INTRODUCTION

Since the history of medicine, Diabetes Mellitus (DM) is known to be complicated by diseases of heart, kidney, retina, nerve, liver etc. But recently debate have been raised, whether DM has got any relation with cancers or not. DM and cancer both are the common killer of humankind. DM particularly type 2 (T2DM) are at higher risk of developing some cancers and at lower risk of few. Moreover few antidiabetic agents have shown the potentiality to increase or decrease some cancers.

But till now the interaction between diabetes and cancer is not clear and doubt exist on different issues.¹

Epidemiology

In recent times both cancer and DM are increasing because of urbanization, industrialization, lifestyle changes, population growth and increased life expectancy. Cancer prevalence in India is near about 2.5 million with 8 lacs of new cases and 5.5 lacs of death occurring each year.² Among the men, cancer of lung, oesophagus, stomach, oral cavity, pharynx are more common. But in women cancers of cervix and breast are common followed by of stomach and oesophagus. In India there is regional variation in the nature of organ involvement in cancer³ as follows.

* Oesophageal Cancers : Karnataka, Tamilnadu, Gujrat, Maharashtra
* Stomach Cancers : Southern India, highest in Chennai
* Pharyngeal Cancers : Mumbai
* Thyroid Cancers : Kerala
* Gall bladder Cancers : Delhi and West Bengal

The observed trend in the incidence of cancer in India is that its overall occurrence is increasing among the women with greater incidence of cancer of breast and colon. In male increasing incidence is seen with cancers of prostate and kidney. In both male and female increasing incidence is observed with lymphoma, urinary bladder, gall bladder and brain with diminishing incidence of oesophageal and gastric carcinoma. In female cervical carcinoma is also diminishing in incidence⁴.

The most common cancers seen as a whole are those of the lung/bronchus, breast, and colorectum, whereas the common cancer deaths are from lung, stomach, and liver cancer. Worldwide, cancer is the 2nd and diabetes is the 12th leading cause of death.⁵ In the United States, cancer is the 2nd and diabetes is the 7th leading cause of death.⁶ But the pathophysiology underlying both cancer and diabetes are improperly understood.

In 80-90% cases of cancer occurrence, environmental factors particularly life style disorders is responsible, which also account for higher number of diabetes cases. Appropriate changes in life style has shown reduction in mortality and morbidity of both the diseases.

Association Between Diabetes and Cancer Incidence or Prognosis

As early as 1959, Joslin et al¹ noted the association between diabetes and cancer. Some cancers develop more in diabetes (predominantly type 2), whereas prostate cancer occurs less. The relative risks imparted by diabetes are greatest for
cancers of the liver, pancreas, and endometrium, and lesser for colon/rectum, breast, and bladder. Other cancers (of lung) do not appear to be associated with an increased risk in diabetes, and the evidence for others (kidney and non-Hodgkin lymphoma) is inconclusive. Till date, few studies have explored links with type 1 diabetes1.

Both the liver and the pancreas are exposed to high concentrations of endogenously produced insulin. Diabetes-related factors including steatosis, nonalcoholic fatty liver disease, and cirrhosis may also predispose to liver cancer. Abnormal glucose metabolism may be a consequence of pancreatic cancer.

Diabetes is associated with a lower risk of prostate cancer, probably due to reduced testosterone. Obesity is not associated, and in some studies is even reported to be inversely associated, with prostate cancer incidence. Obese with prostate cancer have higher cancer mortality rates than those of normal weight.7 Obesity in addition to hyperinsulinemia, may be associated with delayed diagnosis and poorer treatment, leading to worsened prognosis1.

Epidemiological studies suggest that diabetes may significantly increase mortality in patients with cancer. 5-year mortality rates were significantly higher in patients diagnosed with both breast cancer with diabetes than without diabetes.8 Because diabetes is associated with excess age-adjusted mortality, whether the apparent excess mortality associated with diabetes in cancer patients is greater than the excess mortality observed among diabetic patients without cancer is unclear.

It is not evident, whether the association between diabetes and cancer is direct (eg, due to hyperglycemia), whether diabetes is a marker of underlying biologic factors that alter cancer risk (eg, insulin resistance and hyperinsulinemia), or the association between cancer and diabetes is indirect and due to common risk factors such as obesity. We do not know if cancer risk is influenced by the duration of diabetes and may be complicated further by the multidrug therapy often necessary for diabetes treatment.

Evaluation of other diabetes-related biomarkers (eg, adiponectin, hyperglycemia) is also essential. Common confounders (such as body weight, physical activity) must also be assessed. Better characterization of aspects of diabetes (diabetes duration, therapy, and degree of glycemic control) in relation to cancer is needed1.

Risk Factors Common to Both Cancer and Diabetes
Potential risk factors (modifiable and nonmodifiable) common to both cancer and diabetes include age, sex, obesity, physical activity, diet, alcohol, and smoking.

Nonmodifiable Risk Factors
Age
In economically developed countries, approximately 78% of all newly diagnosed cancer occurs among individuals above 55 years.1. Diabetes also becomes increasingly common with age, with a prevalence of 2.6% in American adults aged 20 to 39 years and 10.8% in 40 to 59 years, and increases to 23.8% in those aged 60 years or older.6

Sex
Certain cancers are sex-specific, but occurs more frequently in men who also have a slightly higher age-adjusted risk of diabetes than women.6

Race/Ethnicity
In the United States, African Americans are more likely to develop and die of cancer than others. After African Americans are non-Hispanic whites, with Hispanics, Native Americans, and Asian Americans/Pacific Islanders have lower cancer incidence and mortality.9 This racial/ethnic variability in cancer incidence in the is attributed, at least in part, to socioeconomic and other disparities. Hormone levels that vary by race, also may play a role1.

In the United States, type 2 diabetes and its complications disproportionately affect several specific populations, including African Americans, Native Americans, Hispanics, and Asian Americans/Pacific Islanders compared with non-Hispanic whites.6 Genetic, socioeconomic, lifestyle, and other environmental factors are believed to contribute to these disparities.

Modifiable Risk Factors
Overweight, Obesity, and Weight Change
Overweight or obese individuals have a higher risk of cancer compared with individuals with normal BMI.10 The cancers most frequently seen with obesity are those of the breast (in postmenopausal women), colon/rectum, endometrium, pancreas, oesophagus, kidney, gallbladder, and liver. Obesity may also increase the risk of mortality from prostate cancers.7

For type 2 diabetes as well as certain cancers (eg, colon) studies suggest that waist circumference, waist-to-hip ratio,
or direct measures of visceral adiposity are associated with risk independently of BMI and weight loss lowers disease risk. The association between weight loss and subsequent cancer risk is less clear. In the Nurses’ Health Study, a statistically significant inverse relation between adult weight loss and postmenopausal breast cancer was found only when the weight loss had been maintained for 4 years. But weight loss may be a sign of undiagnosed cancer.

**Diet**

Diet low in red and processed meats and higher in vegetables, fruits, and whole grains are associated with a lower risk of many types of cancer and may protect against type 2 diabetes, possibly through improving insulin sensitivity.

Diet high in glycemic index or load are associated with an increased risk of type 2 diabetes, but evidence of their associations with cancer risk is mixed.

**Physical Activity**

Higher levels of physical activity are associated with a lower risk of colon, postmenopausal breast, and endometrial cancer and may also help prevent other cancers, including lung and aggressive prostate cancer. But a clear link has not been established up till now. Physical activity after diagnosis may improve survival for cancers of breast, colon and rectum.

A protective role for increased physical activity in diabetes metabolism and outcome substantially reduces (approximately 25-36%) the risk of developing type 2 diabetes.

**Tobacco-Smoking**

Tobacco smoking accounts for 71% of all trachea, bronchus, and lung cancer deaths. Cancers strongly associated with smoking are those of the larynx, upper digestive tract, bladder, kidney, pancreas, leukemia, liver, stomach, and uterine cervix. Smoking is also an independent risk factor for the development of diabetes and increase the risk of cardiovascular disease, retinopathy, and other complications of diabetes.

**Alcohol**

Alcohol even in moderate amounts, increases the risk of cancer of the oral cavity, pharynx, larynx, esophagus, liver, colon/rectum, and female breast. Although excess alcohol consumption is a risk factor for diabetes, moderate alcohol consumption has been associated with reduced diabetes incidence in both men and women.

Whether the association between diabetes and the risk of certain cancers is largely due to shared risk factors (obesity, poor diet, physical inactivity, and aging), or whether diabetes itself, and the specific metabolic derangements (eg, hyperglycemia, insulin resistance, and hyperinsulinemia), increases the risk of some types of cancer has not been solved. Lower levels of adiposity, a healthy diet, and regular physical activity are associated with a reduced risk of both type 2 diabetes and several common types of cancer. But these factors are interrelated, and the contribution of each is difficult to assess.

Little is known to us, how modifiable lifestyle factors influence prognosis in cancer patients. How genetics influence the diverse aspects of diabetes (eg, insulin resistance and β-cell depletion) and affect cancer risk, may provide information about the association between diabetes and cancer. Long-term trials such as the Look AHEAD trial of the effects of weight loss on cardiovascular outcomes in patients with diabetes and follow-up of cohorts in lifestyle studies such as the Diabetes Prevention Program, may provide further evidence of the impact of lifestyle improvements on cancer incidence.

**Biologic Links Between Diabetes and Cancer Risk**

Carcinogenesis is a complex process. Normal cells must undergo multiple genetic attacks, before the full neoplastic phenotype of growth, invasion, and metastasis occurs. Factors that affect one or more steps of this pathway like initiation, promotion, and progression could be associated with cancer incidence or mortality. Diabetes may influence the neoplastic process by several mechanisms, including hyperinsulinemia (either endogenous due to insulin resistance or exogenous due to administered insulin or insulin secretagogues), hyperglycaemia, or chronic inflammation.

**Insulin/Insulin-Like Growth Factor Axis**

Majority cells in cancer express insulin and IGF-I receptors; the A isoform of the insulin receptor is important and can stimulate insulin-mediated mitogenesis, even in cells deficient in IGF-I receptors. Other than metabolic functions, the insulin receptor is also capable of stimulating cancer cell proliferation and metastasis. Glucose uptake in cancer cells is constitutively high and independent of insulin binding to its receptor. The effects of insulin receptor activation on neoplastic cells may relate more to cell survival and mitogenesis than to enhanced glucose uptake.
Multiple signaling pathways are activated after insulin receptors or IGF-I receptors interact with their ligands. By phosphorylating adaptor proteins, particularly the insulin receptor substrate family, the initial kinase event is linked to downstream signaling pathways. After activation, these signaling pathways can stimulate proliferation, protection from apoptotic stimuli, invasion, and metastasis. This enhances the promotion and progression of many types of cancer cells. Insulin/IGF may stimulate normal cells that are involved in cancer progression. For example, hyperglycemia allows IGF-I to stimulate vascular smooth muscle cell proliferation and migration.

Hyperinsulinemia may stimulate carcinogenesis indirectly through its effects on IGF-I. Insulin reduces the hepatic production of IGF binding protein (IGFBP)-1 and possibly IGFBP-2, and increases circulating free, bioactive IGF-I, and act as a growth stimulus in pre-neoplastic and neoplastic cells that express insulin, IGF-I, and hybrid receptors. Each of them might play an etiologic role in the pathogenesis of other cancers. Therefore, hyperglycemia may facilitate neoplastic proliferation. Most cancers have highly effective upregulated, insulin-independent glucose uptake mechanisms and therefore may not derive a further growth advantage from hyperglycemia.

Reduced tumor growth in the presence of type 1 diabetes suggests that hyperglycemia does not lead to increased neoplastic growth, at least during insulin deficiency. Studies indicate that glucose mediates the correlation; rather, hyperglycemia may serve as a surrogate for a causative factor such as hyperinsulinemia. Probably for a subset of tumors, hyperglycemia offers a growth advantage. Adequate therapy for diabetes can limit tumor growth, but insulin receptor activation may be a more important variable than hyperglycemia in determining tumor growth.

Inflammatory Cytokines, Diabetes, and Cancer Risk

In addition to the direct effects of insulin, type 2 diabetes and/or obesity might enhance other pathways, resulting in malignant progression. Adipose tissue is an active endocrine organ, producing free fatty acids, interleukin-6 (IL-6), monocyte chemotactant protein, plasminogen activator inhibitor-1 (PAI-1), adiponectin, leptin, and tumor necrosis factor-α. Each of them might play an etiologic role in regulating malignant transformation or progression. In some cases, the role of these molecules is well known.

Expression of PAI-1 have been linked to poor outcome in patients with breast cancer. Activation of signal transducer and activator of transcription protein (STAT) signaling, via cytokines such as IL-6, enhance cancer cell proliferation, survival, and invasion and also suppress host antitumor immunity. Certain experimental cancers tend to behave more aggressively with calorie and less aggressively with calorie restriction. Thus diet-induced changes in IL-6 and/or insulin may mediate the effect of diet on neoplasia and
specific signaling pathways of the tumors determine the nature of tumor behavior.¹

**Major Unanswered Questions**

The association between diabetes and the incidence and/or prognosis of some cancers may not be causal; diabetes and cancer may be associated simply because they share common predisposing risk factors such as obesity. However, several plausible biologic mechanisms have been described that may account for this link, including the effects of hyperglycemia, hyperinsulinemia, and inflammation on cancer etiology and progression. Another important area for investigation concerns the issue of insulin resistance in type 2 diabetes in cells of nonclassic insulin target organs, such as the breast, colon, or prostate. Probably in the setting of insulin resistance in classic insulin target organs (liver, muscle, and adipose tissue) at least a subset of cancers remain insulin sensitive, or that insulin insensitivity to metabolic pathways does not extend to resistance to growth-promoting properties.

**Influence of Diabetes Treatment on Cancer Risk or Cancer Prognosis**

Individuals with type 1 diabetes represent approximately 5% of the diabetes population worldwide with the need for immediate and lifelong insulin therapy. But type 2 diabetes is much common and is generally associated with overweight and obesity. This requires increasing use of pharmacologic agents over time and the eventual need for insulin therapy in approximately half of all patients.

**Metformin**

Metformin has been shown to inhibit cell proliferation, reduce colony formation, and cause partial cell cycle arrest in cancer cell lines. Metformin-induced activation of 5’ adenosine monophosphate-activated protein (AMP)-activated protein kinase (AMPK) in tumor cells may lead to growth inhibition, by inhibiting protein synthesis. The insulin-lowering action of metformin may contribute to its antineoplastic activity, and that it may have less impact on cancers occurring in less hyperinsulinemic patients. Metformin may selectively kill cancer stem cells and enhance the effectiveness of breast cancer treatment regimens. Metformin has also been shown to reduce mammary tumor growth in rodent models¹.

Human studies suggest that treatment with metformin (compared with other glucose-lowering therapies) is associated with a reduced risk of cancer¹⁸ or cancer mortality. Additional observational data suggest that metformin might improve cancer prognosis. Metformin treatment was found to be associated with higher pathologic complete response among patients with early stage breast cancer who were receiving neoadjuvant therapy¹.

**Thiazolidinediones (TZD)**

PPARγ agonists have several anticancer activities, such as inhibiting growth and inducing apoptosis and cell differentiation, and PPARγ is currently considered a potential target for both chemoprevention and cancer therapy based on other preclinical studies.¹⁹ However, because recent in vitro studies have indicated that the effects of PPARγ agonists on cell growth are often independent of the presence of PPARγ, 100 the clinical relevance of the findings of in vitro studies is unclear. Studies in rodents have shown that PPAR agonists can potentiate tumorigenesis, and are multispecies, multisex carcinogens. Therefore, TZDs may increase, decrease, or have a neutral effect on the risk of cancer or cancer progression in humans²⁰.

Definitive human data regarding the cancer risk associated with TZDs are not available. Meta-analysis of clinical trials of rosiglitazone demonstrated no statistically significant increase or decrease in the risk of cancer though the numbers of cancer cases at these specific sites were small.²¹ This epidemiologic studies examined only short-term exposure, due to recent introduction of these medications and the shorter duration of many trials. Few clinical trials conducted of TZDs for cancer treatment, show negative results.

**Insulin Secretagogues**

Secretagogues, include sulfonylureas and the rapid-acting glinides. Some observational studies observed a higher risk of cancer or cancer death among diabetes patients treated with sulfonylureas compared with other diabetes medications.²² But most of these studies had very few cancer cases among users of sulfonylureas, and therefore power was limited to examine associations with specific cancer sites. Studies regarding dose, duration, recency, and persistence of use are scanty.

Though the association between sulfonylureas and cancer risk is genuine, it is clear whether the findings reflect excess cancer among users of the secretagogues or a reduced risk in those using comparator drugs, which often include metformin. Furthermore, if the association was to be confirmed, it remains to be determined whether the mechanism involves direct actions of the agents on transformed cells or cells at risk of carcinogenesis, compared with indirect effects mediated by increased insulin levels.
Till now no published data to date that support an association between the glinide secretagogues and cancer risk.

Incretin-Based Therapies
Liraglutide increase the risk of medullary thyroid cancer in rats and mice in preclinical tests and was associated with slight increases in serum calcitonin in human trials. Exenatide, liraglutide, and DPP-4 inhibitors increased β-cell proliferation in animal studies, and in one small study of a transgenic rodent model, sitagliptin was demonstrated to increase pancreatic ductal hyperplasia. No impact of incretin-based agents on human cancer incidence has been reported, because of the drug have not been used in sufficient numbers of patients or for long enough periods.

Insulin and Insulin Analogs
Administraton of insulin results in significantly higher levels of circulating insulin in the systemic circulation than endogenous insulin secretion, and possibly amplify links between hyperinsulinemia and cancer risk.

Sever several epidemiologic analyses examined a possible association between insulin use and/or use of the long-acting insulin analog glargine and increased risk of cancer. Insulin glargine may have a disparate impact on cancer risk through its binding to IGF-1 receptors. But there are doubts and debates about the potential strengths and weaknesses of these studies. For example, insulin is mostly used in patients with a longer duration of type 2 diabetes and more often in those with one or more comorbid conditions that preclude the use of comparator medications. But these or other potential confounders (BMI, actual insulin dose, degree of glucose control, glucose variability, and other patient characteristics) been fully accounted for in the study designs or analyses.

Randomized clinical trial data from an open-label, 5-year trial of insulin glargine versus NPH insulin did not find evidence of excess cancer risk with insulin glargine. The ongoing randomized ORIGIN trial (glargine vs placebo) is much larger. It is important to note that this trial was powered for cardiovascular outcomes and may still not provide definitive evidence regarding cancer incidence, especially for specific cancers.

Link Between Exogenous Insulin, Insulin Analogs, and Cancer
Suspected mechanisms by which the administration of insulin or insulin analogs might influence neoplastic disease include both direct and indirect actions. Direct actions are interactions of the administered ligands (or their metabolites) with cancer cells, partially transformed cells, or cells at risk of transformation. Indirect mechanisms involve interactions of signaling molecules whose levels (eg, glucagon, adiponectin, or IGFBPs) or activity are influenced by the administration of insulin into these target cells.

Earlier research has focused on the differences between human insulin and analogs with respect to binding affinity to the IGF-1 receptor, including evidence that insulin glargine has much higher affinity, and higher mitogenic potency, than human insulin or other analogs. The affinity of particular analog insulins for the IGF-1 receptor is an important issue in view of evidence that knockdown of the IGF-1 receptor, but not the insulin receptor, abolished the proliferation of malignant cell lines in response to insulin glargine. But an insulin or analog that retains specificity for the insulin receptor over the IGF-1 receptor is unlikely to have important mitogenic effects or effects on neoplasia and may appear as diluted and too simplistic in the presence of recent researches, that indicate that the insulin receptor is present on neoplastic cells and may itself influence neoplastic behavior in certain contexts.

It is not clear whether there is a biologic difference between the exposure of neoplastic cells to fluctuating levels of endogenous insulin observed under normal physiologic conditions compared with the levels of endogenous insulin noted in obesity, type 2 diabetes, and/or after the administration of exogenous human or synthetic insulins. Subcutaneous human insulin involves transient exposures to very high insulin levels, whereas the subcutaneous administration of some synthetic insulins results (by design) in longer term exposure to higher insulin concentrations. As such, simple pharmacokinetics may not fully explain observed changes in the behavior of neoplastic tissues. It also is critical to recognize that cancer cells in patients with type 2 diabetes may be exposed to abnormally high levels of endogenous insulin for many years prior to the administration of exogenous insulin.

Unanswered Questions
It is extremely difficult to assess the independent association between a specific medication and cancer risk relative to no medication. For example, if some medications increase risk whereas others decrease or have no effect on risk, different comparator drugs will likely lead to different associations and may explain some of the observed inconsistencies.
across studies. Few studies have examined the risk associated with the dose, duration, or recency of medication use, which might inform the biologic plausibility of observed associations. Many agents that affect carcinogenesis have long latencies or require a minimum exposure level, and the risk associated with some agents may return to baseline after the exposure has been terminated for a period of time. Some medications newt (eg, TZDs, insulin analogs, and incretin-based therapies), and studies can only assess the cancer risk associated with relatively short-term use. Multiple well-conducted and appropriately designed prospective observational studies are needed. Results of in vitro and preclinical studies should inform design considerations for observational studies, but by themselves cannot be considered conclusive.

CONCLUSION

We cannot neglect the growing concept of the inter-relation between DM and cancer. Until it is proved beyond doubt by definitive studies, we should at least implement screening for one disease in presence of the other, strictly implement life style modification which is probably beneficial for both. During choosing therapy, metformin can be given priority if it really reduces cancer.

REFERENCES