Metformin Treatment and Cancer Risk: Cox Regression Analysis with Time-Dependent Covariates of 320,000 Individuals with Incident Diabetes Mellitus

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Running head: Metformin Treatment for Diabetes and Cancer Risk

Abstract

There is conflicting evidence regarding the association between metformin use and cancer risk in diabetic patients. During 2002-2012, we followed a cohort of 315,890 incident diabetic individuals aged 21-87 years insured in the largest health maintenance organization in Israel. We used a discrete form of the weighted

cumulative metformin exposure to evaluate its association with cancer incidence. This was implemented in a time-dependent covariate Cox model, adjusting for treatments with other glucose lowering medications, as well as age, sex, ethnic background, socioeconomic status, smoking (for bladder and lung cancer) and parity (for breast cancer). We excluded from the analysis the metformin exposure in the year before cancer diagnosis to minimize reverse causation of cancer on changes in medication. Estimated hazard ratios (HRs) that were associated with exposure to 1 defined daily dose of metformin over the previous 2-7 years were: for all-sites cancer (excluding prostate and pancreas) HR=0.98 (95% confidence interval (CI) 0.82, 1.18); colon cancer, HR=1.05 (95%CI 0.67, 1.63); bladder cancer, HR=0.98 (95%CI 0.49, 1.97); lung cancer, HR=1.02 (95%CI 0.59, 1.78); and female breast cancer, HR=0.88 (95%CI 0.56, 1.39). Our results do not support an association of metformin treatment with the incidence of major cancers (excluding prostate and pancreas).

Keywords: Bladder cancer; Breast cancer; Colorectal cancer; Diabetes Mellitus; Lung cancer; Metformin; Time varying treatment; Weighted cumulative exposure.

Abbreviations:
BMI – body mass index
CI – confidence interval
DDD – Defined Daily Dose
GLMs - glucose lowering medications
HR - hazard ratio
WCE - weighted cumulative exposure

The evaluation of associations of glucose lowering medications (GLMs) with cancer risk has increased dramatically; metformin is the predominant drug investigated in this context. This biguanide has a well-established safety profile, and has been used as treatment for hyperglycemia during more than half a century (1). Metformin is the most commonly prescribed oral GLM worldwide and is recommended as first-line

therapy in type-2 diabetes (2). Several studies, starting in 2005, have suggested a possible protective effect of metformin with cancer (3). Such effect was concluded by a meta-analysis of 66 studies; however, heterogeneity was high between them: I^2=89%); further, this association was not supported by a sub-meta-analysis that comprised the 23 randomized controlled trials of the full meta-analysis (4). Time-related biases and insufficient attention to the natural history of type-2 diabetes have been claimed to be at the basis of the metformin negative association demonstrated in observational studies (5). Accordingly, a systematic review of observational studies showed that among those with low possibility of bias, a causal effect of metformin on all-sites or specific cancer risk was not evident (6).

We investigated the association of metformin treatment as a time dependent exposure, with cancer incidence, in a population-based cohort of type-2 diabetes incident patients, while accounting for major time related biases and for the various diabetes treatments as they change over time. An important feature of our investigation is the use of Cox regression that includes the history of metformin treatment together with the history of other GLMs as time-dependent covariates. Sylvestre and Abrahamowicz (7) described the use of weighted cumulative exposure (WCE) functions for evaluating the effects of the history of a medication on the incidence of a disease in continuous time. In this paper, we describe a simplified, discrete-time version of the WCE.

METHODS

Study population: Our study is based on electronic records from the largest health maintenance organization in Israel, Clalit Health Services, insuring 53% (4.3 million) of the nation's population. All persons 21-87 years old on January 1 2002, free of diabetes and cancer at study entry, were included in a closed cohort, followed until

December 31 2012 for diabetes incidence. In the present analysis, only patients who developed diabetes during follow-up were included and they were subsequently followed for cancer incidence. The cohort data file, comprising abundant high quality demographic, clinical, and pharmaceutical information, was linked to the Israel National Cancer Registry for cancer morbidity.

Incident diabetes was defined as the fulfilment of at least one of the following 6 criteria during the period from January 1 2002 to December 31 2012: (1) A record of diabetes in the Clalit Chronic Disease Registry; (2) A physician's diagnosis of diabetes together with a plasma glucose test $\geq$ 126 mg/dL within 12 months; (3) HbA1c of 6.5% or higher; (4) Two-hour plasma glucose during an oral glucose tolerance test ≥ 200 mg/dL; (5) Two plasma glucose measurements $\geq$ 126 mg/dL within 12 months; (6) Three or more purchases of glucose lowering medications within 12 months.

Cancer incidence was ascertained by record linkage to the Israel National Cancer Registry, established in 1960. The registry has benefited since 1982 from a national law mandating registration of cancer, and has a 97% coverage of solid tumors, and approximately 88% coverage of hematologic cancers (8).

In this paper, we report associations, in incident diabetic patients, between metformin treatment and the following cancers: all-sites excluding pancreatic and prostate cancers (see reasons for exclusion below), and colorectal, bladder, lung, and breast, chosen as the cancers with the largest incidence in Israel.

We excluded from the present analysis cancers of the pancreas and the prostate, since in previous analyses of our cohort of persons with diabetes, we found strong associations between glucose levels and these cancers (9), whereas we found no such associations with other cancers. In view of these associations, any

assessment of the effect of GLMs on cancers of the pancreas and prostate requires more complex modeling that includes the history of glucose levels as well as medication history (6). Analysis of the associations between metformin and these cancers is therefore being studied separately.

Metformin exposure was defined by metformin use alone or in combination with dipeptidyl peptidase-4 inhibitors. The latter combination entered the market in the last quarter of 2009, comprising 1% of all metformin purchases, and gradually increased to 6% in subsequent years, but the predominant form of metformin use in this study is as taken alone. We adjusted for all other GLMs, including treatment with insulin, alfa glucosidase inhibitors, rosiglitazone, sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and meglitinides. The doses considered for metformin and these other GLMs were according to purchasing data. We recognize that some persons may not have consumed all the medication that they purchased. However, in the absence of information on the amount of missed medications, our analysis is based on the assumption that the amount purchased was the amount consumed.

GLM doses were summarized according to the defined daily dose (DDD). The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or the prescribed daily dose. Therapeutic doses for individual patients and patient groups often differ from the DDD as they are based on individual characteristics (such as age, weight, ethnicity, type and severity of disease) and pharmacokinetic considerations. DDDs provide a fixed unit of measurement independent of price, currency, package size and strength,

enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups.

The Sheba Medical Center's review board and the Clalit services review board approved the study proposal, and exempted the study from obtaining informed consent from each patient due to the historical nature and the source of data from electronic records of a large population.

Statistical analysis

We evaluated the association of metformin with the risk of all site and selected site-specific cancers among incident diabetes patients using Cox regression models with time-dependent covariates. The time origin for the Cox model was two years after the date of diabetes diagnosis. Thus, incident diabetes patients who died, developed cancer or completed their follow-up within 2 years of diabetes diagnosis were excluded from the analysis. In addition, upon reaching age 90 years, individuals were censored from the study. The time axis was divided into quarterly (3-month) periods, and in each period the mean daily DDD metformin level was calculated for each individual.

A major challenge in this work was to find a flexible way of relating a medication history to the risk of cancer. If t denotes the current quarter (t is labeled from 1, the quarter that starts from the date of diabetes diagnosis, to a possible maximum of 44), then an individual's risk of cancer in quarter t may be affected by the dose of medication taken in quarters t-1, t-2, t-3, …., back to quarter 1. (Note that using this notation, follow-up for cancer starts at t=9, the first quarter that is 2 years after diabetes diagnosis). Let D(t) be the mean daily dose of the medication in quarter t. We express the overall exposure of the medication history as a weighted sum of the past doses,

$$\sum_{u=1}^{t-1} w(u)D(t-u) \qquad (1)$$

going back to the first quarter after diagnosis. This sum is called the weighted cumulative exposure at time t, denoted WCE(t). Sylvestre and Abrahamowicz (7) defined this term as an integral over continuous time, but the expression (1) is a sum over the previous quarters. Because the "lag time" of the effect of the medication on cancer risk in quarter t is unknown, the relative weights for past doses are similarly unknown. In our analysis we can estimate the weights as part of the Cox model analysis, viewing each weight as a regression coefficient. However, this would require estimating 36 different weights, corresponding to the 44 quarters. In our application, we have simplified the estimation procedure by assuming that certain groups of weights are equal, namely for the quarters of the previous year (u= 1-4), for years 2-4 previously (u = 5-16), for years 5-7 previously (u = 17-28) and for years 7-10 previously (u=29-40). In this way, expression (1) simplifies to:

$$WCE(t) = w_1 \sum_{u=1}^{4} D(t-u) + w_2 \sum_{u=5}^{16} D(t-u) + w_3 \sum_{u=17}^{28} D(t-u) + w_4 \sum_{u=29}^{40} D(t-u),$$

with only 4 unknown weights instead of 36. In the above expression, if t-u is less than 1 then D(t-u) is set to zero. We did not extend WCE back beyond 10 years since the data were too sparse to estimate adequately the weights for these years.

We incorporated the WCE into the Cox risk model as follows:

$$\lambda(t) = \lambda_0(t)\exp\{\beta_W WCE(t) + \beta_C C\}$$

where $\lambda(t)$ is the individual's hazard rate at time t for the cancer of interest, $\lambda_0(t)$ is the baseline hazard rate, β_W is the coefficient of WCE(t), C are the baseline confounders,

and β_C are their coefficients. With our simplifying assumption, the model reduces to the following Cox model

$$\lambda(t) = \lambda_0(t)\exp\{\beta_1 D_1(t) + \beta_2 D_2(t) + \beta_3 D_3(t) + \beta_4 D_4(t) + \beta_C C\}, \quad (2)$$

where D1(t), D2(t), D3(t) and D4(t) are the mean daily doses over the year previous to quarter t, years 2-4 previous to t, years 5-7 previous to t, and years 7-10 previous to t, respectively (see Web Appendix 1 for details). The doses referred to are those of metformin. Model (2) may be expanded to include additive terms for other medications, each medication comprising four additive terms, as for metformin. In our main analyses, we included also the following GLMs, grouped into 4 main categories according to their mechanism of action: Insulin (fast acting, long acting , intermediate acting, combination of fast and intermediate); drugs affecting endogenic insulin levels, i.e. insulin secretagogues (Sulfonylureas, Meglitinides) and incretin mimetics (dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists); Alfa glucosidase inhibitor; and Roziglitazone (GlaxoSmithKline (Israel) LTD, Petach Tikva, Israel) – the thiazolidinedione used in Israel during the study period.

The confounding variables, C, included in our model were: age in 5-year groups (according to age at entry, i.e. two years after diabetes diagnosis), gender (except for breast cancer), socioeconomic status according to locality of the Health Maintenance Organization clinic [low, medium, high, and "missing" (2.7% had a missing value)], and race/ethnicity (country of birth or mother's country of birth: Ashkenazi Jews [those born in Russia, Eastern Europe, Europe, America or South Africa]; Sephardi Jews [those born in northern Africa or the Middle East]; Yemenite Jews; Ethiopian and Central African Jews; Israeli Jews [including also Israel-born Jews whose mothers' birthplace was unknown]; and Israeli Arabs). In breast cancer

analyses, adjustment was also made for parity, and in lung and bladder cancer analyses, for smoking status (ever smoked versus never smoked/not known).

As mentioned above, we allowed a gap of two years between diabetes diagnosis and start of follow-up for cancer. This was done to minimize effects of ascertainment bias and reverse causation of cancer diagnosis on diabetes diagnosis. Similarly, when evaluating the association of metformin with cancer risk, we ignored the coefficient β_1 representing the association between metformin use in the previous year, since the cancer may have led to a change in metformin dose immediately prior to diagnosis. Accordingly, we report two estimated hazard ratios for cancer associated with metformin use: firstly, the ratio of the hazard rate of someone who used a mean dose of x+1 DDD's in years 2-4 previous to the current quarter versus the hazard rate of someone who was similar in all other characteristics but used a mean dose of x DDD's in that period; and secondly, the ratio of the hazard rate of someone who used a mean dose of x+1 DDD's in years 2-7 previous to the current quarter versus the hazard rate of someone who was similar in all other characteristics but used a mean dose of x DDD's in that period. These hazard ratios are estimated by $\exp(b_2)$ and $\exp(b_2+b_3)$, respectively, where b_2 and b_3 are the estimates of the coefficients β_2 and β_3 in the extended model (2). A simpler interpretation of these hazard ratios is given by considering the case of x=0 in the above definitions. In this case the hazard ratios relate to using a mean metformin dose of 1 DDD over the period in question versus no use of metformin over that period. We aimed to present also hazard ratios for metformin use over the period 2-10 years back, but the data for years 7-10 were insufficient to estimate these with reasonable accuracy.

RESULTS

The characteristics of the individuals included in the cohort are presented in Table 1. Close to 1.33 million person years of follow-up accrued during 2004-2012 among the 315,890 adults who developed diabetes under the age of 88y. Of these, 304,582 were without a previous diagnosis of cancer.

Table 2 presents the number of patients remaining at risk for cancer each year from the time of diabetes diagnosis and their use of metformin and other GLMs. Overall, 172,948 (54.7%) of the patients took metformin at some time during their follow-up. Of those remaining in follow-up, the percentage taking metformin rose steadily, from 29% in the first year following diagnosis of diabetes to 65% in the 11th year (see Figure 1). A total of 94,630 (30%) of the patients took other GLMs at some time during their follow-up. Of those remaining in follow-up, the percentage taking other GLMs rose steadily, from 11% in the first year following diagnosis of diabetes to 46% in the 11th year (see Figure 1).

Results of the Cox regression model for each cancer site are presented in Web Tables 1-5 and the results for metformin exposure summarized in Table 3. The number of individuals included in each analysis differs because we excluded only those patients who had developed the specific cancer of interest within 2 years of their diabetes diagnosis. The main confounders were found to be age, ethnic group, and, for lung and bladder cancers, smoking. Overall, the use of non-metformin GLMs was not found to be associated with the cancers investigated. From the regression coefficients for metformin shown in Web Tables 1-5, hazard ratios for 1 DDD of metformin taken over the periods 2-4 years and 2-7 years previously (Table 3) were calculated as described in the Methods section. The 95% confidence intervals for these hazard ratios included the null value of 1.0 (Table 3), indicating that there was

no clear evidence of an association between the use of metformin and the incidence of these cancers.

DISCUSSION

In this study, we found no clear association between the use of metformin and all-sites cancer (excluding prostate and pancreas), nor with cancers of the colon, breast, lung and bladder.

Several laboratory studies have suggested that metformin may reduce the incidence of cancer. Pleiotropic anti-cancer effects of metformin have been demonstrated both in-vitro and in-vivo, on a number of main molecular pathways, and cellular and metabolic processes (10). Metformin has been shown to specifically target cancer stem cells, as well as to augment the benefit of anti-cancer drugs (11). In a rat model of postmenopausal breast cancer, metformin was shown to inhibit the formation of new tumors, as well as to decrease the size of mammary tumors (12). However, to date, the published results from ongoing clinical trials that have addressed the hypothesis that metformin has antineoplastic activity, have related only to surrogate markers, or have shown negative results (13, 14).

The findings of several observational studies have suggested a protective effect of metformin on cancer development and progression. Metformin was reported to be associated with significant reductions in the risk of cancer overall (15, 16, 17), as well as cancers of the breast (18), liver (19), colorectum (18, 19, 20), pancreas (19), stomach (19), prostate (21), and esophagus (19). Other studies did not find reduced risks for at least some of the cancer types investigated (19, 22, 23). However, it has been claimed that the metformin negative association reported in many observational studies resulted from time-related biases, occurring when allotting

time-at-risk to different exposure categories or when overlooking the effect of the natural history of type 2 diabetes (5, 24). These biases have been described as a) time-window bias, a bias introduced because of differential exposure opportunity time windows between subjects; b) immortal time bias, a bias introduced with time-fixed cohort analyses that misclassify unexposed time as exposed; and c) time-lag bias, a bias introduced by comparing treatments given at different stages of the disease, i.e. when a longer duration of diabetes in the comparator group confounds the association. Time-related biases have been shown to exaggerate downward the association of a drug with disease, thus making a drug appear protective when it really has no effect (5).

Like the study reported in this paper, a number of more recently published studies that accounted for time-related biases did not find negative associations of metformin use with the incidence of lung, colorectal, breast, or bladder cancers (25-28). On the other hand, the use of metformin during a period of at least five years was found to be associated with reduced incidence of colorectal cancer in men (29).

The strengths of the current study are the use of a large population-based database that has high quality data on medication purchases, linkage to data from a national cancer registry with 95% coverage of cancer diagnoses, the use of time-dependent Cox models that overcome the problem of time-related biases and the use of a flexible weighted cumulative exposure (WCE) approach that enables examination of different time periods and doses of exposure, and, in particular, the exclusion of periods of exposure shortly before cancer diagnosis. Using the WCE concept in continuous time requires special programming. Our adaptation of the method to

discrete-time periods (i.e. quarters) enabled implementation of the WCE approach naturally, within the usual Cox regression framework, with a considerable reduction in programming-burden. Additionally, the adjustment for other GLM use as time-dependent variables enabled us to capture more fully the complexity of diabetes treatment and to account for these potential confounding exposures.
The characteristics of the study cohort reflect those of individuals with diabetes in the Israeli population assuring a high external validity (30).

Limitations of the study include reliance on medication purchase data as a surrogate for medication use, a relatively short study duration, and limited data on confounding risk factors for cancer. The relatively short study duration, apart from limiting our ability to examine the association of longer-term use of metformin with cancer, also reduces the power to detect shorter-term associations. Thus, while the estimated hazard ratios are generally small and near the null value of 1.00, their confidence intervals are relatively wide.

Information on a number of potentially important confounders was not available in our database. We were not able to include body mass index (BMI), physical activity, or aspirin or statin medication as adjusting covariates in our models. The cancer most likely to be impacted by this lack of adjustment is colorectal cancer. Confounding by BMI and physical activity would tend to cause overestimation of the hazard ratio for metformin use for this cancer. On the other hand, if more metformin use also took more aspirin or statins then this would cause an underestimate. It is therefore possible that these potential biases would partially cancel each other.

Data were not available to distinguish between the types of diabetes; thus, individuals with type 1 diabetes were included in the diabetes groups. However, the proportion of such cases is expected to have been small, and their inclusion is therefore not expected to have had considerable impact on the results. Only 3.5% of adults with diabetes in Western countries are estimated to have type 1 diabetes. In addition, patients with type 1 diabetes are usually medicated with insulin, and since we adjust for insulin medication in our model, we also partially control for the inclusion of these patients.

We expect the database to become even more valuable as follow-up is extended and the quality of data on risk factors is improved.

In conclusion, our analysis, accounting for major time-related biases and for diabetes treatment varying over time, did not support an association of metformin treatment with the incidence of cancers (excluding prostate and pancreas) in diabetic patients. Long-term controlled trials, following diabetic patients from the time of diabetes diagnosis and randomizing them to metformin or to other GLMs with re-randomization to an added GLM in case of failure to control plasma glucose, would be the most reliable method to answer this question, but are probably not feasible.

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Table 1. Characteristics of 315,890 Israeli Individuals with Incident Diabetes aged 21-87 years, followed between 2002 and 2012 for cancer incidence for a total of 1,934,333 person years.

Characteristic	%
Age at baseline (years) [a] [b]	58.6 (14.9)
Sex	
Men	47.0
Women	53.0
Ethnic origin	
Ashkenazi Jews	31.3
Sephardic Jews	27.2
Yemenite, Ethiopian and Central African	5.3
Israeli Jews	18.0
Israeli Arabs	18.1
Socioeconomic status	
Low	43.7
Medium	37.5
High	16.1
Missing	2.7
Smoking	
Never smoked + missing	64.3
Past + current smoker	35.7
Number of children	
0	22.1
1	16.4
2 or 3	35.8
4+	25.7

[a] At time of diabetes diagnosis; [b] Values are expressed as mean (standard deviation)

Table 2. Israeli Individuals with Diabetes Mellitus at Risk for Cancer according to the Time from Diabetes Diagnosis (Years) and Characteristics of the Use of Metformin and Other Glucose Lowering Medications during 2002-2012 [a]

Time from Diabetes Diagnosis, years	No. Alive Without Any Cancer at the Beginning of the Period [b]	No. Who Began Metformin Treatment [c]	No. Who Continued Metformin Treatment [d]	DDD of Metformin [e]	No. Who Began Other GLM Treatment [f]	No. Who Continued Other GLM Treatment [g]	Not Treated With Any GLM
0.0-0.9	304,582	86,913	-	0.27	33,551	-	203,493
1.0-1.9	298,984	26,363	70,357	0.36	12,590	22,217	171,699
2.0-2.9	276,902	19,211	83,588	0.40	11,461	29,131	139,794
3.0-3.9	242,254	13,810	86,850	0.45	10,084	34,052	108,380
4.0-4.9	208,035	9,748	84,844	0.49	8,240	37,239	83,093
5.0-5.9	171,243	6,753	77,260	0.52	6,548	37,698	60,898
6.0-6.9	138,695	4,546	67,553	0.56	4,947	36,195	44,538
7.0-7.9	107,186	2,932	55,571	0.59	3,625	32,658	31,161
8.0-8.9	77,333	1,650	42,362	0.62	2,163	26,090	20,176
9.0-9.9	48,788	836	28,599	0.65	1,148	19,065	10,709
10.0-10.9	13,487	186	8,544	0.68	273	5,953	2,263

DDD – Defined Daily Dose: *The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.* GLM - Glucose Lowering Medications.

[a] Other GLMs, including treatment with insulin, alfa glucosidase inhibitors, rosiglitazone, sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and meglitinides; [b] The succeeding columns do not sum to this total column because some patients take both metformin and other GLMs; [c] If a patient had not taken metformin before this period and started to take metformin in this period, s/he was entered in this cell; [d] If a patient took metformin before this period and also during this period, s/he was entered in this cell; [e] The sum of the total DDDs of metformin over these patients and divided by 365.25 and then by the total number of patients in the two preceding columns. The DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose; [f] If a patient started any GLM other than metformin and had not taken any such medication before, s/he was entered in this cell; [g] If a patient took any GLM other than metformin before this period and also took any GLM other than metformin in this period, s/he was entered in this cell.

Table 3. The Association Between Metformin Treatment (1 Defined Daily Dose increment) and Incidence of All-Sites and Specific Cancers During 2004-2012 in Israeli Individuals with Diabetes, Controlling for All Other Glucose Lowering Medications [a], and Adjusting for Confounding Variables [b]

Cancer site	No. at Risk [c]	No. of Cancer Events	Period of Metformin treatment previous to the current quarter			
			Years 2-4 [d]		Years 2-7 [d]	
			aHR	95%CI	aHR	95%CI
All sites [e]	294,770	11,898	0.96	0.82, 1.12	0.98	0.82, 1.18
Colon	310,698	2,131	1.13	0.79, 1.63	1.05	0.67, 1.63
Bladder	313,133	764	0.91	0.50, 1.68	0.98	0.49, 1.97
Lung	313,460	1,265	0.85	0.53, 1.38	1.02	0.59, 1.78
Breast (women only)	163,461	1,835	0.95	0.64, 1.40	0.88	0.56, 1.39

[a] adjusted for: insulin, alfa glucosidase inhibitor, rosiglitazone, sulfonylureas, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, meglitinides; [b] Confounding variables: age, sex, socioeconomic status, ethnic origin, smoking (for bladder and lung cancers), parity (for breast cancer); [c] the numbers reflect patients at risk for the particular cancer at the time they were diagnosed with diabetes (and were without any previous cancer diagnosis), excluding those who completed follow-up within two years of their diabetes diagnosis; [d] Excluding the first year previous to the current period, because an undiagnosed cancer could cause perturbations in glucose levels particularly in the year prior to diagnosis; [e] without prostate and pancreatic cancers.

Figure 1. Percentage of Israeli Individuals with Diabetes Mellitus-at-Cancer-Risk Taking Metformin (continuous curve) and Other Glucose-Lowering Medications (dashed curve) by Years Since Diabetes Diagnosis (for the period 2002-2012)

Figure 1 legend:
See Table 2, 3^{rd}+4^{th} columns divided by 2^{nd} column for metformin trajectory, 6^{th}+7^{th} columns divided by 2^{nd} column for other glucose-lowering medication trajectory.