

## RESEARCH ARTICLE

# Demographic Characteristics, Survival and Prognostic Factors of Early Breast Cancer Patients with Type 2 Diabetes Mellitus: A Hospital-Based Cohort Study

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### Abstract

**Objective:** With increasing prevalence of type 2 diabetes mellitus and breast cancer in Iran, we aimed to search hospital registries of breast cancer patients to investigate type 2 diabetes mellitus association with survival outcomes of early breast cancer after adjustment of confounding factors. **Methods:** In a retrospective cohort study conducted from July 2003 to Feb 2014 and followed up until death or December 2016, female patients with early breast cancer who have been treated for the first time at the Cancer Institute of Iran, were divided to diabetic and non-diabetic groups. Primary and secondary outcomes were relapse free survival (RFS) and overall survival (OS). SPSS version 23 was used for analysis of data. Other variables included age, tumor stage, hormone receptor status, tumor subtype, and patient's body mass index (BMI). **Result:** From a total of 1021 patients, 218 (21.4%) had type 2 diabetes mellitus. Diabetic patients had a higher mean age (53.31 vs 47.00), higher mean BMI (31.13 vs 29.15), lower HER2 expression (20.8% vs 32.1%) and higher frequency of luminal A subtype (61.1% vs 51.0). Overall, after adjustment of other variables, diabetes status did not affect RFS or OS independently. However, in luminal A subgroup, patients with diabetes mellitus had significantly lower survival outcomes of OS (135.277 vs 154.701) and RFS (114.107 vs 133.612) as well as OS higher hazard ratio of 1.830 and RFS hazard ratio of 1.663 compared to non-diabetic patients. BMI, hormone receptor status and tumor stage significantly affected the survival of the patients. **Conclusion:** In the present study, in addition to known breast cancer risk factors, BMI and type 2 diabetes mellitus had an independent impact on survival of the patients, highlighting the importance of health issues such as obesity and diabetes suboptimal performance in the treatment outcomes of early breast cancer patients in Iran.

**Keywords:** Type 2 diabetes mellitus- breast cancer- demographics- survival outcomes- prognostic factors

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### Introduction

Diabetes mellitus is a major health burden which directly results in 1.5 million deaths worldwide and is the fifth leading cause of death in women (WHO, 2015). Based on WHO estimates, diabetes is affecting 422 million adults aged over 18 years globally (8.5%) with the highest prevalence (13.7%) and rise in prevalence of diabetes being experienced in WHO Eastern Mediterranean Region, which includes Iran (NCD-RisC, 2016; WHO, 2016). High prevalence of diabetes has been recorded in Iran with one study estimating it to be 16.3% in adults aged over 30 in Yazd Province (Lotfi et al., 2014). Another study reported 18.6% diagnosed and 7.5% undiagnosed type 2 diabetes prevalence in adult Zoroastrians in Yazd (Khalilzadeh et al., 2015).

Breast cancer is another global health burden, which remains the leading cause of death in woman worldwide (Torre et al., 2015). In Iran, increasing trend of breast

cancer mortality has been detected (Taghavi et al., 2012). Obesity, aging, and physical inactivity are among common risk factors linking type 2 diabetes mellitus and breast cancer. Previous meta-analysis showed increased risk of breast cancer in woman with type 2 diabetes but not type 1 diabetes (Redaniel et al., 2012). Complex results regarding the association of type 2 diabetes mellitus and risk of breast cancer have been reported. A meta-analysis reported that diabetes was associated with statistically significant 23% increased risk of breast cancer in women in Europe and US but not in Asia (Liao et al., 2011). Another study observed association between diabetes and breast cancer but reported it could be due to potential detection bias and confounders (Tseng, 2014).

Association between breast cancer mortality and diabetes is even more controversial. Findings from a meta-analysis indicated increased risk of breast cancer in diabetic patients, but did not find significant association between diabetes and breast cancer mortality and reported

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significant heterogeneity among the mortality studies (Larsson et al., 2007). Another meta-analysis indicated increased incidence and mortality among breast cancer patients with pre-existing diabetes (Renehan et al., 2012). There are also reports of significant association of diabetes with survival but not relapse of early breast cancer (Zhao and Ren, 2016).

To clarify the association between type 2 diabetes mellitus and breast cancer outcome in Iran, a hospital-based cohort study was performed. The aim of the study was to determine the demographic and clinicopathological characteristics of breast cancer patients with type 2 diabetes and to compare the patients' survival outcomes with non-diabetic counterparts. Variables in the present study included patients' age, weight and body mass index (BMI), hormone receptor status, tumor subtype and stage.

## Materials and Methods

This study was conducted based on Helsinki convention principles (World Medical Association, 2013) and approved by the ethics committee of Tehran University Medical Sciences (TUMS) Research Deputy with study code 23828.

### Patient Population

We carried out a retrospective cohort study on early breast cancer patients, stages I–III, who have been treated with chemotherapy and/or hormonal therapy in the Medical Oncology Department of Iran Cancer Institute from July 2003 to Feb 2014 and followed up until death or December 2016. Female patients with confirmed pathology diagnosis of invasive ductal carcinoma and documented follow-up were registered in the study. Patients with diagnosis of stage IV before chemotherapy or subsequent diagnosis of diabetes after breast cancer treatment, pregnant patients and those with type 1 diabetes mellitus or steroid-induced diabetes were excluded. Diabetes status was determined from patient self-report, history of prescriptions of anti-diabetic medications and blood tests compatible with American Diabetic Association qualification of type 2 diabetes mellitus (American Diabetes Association, 2010). Patients were divided into two groups of diabetic and non-diabetic.

### Pathologic Evaluation

TNM breast cancer staging were performed according to the American Joint Committee on Cancer (AJCC) seventh edition manual (Edge and Compton, 2010). Molecular subtypes were categorized based on Estrogen Receptor (ER), Progesterone Receptor (PR) and HER2 Receptor status as luminal A (ER positive and/or PR positive, HER2 negative), luminal B (ER positive and/or PR positive, HER2 positive), HER2 enhanced type (ER negative, PR negative, HER2 positive), and triple-negative (ER negative, PR negative, HER2 negative). ER and PR status was identified by Immunohistochemistry (IHC) procedures based on ASCO/CAP Guidelines (Hammond et al., 2010). Diagnosis of HER2-positive patients was based on either 3+ receptor overexpression on IHC staining or fluorescent in situ hybridization (FISH) amplification

(Wolff et al., 2013). All pathology slides were centrally reviewed.

### Statistical analysis

Difference between baseline characteristics of diabetic patients in comparison to non-diabetics was examined by performing Chi-square test on categorical variables and one-way ANOVA on continuous variables. Time to event variables were calculated in months from the first pathology diagnosis and censored at the end of follow-up if events were not observed. Recurrence-free survival (RFS) and overall survival (OS) were defined retrospectively as the time from first pathology report of breast cancer until first recurrence or death from any cause. Kaplan-Meier test was used to investigate the association of RFS and OS with all variables and was compared by log-rank statistics. Effect of diabetes on RFS and OS was further analyzed by Cox Regression method after adjusting for TNM stage, molecular subtypes, age and BMI. All statistical analyses were performed using IBM SPSS Statistics 23 and P-values less than 0.05 were considered significant.

## Results

From a total of 1021 patients with early invasive breast cancer included in this study, 803 (78.6%) were without diabetes and 218 (21.4%) had type 2 diabetes. Demographics and prognostic factors of diabetic and non-diabetic patients are compared in Table 1. In average, patients in the diabetic group were 6.3 years older ( $p < 0.001$ ), weighted 2.8 kg more ( $p = 0.005$ ), and their BMI was 2.0 units higher ( $p < 0.001$ ) than those in the non-diabetic group. With 20.8% of diabetic patients expressing HER2 receptor, diabetic group had a lower HER2 expression than the non-diabetic group with 32.1% HER2 expression ( $p = 0.001$ ). Molecular subtypes of breast cancer were also significantly different between groups with higher frequency of luminal A (61.1% vs 51.0%) and lower frequency of luminal B subtypes (8.8% vs 17.2%) seen in diabetic patients ( $p = 0.007$ ). No significant difference was detected in ER and PR expression, tumor stage, and chemotherapy protocol between two groups.

The mean follow-up of patients who were still alive was 61 months (range 1–161 months). From the total of 150 (14.7%) deaths, 37 (17.0%) patients died in the diabetic group, while 113 (14.1%) died in the non-diabetic group. Overall, there were 48 (4.7%) local relapses and 217 (21.3%) distant metastasis, including 10 (4.6%) local and 52 (23.9%) metastatic recurrences in the diabetic group compared to 38 (4.7%) local and 165 (20.5%) distant relapses in the non-diabetic group.

Kaplan–Meier estimates of survival outcomes for different subgroups are depicted in Table 2. With mean RFS estimate of 114.6 months (95% CI, 102.9–126.4) and mean OS estimate of 135.1 months (95% CI, 124.9–145.2), diabetic patients were observed to have similar survival to non-diabetic patients with mean RFS of 117.7 (95% CI, 110.2–125.2) and mean OS of 137.8 (95% CI, 124.1–151.5). However, in the luminal A subgroup, diabetic patients were evaluated to have lower mean OS of 135.277 months (95%CI, 123.397–147.157) than

Table 1. Patient Demographics and Prognostic Factors in Diabetic and Nondiabetic Groups

Factor	Total (N=1021)	Nondiabetic (N=803)	Diabetic (N=218)	P
Age at diagnosis, yr				
Mean [95% CI]	48.34	47.00 [46.23-47.78]	53.31 [51.82-54.80]	<0.001
≤50	569 (56.0%)	489 (61.1%)	80 (37.0%)	
>50	447 (44.0%)	311 (38.9%)	136 (63.0%)	<0.001
Body weight, Kg				
Mean [95% CI]	71.927	71.294 [70.392-72.196]	74.118 [72.257-75.979]	0.005
Height, cm				
Mean [95% CI]	155.98	156.42 [155.97-156.86]	154.46 [153.57-155.36]	<0.001
Body Mass Index				
Mean [95% CI]	29.59	29.15 [28.79-29.50]	31.13 [30.35-31.92]	<0.001
Normal weight <25	187 (19.8%)	158 (21.5%)	29 (13.7%)	
25≤ Overweight <30	334 (35.3%)	272 (37.1%)	62 (29.2%)	
30 ≤ Obese	425 (44.9%)	304 (41.4%)	121 (57.1%)	<0.001
ER				
Negative	325 (32.0%)	260 (32.6%)	65 (30.0%)	
Positive	690 (68.0%)	538 (67.4%)	152 (70.0%)	0.462
PR				
Negative	395 (38.9%)	316 (39.6%)	79 (36.4%)	
Positive	620 (61.1%)	482 (60.4%)	138 (63.6%)	0.392
HER2				
Negative	713 (70.3%)	542 (67.9%)	171 (79.2%)	
Positive	301(29.7%)	256 (32.1%)	45 (20.8%)	0.001
Subtype				
Luminal-A	539 (53.2%)	407 (51.0%)	132 (61.1%)	
Luminal-B	156 (15.4%)	137 (17.2%)	19 (8.8%)	
Triple-Negative	174 (17.2%)	135 (16.9%)	39 (18.1%)	
HER2type	145 (14.3%)	119 (14.9%)	26 (12.0%)	0.007
Chemotherapy				
Adjuvant	910 (89.1%)	713 (88.8%)	197 (90.4%)	
neoadjuvant	111 (10.9%)	90 (11.2%)	21 (9.6%)	0.508
Stage				
I	143 (14.4%)	108 (13.8%)	35 (16.5%)	
IIA	290 (29.1%)	234 (29.8%)	56 (26.4%)	
IIB	216 (21.7%)	170 (21.7%)	46 (21.7%)	
IIIA	189 (19.0%)	145 (18.5%)	44 (20.8%)	
IIIB	75 (7.5%)	61 (7.8%)	14 (6.6%)	
IIIC	83 (8.3%)	66 (8.4%)	17 (8.0%)	0.802

non-diabetic patients with mean OS of 154.701 months (95% CI, 144.876-164.525) based on Kaplan–Meier analysis (p=0.020). Similarly, RFS of diabetic patients in this subgroup was estimated to be 114.107 (95% CI, 99.941-128.274) which was significantly lower than RFS estimate of 133.612 (95% CI, 125.531-141.693) in the non-diabetic group (p=0.010). Other factors significantly affecting both survival outcomes in Kaplan-Meier analysis were ER, PR, molecular subtype and Tumor stage (p<0.001). Higher bodyweight (p=0.004) and BMI (p=0.011) significantly reduced estimate of OS but not RFS.

In Table 3, the result of Multivariate Survival

Analysis using Cox's Regression Model performed on independent prognostic factors of diabetic status, tumor stage, molecular subtype, age, and BMI is shown. Diabetes status was found not significantly affecting RFS or OS hazard ratio in total patients. Tumor stage and molecular subtype significantly impacted both RFS and OS survival outcomes (p<0.001), while 5.8% higher risk of mortality was observed with each unit increase in BMI (p<0.001). In luminal A subgroup, compared to non-diabetic counterparts, diabetic patients had significantly higher RFS hazard ratio of 1.663 (95% CI, 0.779-1.436 [p=0.720]) and OS hazard ratio of 1.830 (95% CI, 1.129 -2.450 [p=0.010]).

Table 2. Kaplan- Meier Estimates of Survival Outcomes for Different Subgroups

Factor	RFS Mean survival (month)	95% CI	P	OS Mean survival (month)	95% CI	P
<b>Group</b>						
Non-diabetic	117.73	[110.226-125.234]		137.811	[124.081-151.542]	
Diabetic	114.64	[102.869-126.412]	0.543	135.076	[124.949-145.203]	0.553
<b>ER</b>						
Negative	87.586	[80.440-94.731]		110.695	[102.158-119.232]	
Positive	126.376	[119.759-132.992]	<0.001	152.727	[145.175-160.278]	<0.001
<b>PR</b>						
Negative	97.913	[84.084-111.741]		119.817	[109.082-130.552]	
Positive	126.883	[119.794-133.972]	<0.001	152.209	[144.090-160.328]	<0.001
<b>HER2</b>						
Negative	119.708	[112.559-126.857]		141.887	[131.452-152.322]	
Positive	109.878	[99.548-120.208]	0.96	128.607	[116.821-140.393]	0.402
<b>Subtype</b>						
Luminal-A	128.936	[121.716-136.156]		152.918	[144.694-161.142]	
Luminal-B	109.841	[95.631-124.051]		133.74	[120.604-146.875]	
Triple-Negative	82.977	[73.996-91.957]		108.034	[98.058-118.010]	
HER2type	79.529	[71.866-87.191]	<0.001	88.695	[80.828-96.561]	<0.001
<b>Age at diagnosis, yr</b>						
≤50	116.546	[107.990-125.102]		143.824	[132.355-155.292]	
>50	117.383	[109.219-125.546]	0.877	130.995	[122.646-139.345]	0.26
<b>Body weight, Kg</b>						
≤63	101.292	[92.896-109.689]		123.53	[117.184-129.877]	
63.1-79	119.188	[111.219-127.158]		134.101	[126.152-142.049]	
>79	111.374	[99.484-123.263]	0.506	129.121	[114.913-143.329]	0.004
<b>Height, cm</b>						
≤150	114.735	[104.150-125.321]		130.492	[119.965-141.019]	
151-159	99.273	[92.711-105.835]		117.744	[109.731-125.757]	
≥160	121.434	[111.061-131.807]	0.469	155.045	[145.536-164.554]	0.139
<b>Body Mass Index</b>						
Normal weight < 25	100.019	[90.624-109.413]		124.022	[117.766-130.278]	
25 ≤ Overweight < 30	126.504	[118.538-134.470]		148.034	[137.511-158.558]	
30 ≤ Obese	109.274	[99.940-118.608]	0.227	124.202	[115.259-133.144]	0.011
<b>Stage</b>						
I	150.716	[140.758-160.673]		159.748	[143.213-176.284]	
IIA	134.01	[124.658-143.363]		154.103	[147.408-160.799]	
IIB	115.108	[103.419-126.798]		121.604	[108.916-134.291]	
IIIA	99.395	[87.662-111.128]		122.82	[111.781-133.860]	
IIIB	65.468	[51.895-79.040]		79.156	[65.907-92.405]	
IIIC	67.543	[53.600-81.486]	<0.001	85.72	[67.613-103.828]	<0.001

## Discussion

In the present retrospective cohort study, significant difference in demographic and clinicopathological characteristics was detected between two groups. Non-diabetic patients were younger, tinier and had lower BMI. In the diabetic group, we found significantly lower expression of HER2 receptor. Similarly, higher frequency of HER2-negative patients was detected in

premenopausal women with diabetes in a cross-sectional study (Bronsveld et al., 2017). While we did not detect significant difference in ER or PR expression between two groups, premenopausal diabetic patients were more often PR-negative in the mentioned study (Bronsveld et al., 2017). However, significant difference in subtypes of breast cancer was detected between diabetic and non-diabetic patients with diabetic patients showing higher frequency of luminal A and lower frequency of luminal

Table 3. Cox Regression Table of Association between Prognostic Factors and Survival Outcomes

Group	RFS			OS		
	HR	95% CI	P	HR	95% CI	P
Non-diabetic	1			1		
Diabetic	1.057	[0.779-1.436]	0.72	.984	[0.659-1.469]	0.984
Subtype						
Luminal-A	1		<.001	1		<.001
Luminal-B	1.621	[1.086-2.418]	0.018	1.214	[.647-2.277]	0.546
Triple-Negative	2.461	[1.818-3.331]	<0.001	3.155	[2.151-4.627]	<0.001
HER2type	1.52	[1.011-2.284]	0.044	1.841	[1.079-3.141]	0.025
Stage						
I	1		<.001	1		<.001
IIA	1.582	[.851-2.942]	0.147	0.668	[.289-1.546]	0.346
IIB	2.928	[1.594-5.380]	0.001	2.914	[1.403-6.054]	0.004
IIIA	3.817	[2.087-6.981]	<0.001	2.791	[1.324-5.885]	0.007
IIIB	9.089	[4.724-17.488]	<0.001	8.31	[3.786-18.243]	<0.001
IIIC	10.477	[5.636-19.474]	<0.001	9.255	[4.363-19.632]	<0.001
Body Mass Index	1.017	[0.992-1.042]	0.178	1.058	[1.027-1.090]	<0.001
Age at diagnosis, yr	0.997	[0.985-1.009]	0.626	1.011	[0.996-1.026]	0.167

B subtypes in our study.

Although there are reports of more advanced stages of breast cancer and less frequent adjuvant chemotherapy treatment among diabetic patients compared with non-diabetic counterparts (van de Poll-Franse et al., 2007; Peairs et al., 2011; Renehan et al., 2012; Lipscombe et al., 2015), in the present study, no significant difference in pathologic stage or chemotherapy treatment was detected between these two cohorts of early breast cancer cases. It seems that our result of worse survival outcome in luminal A subgroup of patients with diabetes is related to causes other than unfavorable primary characteristics of tumor, especially higher stage or less effective adjuvant therapy. This result can suggest other probable effects of diabetes such as hyperinsulinemia, insulin resistance (Perseghin et al., 2012), endogenous sex hormones and proinflammatory markers (Zhao and Ren, 2016) as potential mortality factors.

In this study, type 2 diabetes mellitus was associated with respectively 1.7 and 1.8-fold increased risk of relapse and mortality in luminal A subtype of breast cancer patients who were ER positive and/or PR positive and HER2 negative. This finding is consistent with the previous study showing elevated incidence of breast cancer among women with ER positive tumors but not ER negative tumors (Michels et al., 2003). Likewise, in another study, type 2 diabetes mellitus association with poor prognosis was only significant in breast cancer patients who were ER and/or PR positive or HER2 negative (He et al., 2015). In the present study, diabetes was not significantly associated with all-cause mortality of the whole cohort population as reported in some studies (Boyle et al., 2012; Redaniel et al., 2012; Oppong et al., 2014).

Another debate about relation of diabetes and breast cancer outcomes is the difference between disease free

survival (DFS) as the time interval between diagnosis of breast cancer and relapse or death, and relapse free period (RFP) as the time length from diagnosis and relapse but not death. A meta-analysis suggested that while preexisting diabetes is significantly associated with poor OS and DFS, the impact of diabetes on RFP needs further clarification by prospective studies which consider glycemic control and type of anti-hyperglycemic drugs used (Zhao and Ren, 2016).

Although our result of the type 2 diabetes mellitus prevalence is not based on population registry, the high prevalence of diabetes (21%) and obesity (45%, BMI  $\geq$ 30) among breast cancer patients is noticeable. Does changing life-style of Iranian people toward the western world have a role in the increase of these conditions in the society? There are a lot of reports of high rates of diabetes and obesity in general Perisan adults and even adolescent population (Lotfi et al., 2014; Khalilzadeh et al., 2015; Rahmani et al., 2015; Bakhshi et al., 2016). As mentioned throughout the literature, cancer treatment requires a multidisciplinary care (Ko and Chaudhry, 2002). It is essential to pay attention to diabetes treatment effect on outcome of breast cancer; especially important probable positive effect of metformin drug on overweight and obese diabetic patients should be considered. There are reports of anti-proliferative effects of metformin on other gynecologic cancers such as endometrial and ovary carcinomas (Gadducci et al., 2016; Tang et al., 2017; Yu et al., 2017).

Heterogeneity among studies on survival outcomes of breast cancer patients with preexisting diabetes has been detected based on follow-up duration of more than five years in comparison to shorter follow-ups (Zhao and Ren, 2016). The present study with average follow-up of more than five years, did not find significant association between

type 2 diabetes mellitus status and survival outcome of the whole group of the patients after adjustment of confounder factors. Therefore, we emphasize the great value and importance of the best control of hyperinsulinemia, obesity and other co-factors in increasing breast cancer patients' survival irrespective of diagnosis of type 2 diabetes mellitus.

One limitation of this study is that the date of diagnosis of type 2 diabetes mellitus was not recorded. To minimize the possible bias associated with time interval between diagnosis of diabetes and breast cancer occurrence, patients with diagnosis of diabetes after breast cancer treatment were excluded. Another probable co-founder is the diabetes-targeted treatment. It has been shown that metformin prescription even for a short interval can result in reduction of Ki-67 and tumor proliferation (Hadad et al., 2011; Sadighi et al., 2016; Bradley., 2017). Future studies which include metformin treatment effect on survival of non-diabetic patients, may further clarify the association of metformin and breast cancer (Sonnenblick et al., 2017).

In summary, the present study suggested high rate of type 2 diabetes mellitus and obesity in breast cancer patients in Iran. Breast cancer patients were significantly older and more likely to be overweight. The study demonstrated worse survival outcomes of diabetic patients in luminal A subgroup.

We emphasize the importance of multidisciplinary care of early breast carcinoma patients. It requires participation of not only different cancer specialist groups from pathologists to medical, radiation, and surgical oncologists, but also public health professionals and other medical groups that focus on non-cancer health issues with direct effect on treatment outcomes.

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#### References

- American diabetes association (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, **33**, 62-9.
- Bakhshi E, Etemad K, Seifi B, et al (2016). Changes in obesity odds ratio among Iranian adults, since 2000: Quadratic inference functions method. *Comput Math Methods Med*, **2016**, 7101343.
- Boyle P, Boniol M, Koechlin A, et al (2012). Diabetes and breast cancer risk: a meta-analysis. *Br J Cancer*, **107**, 1608-17.
- Bradley CA (2017). Metformin in breast cancer. *Nat Rev Endocrinol*, **2017**, 37.
- Bronsveld HK, Jensen V, Vahl P, et al (2017). Diabetes and breast cancer subtypes. *PLoS One*, **12**, e0170084.
- Edge SB, Compton CC (2010). The American joint committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*, **17**, 1471-4.
- Gadducci A, Biglia N, Tana R, Cosio S, Gallo M (2016). Metformin use and gynecological cancers: A novel treatment option emerging from drug repositioning. *Crit Rev Oncol Hematol*, **105**, 73-83.
- Hadad S, Iwamoto T, Jordan L, et al (2011). Evidence for biological effects of metformin in operable breast cancer: a pre-operative, window-of-opportunity, randomized trial. *Breast Cancer Res Treat*, **128**, 783-94.
- Hammond ME, Hayes DF, Dowsett M, et al (2010). American society of clinical oncology/college of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*, **28**, 2784-95.
- He DE, Bai JW, Liu J, et al (2015). Clinicopathological characteristics and prognosis of breast cancer patients with type 2 diabetes mellitus. *Mol Clin Oncol*, **3**, 607-12.
- Khalilzadeh S, Afkhami-Ardekani M, Afrand M (2015). High prevalence of type 2 diabetes and pre-diabetes in adult Zoroastrians in Yazd, Iran: a cross-sectional study. *Electron Physician*, **7**, 998-1004.
- Ko C, Chaudhry S (2002). The need for a multidisciplinary approach to cancer care. *J Surg Res*, **105**, 53-7.
- Larsson SC, Mantzoros CS, Wolk A (2007). Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer*, **121**, 856-62.
- Liao SC, Li JX, Wei W, et al (2011). Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. *Asian Pac J Cancer Prev*, **12**, 1061-5.
- Lipscombe LL, Fischer HD, Austin PC, et al (2015). The association between diabetes and breast cancer stage at diagnosis: a population-based study. *Breast Cancer Res Treat*, **150**, 613-20.
- Lotfi MH, Saadati H, Afzali M (2014). Prevalence of diabetes in people aged  $\geq 30$  years: The results of screening program of Yazd province, Iran, in 2012. *J Res Health Sci*, **1414**, 88-9288.
- Michels KB, Solomon CG, Hu FB, et al (2003). Type 2 diabetes and subsequent incidence of breast cancer in the nurses' health study. *Diabetes Care*, **26**, 1752-8.
- NCD risk factor collaboration (NCD-RisC) (2016). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*, **387**, 1513-30.
- Oppong BA, Pharmed LA, Oskar S, et al (2014). The effect of metformin on breast cancer outcomes in patients with type 2 diabetes. *Cancer Med*, **3**, 1025-34.
- Peairs KS, Barone BB, Snyder CF, et al (2011). Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol*, **29**, 40-6.
- Perseghin G, Calori G, Lattuada G, et al (2012). Insulin resistance/hyperinsulinemia and cancer mortality: the Cremona study at the 15th year of follow-up. *Acta Diabetol*, **49**, 421-8.
- Rahmani A, Sayehmiri K, Asadollahi K, et al (2015). Investigation of the prevalence of obesity in Iran: a Systematic review and meta-analysis study. *Acta Med Iran*, **53**, 596-607.
- Redaniel MT, Jeffreys M, May MT, et al (2012). Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. *Cancer Causes Control*, **23**, 1785-95.
- Rehnan AG, Yeh HC, Johnson JA, et al (2012). Diabetes and cancer (2): evaluating the impact of diabetes on mortality in patients with cancer. *Diabetologia*, **55**, 1619-32.
- Sadighi S, Saberian M, Nagafi M, et al (2016). Metformin anti-proliferative effect on a cohort of non-diabetic breast

- cancer patients. *Ann Oncol*, **27**, Issue suppl\_6.
- Sonnenblick A, Agbor-Tarh D, Bradbury I, et al (2017). Impact of diabetes, insulin, and metformin use on the outcome of patients with human epidermal growth factor receptor 2-positive primary breast cancer: Analysis from the ALTTO phase III randomized trial. *J Clin Oncol*, **35**, 1421-9.
- Taghavi A, Fazeli Z, Vahedi M, et al (2012). Increased trend of breast cancer mortality in Iran. *Asian Pac J Cancer Prev*, **13**, 367-70.
- Tang YL, Zhu LY, Li Y, et al (2017). Metformin use is associated with reduced incidence and improved survival of endometrial cancer: A meta-analysis. *Biomed Res Int*, **2017**, 5905384.
- Torre LA, Bray F, Siegel RL, et al (2015). *Global cancer statistics, 2012*. *CA Cancer J Clin*, **65**, 87-108.
- Tseng CH (2014). Diabetes and breast cancer in Taiwanese women: a detection bias?. *Eur J Clin Invest*, **44**, 910-7.
- van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, et al (2007). Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer*, **120**, 1986-92.
- Wolff AC, Hammond ME, Hicks DG, et al (2013). Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of American pathologists clinical practice guideline update. *J Clin Oncol*, **31**, 3997-4013.
- World health organization (WHO) (2015). WHO mortality database [online database]. ([http://apps.who.int/healthinfo/statistics/mortality/causeofdeath\\_query/](http://apps.who.int/healthinfo/statistics/mortality/causeofdeath_query/), accessed 12 January 2016).
- World health organization (WHO) (2016). Global report on diabetes. ([http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf)).
- World medical association (2013). World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*, **310**, 2191-4
- Yu X, Mao W, Zhai Y, et al (2017). Anti-tumor activity of metformin: from metabolic and epigenetic perspectives. *Oncotarget*, **8**, 5619-28.
- Zhao XB, Ren GS (2016). Diabetes mellitus and prognosis in women with breast cancer: A systematic review and meta-analysis. *Medicine (Baltimore)*, **95**, e5602.