Turk J Public Health
Available online at: http://dergipark.org.tr/tjph/
Doi: 10.20518/tjph.1475986

TURKISH JOURNAL OF PUBLIC HEALTH

ORIGINAL ARTICLE

Malignancy risk in diabetes; a population study based on electronic health records

Mustafa Mahir Ülgü[1], Mestan Emek[2] , Mustafa Kemal Balcı[3], Kemal Hakan Gülkesen[4]

[1]Assoc. Prof., Ministry of Health, Ankara, Türkiye
[2]Assist.Prof., Department of Public Health, Faculty of Medicine, Akdeniz University, Antalya, Türkiye
[3]Prof., Division of Endocrinology, Faculty of Medicine, Akdeniz University, Antalya, Türkiye
[4] Assoc. Prof., Department of Biostatistics and Medical Informatics, Faculty of Medicine, Akdeniz University, Antalya, Türkiye

Received: 20.05.2024, **Accepted:** 14.11.2024

Abstract

Objective: To document the risk of the most common types of malignancies in people with diabetes compared to the people without diabetes.

Methods: The data source of this study is the national electronic health records system of Türkiye (e-Nabız). We analysed only the data of people over 14 years old in 2019. All the people with ICD-O-3 codes recorded for the first time in 2019 were accepted as new tumour cases. Tumours with /3 behaviour codes were accepted as malignant.

Results: We detected 6,775,054 (10.6%) people with diabetes and 57,167,598 people without diabetes in our database. There were 63,696 new malignant cases in the group with diabetes and 123,662 new malignant cases in the group without diabetes. The total number of malignant tumours was 187,358. All types of major tumours seem to have increased risk. Pancreas cancer has the highest OR (odds ratio), 4.02 (3.71-4.36, 95% confidence interval), and larynx cancer has the lowest OR, 1.29 (1.19-1.41). OR for the presence of any malignancy in a person with diabetes is 1.87 (1.85-1.89).

Conclusion: All major types of malignant tumours have an increased incidence in people with diabetes. The results confirm the presence of a relationship between diabetes and malignancy.

Keywords: Neoplasms, Malignant, Diabetes Mellitus, Electronic Health Records

Correspondence: Assoc. Prof., Kemal Hakan Gülkesen, Department of Biostatistics and Medical Informatics, Faculty of Medicine, Akdeniz University, Antalya, Türkiye. **E-mail:** hgulkesen@gmail.com, **Phone**: +90 532 775 79 10

Cite This Article: Ülgü MM, Emek M, Balcı MK, Gülkesen KH. Malignancy risk in diabetes; a population study based on electronic health records. Turk J Public Health 2024;22(3): 255-262.

INTRODUCTION

Diabetes mellitus is a systemic disease that has harmful effects on a series of physiologic processes in the human body. An increased risk of malignancy in diabetes was identified in the 1960s in population-based studies. There are some explanations for the mechanism of the development of malignancy in diabetes. Some researchers suspect shared risk factors in both diseases, such as age, sex, obesity, and dyslipidemia. There are several other suggested mechanisms for carcinogenesis in diabetes, including the direct effect of hyperglycemia, but their mechanisms are unclear yet[1]. Some studies have shown increased risks of some cancers after adjusting for other confounding factors, such as obesity and dyslipidemia. Possibly both types of factors are responsible together for carcinogenesis. Growth hormones, insulin resistance, inflammatory cytokines, adipokines, and hyperlipidemia are some of the variables that influence the development of obesity and diabetes. By controlling several signaling pathways, the metabolic anomalies linked to variations in these components' levels in obesity and diabetes may play a major role in the initiation and spread of cancer[2]. Insulin resistance linked to type 2 diabetes is known to adversely affect some important genetic and metabolic factors that may ultimately result in neoplastic transformation[3]. Additionally, some antidiabetics may increase the risk of cancer. There are also studies reporting a decreased risk of cancer by metformin[4].

Cancer risk is increased in both type 1 and type 2 diabetes mellitus. Studies suggest an association between type II diabetes and cancer in many organs, such as the endometrium, breast, stomach, colorectum, pancreas, liver, and blood[5]. Interestingly, prostate cancer is reported to have a lower incidence in people with diabetes[6]. Overall cancer incidence among people with diabetes is 10–20% higher than among those without diabetes[7]. Previous reports on the risk of major cancer types in diabetes are summarized in Table 1.

There may be also a sex difference on the effect of diabetes on cancer. According to a meta-analysis, the pooled adjusted RR for all-site cancer associated with diabetes was 1.27 (95% CI 1.21, 1.32) in women and 1.19 (1.13, 1.25) in men. Women with diabetes had 6% greater risk compared with men with diabetes (the pooled RRR was 1.06, 95% CI 1.03, 1.09)[24].

Türkiye has cancer registry centers, and the Ministry of Health publishes annual cancer statistics. The last cancer statistics book presented the data for 2018[25]. According to this report, cancer incidence is 283 for men and 232 for women per 100,000. The most common cancer types are lung, prostate, and colorectal in men and breast, thyroid, and colorectal in women.

The incidence of diabetes-related cancer has not been sufficiently studied in the Turkish population. There is only one study, a cohort study, conducted in the İzmir region[26]. In total, 1643 people with diabetes and 14,226 people without diabetes were followed up for diabetes-related cancer development in the following six years. According to the results of the study, diabetes-related cancer incidence was significantly higher in men with diabetes than without diabetes. No statistically significant increase in malignancy in women with diabetes compared to women without diabetes was observed.

This study aims to document the risk of the most common types of malignancies in people with diabetes compared to people without diabetes based on national electronic health records (EHR).

Table 1. Summary of some studies reporting the risk of malignancy in diabetes. OR: Odds ratio, RR: Relative risk, SIR: Adjusted standardized incidence ratio

Type of malignancy	Year	Type of diabetes	Study design	Risk (95% CI)
Oral	2021	Both	Meta-analysis	OR: 1.41 (1.10-1.81)[8]
Head and neck	2021	Type 2	Meta-analysis	RR: 1.04 (0.88-1.23)[9]
Pharynx	2021	Type 2	Meta-analysis	RR: 1.18 (0.94-1.49)[8]
Stomach	2022	Both	Meta-analysis	RR: 1.17 (1.02-1.34)[10]
Colon	2011	Both	Meta-analysis	RR: 1.27 (1.21-1.34)[11]
Liver	2012	Both	Meta-analysis	RR: 2.31 (1.87-2.84)[12]
Pancreas	2011	Both	Meta-analysis	RR: 1.94 (1.66-2.27)[13]
Larynx	2021	Type 2	Meta-analysis	RR: 1.03 (0.88-1.22)[9]
Lung	2020	Both	Meta-analysis	RR: 1.10 (0.99-1.23)[14]
Malignant melanoma	2014	Type 2	Meta-analysis	RR: 1.15 (1.00-1.32)[15]
Breast	2023	Type 2	Meta-analysis	RR: 1.20 (1.05-1.36)[16]
Uterus	2019	Both	Meta-analysis	RR: 1.72 (1.48-2.01)[17]
Ovary	2020	Both	Meta-analysis	RR: 1.20 (1.10-1.31)[18]
Prostate	2013	Type 2	Meta-analysis	RR: 0.86 (0.80-0.92)[6]
Kidney	2013	Both	Meta-analysis	RR: 1.40 (1.16-1.69)[19]
Bladder	2013	Both	Meta-analysis	RR: 1.35 (1.17-1.56)[20]
Thyroid	2017	Both	Meta-analysis	RR: 1.20 (1.09-1.33)[21]
Hodgkin disease	2012	Type 2	Meta-analysis	OR: 1.02 (0.86-1.19)[22]
Non-Hodgkin lymphoma	2020	Type 1	Meta-analysis	RR: 1.55 (1.15-2.08)[23]
Non-Hodgkin lymphoma	2020	Type 2	Meta-analysis	RR: 1.20 (1.12-1.30)[23]

METHOD

This study has been reported according to the RECORD Statement. The data source of this study is the national EHR system of Türkiye, e-Nabız (https://enabiz.gov.tr/). At the end of 2019, the system was storing the health data of 62,442,436 (97.7%) of 63,942,652 citizens over 14 years old.

We analysed only the data of people over 14 years old in 2019. First, we detected all the people who had diabetes. Our criteria for having diabetes mellitus were 1) having an HbA1c over 48 mmol/mol (6.5%) or 2) having a prescription with a diabetes mellitus diagnosis, with ICD-10 codes E10-E14. If only metformin is prescribed, the person is considered not to have diabetes because it is used in "prediabetes" and other indications[27], or 3) having at least two fasting blood sugar measurements over 126 mg/dl. The fasting blood sugars that were ordered from an emergency department or between 13.00 and 8:00 were excluded. The data was scanned from April 2015 to the end of 2019. e-Nabız system started in April 2015, and we do not have reliable data before this date. All the citizens without diabetes over 14 years old are in the comparison group. The pathology reports in the system were checked for the presence of any ICD-O-3 codes. If a patient had an ICD-O-3 code in 2019, their data were checked for the presence of the same code in previous years (2015-2018). All the people with ICD-O-3 codes recorded for the first time in 2019 were accepted as new tumour cases

for calculating 2019 incidences. Tumours with /3 behaviour codes were accepted as malignant.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Clinical Research Ethics Committee of the Medical Faculty of Akdeniz University.

The data were analysed by Microsoft Excel 2016. Calculating the pooled (age and sex-adjusted) odds ratio and its confidence intervals were performed by the logit method Morris and Gardner described[28]. In the case of zero cases in any category, the number was entered as 0.001 in Excel to prevent division by zero errors. Odds ratios with their 95% confidence Intervals have been calculated.

RESULTS

We detected 6,775,054 (10.6%) people with diabetes and 57,167,598 people without diabetes in our database. There were 63,696 new malignant cases; 29,663 women and 34,033 men in the group with diabetes. There were 123,662 new malignant cases; 56,971 women and 66,691 men in the group without diabetes. The total number of malignant tumours was 187,358.

Age and sex-adjusted incidences of tumours in the population with diabetes and the population without diabetes are compared in Table II and Figure 1. All the tumours seem to have an increased risk. Pancreas cancer has the highest OR, 4.02 (3.71-4.36), and larynx cancer has the lowest OR, 1.29 (1.19-1.41). Men are more likely than women to develop certain cancers, such as colorectal, liver, pancreatic, thyroid, and other malignancies, as well as Hodgkin disease and non-Hodgkin lymphomas. Age and sex-specific incidences and ORs for each type of malignancy are presented in supplementary file.

Table 2. Age and sex-adjusted incidence (per 100,000) and pooled odds ratio of some malignant tumours in the populations with diabetes and without diabetes.

Type of tumour	Female			Male			Total		
	DM	Non-DM	OR (95% CI)	DM	Non-DM	OR (95% CI)	DM	Non-DM	OR (95% CI)
Oral and pharynx cancers (C00-C14)	9.8	4.7	1.70 (1.53-1.88)	19.8	7.4	1.86 (1.72-2.03)	14.8	6.1	**1.80 (**1.69-1.92**)**
Stomach cancer (C16)	21.2	10.0	1.73 (1.61-1.85)	36.0	18.0	1.72 (1.63-1.81)	28.5	14.0	**1.72** (1.65-1.79)
Colorectal cancer (C18-C20)	35.7	16.9	1.94 (1.84-2.03)	65.7	24.7	2.26 (2.17-2.35)	50.6	20.8	**2.12** (2.06-2.19)
Liver cancer (C22)	10.5	4.4	2.17 (1.97-2.39)	19.1	6.2	2.72 (2.51-2.94)	14.8	5.3	**2.48** (2.34-2.64)
Pancreas cancer (C25)	7.4	2.1	3.47 (3.06-3.93)	12.8	2.6	4.49 (4.03-5.00)	10.1	2.3	**4.02** (3.71-4.36)
Larynx cancer (C32)	0.9	0.6	1.42 (1.03-1.95)	9.8	7.2	1.29 (1.18-1.41)	5.3	3.9	**1.29** (1.19-1.41)
Lung cancer (C34)	22.1	11.8	1.67 (1.57-1.78)	91.5	52.1	1.55 (1.50-1.60)	56.7	31.9	**1.57** (1.53-1.62)
Malignant melanoma (C44)	1.4	0.9	1.48 (1.14-1.91)	2.5	1.1	1.95 (1.56-2.43)	1.9	1.0	**1.73** (1.46-2.05)
Breast cancer (C50)	108.7	58.2	1.70 (1.65-1.76)	1.9	0.8	1.82 (1.40-2.36)	55.5	29.6	**1.70** (1.65-1.76)
Uterus cancer (C54)	19.8	8.0	-	-	-	-	-	-	**2.38** (2.22-2.56)
Ovary cancer (C56)	9.4	3.4	-	-	-	-	-	-	**2.26** (2.00-2.54)

Table 2. (countinue) Age and sex-adjusted incidence (per 100,000) and pooled odds ratio of some malignant tumours in the populations with diabetes and without diabetes.

Prostate cancer (C61)	-	-	-	55.7	40.7	-	-	-	**1.35** (1.30-1.40)
Kidney cancer (C64)	8.0	3.4	1.96 (1.75-2.20)	19.0	7.1	2.17 (2.00-2.35)	13.5	5.3	**2.10** (1.96-2.24)
Bladder cancer (C67)	5.6	3.8	1.41 (1.26-1.58)	41.0	23.2	1.64 (1.57-1.62)	23.2	13.5	**1.61** (1.54-1.68)
Thyroid cancer (C73)	44.0	22.0	1.74 (1.64-1.84)	20.4	6.4	2.21 (2.01-2.44)	32.3	14.2	**1.84** (1.76-1.94)
Hodgkin disease (C81)	5.3	1.3	2.84 (2.26-2,58)	17.2	1.8	4.72 (3.97-5.62)	11.2	1.5	**3.93** (3.42-4.52)
Non Hodgkin lymphoma (C82–C86, C96)	9.7	4.0	1.92 (1.73-2.14)	23.8	5.3	2.61 (2.38-2.86)	16.7	4.6	**2.29** (2.14-2.46)
Other malignant tumours	180.2	74.0	1.96 (1.91-2.01)	282.2	67.0	2.24 (2.18-2.30)	231.1	70.5	**2.09** (2.05-2.13)
All malignant tumours (C00-C97)	499.6	229.6	1.87 (1.84-1.90)	718.2	271.5	1.88 (1.85-1.90)	608.5	250.5	**1.87** (1.85-1.89)

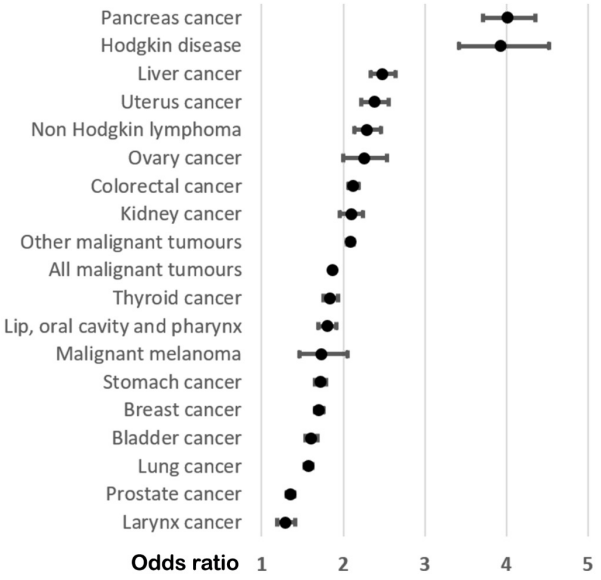

Figure 1: Age and sex-adjusted odds ratios of major malignancies in 6.8 million people with diabetes compared to 57.2 million people without diabetes. Lines representing confidence intervals are not visible for some tumours due to being too narrow.

DISCUSSION

The incidences of all the common malignancies were higher in people with diabetes compared to people without diabetes. Larynx cancer has the lowest OR, while pancreatic cancer has the highest. The odds ratio for the presence of any malignancy in a person with diabetes is 1.87 (1.85-1.89).

We preferred to use the odds ratio as the risk factor to apply the pooled odds ratio method in Morris and Gardner's study to adjust it for age and sex[28]. OR is very close to RR when incidence is low, so they can be accepted as the same in practice, to compare our results to the literature.

Liver, colon, pancreas, breast, endometrium, ovary, kidney, bladder, thyroid malignancies, and non-Hodgkin lymphoma were known to have a high risk in diabetes. A meta-analysis on pancreas cancer[13] reports 1.9 RR, which is quite lower than our results. However, another meta-analysis with only Chinese studies[29] reports a 3.7 RR, which is close to our result. This situation suggests the presence of genetic and/or environmental factors in the pathogenesis of pancreas cancer in diabetes. Our results are very close to the previous meta-analyses of liver[12], and bladder[20]. The risk of colorectal carcinoma (2.1 vs. 1.3)[11], breast cancer (1.7 vs. 1.2)[16], ovary cancer (2.3 vs. 1.2)[18], kidney cancer (2.1 vs. 1.4)[19], thyroid cancer (1.8 vs. 1.2)[21], and non-Hodgkin lymphoma (2.3 vs. 1.2)[23] are higher than the reported risks in the literature.

Some of the malignancies such as stomach (1.72 in our study vs. 1.10[10] in the literature), larynx (1.29 vs. 1.03[9]), lung (1.57 vs. 1.10[14]), malignant melanoma (1.73 vs. 1.15[15]), and Hodgkin's disease (3.93 vs. 1.02[22]), were reported as having no risk or a minimal increase in risk in diabetes. However, all these tumours have an increased risk in our data. Additionally, the total incidence of malignancy is increased by an OR of 1.87 (1.85-1.89), in contrast to the suggested 10-20% increase[7].

Prostate cancer was reported to have a lower risk in people with diabetes[6], but we have found an increased risk with an OR of 1.35 (1.30-1.40). This result is confusing, but it may be due to genetic or environmental factors. An increased risk of prostate cancer in Asian men (RR: 1.72) was reported in a meta-analysis[30].

We also analyzed if there is a sex difference in the effect of diabetes on cancer. According to a previous meta-analysis[24], women with diabetes had 6% greater risk compared with men with diabetes. We did not observe a general risk difference between men and women. In the meta-analysis, they observed a higher liver cancer risk in men. We observed the same pattern in our dataset. Additionally, we observed that men are more likely than women to develop colorectal, pancreatic, thyroid, and other malignancies, as well as Hodgkin disease and non-Hodgkin lymphomas. On the other hand, they observed an increased risk of oral, kidney, and stomach cancers in women, but our results have not confirmed this relation. The differences in these results may be due to genetic and environmental differences, sample size, and the absence of some confounding factors in our dataset.

This study examined the relationship between diabetes and cancer in Türkiye for the first time through national health records. Although the study has limitations, it provides us with valuable information due to the large volume of data. As the study was carried out on a large population, confidence intervals are very narrow. Some malignancies that revealed suspicious results in previous studies showed prominently increased risks. The increased risks in this study may be related to local and genetic factors for some of the malignancies and may not be generalizable to other countries. EHR systems are relatively new, and the quality of data in these systems is not excellent yet. Our system is also unsuitable for investigating causal relations because the data starts from 2015. In the future, with the accumulation of longitudinal data and better data quality in EHRs, we expect the scientific community to produce more information about diabetes and other diseases.

When we were extracting data for the study, the 2020 data was complete; however, we considered that the incidence of tumours must be lower than usual because of decreased patient admission during the COVID pandemic. Therefore, we preferred to work with 2019 data. Because this data is derived from the EHR, there may be questions about the reliability of the incidences in the present report. We compared our incidences to official 2018 statistics[25]. For example, in men, cancer incidence is 316 vs. 283 (per 100,000, our report vs. 2018 report), 58 vs. 60 for lung, 44 vs. 42 for prostate, and 31 vs. 28 for colorectal cancers. In women, cancer incidence is 270 vs. 232, 66 vs. 60 for breast, 21 vs. 20 for colorectal, and 24 vs. 27 for thyroid cancer. Our incidences are close to the official cancer registry data, although

there are differences of various magnitudes. The source of these differences may be the possibility of detecting old cases with new biopsies (the EHR system started in 2015, and its coverage was lower before 2019) or the possibility of some missed cases in the cancer registry. On the other hand, our method should have missed some cases because of the absence of a pathology report. According to official statistics, 91.3% of the cases have histopathological confirmation. However, these problems are valid for both people with and without diabetes. Our study is based on the data extracted from the national EHR, and this system is not specifically designed as a diabetes or cancer registry. We extracted the data from a daily operational database that may contain errors. Additionally, some data may be absent in the database, so it is possible that we could not include some diabetes or tumour cases. On the other hand, type 1 and type 2 diabetes may pose different risks to different tumours. However, we are not able to differentiate the type of diabetes in our dataset. So the results are a mixture of type 1 and predominantly type 2 diabetes. Another limitation is the absence of data related to possible confounding factors such as infections, alcohol, and smoking.

CONCLUSION

According to the results of the present study, all major types of malignant tumours have an increased incidence in people with diabetes. The population analysed in this study was larger than most previous studies, and ORs with quite narrow confidence intervals were obtained because the study is based on a national EHR system that contains 6,7 million people with diabetes and 57,2 million people without diabetes. The common risk factors for diabetes and malignancy, namely obesity and the absence of glycemic control, are serious public health problems to be fought. Health policymakers must also develop strategies for the early detection of malignancies in patients with diabetes.

ACKNOWLEDGEMENTS

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Financial Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Declaration: In order to conduct the study. Ethics committee approval (dated 18.10.2020 and decision number KAEK-768) from Clinical Research Ethics Committee of the Medical Faculty of Akdeniz University and written informed consent was obtained from the individuals participating in the study via online forms.

Author Contrubition: Concept: MMÜ, MKB, KHG, Design: MMÜ, MKB, KHG, Supervising: MKB, Data collection and entry: MMÜ, Analysis and interpretation: MMÜ, ME, KHG, Literature search: MMÜ, ME, KHG, Writing: MMÜ, KHG, Critical review: ME, MKB.

REFERENCES

1. Kim DS, Scherer PE. Obesity, Diabetes, and Increased Cancer Progression. Diabetes Metab J. 2021 Nov;45(6):799-812.
2. Cebioglu M, Schild HH, Golubnitschaja O. Diabetes mellitus as a risk factor for cancer: Stress or viral etiology? Infect Disord Drug Targets. 2008;8:76–87.
3. Vulichi SR, Runthala A, Begari N, Rupak K, Chunduri VR, Kapur S, Chippada AR, Sistla DSM. Type-2 diabetes mellitus-associated cancer risk: In pursuit of understanding the possible link. Diabetes Metab Syndr. 2022 Sep;16(9):102591.
4. Lv Z, Guo Y. Metformin and Its Benefits for Various Diseases. Front Endocrinol (Lausanne). 2020;11:191.

5. Blonde L, Umpierrez GE, Reddy SS, McGill JB, Berga SL, Bush M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022 Oct;28(10):923-1049.

6. Peila R, Rohan TE. Diabetes, Glycated Hemoglobin, and Risk of Cancer in the UK Biobank Study. Cancer Epidemiol Biomarkers Prev. 2020 Jun;29(6):1107-1119

7. Suh S, Kim KW. Diabetes and Cancer: Cancer Should Be Screened in Routine Diabetes Assessment. Diabetes Metab J. 2019 Dec;43(6):733-743.

8. Ramos-Garcia P, Roca-Rodriguez MDM, Aguilar-Diosdado M, Gonzalez-Moles MA. Diabetes mellitus and oral cancer/oral potentially malignant disorders: A systematic review and meta-analysis. Oral Dis. 2021;27:404-421.

9. Yan P, Wang Y, Yu X, Liu Y, Zhang ZJ. Type 2 diabetes mellitus and risk of head and neck cancer subtypes: a systematic review and meta-analysis of observational studies. Acta Diabetol. 2021;58:549-565.

10. Bae JM. Diabetes History and Gastric Cancer Risk: Different Results by Types of Follow-Up Studies. Asian Pac J Cancer Prev. 2022 May 1;23(5):1523-1528.

11. Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. Eur J Epidemiol. 2011;26:863-876.

12. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2012;28:109-122.

13. Ben Q, Xu M, Ning X, et al. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. Eur J Cancer. 2011;47:1928-1937. Yi ZH, Luther Y, Xiong GH, et al. Association between diabetes mellitus and lung cancer: Meta-analysis. Eur J Clin Invest. 2020;50:e13332.

14. Qi L, Qi X, Xiong H, et al. Type 2 diabetes mellitus and risk of malignant melanoma: a systematic review and meta-analysis of cohort studies. Iran J Public Health. 2014;43:857-866

15. Lu Y, Hajjar A, Cryns VL, Trentham-Dietz A, Gangnon RE, Heckman-Stoddard BM, Alagoz O. Breast cancer risk for women with diabetes and the impact of metformin: A meta-analysis. Cancer Med. 2023 May;12(10):11703

16. Saed L, Varse F, Baradaran HR, Moradi Y, Khateri S, Friberg E, et al. The effect of diabetes on the risk of endometrial Cancer: an updated a systematic review and meta-analysis. BMC Cancer. 2019 May 31;19(1):527.

17. Wang L, Zhong L, Xu B, Chen M, Huang H. Diabetes mellitus and the risk of ovarian cancer: a systematic review and meta-analysis of cohort and case-control studies. BMJ Open. 2020 Dec 29;10(12):e040137.

18. Bao C, Yang X, Xu W, et al. Diabetes mellitus and incidence and mortality of kidney cancer: a meta-analysis. J Diabetes Complications. 2013;27:357-364.

19. Zhu Z, Wang X, Shen Z et al. Risk of bladder cancer in patients with diabetes mellitus: an updated meta-analysis of 36 observational studies. BMC Cancer. 2013;13:310.

20. Li H, Qian J. Association of diabetes mellitus with thyroid cancer risk: A meta-analysis of cohort studies. Medicine (Baltimore). 2017;96:e8230.

21. Castillo JJ, Mull N, Reagan JL, Nemr S, Mitri J. Increased incidence of non-Hodgkin lymphoma, leukemia, and myeloma in patients with diabetes mellitus type 2: a meta-analysis of observational studies. Blood. 2012;119:4845-4850.

22. Wang Y, Liu X, Yan P, Bi Y, Liu Y, Zhang ZJ. Association between type 1 and type 2 diabetes and risk of non-Hodgkin's lymphoma: A meta-analysis of cohort studies. Diabetes Metab. 2020;46:8-19.

23. Ohkuma T, Peters SAE, Woodward M. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events. Diabetologia 61, 2140–2154 (2018).

24. Tolunay T, Kaygusuz S, Keskinkılıç B, Özsarı S, Gökler ME. Türkiye Kanser İstatistikleri 2018. Ankara, Halk Sağlığı Genel Müdürlüğü (General Directorate of Public Health);2022, Ankara. https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/Dokumanlar/Istatistikler/Kanser_Rapor_2018.pdf

25. Yilmaz Kavcar SR, Acikgoz A, Ergor G, Unal B. Evaluating the Relationship between Diabetes and Cancer in a Cohort. Asian Pac J Cancer Prev. 2022;23:1223–1229.

26. Bailey CJ. Metformin: historical overview. Diabetologia. 2017;60:1566-1576.

27. Morris JA, Gardner MJ. Calculating confidence intervals for relative risks (odds ratios) and standardised ratios and rates. Br Med J (Clin Res Ed). 1988;296:1313-1316.

28. Zhang JJ, Jia JP, Shao Q, Wang YK. Diabetes mellitus and risk of pancreatic cancer in China: A meta-analysis based on 26 case-control studies. Prim Care Diabetes. 2019;13:276-282. Gang PJ, Mo L, Lu Y, Runqi L, Xing Z. Diabetes mellitus and the risk of prostate cancer: an update and cumulative meta-analysis. Endocrine Research. 2015;40:54-61.