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Incidence of malignancies in patients with diabetes mellitus and correlation with treatment modalities in a large Israeli health maintenance organization: a historical cohort study

Andreas E. Buchs[a,*], *Barbara G. Silverman*[b]

[a] *Department of Medicine D, Assaf Harofe Medical Center, Zerifin, Israel and Sackler School of Medicine, Tel Aviv University, Israel*
[b] *Department of Research and Evaluation, Maccabi Healthcare Services, Tel Aviv, Israel*

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ABSTRACT

It has been hypothesized that incidence of and mortality from several malignancies are increased among diabetic patients. Whether certain treatment modalities, including use of metformin, sulfonylureas, or insulins, affect cancer incidence or mortality and whether use of long-acting insulin analogues glargine and detemir may increase cancer incidence more than traditional human insulins are debated. The objective was to investigate the association between specific glucose-lowering agents and cancer incidence in diabetic members of an Israeli health maintenance organization. We studied a cohort of 36 342 diabetic patients aged at least 18 years with no history of cancer or treatment with insulin as of January 1, 2003. For the period from January 2003 to December 2007, we searched pharmacy records for purchases of glucose-lowering agents, including metformin, sulfonylureas, human insulin, and analogue insulins. Incident cancer diagnoses were identified from the health maintenance organization cancer registry. We studied the association of cancer incidence with the use of specific glucose-lowering agents, controlling for age, sex, and baseline glycohemoglobin measurement. Cancer was diagnosed in 6% of the study cohort during 164 652 person-years of follow-up time. Cancer incidence increased with age and varied with medication purchasing patterns. On multivariate analysis, age (hazard ratio [HR], 1.049; confidence interval [CI], 1.045-1.052), male sex (HR, 1.16; CI, 1.065-1.264), and number of insulin purchases (HR, 1.007; CI, 1.001-1.012) were significantly associated with increased cancer risk, whereas number of metformin purchases was associated with reduced cancer risk (HR, 0.996; CI, 0.994-0.998). Male sex, age, and human insulin purchases were associated with increased cancer incidence, whereas metformin purchases were associated with decreased cancer risk. There was a trend for increased cancer incidence associated with use of long-acting insulin analogues, but the number of long-acting insulin analogue users was too small for risk estimates to be conclusive.

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* *Corresponding author*. Department of Medicine D, Assaf Harofe Medical Center, 70300 Zerifin, Israel. Tel.: +972 8 9779302; fax: 972 8 9779317.

E-mail address: abuchs@asaf.health.gov.il (A.E. Buchs).

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1. Background

The incidence of solid cancers originating from the colon, breast, pancreas, and liver and the related mortality are increased in patients with type 2 diabetes mellitus [1-7]. Age, sex, body weight, and glycemic control in addition to treatment with some glucose-lowering agents such as insulin and sulfonylureas are associated with increased cancer risk, whereas metformin is associated with decreased risk [8-15]. Whether long-acting insulin analogues are associated with an increased incidence of cancer even more than human insulins is disputed [16-21].

The purpose of this study was to investigate the correlation of clinical and demographic factors, glucose-lowering agents, and insulin analogues on the incidence of cancer in diabetic members of a large Israeli health organization.

2. Methods

2.1. Data source

This study was based on the computerized databases of Maccabi Healthcare Services, Israel (MHS). The MHS is Israel's second-largest health maintenance organization (HMO), serving more than 1.8 million members, approximately 25% of the Israeli population. The HMO data systems capture most encounters with the health care system, including visits in hospitals and outpatient clinics, contacts with physicians and other health professionals, prescription drug purchases, laboratory testing, and imaging studies. Utilization data are linked by a unique patient identifier. Pharmacy purchasing data include information on all prescription drug purchases, including identification numbers for the patient and prescribing physician, date and place of purchase, and a drug classification number that identifies the brand and generic drug names, form, dosage strength, and units per package. Membership files provide date of birth, sex, area of residence, date of entry into the HMO, current membership status (active, inactive, or deceased), and date of death or exit from the HMO, if applicable. Vital status is updated monthly on the basis of information provided by the National Insurance Institute. The MHS maintains registries for a number of chronic diseases, including cancer and diabetes. The cancer registry draws data from the Israel National Cancer Registry (INCR). The INCR has been in operation since 1961, and reporting of all cancer cases by medical facilities and pathology laboratories to the INCR has been mandatory since 1982. Registry staff review cases reported by laboratories and medical facilities, determine primary site and morphology, and assign diagnosis codes according to the International Classification of Diseases for Oncology. Data supplied by the INCR to the MHS include national identification number of the member, diagnosis code, and date of diagnosis [22,23]. These data are updated at least annually. Additional cancer cases are identified through approvals for specific drugs for the treatment of cancer. We included all cancer types in the registry in calculating cancer risk.

The HMO diabetes registry draws on laboratory, pharmacy purchasing, and physician and hospital diagnosis data to identify diabetes, using the following criteria [24]:

1. Glycohemoglobin greater than or equal to 7.25% OR
2. Glucose greater than or equal to 200 mg/dL AND recorded diabetes diagnosis within 6 months of the date of the glucose test OR
3. At least 2 purchases of hypoglycemic medications OR
4. Glycohemoglobin greater than or equal to 6.5% or glucose greater than or equal to 125 mg/dL AND any history of diabetes diagnosis.

2.2. Study cohort

The study population consisted of all active MHS members 18 years and older as of January 1, 2003, who met the following additional criteria: (1) had joined the HMO and were continuously active from January 1, 2000, or earlier; (2) entered the diabetes registry before January 1, 2003; (3) had no history of cancer as of January 1, 2003; and (4) had made fewer than 3 insulin purchases before January 1, 2003. The last date of observation for members of the study cohort was defined as the earliest of the following dates: (1) date of death, (2) date leaving the HMO, or (3) December 31, 2007.

We searched pharmacy purchasing records for all purchases of insulin and other hypoglycemic drugs made by members of the study population during the period from 2000 through 2007 and used these to establish medication use during the "baseline" (years 2000 through 2002) and "follow-up" periods. Subjects who had made fewer than 3 purchases of any diabetes drug in the baseline period were characterized as "untreated" at baseline; the remaining subjects were was characterized as treated with oral drugs only. For the follow-up period, we calculated total purchases of each of the following medication groups: all types of insulin, all types of oral drugs, insulin detemir, insulin glargine, other insulins, metformin (alone or combined with other medications), and sulfonylureas. Because only 1% of the study population was treated exclusively with oral medications other than sulfonylureas or metformin, those were not evaluated separately in our analysis. Medication use during the follow-up period was defined as at least 2 purchases of metformin, sulfonylureas, human insulin, glargine, or detemir in any calendar year from 2003 to 2007. We extracted all glycohemoglobin (HbA_{1c}) measures for the study cohort from the HMO laboratory data file. The last HbA_{1c} measurement performed before January 1, 2003, was taken as the baseline measurement. The follow-up HbA_{1c} value was the last measurement performed before the last date of observation.

2.3. Statistical analysis

We used t tests to compare continuous variables such as age and laboratory parameters in different treatment subgroups; χ^2 analysis was used to compare categorical variables in treatment subgroups. Cox proportional hazards analysis was used to estimate the effect of total number of purchases of long-acting insulin analogues, other insulins, metformin, and sulfonylureas on cancer incidence during the follow-up period. Statistical significance was assumed with a P value

of .05 or lower. All analyses were performed using SPSS (Chicago, IL) Version 17.0.

This project received approval from the HMO Helsinki Committee for Research Involving Human Subjects.

3. Results

3.1. Study cohort

As of January 1, 2003, there were 53 178 diabetic patients in the MHS registry. Of those, 44 856 had been members from the year 2000 and onward; and 41 386 had no cancer diagnosis as of January 1, 2003. One hundred fifty-four patients were manually removed from the diabetes registry after the diagnosis could not be verified, resulting in 41 232 members. At baseline (January 1, 2003), 12 780 (31%) of the study population patients had not purchased hypoglycemic agents, 23 633 (57%) had purchased only oral hypoglycemic agents, and 4819 (12%) patients had purchased insulin. None of these patients used detemir or glargine insulin at this time, as these drugs were not yet available in Israel. Users of insulin and members younger than 18 years at baseline were excluded from further analysis, resulting in a final study sample of 36 342 members with a total of 164 652 years of follow-up time (mean follow-up time, 4.5 years). During the follow-up period, cancer was diagnosed in 2168 (6%) of the study cohort, 4036 died, and 1059 left the HMO (Fig. 1). Mean age at baseline was 60 years. Forty-five percent of the study population was male. At least one HbA_{1c} measurement was available for 88% of subjects in the baseline period and for 90% in the follow-up period. Of those tested, 52% had an HbA_{1c} value less than 7% during the baseline period; and 48%, during the follow-up period.

Annual purchasing patterns of hypoglycemic medications are shown in Table 1. Metformin was the most frequently purchased medication in all years, followed by sulfonylureas and insulin. When limiting the definition of a *user* of a group of medications to 2 or more purchases in a calender year, 73.8% of the cohort had used metformin, 53.2% had used sulfonylureas, and 11.5% had used insulin of any kind. Use of long-acting insulin analogues was not widespread; 1137 subjects purchased glargine insulin and 228 purchased detemir at some time during the follow-up period.

3.1.1. Cancer events

Crude cancer incidence during the follow-up period was 13.2 cases per 1000 person-years of follow-up. In women, the most common cancer diagnoses were breast cancer and cancers of the gastrointestinal system (29.1% and 18.0% of total cancer cases, respectively); and in men, cancers of the prostate and gastrointestinal system (23.4% and 22.5%, respectively) (Table 2). Among both women and men, crude cancer incidence during the follow-up period increased with age at baseline, from 3.9% among those aged 18 to 64 years to 9.2% in those aged at least 65 years.

Cancer incidence during the follow-up period varied with medication purchasing patterns. Members purchasing sulfonylureas or human insulin were significantly more likely to be diagnosed with cancer than those not purchasing these medications (sulfonylureas, 6.5% vs 5.4%, $P < .001$; insulins, 7.1% vs 5.8, $P = .002$). Metformin use was not associated with increased cancer incidence during the follow-up period (Table 3).

3.1.2. Glucose control

Eighty-eight percent of the study population had at least one HbA_{1c} measurement during the baseline period; and 94%, during the follow-up period. Glucose control was similar in the baseline and follow-up periods; of those tested during the baseline period, the last HbA_{1c} measurement recorded was less than 7% in 46%; in the follow-up period, this figure was

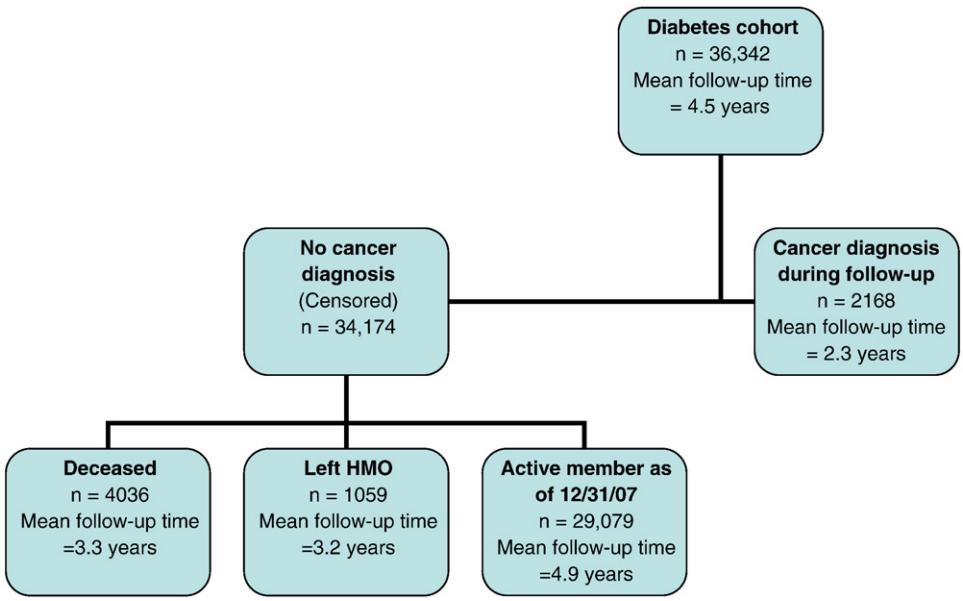

Fig. 1 – Events during follow-up and survival times by group, diabetes cohort, MHS, 2003-2007.

Table 1 – Number of users and mean number of purchases of selected groups of diabetes medications per year in a diabetic cohort, MHS, 2003-2007

	2003		2004		2005		2006		2007	
	No. of users	Mean no. of purchases	No. of users	Mean no. of purchases	No. of users	Mean no. of purchases	No. of users	Mean no. of purchases	No. of users	Mean no. of purchases
Insulin	927	4.6	1646	6.1	2327	6.9	3080	7.6	3885	8.3
Metformin	20 874	7.8	21 878	8.3	22 282	8.0	22 645	8.5	22 901	8.6
Sulfonylureas	15 605	7.6	15 440	7.7	14 858	7.6	14 365	7.7	13 815	7.6
Glargine	40	2.2	192	3.8	517	4.4	741	5.7	1131	5.9
Detemir					17	2.0	155	3.9	247	6.0

45%. Cancer incidence during the follow-up period was significantly higher in the subgroup with baseline or follow-up HbA_{1c} less than 7% (baseline, 6.4% vs 5.8%, $P = .019$; follow-up, 6.7% vs 5.4%, $P < .001$).

Cox proportional hazards analysis taking into account age, sex, and number of purchases in each medication group during the follow-up period indicated that only age (hazard ratio [HR], 1.049), male sex (HR, 1.16), and number of insulin purchases (HR, 1.007) were significantly associated with increased cancer risk, whereas cancer risk dropped with number of metformin purchases (HR, 0.996) (Table 4). Neither baseline nor follow-up HbA_{1c} values were found to be associated with cancer incidence in the multivariate model.

4. Discussion

We followed a large cohort of diabetic patients previously untreated with insulin to examine the effects of different treatment modalities on cancer risk. Mean follow-up time during the study period was 4.5 years. Multivariate analysis indicated that age, male sex, and purchases of human insulin were significantly associated with an increased risk of cancer and that purchases of metformin were associated with decreased risk. Neither the purchase of long-acting insulin analogues nor HbA_{1c} level at baseline or follow-up was found to be associated with cancer risk.

Table 2 – Cancer diagnoses by sex and site in a diabetic cohort, MHS, 2003-2007

Cancer site	Sex					
	Female		Male		Total	
	n	%	n	%	n	%
Prostate	0	.0	279	23.4	279	12.9
Breast	284	29.1	6	.5	290	13.4
Gastrointestinal	176	18.0	268	22.5	444	20.5
Urinary	48	4.9	150	12.6	198	9.1
Hematologic	91	9.3	117	9.8	208	9.6
Respiratory	41	4.2	104	8.7	145	6.7
Skin	44	4.5	82	6.9	126	5.8
Pancreas	42	4.3	38	3.2	80	3.7
Head and neck	12	1.2	25	2.1	37	1.7
Bone	2	.2	9	.8	11	.5
Brain	12	1.2	12	1.0	24	1.1
Female genital	132	13.5	1	.1	133	6.1
Male genital	0	.0	5	.4	5	.2
Metastatic to any site	27	2.8	32	2.7	59	2.7
Other	65	6.7	64	5.4	129	6.0
Total	976	100.0	1192	100.0	2168	100.0

Studies of the effect of insulin in general and long-acting insulin analogues in particular on the risk of cancer have produced mixed results [16-21]. Glargine and detemir insulins have been available to the Maccabi patient population since 2004 and 2005, respectively, and were subject to stringent guidelines in the first years of their availability. Therefore, in comparison to human insulins, their rate of utilization was relatively low in our study population, limiting our power to detect a possible correlation with cancer incidence Grouping both long-acting insulin analogues together in the multivariate analysis had no effect on the model. We cannot exclude the possibility that as the use of glargine and detemir insulins increases in our study population, future analysis with larger numbers of patients will reveal different outcomes.

Lifestyle changes and the use of metformin are cornerstones of treatment aimed at achieving good glycemic control. With its positive effect on the lipid profile, metformin is considered to have a cardioprotective effect as well. Our findings are consistent with those of other studies indicating a decreased cancer risk associated with the use of metformin [13,25,26]. The mechanism of the apparent protective effect of metformin is presumably through the activation of the adenosine monophosphate–activated protein kinase [27,28]. In view of this information, metformin should be part of a treatment regimen for type 2 diabetes mellitus from initiation of therapy in the absence of contraindications for its use. Metformin use should not, however, prevent the addition of further medications to reach optimal glucose control.

It is unsettled to what degree glycemic control plays an active role in cancer genesis. Some studies reported an increased risk in gastrointestinal cancers with increasing HbA_{1c} values, whereas others failed to do so [9,29-31]. Our analysis failed to reveal an association between glycemic control, as reflected by HbA_{1c}, and cancer incidence. Because we used the last recorded HbA_{1c} values in the follow-up period in our analysis, it is possible that they reflected the condition of patients after cancer diagnosis, rather than functioning as an indicator of baseline glycemic control. Furthermore, it is conceivable that stricter glucose control was a result of aggressive treatment by the addition of sulfonylurea and insulin, which themselves could increase the incidence of cancer.

Use of administrative data such as are available for an HMO with a stable member population offers several advantages,

Table 3 – Cancer incidence by sex, age group, and drug use category in a diabetic cohort, MHS, 2003-2007

		n	% With cancer diagnosis in follow-up period	RR	LCL (95%)	UCL (95%)	P value
Sex	Male	19 971	5.97%	1.001	.922	1.087	.000
	Female	16 371	5.96%				
Age group at baseline	65+	14 207	9.25%	2.397	2.205	2.606	<.001
	18-65	22 135	3.86%				
Metformin purchase during follow-up period	Yes	28 253	5.94%	.978	.887	1.078	.653
	No	8089	6.07%				
Insulin glargine purchases during follow-up period	Yes	1137	5.72%	.957	.753	1.216	.719
	No	35 205	5.97%				
Insulin detemir purchase during follow-up period	Yes	228	7.46%	1.252	.791	1.981	.909
	No	36 114	5.96%				
Other insulin purchase during follow-up period	Yes	3884	7.08%	1.214	1.075	1.372	.002
	No	32 458	5.83%				
Sulfonylurea purchase during follow-up period	Yes	19 349	6.46%	1.194	1.099	1.296	<.001
	No	16 993	5.41%				

LCL indicates lower confidence limit; UCL, upper confidence limit.

among others the opportunity for long-term follow-up of the study cohort. Mean follow-up time for our cohort was 4.5 years compared with a maximum of 3 years in other recently published studies of the association between insulins and cancer risk. Our inclusion criteria included the requirement that patients have an established history of diabetes, be 18 years or older at baseline, and have no history of insulin use, providing reasonable certainty that the cohort consists of predominantly type 2 diabetes mellitus patients. Care for diabetes mellitus is quite similar in Israel and the United States [32]. For this reason, we assume that our results can be generalized to populations of type 2 diabetes mellitus patients in other developed countries.

Observational studies carry with them certain limitations, the most important of which is that subjects are not randomly assigned to treatment groups. The choice of treatment of diabetes is based on a number of factors, including disease severity, level of glycemic control, and the presence of comorbid conditions, factors that are likely to be related to the risk of cancer. Differentiating between the effect of underlying health status and that of treatment is therefore difficult. Although body mass index measurements are now a standard component of the HMO medical record, they were less widely recorded during the early period of this study and therefore were not available for sufficient numbers of subjects to be included in the analysis. For this reason, we were unable to investigate the independent contribution of obesity to cancer risk. In addition, the HMO database does not maintain accurate information on smoking and family history of cancer; therefore, we were unable to take these factors into account. Another concern is the potential for bias in the identification of diabetic patients by the registry. The registry criteria specify purchases of antidiabetic medications and/or elevated glucose and HbA_{1c} measurements as indicators for inclusion, potentially excluding diabetic patients who are well controlled on diet alone. Although the number of such

Table 4 – Cox proportional hazard model analysis, factors associated with cancer incidence in diabetic cohort, MHS, 2003-2007 diabetic cohort

Factor	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	HR, 95% CI	P value	HR, 95% CI	P value	HR, 95% CI	P value	HR, 95% CI	P value
Age	1.048 (1.044-1.052)	<.001	1.048 (1.044-1.053)	<.001	1.049 (1.045-1.052)	<.001	1.049 (1.045-1.052)	<.001
Male sex	1.171 (1.075-1.276)	<.001	1.159 (1.060-1.268)	.001	1.159 (1.064-1.263)	.001	1.160 (1.065-1.264)	.001
Baseline $HbA_{1c} \leq 7.0\%$			1.016 (0.929-1.111)	.727				
Metformin purchases					0.996 (0.994-0.998)	.001	0.996 (0.994-0.998)	.001
Sulfonylurea purchases					0.998 (0.996-1.001)	.143	0.998 (0.996-1.001)	.141
Glargine and detemir purchases					1.012 (0.998-1.027)	.097		
Glargine purchases							1.011 (0.995-1.026)	.187
Detemir purchases							1.032 (0.989-1.077)	.149
Other insulin purchases					1.007 (1.002-1.012)	.012	1.007 (1.001-1.012)	.014

[a] Age and sex.
[b] Age, sex, and baseline HbA_{1c}.
[c] Age, sex, metformin purchases, sulfonylurea purchases, all long-acting insulin purchases, other insulin purchases.
[d] Final model—age sex, metformin purchases, sulfonylurea purchases, glargine purchases, detemir purchases, other insulin purchases.

subjects is likely to be small, the effect of excluding them from analysis would be to overestimate the percentage of patients receiving drug treatment. Finally, our use of prescription purchases as a proxy for medication could result in either overestimation (in cases in which patients purchase, but do not use the medications of interest) or underestimation (in cases in which patients purchase medication outside the system) of true utilization. Given that all members have a prescription drug benefit involving a modest copayment, we consider it unlikely that they would choose to purchase medications outside of the system. To minimize overestimation of medication use, we required at least 2 medication purchases in any calendar year, under the assumption that members would be unlikely to repeatedly purchase medications they did not use.

Large international, randomized, blinded studies would be required to definitively determine the extent to which long-acting insulin analogues contribute to the risk of cancer. Given the ethical concerns that would be inherent in such trials, they are unlikely to be performed. Because long-acting insulins were introduced relatively recently and with stringent limitations on their use in our population, our numbers of members treated were small. For this reason, we are unable to estimate the true risk of cancer associated with these products. Further study of this population, with increased numbers of treated patients and longer follow-up time, is planned. In the absence of clinical trials data, long-term observational studies of large populations of diabetic patients are a valuable source of data to direct clinical decision-making.

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