Incidence of Cancer among Diabetic and Non-Diabetic Adult Israeli Arabs

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ABSTRACT: **Background:** A worldwide epidemic of type 2 diabetes mellitus (T2DM) is in progress. This disease carries a heavy socio-economic burden.

Objectives: To compare the incidence rate of overall and site-specific cancers among Israeli Arabs with T2DM to that of Israeli Arabs without.

Methods: A retrospective cohort study of all adult Arab members of Clalit Health Care Services in northern Israel was conducted over a 10 year period (1999–2008).

Results: During the study period 752 and 2045 incident cases of cancer were diagnosed among 13,450 adults with diabetes and 74,484 without, respectively. The follow-up time involved 817,506 person-years. Diabetes was associated with a standard incidence ratio (SIR) of 3.27 (95%CI 1.49–5.05) and 2.87 (95%CI 1.25–4.50) for pancreatic cancer in men and women, respectively. A significantly reduced SIR (0.67, 95%CI 0.36–0.99) was observed for esophageal, stomach and intestinal cancers in men.

Conclusions: Our findings support an association between T2DM and increased risk of cancer of the pancreas in Arab men and women. A significantly reduced risk of all other cancers was observed only in Arab men. Our findings underscore the need for effective diabetes and cancer prevention and intervention programs.

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KEY WORDS: cohort studies, type 2 diabetes mellitus (T2DM), cancer incidence, Israeli Arabs, computerized databases

Type 2 diabetes mellitus is a major and growing health problem worldwide. It is associated with severely acute and chronic complications that negatively impact both the quality of life and the survival of affected individuals [1]. Patients diagnosed with cancer who have preexisting diabetes are at an increased risk for long-term all-cause mortality as compared to those without diabetes [1-3]. Several epidemiological studies in various countries have found a higher relative risk for development of malignant diseases among diabetic patients, with the strongest association between diabetes and increased risk of liver, pancreatic, colon, rectal, uterine and breast cancers [1-5]. However, the association between diabetes and cancer is still in dispute, and various mechanisms have been suggested to explain the potentially causal relationship between diabetes and cancer. The former is associated with insulin resistance, relative insulin deficiency, insulin secretor defect, or both. Insulin may stimulate cell proliferation through activation of the insulin receptor or insulin-like growth factor receptor [4]. Studies have also shown greater oxidative damage to DNA in diabetic patients, as measured by the concentration of 8-hydroxydeoxyguanosine in mononuclear cells [6].

Deregulations in insulin and insulin-like growth factor pathways may contribute to the development of hepatocellular carcinoma. Intracellular insulin receptor substrate-2 is the main effector of insulin signaling in the liver and is overexpressed in human hepatocellular carcinoma. The emergence of IRS-2 overexpression at pre-neoplastic stages during experimental hepatocarcinogenesis and its protective effect against apoptosis suggest that IRS-2 contributes to the progression of liver tumor [7,8].

Most previous epidemiological studies on diabetes and cancer were limited due to the use of self-reported information about diabetes status, relatively small study populations, or short follow-up periods. In addition, many studies examined cancer mortality rather than incidence. Since diabetic patients with cancer have a poorer survival rate [2,9] independent of tumor stage and grade, cancer mortality may not represent true risk estimates, particularly for rarer cancers and cancers with low fatality rates.

Throughout the world, the incidence of pancreatic cancer is highest in countries with a westernized lifestyle, including Israel. Even so, pancreatic cancer is not a common malignancy, being the 12th and 15th most common malignancy among Israeli Jewish men and women, respectively, and 10th and 19th among Arab men and women [10,11]. In contrast, it ranks 6th and 13th in the United States for men and women,

IRS-2 = insulin receptor substrate-2

respectively. Cancer of the pancreas accounts for only 3% of all cancers worldwide. However, due to its poor prognosis it is the eighth cancer-related death worldwide [11]. Pancreatic cancer mortality ranks third in Israel and fourth in the USA [10-13]. From 1982 to 2002, a 9.9% reduction in incidence rates of pancreatic cancer was observed in the Israeli general population. Rates declined significantly among both men and women – a decrease of 12.2% and 5.7%, respectively. This decline in pancreatic cancer incidence rates was noted only among Jews: the annual incidence rates declined by 0.8% and 0.4% per year among Jewish men and women respectively. In contrast, during this period, the incidence rate rose among Arab men and women [11].

The main goal of the current retrospective cohort study was to evaluate the incidence of overall and site-specific cancer among Israeli Arabs with and without diabetes who are members of a large health insurance fund in northern Israel.

PATIENTS AND METHODS

Clalit Health Care Services is the major health insurance fund in the country, covering approximately 90% of the population until 1995, after which it gradually declined in membership in the general Israeli population to just over 50% in 2010. This decline is much less prominent among the Arabs of northern Israel, and in 2010 about 70% of the Arabs in northern Israel were members of Clalit. Israeli Arabs constitute approximately 20% of the total Israeli population and about 48% in the country's northern region.

DIABETES MELLITUS

We identified T2DM patients by using the Clalit Health Care Services computerized registry of diabetic patients that was established in 1999, and the computerized medical records of each member (a computerized personal file in the office of all primary care physicians), using the disease classification criteria suggested by the American Diabetes Association [14]. These criteria include fasting plasma glucose > 125 mg/dl (7.0 Mm 1/1), or casual (namely, without regard to time since the last meal) plasma glucose concentration ≥ 200 mg/dl, hemoglobin A1C ≥ 6.5, or purchase of at least two hypoglycemic medications or single insulin dose during a 6 month period.

All prevalent diabetes cases aged 25 or older who were identified prior to the index date (1 January 1999) and continuously insured by Clalit in the Haifa and Western Galilee region for the subsequent 10 years were included in the cohort. The non-diabetes group comprised cancer-free members of Clalit prior to the start of the follow-up period, who were never diagnosed with diabetes and had no laboratory test results in their personal file suggestive of diabetes or glucose intolerance.

T2DM = type 2 diabetes mellitus

COHORT MEMBERS AND FOLLOW-UP

The number of Arab members of Clalit in the relevant district at the end of the study period was 257,916, as compared with a total Arab population in Israel of 1,499,000 (17%). Arab members over the age of 25 in the region numbered 93,000 as compared with 680,700 in the total Arab population (14%).

About 5066 persons were excluded because they had cancer prior to 1999 or during the first year of follow-up. Also excluded were persons who had diabetes but their cancer appeared before the diagnosis of diabetes or up to 1 year after. The rationale for this was to neutralize the possibility that diabetes was an early expression of cancer, as both diabetes and cancer are diseases with long latency periods.

The final study group comprised 13,450 (15.3%) adult Arabs with diabetes and 74,484 (84.7%) without. Males constituted 46.4% of the diabetes group and 50.2% of the non-diabetes group.

The follow-up period was from 1 January 1999 (index date) to the date of the incident cancer diagnosis, death, discontinuation of coverage by the health fund, or 31 December 2008 (whichever occurred first). The follow-up period involved 817,506 person-years, of which 54,491 were contributed by diabetic males and 65,131 by diabetic females, as compared with 349,131 person-years by non-diabetic males and 348,753 by non-diabetic females.

CANCER INCIDENCE DATA

Data on cancer occurrence during the follow-up period was obtained from the Israel National Cancer Registry. Established in 1960, this registry collects information of diagnosed cancer cases from all medical institutions in the country, covering more than 90% of diagnosed cancer cases [15]. All cancer cases were classified according to the International Classification of Diseases for Oncology (ICD-O, Version 3) and include histological findings [15]. The diabetes registry of Clalit Health Care Services and the Israel National Cancer Registry database were cross-linked by the unique identity number assigned to each Israeli resident.

STATISTICAL ANALYSIS

Standardized incidence rates were computed per 100,000 population, standardized to the "Israeli Arab Standard Population." Rates were computed for all and site-specific cancers. Israeli Arab population data, by age group and gender, were retrieved from the Central Bureau of Statistics. Tests of significance used confidence intervals of 95% and a result was considered significant when $P < 0.05$. The earliest measurement of body mass index prior to the end of follow-up was obtained from medical records and categorized as follows: < 25 kg/m^2, 25–29.9 kg/m^2, and 30 kg/m^2. Student's *t*-test was used to compare mean differences. This study was approved by the Clalit ethics com-

mittee. All statistical analyses were conducted using Excel, SAS and SPSS software packages.

RESULTS

DIABETES IN THE STUDY POPULATION

Type 2 diabetes mellitus usually appears in older adults, in both genders, and the prevalence of the disease increases progressively with age. Approximately 17% of the diabetics in the study group were younger than 50 years and about 55% were older than 60, compared to the non-diabetes group, 61.7% and 19.3%, respectively. The overall prevalence rate of diabetes in the study group (adult Arabs older than 25) during the 10 years of follow-up was 14.3% for men and 16.3% for women.

MALIGNANCY IN THE STUDY POPULATION

During the 10 year follow-up period, 752 cases of malignant disease were observed in diabetics (crude rate 628/100,000) and 2045 cases (crude rate 293/100,000) in the non-diabetic group, resulting in a rate ratio of 2.56.

Table 1. Mean age of study participants by diagnosis (DM vs. non-DM) and gender (at the end of the follow-up period, 1999–2008)

	Diabetic patients (n=13,450)	Non-diabetic patients (n=74,484)	*P*
Age (yr) (mean ± SD)	62.5 ± 12.3	49.5 ± 13.4	0.001
Female age (yr) (mean ± SD)	63.2 ± 12.7	49.4 ± 13.4	0.001
Male age (yr) (mean ± SD)	61.6 ± 12.5	49.5 ± 13.4	0.001
Gender (% men)	46.4 %	50.2%	0.001
Body mass index (kg/m²)			
< 25	13.3%	26.4%	0.001
25–30	34.0%	34.6%	NS
30+	50.5%	27.5%	0.001
Smoking			
Never smoker	15.1%	13.2%	NS
Past smoker	6.2%	0.7%	0.001
Current smoker	2.9%	6.3%	0.001

Table 2. Cancer incidence rate, diabetics vs. non-diabetics, 1999–2008

	Gender	Observed	Expected	SIR	95%CI		*P* value
All cancers	Male	385	425.94	0.90	0.81	0.99	0.018
	Female	367	335.78	1.09	0.98	1.20	0.053
	Male & female	752	761.72	0.99	0.92	1.06	0.062
Pancreas	Male	13	3.97	3.27	1.49	5.05	0.006
	Female	12	4.18	2.87	1.25	4.50	0.011
	Male & female	25	8.15	3.07	1.87	4.27	0.032
Esophagus, stomach & small intestine	Male	18	26.71	0.67	0.36	0.99	0.020
	Female	11	15.17	0.73	0.30	1.15	NS
Genital	Female	45	52.16	0.86	0.61	1.11	NS
Breast	Female	102	93.62	1.09	0.88	1.30	NS
Colorectal	Male	51	48.42	1.05	0.76	1.34	NS
	Female	64	49.17	1.30	0.98	1.62	NS
	Male & female	115	97.59	1.18	0.96	1.39	NS

MEAN AGE OF THE STUDY POPULATION

Table 1 shows that both diabetic men and women were significantly older (about 12–13 years) at the end of the follow-up period (index date) than non-diabetic persons. This difference was highly statistically significant (t = 107.369, 95% confidence interval 12.78–13.25, P = 0.000). The mean age of diabetic men was 61.6 ± 12.5 years and of non-diabetic men 49.5 ± 13.4 years. The mean age of diabetic women was 63.2 ± 12.7 years and of non-diabetic women 49.4 ± 13.4 years.

There was no statistically significant difference between the mean age of non-diabetic men and women (t = 0.94, 95%CI 0.1–0.29, P = 0.35). In contrast, diabetic men were about 18 months younger than diabetic women (t = -7.607, 95%CI -2.01–1.18, P = 0.00). There was no statistically significant difference between the study population and the general adult Arab population in Israel in terms of age and gender distribution.

STANDARDIZED INCIDENCE RATIOS

The overall cancer incidence among diabetic Arab women showed a borderline increase as compared with non-diabetic women, but it was not significant (SIR 1.09, 95%CI 0.98–1.20, P = 0.053). In contrast, the overall cancer incidence was significantly lower in diabetic Arab men as compared to non-diabetic men (SIR 0.90, 95%CI 0.81–0.99, P = 0.018).

Diabetes was associated with a standardized incidence ratio of 3.27 (95%CI 1.49–5.05) and 2.87 (95%CI 1.25–4.50) for cancer of the pancreas in men and women, respectively. A borderline non-significant increased SIR value was observed also for colorectal cancer in female diabetics, SIR 1.3 (95%CI 0.98–1.62, P = 0.056) while in men the increase rate was not statistically significant, SIR 1.05 (95%CI 0.76–1.34).

For breast and genital cancers in female diabetics, SIR was not significantly increased, 1.09 (95%CI 0.88-1.30) and 0.86 (95%CI 0.61–1.11), respectively. Significantly reduced SIR values were observed for esophageal, stomach, intestinal and all cancers for diabetic men: SIR 0.67 (95%CI 0.36–0.99) and 0.90 (95%CI 0.81–0.99), respectively [Table 2].

Cancer incidence rates rose continuously with age in both diabetic and non-diabetic men during the follow-up period. The rate ratio of person-years incidence rate of cancer in diabetic subjects and non-diabetic subjects under age 50 was higher in diabetic males and females than in non-diabetics [Table 3].

During the 10 years of follow-up 385 and 1127 incident cancer cases occurred among diabetic and non-diabetic men, respectively, and 367 and 918 incident cancer cases were diagnosed among diabetic and non-diabetic women, respectively. The 10 year incidence rate of various types of cancer in dia-

CI = confidence interval
SIR = standardized incidence ratio

Table 3. Rate ratio of person-year cancer incidence rate among diabetic and non-diabetic subjects by age groups and gender

	Rate ratio	
Age (yr)	**Male**	**Female**
35–39	1.36	1.8
40–44	1.40	2.0
45–49	1.58	1.2
50–54	1.03	0.97
55–59	1.01	0.99
60–64	0.86	1.56
65–69	0.96	0.83
70–74	0.86	0.86
75+	0.66	0.76

betic and non-diabetic male and female Arabs in the region is shown in Table 4A for men and 4B for women. Breast cancer was the leading malignant disease in women, both diabetic and non-diabetic, 28% and 32.6% of all cancer cases, respectively. The second most prevalent cancer in diabetic women was colorectal (17.4%), followed by cervical-uterine (10.0%). Among non-diabetic women, cervical-uterine cancer ranked second (16.1%) and colorectal cancer third (11.4%).

Lung cancer was the most common cancer in both diabetic and non-diabetic men, 16.3% and 20%, respectively, followed by prostate cancer (14.5% vs. 11.8%), colorectal cancer (13.2% vs. 10.5%), and bladder cancer (12.5% vs. 10.8%). Pancreatic cancer incidence was three times higher among diabetic than among non-diabetic persons (3.4% vs. 1.1%, respectively).

Table 4A. Ten year cancer incidence in diabetic and non-diabetic Arab men, 1999–2008

	Diabetic subjects		Non-diabetic subjects	
Site	**No.**	**%**	**No.**	**%**
All cancers	385	100%	1127	100%
Lung	63	16.3%	226	20%
Prostate	56	14.5%	133	11.8%
Colorectal	51	13.2%	119	10.5%
Bladder	48	12.5%	122	10.8%
Leukemia	21	5.5%	34	3.0%
Pancreas	13	3.4%	12	1.1%
Melanoma	13	3.4%	30	2.7%
Kidney	9	2.3%	27	2.4%

Table 4B. Ten year cancer incidence in diabetic and non-diabetic Arab females, 1999–2008

	Diabetic subjects		Non-diabetic subjects	
Site	**No.**	**%**	**No.**	**%**
All cancers	367	100%	918	100%
Breast	102	28%	299	32.6%
Colorectal	64	17.4%	105	11.4%
Cervical-uterine	37	10%	148	16.1%
Bladder	14	3.8%	29	3.2%
Pancreas	12	3.2%	8	0.9%
Kidney	7	1.9%	4	0.4%
Leukemia	6	1.6%	20	2.2%
Melanoma	7	1.9%	15	1.6%
Liver	20	5.4%	4	0.4%

DISCUSSION

This study provides the first reported estimates of cancer incidence in diabetic adult Israeli Arabs. The overall prevalence rate of diabetes in Arab adults (over 25 years) in our study was about 15%, slightly higher in women than in men. This rate is similar to that of the overall Arab population in Israel [16]. The overall cancer person-years incidence rate in our cohort of adult diabetic Arabs was 706/100,000 for males and 563/100,000 for females, while the rates in non-diabetics were lower, 323/100,000 and 263/100,000, respectively.

The findings indicate that the standardized incidence ratio of pancreatic cancer in Israeli Arabs over the age of 25 is higher among diabetic than non-diabetic subjects. Thus, the results of this large, population-based retrospective cohort study suggest that among Israeli Arabs diabetes is an independent risk factor for pancreatic cancer. When analyses were limited for patients with more than 5 years follow-up, the association between diabetes status and pancreatic cancer in men and women remained high, supporting a causal relationship between diabetes and pancreatic cancer. Chodick et al. [17], in their large cohort study of Israeli Jews, found that the mean age for both diabetic patients and non-diabetic subjects was 62 years (SD ± 13 years). In our study, we noticed a 12 year gap between the mean age of diabetic and non-diabetic subjects (62.5 ± 12.3 vs. 49.5 ± 13.4 years). The gender divide was equal in the non-diabetic group, while women accounted for about 54% of the diabetic group. In Chodick's study [17] women constituted only 47% of the study population.

T2DM occurs three times more often among Israeli Arabs between the ages 35 and 64 as compared with Israeli Jews in the same age group, for both genders. Due to lifestyle changes among Israeli Arabs in recent decades (westernization), a marked increase in the incidence rate of T2DM in this group was observed. The most influential risk factors are unhealthy diet, lack of physical activity, and tobacco smoking [18]. The Israeli Arab population is relatively young, with 42% of Arabs under the age of 15 [19].

Chodick and co-authors [17] found that in Israeli (urban) Jewish men and women, breast cancer and prostate cancer comprised 26.8% and 26.0% of all cancers, respectively. In our study of Israeli Arab adults, breast cancer and prostate cancer comprised only 14.6% and 6.8% of all cancers, respectively. Cancers of the digestive system organs comprised 23.2% of all cancers among men vs. 24.6% among women in Chodick's cohort study. In our study of Arab subjects, cancers of the digestive system organs comprised 11.0% of all cancers among men vs. 9.1% among women.

Since the 1990s the age-adjusted incidence rate of cancer is increasing, particularly among Israeli Arabs. During 2000–2007, the rate increased by 21% among Arab males, mainly cancer of the prostate, colon and rectum, and by 11% among Arab females, mainly cancer of the breast, corpus uteri and colon [20,21]. These increasing rates were partially explained by improved and more accessible diagnostic technologies currently available to the Arab population.

Among Israeli Jewish and Arab women, the most common cancer is breast cancer and the second most common is colorectal [14]. The incidence rate of breast cancer among Jewish women in 2008 was 87.4/100,000 compared to 56.5/100,000 among Arab women. Between 1980 and 2000, the breast cancer incidence rate increased by 140% among Arab women and only 37% among Jewish women [20]. Breast cancer accounted for one-third of the age-adjusted incidence rate of all malignancies among Jewish and Arab women. Since 2000, the rate has decreased among Jews but increased among Arabs [21].

A meta-analysis of 17 case-control and 19 cohort or nested case-control studies showed that T2DM was associated with increased risk of pancreatic cancer with odds ratios of 1.48 and 1.57 among men and women, respectively [22]. Cigarette smoking and possibly obesity have been identified as causally associated with pancreatic cancer [22]. Among individuals with chronic diabetes (over 45 years) the increased risk of pancreatic cancer supports a causal relationship between diabetes and pancreatic cancer. This is true when considering that in individuals with a long history of diabetes (over 45 years), it is unlikely that a malignancy with a particularly low 1 year survival rate (fewer than 20% of individuals are alive at 1 year following diagnosis) could induce diabetes many years prior to its diagnosis. In addition, the presence of a graded dose-response association between fasting glucose and pancreatic cancer reported by some large prospective studies supports a causal relationship [22,23].

T2DM, cigarette smoking, and possibly obesity, are known risk factors causally associated with pancreatic cancer. Unless a substantial reduction in these risk factors in the concerned group is achieved the incidence of pancreatic cancer will continue to rise [22,23].

Smoking trends in Israel follow the pattern of smoking in the developed world. Smoking rates have been decreasing during the last decade in the Jewish population, whereas in the minority population (Arab men) the rates are still increasing. The rates of smoking among Arab men are nearly double those among Jewish men. Current smoking patterns among Arabs are similar to those of the first stages of the cigarette epidemic, with high rates of smoking among men and low rates among women [24].

An inverse relationship between diabetes and prostate cancer was found in several earlier studies. High testosterone levels may increase the risk of prostate cancer and, therefore, low testosterone levels may actually be protective [17,25]. Similar results were found in a population-based cohort study [25].

In their cohort study, Chodick et al. suggested that T2DM in women may be an independent risk factor for cancer of digestive system organs (pancreas, colon, liver, gall bladder) and genital organs (uterus and ovaries). Men with diabetes do not have a significantly increased risk of developing digestive system cancers and are also less likely to develop prostate cancer [17]. The findings of our study of a significantly reduced SIR for esophageal, stomach, intestinal and all other cancers in diabetic men – 0.67 (95%CI 0.36–0.99) and 0.90 (095%CI 0.81–0.99), respectively – were not observed in earlier studies. A review of the literature did not reveal articles indicating reduced cancer risk in men with diabetes other than for prostate cancer.

Our results have important clinical and public health implications. In Israel about 8% of the Arab population has diabetes [16] and it has been predicted that the number of Israeli Arabs with diagnosed diabetes will increase in the future. The prevalence of diabetes will probably increase as a result of the obesity epidemic and, thus, this disease may further contribute to the development of additional cases of cancers in the future. Our findings underscore the need for effective diabetes and cancer prevention and intervention programs, especially since a worldwide epidemic of diabetes is in progress, carrying with it a heavy subsequent socioeconomic burden.

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Capsule

Receptor binding by a ferret-transmissible H5 avian influenza virus

Cell surface-receptor binding by influenza viruses is a key determinant of their transmissibility, both from avian and animal species to humans as well as from human to human. Highly pathogenic avian H5N1 viruses that are a threat to public health have been observed to acquire affinity for human receptors, and transmissible-mutant-selection experiments have identified a virus that is transmissible in ferrets, the generally accepted experimental model for influenza in humans. Xiong and collaborators showed that quantitative biophysical measurements of the receptor-binding properties of hemagglutinin (HA) from the transmissible mutant indicate a small increase in affinity for human receptor and a marked decrease in affinity for avian receptor. From analysis of virus and HA binding data the authors have derived an algorithm that predicts virus avidity from the affinity of individual HA-receptor interactions. It reveals that the transmissible mutant virus has a 200-fold preference for binding human over avian receptors. The crystal structure of the transmissible mutant HA in complex with receptor analogues shows that it has acquired the ability to bind human receptor in the same folded-back conformation as seen for HA from the 1918, 1957, 1968 and 2009 pandemic viruses. This binding mode is substantially different from that by which non-transmissible wild-type H5 virus HA binds human receptor. The structure of the complex also explains how the change in preference from avian to human receptors arises from the Gln226Leu substitution, which facilitates binding to human receptor but restricts binding to avian receptor. Both features probably contribute to the acquisition of transmissibility by this mutant virus.

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Eitan Israeli

"For any student of history, change is the law of life. Any attempt to contain it guarantees an explosion down the road; the more rigid the adherence to the status quo, the more violent the ultimate outcome will be"

Henry Kissinger (born 1923), German-born American writer, political scientist, diplomat and Nobel Peace Prize laureate. He served as National Security Advisor and later as Secretary of State in the administrations of Presidents Richard Nixon and Gerald Ford. After his term, his opinion was still sought by some subsequent U.S. presidents and other world leaders. A proponent of *Realpolitik*, Kissinger pioneered the policy of *détente* with the Soviet Union, orchestrated the opening of relations with the People's Republic of China, and negotiated the Paris Peace Accords, ending American involvement in the Vietnam War. He is still considered an influential public figure