Population-based estimation of mortality and occurrence of cancer in patients with and without diabetes in Pune

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Diabetes has been implicated as an altered risk for development of various cancer types. Aim of the present study was to compare the mortality from malignancies in diabetic and non-diabetic population and to understand the interrelationship between diabetes and cancer. Retrospective observational analysis of data obtained from death certificate providing information about the cause of death, age, sex and identity of decedents from Pune city, excluding the suburbs, was undertaken. Death certificates from January 2006 to December 2006 were analysed. Thirty-two different cancer types were detected in a deceased population of 14,838 with 8% and 6.8% suffering from diabetes and cancer respectively. Out of the total population, 7% of diabetics and 6.8% of the non-diabetics had cancer. Liver (OR = 2.05, 95% CI (1.04–4.04), $P = 0.033$) and pancreatic (OR = 3.78, 95% CI (1.84–7.73), $P = 0.0001$) cancer were the major cancer types in diabetic population. Average survival age of breast cancer patients with diabetes was 70.3 years and it was 57.9 years for non-diabetics. We observed that in a given population, there is an increase in the occurrence of certain cancer types under diabetic condition. The present study hints that the interplay between diabetes and cancer in Indian population may be complex and provides impetus for a detailed cohort study.

Keywords: Cancer, death certificate, diabetes, Indian population, mortality.

BOTH cancer and diabetes are a major concern for the health of adult population in India[1–3]. Several studies have suggested that diabetes mellitus may alter the risk of developing a variety of cancers, and the associations are biologically plausible[4–8]. Though the association between diabetes and cancer has been the subject matter of research over a century, it is the recent epidemiological studies conducted in a number of countries that substantiates an interrelation between these two diseases[4–11]. The greatest risk has been reported for primary liver cancer, moderately elevated for pancreatic, and relatively low for colorectal, endometrial, breast and renal cancers[7]. However, risk of developing other cancer types in diabetics is obscure. Since the magnitude of both these health problems in India is growing at an alarming rate, effective management of these health problems warrants studies related to the prevalence of various cancers in diabetic population, which at present are lacking. We evaluated the percentage occurrence of various cancer types in diabetic and non-diabetic deceased population with an objective to study the influence of diabetes.

The study designed is a retrospective observational study of deceased population of Pune city, excluding suburbs, by probing into one-year death certificate data provided by the State Bureau of Health Intelligence and Vital Statistics (HIVS), Pune, India. Death certificate gives information about the cause of death, age, sex and identity as well as the diseases the patient suffered from.

The study analysed 14,838 death certificates data for 2006 (January 2006 to December 2006). Decedents with diabetes, cancer and diabetes with cancer were defined purely as those with diabetes-related disorders, cancer and diabetes with cancer respectively. This information was used to analyse the association, occurrence and mortality due to different cancer types, percentage occurrence of cancer types and mean survival age, status of sex-specific cancers, in both males and females, with or without diabetes.

Chi-square test was used to assess the significance of increased incidences of liver and pancreatic cancers in diabetic and non-diabetic population. Chi-square values were calculated by utilizing the formula $(ad - bc)^2/efgh \times k$, where a is the number of deceased patients with liver cancer and diabetes, b the number of deceased patients with liver cancer without diabetes, c the number of deceased patients with only diabetes without liver cancer, d the number of deceased without liver cancer and without diabetes, e the total number of diabetics, f the total number of non-diabetic population, g the number of liver cancer deceased patients, h the number of deceased without liver cancer and k is the total sample size. Chi-square value was considered significant for P value of < 0.05. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated to reflect the uncertainty due to missing data and population sampling. In breast cancer cases, the significance of mortality age difference between two groups (diabetics with breast cancer and non-diabetics with breast cancer) was analysed using t-test.

Analysis revealed that 1,212 deceased adults were suffering from diabetes and 1,012 from cancer. These diabetes

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and cancer decedents represented 8% and 6.8% respectively of total medically certified deaths. Fifty seven per cent (694) of deceased diabetics were males and 43% (518) were females. Eighty-five deaths, which constitute 0.6% of total medically certified deaths, were patients suffering from diabetes as well as cancer (Figure 1).

Thirty-two types of cancers were reported in the deceased population (Table 1). Twenty-three forms of cancers were observed in males and 29 in females. Of the total cancer-related mortalities, breast, lung, colon, oral, oesophageal, liver, cervix, leukaemia, non-Hodgkin's lymphoma, ovary were relatively more prevalent. Breast, cervical, ovary, colon, oesophageal, oral, lung and liver cancers were predominant in females, whereas lung, liver, colon, oral cavity, leukaemia, oesophageal, prostate and non-Hodgkin's lymphoma were the major forms of cancer in males (Table 1).

Death certificate analyses revealed that 7.6% of the deceased suffered from diabetes-related disorders and 6.2% of the deceased suffered from cancer (Figure 1). Of the 1212 diabetic patients, 7% patients had cancer, whereas 6.8% of the non-diabetics had cancer (Table 2). Nineteen different forms of cancers were recorded in deceased diabetic patients. Breast, liver, lung, pancreas, oral, non-Hodgkin's lymphoma, leukaemia, CNS tumour, colon were the major cancer types noted in diabetic population. Breast, colon, oesophageal, lung, oral cavity, cervix and liver were the major cancers reported in deceased non-diabetic population. The percentage occurrence of cancer of CNS, urinary bladder, leukaemia, gall bladder, stomach, larynx, prostate and non-Hodgkin's lymphoma in diabetics remained more or less similar to that in non-diabetic population. In contrast, to the above mentioned cancer types, increased percentage occurrence of renal, oral cavity, pancreas, lung, liver and breast cancer were noted in deceased diabetic patients. A statistically significant positive association was observed with diabetic state in case of liver (OR = 2.05, 95% CI (1.04–4.04), $P = 0.033$) and pancreatic cancer (OR = 3.78, 95% CI (1.84–7.73), $P = 0.0001$). In general, the percentage occurrence of majority of cancer types in diabetic and non-diabetic deceased patients did not vary significantly. Interestingly, it was observed that survival age was high in breast and oral cavity cancers.

Of the 17 cancer types recorded in diabetic males, liver, lung, pancreas and oral cavity cancers caused increased mortality. Diabetic males had increased percentage occurrence of liver, lung, pancreas and oral cavity cancer (Table 3). In case of diabetic females breast, lung, liver, oral, CNS tumour, non-Hodgkin's lymphoma and laryngeal cancer were more commonly found in comparison to non-diabetics (Table 3). Mean survival age of diabetic males and females with pancreatic cancer decreased by 7.4 and 13.8 years respectively. Increased occurrence of lung cancer and decrease in survival age was observed in diabetic females. Also, though percentage occurrence remained similar, survival age of diabetic males with oral cavity, leukaemia, colon and stomach cancer increased as compared to non-diabetics. Diabetic females with breast,

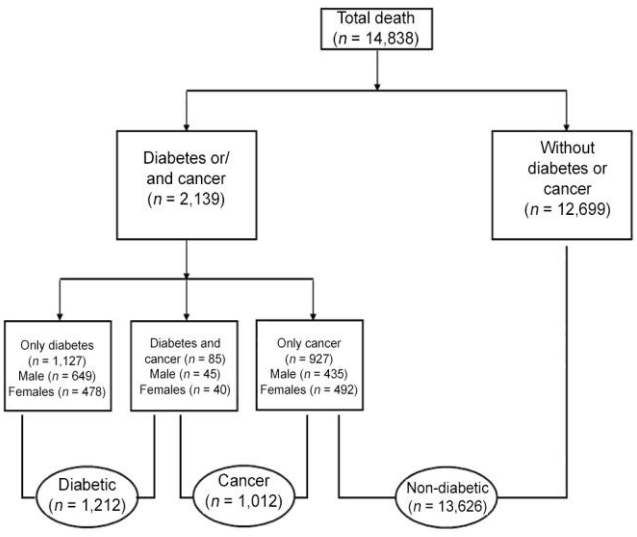

Figure 1. Flow chart representation of occurrence of diabetes and cancer in deceased population. *n* denotes number of deceased.

Table 1. Percentage occurrence of different cancer types in total cancer population ($n = 1012$)

Cancer type	Male (%)	Female (%)	Total (%)
Liver	4.3	2.2	6.4
Lung	5.0	2.4	7.4
Pancreas	2.4	1.5	4.0
Oral	4.0	3.0	6.9
Leukaemia	3.8	1.8	5.5
Colon	4.1	3.4	7.4
Stomach	2.4	1.1	3.5
Non-Hodgkin's lymphoma	3.3	2.1	5.3
Gall bladder	0.5	0.9	1.4
Renal cell	0.7	0.4	1.1
Urinary bladder	1.7	0.6	2.3
CNS tumour	2.5	2.0	4.5
Larynx	2.1	0.9	3.0
Small intestine	0.6	0.1	0.7
Skin	0.9	0.5	1.4
Soft tissue	0.3	0.6	0.9
Multiple myeloma	0.8	1.1	1.9
Oesophageal	3.5	3.2	6.6
Bone	0.5	0.2	0.7
Hodgkin's lymphoma	0.4	0.2	0.6
Thyroid	0.0	0.2	0.2
Lachrymal duct	0.0	0.1	0.1
Metastatic PNET	0.0	0.1	0.1
Adrenal neuroblastoma	0.0	0.1	0.1
Breast	0.0	11.3	11.3
Ovary	0.00	5.2	5.2
Cervix	0.0	5.9	5.9
Vagina	0.0	0.5	0.5
Uterus	0.0	1.3	1.3
Prostate	3.4	0.0	3.4
Penis	0.4	0.0	0.4
Testis	0.2	0.0	0.2

n, Number of deceased.

Table 2. Percentage occurrence of cancer in diabetic and non-diabetic population

	Diabetic (n = 1212)				Non-diabetic (n = 13,626)			
Cancer type	Male mean age (n), range	Female mean age (n), range	Total	Total diabetics (%)	Male mean age (n), range	Female mean age (n), range	Total	Total non-diabetics (%)
Ovary	–	59.20 (02) 55–64	2	0.165	–	59.70 (51) 22–81	51	0.374
CNS tumour	36.00 (01)	67.33 (03) 55–80	4	0.330	49.48 (24) 3–85	47.29 (17) 10–86	41	0.301
Urinary bladder	63.00 (01)	78.00 (01)	2	0.165	70.75 (16) 50–86	82.20 (05)	21	0.154
Renal cell	55.00 (01)	68.00 (01)	2	0.165	55.33 (06) 40–81	52.00 (03) 23–68	09	0.066
Leukaemia	60.00 (03) 41–75	60.00 (01) 3–93	4	0.330	51.57 (35) 3–93	38.23 (17) 2–75	52	0.382
Gall bladder	45.00 (01)	0	1	0.083	62.75 (04) 56–66	50.66 (9) 29–65	13	0.096
Multiple myeloma	0	0	0	0	61.87 (08) 55–87	62.81 (11) 49–78	19	0.139
Oesophagal	0	0	0	0	66.68 (35) 45–90	65.75 (32) 41–88	67	0.492
Stomach	76.50 (02) 63–90	66.00 (01)	3	0.248	59.23 (22) 29–88	64.7 (10) 53–92	32	0.234
Colon	76.66 (03) 76–78	79.00 (01)	4	0.330	62.03 (38) 26–86	62.79 (33) 25–88	71	0.521
Oral	68.75 (04) 55–75	68.33 (03) 60–73	7	0.578	59.16 (36) 32–86	57.85 (27) 35–85	63	0.462
Larynx	46.00 (01)	86.50 (02) 86–87	3	0.248	68.65 (20) 18–87	57.28 (07) 29–82	27	0.198
Prostate	76.33 (03) 59–87	–	3	0.248	73.38 (31) 50–90	–	31	0.228
Liver	64.42 (07) 40–84	66.00 (03) 60–74	10	0.825	65.61 (36) 25–87	64.21(19) 36–85	55	0.404
Pancreas	61.33 (07) 48–76	53.4 (03) 46–62	10	0.825	68.77 (18) 41–85	67.25 (12) 42–81	30	0.220
Lung	61.33 (06) 48–76	59.25 (04) 44–73	10	0.825	63.17 (45) 25–88	67.45 (20) 50–88	65	0.477
Breast	–	70.33 (12) 42–88	12	0.990	–	57.98 (102) 40–97	102	0.749
Cervix	–	0	0	0	–	60.63 (60) 40–97	60	0.440
Vagina	–	0	0	0	–	74.00 (05) 62–84	05	0.037
Small intestine	62.00 (01)	–	1	0.083	61.00 (05) 38–84	70.00 (01)	06	0.044
Uterus	–	0	0	0	–	72.00 (13) 55–83	13	0.095
Penis	0	–	0	0	67.25 (04) 55–78	–	04	0.029
Testis	0	–	0	0	35.50 (02) 25–46	–	02	0.015
Bone	0	0	0	0	41.40 (05) 13–72	26.50 (02) 13–40	07	0.051
Skin	81.00 (01)	0	1	0.083	60.12 (08) 40–81	60.40 (05) 53–64	13	0.095
Thyroid	0	0	0	0	0	49.50 (02) 49–50	02	0.015
Soft tissue	69.00 (01)	0	1	0.083	60.00 (02) 55–65	64.50 (06) 40–85	08	0.059
Non-Hodgkin's lymphoma	53.50 (02) 51–56	63.00 (03) 41–75	5	0.413	57.11 (31) 1.5–88	59.88 (18) 30–84	49	0.360
Hodgkin's lymphoma	0	0	0	0	30.62 (04) 5.5–49	58.00 (02) 44–72	06	0.044
Lacrimal duct	0	0	0	0	0	60.00 (01)	01	0.007
Metastatic PNET	0	0	0	0	0	78.00 (01)	01	0.007
Adrenal neuro-blastoma	0	0	0	0	0	73.00 (01)	01	0.007
							33	
Total cancer	45	40	85	7.01	435	492	927	6.80

n, Number of deceased.

Table 3. Percentage occurrence of cancer in diabetic and non-diabetic males and females

	Male				Female			
	Diabetic		Non-diabetic		Diabetic		Non-diabetic	
Cancer type	Mean age (*n*), range	Diabetic (%) (*n* = 1212)	Mean age (*n*), range	Total non-diabetics (%) (*n* = 13,626)	Mean age (*n*), range	Diabetic (%) (*n* = 1212)	Mean age (*n*), range	Total non-diabetics (%) (*n* = 13,626)
Liver	64.42 (07) 40–84	0.579	65.61 (36) 25–87	0.264	66. 00 (03) 60–74	0.248	64.21 (19) 36–85	0.139
Lung	61.33 (06) 48–76	0.495	63.17 (45) 25–88	0.330	59.25 (04) 44–73	0.33	67.45 (20) 50–88	0.146
Pancreas	61.857 (07) 40–86	0.578	68.77 (18) 41–85	0.132	53.40 (03) 46–62	0.248	73.38 (31) 50–90	0.228
Oral	68.75 (04) 55–75	0.330	59.16 (36) 32–86	0.264	68.33 (03) 60–73	0.248	57.85 (27) 35–85	0.198
Leukaemia	60.00 (03) 41–75	0.248	51.57 (35) 3–93	0.257	60.00 (01) 3–93	0.083	38.23 (17) 2–75	0.125
Colon	76.66 (03) 76–78	0.248	62.03 (38) 26–86	0.279	79.00 (01)	0.083	62.79 (33) 25–88	0.242
Stomach	76.50 (02) 63–90	0.165	59.23 (22) 29–88	0.161	66.00 (01)	0.083	64.70 (10) 53–92	0.073
Non-Hodgkin's lymphoma	53.50 (02) 51–56	0.165	57.11 (02) 1.5–88	0.015	63.00 (03) 41–75	0.248	59.88 (18) 30–84	0.132
Gall bladder	45.00 (01)	0.083	62.75 (04) 56–66	0.029	0	–	50.66 (9) 29–65	0.066
Renal cell	55.00 (01)	0.083	55.33 (06) 40–81	0.044	68.00 (01)	0.083	52.00 (03) 23–68	0.022
Urinary bladder	63.00 (01)	0.083	70.75 (16) 50–86	0.117	78.00 (01)	0.083	82.20 (05)	0.037
CNS tumour	36.00 (01)	0.083	49.48 (24) 3–85	0.176	67.33 (03) 55–80	0.248	47.29 (17) 10–86	0.125
Larynx	46.00 (01)	0.083	68.65 (20) 18–87	0.147	86.50 (02) 86–87	0.165	57.28 (07) 29–82	0.051
Small intestine	62.00 (01)	0.083	61.00 (05) 38–84	0.037	0	–	70.00 (01)	0.007
Skin	81.00 (01)	0.083	60.12 (08) 40–81	0.059	0	–	60.40 (05) 53–64	0.037
Soft tissue	69.00 (01)	0.083	60.00 (02) 55–65	0.015	0	–	64.50 (06) 40–85	0.044
Multiple myeloma	0	–	61.87 (08) 55–87	0.059	0	–	62.81 (11) 49–78	0.080
Oesophagal	0	–	66.68 (35) 45–90	0.257	0	–	65.75 (32) 41–88	0.235
Bone	0	–	41.40 (05) 13–72	0.037	0	–	26.50 (02) 13–40	0.015
Hodgkin's lymphoma	0	–	30.62 (04) 5.5–49	0.029	0	–	58.00 (02) 44–72	0.015
Thyroid	0	–			0	–	49.50 (02) 49–50	0.015
Lacrimal duct	0	–	0	–	0	–	60.00 (01)	0.007
Metastatic PNET	0	–	0	–	0	–	78.00 (01)	0.007
Adrenal neuroblastoma	0	–	0	–	0	–	73.00 (01)	0.007
Penis	0	–	67.25 (04) 55–78	0.029	–	–	–	–
Testis	0	–	35.50 (02) 25–46	0.015	–	–	–	–
Prostate	76.33 (03) 59–87	0.248	73.38 (31) 50–96	0.228	–	–	–	–
Cervix	–	–	–	–	0	–	60.63 (60) 40–97	0.440
Vagina	–	–	–	–	0	–	74.00 (05) 62–84	0.037
Uterus	–	–	–	–	0	–	72.00 (13) 55–83	0.095
Ovary	–	–	–	–	59.20 (02) 55–64	0.165	59.70 (51) 22–81	0.374
Breast	–	–	–	–	70.33 (12) 42–88	0.990	57.98 (102) 40–97	0.748
Total cancer	45	3.7	435	3.19	40	3.3	492	3.6

n, Number of deceased.

oral, CNS tumour and laryngeal cancer survived longer than non-diabetics. However, a significant statistical correlation was observed only in the case of breast cancer ($P = 0.009$).

Male and female specific cancer types accounted for 0.27% and 1.7% respectively of the total population (Table 4). Results indicate that breast, cervix, ovary, uterus and vaginal cancers caused death in about 25% cancer patients. Breast cancer remained a major killer in females, whereas prostate cancer was the major killer in males. Cancer of penis and testis was not recorded in diabetic males. The percentage occurrence of prostate cancer was identical in diabetic and non-diabetic population (0.2% and 0.22% respectively). Surprisingly, in diabetic females, occurrence of only breast and ovarian cancer as sex-specific cancers was recorded. The mean survival age of 102 non-diabetics with breast cancer was 57.98 years, whereas the mean survival age of 12 deceased diabetics having breast cancer was 70.33 years.

The most frequently cited reason for the cause of increased occurrence of cancers in diabetics has been the mitogenic activity of insulin[6]. Smoking is a major risk factor for lung cancer and the risk increases with the increase in the number of years of smoking. Hence, smoking as a confounding factor cannot be ruled out in the present study. Moreover, the interrelationship between diabetes and other site-specific malignancies is difficult to analyse for several reasons. First, cancer from certain sites (colon and rectum, prostate, breast, endometrial and ovary) share some important risk factors such as obesity, high fat diet and sedentary lifestyle[12,13]. Second, as demonstrated in the present study, the occurrence of several types of cancers is very low and it is even lower in diabetic patients.

Table 4. Sex specific cancers

Cancer type	Diabetic mean age (*n*), range	Non-diabetic mean age (*n*), range
Male		
Prostate	76.33 (03) 59–87	73.38(31) 50–90
Penis	0	67.25(04) 55–78
Testis	0	35.50(02) 25–46
Total	3	37
Female		
Breast	70.33 (12) 42–88	57.98(102) 40–97
Ovary	59.20(02) 55–64	59.70(51) 22–81
Cervix	0	60.63 (60) 40–97
Vagina	0	74.00(05) 62–84
Uterus	0	72.00(13) 55–83
Total	14	231

n, Number of deceased.

A positive association between diabetes and liver cancer has been reported where increased cell proliferation may contribute towards excess risk for hepatocellular cancer in patients with chronic hepatitis B virus infection, alcoholic liver disease and liver cirrhosis[14–16]. Moreover, insulin and its precursors have been shown to interact with liver cells and stimulate mutagenesis or carcinogenesis[17–19]. We tried to rule out alcoholism as the confounding factor in establishing association between diabetes and liver cancers by excluding all deceased with diabetes, liver cancer and alcoholic liver disease including liver cirrhosis. However, liver cirrhosis in less severe forms might not be diagnosed and still have a substantial impact on the outcome. Likewise, deceased diabetics with liver cancer as well as hepatitis were excluded. Still, certain undiagnosed and unspecified confounding factors might be important.

The positive association between diabetes and pancreatic cancer as observed in our study is well-established in several population-based studies. However, it is not yet clear whether diabetes is responsible for development of pancreatic cancer or diabetes happens to be an early manifestation[20]. Though this association remains controversial, arguably, increased occurrence of pancreatic cancer is associated quite strongly with diabetes. Insulin sensitivity and overall diabetic state in cancer patients who underwent pancreatic tumour resection is known to improve following surgery[21,22]. A number of experiments have tested the hypothesis that insulin may stimulate the growth of pancreatic cancer[23–26].

The activation of insulin-like growth-factor pathway and regulation of endogenous sex hormones have been postulated to associate diabetes with breast cancer[27]. Association of diabetes with enhanced survival age of breast cancer patients is quiet intriguing which needs verification and further study in different populations. It has been indicated that treatment associated with diabetes decreases the level of an enzyme protein tyrosine phosphatase which is elevated in breast cancers and also in diabetes, and decrease in its levels significantly slows down tumour development[28]. In this study, estrogen and HER receptor status, and the genetic susceptibility of women with breast cancer were not known and may potentially represent confounding factors. In addition, our study hints towards possible association between sex-specific cancers and diabetes with decreased incidences of their occurrence in diabetics.

Death certificate-based research, while potentially providing valuable data, is full of possibilities for bias. We did not validate the cause of death as mentioned on the death certificate. The possibility of misclassification of both diabetes status and cancer type, using only death certificates cannot be ruled out. Information on the onset and cause of diabetes and cancer, the details of anti-diabetic as well as chemotherapeutic drugs used for treatment and duration of treatment were not available. In

addition, the probability of diabetes being recorded on the death certificates is less than half[29]. Therefore, the actual number of diabetics in a given population may be higher and this further signifies the importance of findings in the present study.

Nevertheless, the percentage occurrence of liver, prostate, pancreatic and lung cancer in diabetics is much higher, as compared to their occurrence in non-diabetics. These findings are in accordance with observations in other large cohort studies, suggesting that abnormal glucose metabolism is a general risk factor for development of several cancers[30,31]. Though the population size in the present study is too small to draw a categorical conclusion, it certainly hints that interplay between diabetes and cancer in Indian population may be complex. This highlights the need for more systematic studies with large sample size to draw conclusive inferences.

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