiple subgroups, including age, tumor stage, hormonal status and BMI. After further analysis, we did not detect any differences in mortality outcomes between stage 0 and 1 breast cancer patients in the diabetes and non-diabetic group. Given that patients with stage 0 and I breast cancer tend to live longer, other comorbidities are more likely to influence overall breast cancer mortality outcomes, and thereby attenuate the effects of diabetes on overall survival rates. Not surprisingly, the survival outcomes for stage 4 breast cancer in both groups were poor.

In our present study, stage 3 breast cancer patients in the diabetic group had poor survival outcomes compared to the non-diabetic group. We also discovered that these differences were statistically significant for both overweight and obese diabetic subjects. These results suggest that overweight and obese diabetic stage 3 breast cancer patients have a poor prognosis and may need to be aggressively treated with the best available surgical and chemotherapy options.

It is unclear whether diabetes directly increases breast cancer mortality. Our retrospective study suggests that diabetes is associated with an adverse prognosis in all stages of breast cancer especially at stage 3 presentation. Peiars et al. explored this and described four reasons for why diabetes may be an independent prognostic factor in breast cancer [12]. First, diabetic women typically can present with breast cancer at later stages [10, 14, 15]. Patients with DM are more likely to have other co-morbidities and because of the concomitant management of these chronic conditions by their primary care physicians, they are less likely to be routinely screened for breast cancer [12]. Second, oncologists may consider offering women with DM, a less aggressive treatment, including chemotherapy, radiotherapy, and/or surgery [10, 14]. This may be related to the concern of toxicity from therapy in patients with DM and other co-morbidities. Third, women with pre-existing DM are at higher risk of chemotherapy-related toxicity (eg, febrile neutropenia, infection) [10]. This risk is what possibly affects some oncologists' decision to opt for less aggressive treatment. The fourth possible reason (which may also explain why we noticed that obesity in addition to diabetes is a prognostic factor for breast cancer) is that these patients may have hyperinsulinemia related to the underlying insulin resistance and this might contribute to tumorigenicity. Insulin may act directly on epithelial cells or indirectly by activating insulin-like growth factor pathways or altering endogenous sex hormones [13, 14]. It is clear that further research is needed to clarify these scenarios and identify contributions of these potential contributing factors to the prognosis of breast cancer.

Recent studies have shown that metformin could be safely administered to women with breast cancer and higher insulin levels, resulting in a significant reduction in insulin levels, a modest (though significant) reduction in weight, and improvement in insulin sensitivity [14–18]. An article by Chlebowski et al. conducted a prospective study assessing associations among diabetes, metformin use, and breast cancer in postmenopausal women participating in Women's Health Initiative clinical trials [15]. The conclusion was that metformin use in postmenopausal women with diabetes was associated with lower incidence of invasive breast cancer. These findings are hypothesis generating, and this association requires replication before metformin is routinely introduced into clinical practice to decrease the risk of breast cancer.

This study has some limitations. It is a retrospective study and that limits the level of clinical detail that can be applied to the analysis. The study sample size was small. Laboratory measurements, such as serum insulin, IGF-1, hemoglobin A1C and glucose levels, were not available in our databases. The effect of diabetes treatments such as metformin or insulin on breast cancer risk could not be adequately assessed due to the lack of data.

The main conclusion of our study is that diabetes mellitus is associated with adverse outcomes in all stages of breast cancer, especially in stage 3. Primary caregivers and oncologists alike should start screening the breast cancer patients for DM and vice versa. Stage 3 breast cancer patients with DM may possibly need aggressive treatment of not only the cancer but also of the underlying concomitant DM. It is clear that more studies are necessary to evaluate the potential causal relationship between DM and breast cancer that could possibly be modified to improve the survival outcomes.

Conflict of Interest We do not have any conflict of interest.

References

1. American Cancer Society (2008) Breast cancer facts and figures 2007–2008. American Cancer Society, Atlanta
2. King H, Aubert R, Herman W (1998) Global burden of diabetes, 1995–2025. Diabetes Care 21:1414–1431
3. Wolf I, Rubinek T (2008) Diabetes mellitus and breast cancer. In: Masur K, Thévenod F, Zänker KS (eds) Diabetes and cancer. epidemiological evidence and molecular links. Front diabetes. Vol 19. Karger, Basel, pp 97–113
4. Chapman JA, Meng D, Shepherd L, Parulekar W, Ingle JN, Muss HB et al (2008) Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer. J Natl Cancer Inst 100:252–260
5. Van der Burg B, Rutteman GR, Blankenstein MA, de Laat SW, van Zoelen EJ (1988) Mitogenic stimulation of human breast cancer cells in a growth factor-defined medium: synergistic action of insulin and estrogen. J Cell Physiol 134:101–108
6. Papa V, Costantino A, Belfiore A (1997) Insulin receptor what role in breast cancer? Trends Endocrinol Metab 8:306–312

7. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL (2008) Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 300:2754–2764
8. Larsson SC, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 121:856–862
9. Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr R et al (2011) Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol 29:40–46
10. Kaplan MA, Pekkolay Z, Kucukoner M, Inal A, Urakci Z, Ertugrul H et al (2011) Type 2 diabetes mellitus and prognosis in early stage breast cancer women. Med Oncol 29(3):1576–1580
11. Unterburger P, Sinop A, Noder W, Berger MR, Fink M, Edler L et al (1990) Diabetes mellitus and breast cancer. A retrospective follow-up study. Onkologie 13:17–20
12. Maruthur NM, Bolen S, Brancati FL, Clarke JM (2009) Obesity and mammography: a systematic review and meta-analysis. J Gen Intern Med 24:665–677
13. Calle EE, Kaaks R (2004) Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 4:579–591
14. Pollak MN, Schernhammer ES, Hankinson SE (2004) Insulin-like growth factors and neoplasia. Nat Rev Cancer 4:505–518
15. Chlebowski RT, McTiernan A, Wactawski-Wende J, Manson JE, Aragaki AK, Rohan T et al (2012) Diabetes, metformin, and breast cancer in postmenopausal women. J Clin Oncol 30(23):2844–2852
16. Goodwin PJ, Pritchard KI, Ennis M, Clemons M, Graham M, Fantus IG (2008) Insulin-lowering effects of metformin in women with early breast cancer. Clin Breast Cancer 8:501–505
17. Monami M, Lamanna C, Balzi D, Marchionni N, Mannucci E (2009) Sulphonylureas and cancer: a case–control study. Acta Diabetol 46:279–284
18. Bowker SL, Yasui Y, Veugelers P, Johnson JA (2010) Glucose-lowering agents and cancer mortality rates in type 2 diabetes: assessing effects of time-varying exposure. Diabetologia 53:1631–1637