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Association between Diabetes and Cancer in Indian and US Populations using Longitudinal Study Design

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ASSOCIATION BETWEEN DIABETES AND CANCER IN INDIAN AND US
POPULATIONS USING LONGITUDINAL STUDY DESIGN

by

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DEDICATION

To my parents, family members and all those who believed in me. This journey would be impossible without your support and advice. Thank you for everything you have given me. Dad and Mom, your enthusiasm to study and learn new things has always been and will always be my motivation to progress in my life.

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I cannot thank enough my family members who are important to me in the pursuit of my PhD. Thanks to my parents, who have been with me everyday, every hour of my life, shared my happiness and tears and for just being my parents. Another set of thanks to my brother (Bhai), and sister-in-law for being constantly supportive. Finally; Vedanshi, my love; my niece, for always somehow bringing a smile on my face. You are and always will be very special to me.

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ABSTRACT

Background: There is growing evidence of association between diabetes and cancer. No studies have been conducted in India evaluating this association. With the current epidemiologic, nutritional and economic transition in India, it becomes extremely important to examine this association in an Indian population. Additionally, difference in association exists based on different cancer subtypes. Research has shown that diabetes is associated with an increased risk of colorectal cancer. However most of these studies suggest detection bias to be one of the probable reasons for this association. Additionally, the common risk factors shared by both these conditions are considered to one of the reasons in the association. Furthermore, very few studies have assessed the association between duration of diabetes and either CRC risk or disease aggressiveness. Even more rarely have studies confirmed the status of type 2 diabetes mellitus (T2DM) while determining the diabetes-CRC association.

Methods: For our first objective, we used the Mumbai Cohort Study (MCS)- a longitudinal study. Diabetes information was collected at baseline and cancer information was received via follow-up questionnaire and confirmed using cancer registry. We also evaluated the association between diabetes and cancer subtypes after creating matched datasets for each cancer subtype. We used Cox Proportional model for cancer incidence and conditional logistic regression for cancer subtypes. For our second and third question, we used the Prostate Lung Colorectal Ovarian (PLCO) Cancer screening trial. Diabetes

information was self-reported and collected at baseline and using one of the follow-up questionnaires-supplemental questionnaires. The cancer information was collected using annual survey questionnaire (ASU) administered every year and confirmed using medical records. For our second aim final analysis we use cox proportional hazards model. To evaluate the notion of detection bias, we conducted stratified analysis. In our final question, the diabetes duration was calculated using information on age at diabetes diagnosis. We fit a Cox proportional hazards model for cancer incidence and conducted logistic regression analysis for cancer grade and stage.

Results: In the MCS, we did not observe any significant associations between diabetes and all cancer incidence and cancer subgroups. However the association was in the expected direction. The hazards of all cancer incidence was 1.06 (95%CI=0.75, 1.62) among persons with diabetes as compared to people without diabetes. Among cancer subtypes, there was an increased risk of 'lip/oral/pharyngeal cancer' (OR=1.83; 95%CI=0.86, 3.86) and 'respiratory tract cancer' among people with diabetes (OR=1.28; 95%CI=0.53, 3.13) respectively. Inverse direction was observed for 'digestive organ cancer and 'breast/prostate/uterine/cervical cancer' among people with diabetes compared to people without diabetes (OR=0.59; 95%CI=0.27, 1.32) and (OR=0.66; 95%CI=0.24, 1.84) respectively, but none of these associations reached statistical significance. For our second aim, we observed a 33% higher risk of CRC among people with diabetes as compared to people without diabetes. After stratifying the results by screening arm, we still found a higher risk among both the screening arms, (HR=1.41, 95%CI=1.13, 1.76) among the control arm (HR=1.22, 95%CI=0.94, 1.58). After stratifying by BMI, the risk was still high among people with diabetes in all the groups.

In our final aim, we observed that participants with >10 years of diabetes had a higher risk (HR=1.37; 95%CI: 1.06, 1.77) of CRC incidence compared people without diabetes. An apparently smaller effect was observed among people with <10 years of diabetes duration (HR=1.13; 95%CI: 0.89, 1.43); however, it was not significant. We did not find significant results in the association between cancer aggressiveness and diabetes.

Conclusion: In Indian population, our findings appear to show a higher hazards of all cancer incidence, lip/oral/pharyngeal and respiratory tract cancer among people with diabetes compared to people without diabetes. They direction of the association is consistent with previous study results. However the association is not significant. Future studies needed to explore this association in detail. Secondly, in the PLCO data, our findings showed an association between diabetes and increased risk of colorectal cancer. Detection might not be the reason for this association. Further studies should include information on other factors like diabetic medications. For our final aim, the CRC risk was higher among people with longer duration of diabetes, even after accounting for the potential confounders.

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LIST OF ABBREVIATIONS

ADA .... American Diabetes Association

BMI .... Body Mass Index

CDC .... Early Treatment Failure

CRC .... Colorectal Cancer

DII .... Dietary Inflammatory Index

HDI .... High Development Index

ICD .... International Classification of Disease

IGF-I .... Insulin-like Growth Factor-I

MCS .... Mumbai Cohort Study

PLCO .... Prostate Lung Colorectal Ovarian

SEER .... Surveillance, Epidemiology, and End Results

T2DM .... Type 2 Diabetes Mellitus

CHAPTER 1

INTRODUCTION

Statement of Problem:

Type 2 Diabetes Mellitus (T2DM) and cancer are both among the top 10 leading causes of mortality (1-3). Though to differing extents, both of these diseases can be prevented and controlled by appropriate healthy lifestyle and behavioral changes.

Cancer is a major public health problem and has been studied in many different populations worldwide; however, the incidence, mortality and therefore prevalence of different types of cancer varies across these populations (1, 4). Traditionally, cancer has been considered to be a disease of more developed countries; i.e., those with high development index (HDI). However, recently there has been a change in the trend of these diseases. A decrease in colorectal cancer incidence was observed in the US based on the SEER data (4).

Many developing countries are now experiencing increasing rates of "diseases of affluence" such as cancer and diabetes, while existing communicable diseases also present a public health problem (5-10). Some of these countries' relatively low cancer rates might reflect deficiencies in existing country-wide surveillance systems. Also, the developing world is going through an economic and nutrition transition with increased urbanization and changing lifestyle factors, including poor diet, sedentary lifestyles, and

increased stress leading to a rise in rates of chronic diseases such as diabetes, cancer and heart diseases (1, 4, 5, 7-9, 11-15).

It is the one of the commonly diagnosed cancer among both males and females (16-18). Based on Globocan estimations worldwide, CRC ranks third among males, and second among females (19). Around 1.2 million Americans are living with a diagnosis of CRC. There has been a decrease in the incidence of CRC since mid-1980s due to identification and removal of adenomatous polyps screening (17). Despite improvements in screening techniques; compared to other cancers, incidence and prevalence of CRC remains high. CRC remains one of the top 3 causes of cancer deaths in both men and women (20). Lung cancer ranks the first in both followed by breast cancer among females and prostate cancer among males.

In 2010, the expenses for cancer care in the United States were around $125 billion (21, 22). These costs can be reduced by improving access to screening available facilities to everyone, educating people about it and improving dietary and lifestyle habits. The risk factors linked with CRC include higher age, unhealthy dietary habits, physical inactivity, obesity, smoking, alcohol use, personal history of polyps, and family history of CRC, (17, 22-27). Studies also have shown that T2DM is associated with increased risk of CRC (3, 28-44).

T2DM is a type of diabetes, characterized by hyperglycemia due to either inadequate insulin secretion or its utilization or both. Worldwide, T2DM rates are increasing rapidly (45-47). The estimated prevalence of T2DM was 9% in 2014 in 18+ years age group, worldwide. In 2012, around 1.5 million deaths were due to T2DM. The

prevalence of T2DM is estimated to almost double in 2030 (4.4%) from that observed in 2000 (2.8%) (46, 47). At the same time, and especially in Asia, T2DM is emerging as an epidemic (46-51).

Diagnosed diabetes accounts for an estimated $245 billion cost to U.S. society consisting of $176 billion direct and $69 billion in reduced productivity (52). Besides this, chronic long-term diabetes is associated with functional damage of several other organs especially kidneys, eyes and organs of the cardiovascular system (53-56).

Existing research suggest an association between T2DM and cancer (3, 28-30, 33-35, 37, 39, 41-44, 57-64). Both these diseases place a burden on individual health and the nation's overall health and economic status. Among all the cancers, CRC is the most strongly associated with T2DM (57, 58, 60, 64-66). Many known risk factors are common to both these diseases; for example, obesity, unhealthy diet and physical inactivity (3, 28-30, 33-35, 37-42, 67-74). Various patho-physiological mechanisms have been hypothesized to explain the association between T2DM and CRC. Diabetes can have an influence on colorectal cancer through these mechanisms: hyperinsulinemia, chronic inflammation and hyperglycemia (3, 17, 29, 33, 36, 37, 39, 42, 44, 61, 75, 76). Insulin and Insulin-like growth factor (IGF-I) have a proliferative effect of the colonic epithelium leading to mutations. Thus insulin plays a role in initiation and progression of colon carcinogenesis. Research is even conducted on the diabetic medication use and its impact on risk of cancer. Inconsistent findings are seen among users of subcutaneous injections of insulin and insulin analogs. Few studies suggest an increased risk especially with long-acting drug glargine while some suggest no association (77-81). Insulin resistance leads to hyperinsulinemia thus promoting carcinogenesis indirectly (61, 75, 82-

84). Apart from hyperinsulinemia, chronic low grade inflammation is one of the reasons for the association between T2DM and CRC. (36, 43). Inflammation has also been shown to predict development of T2DM (85-90). Elevated levels of inflammatory markers; C-reactive protein and IL-6 were observed among diabetics (65, 91-94). Inflammatory cytokines like TNF-α, IL-6, stimulate insulin sensitivity, continuing low-grade inflammation, insulin resistance and thereby playing a role in carcinogenesis (95, 96).

Diet and physical activity also are shown to affect insulin levels (61, 67-69, 97-101). All these factors have pro/anti inflammatory effect on the body depending on the adapted lifestyle. Unhealthy diet and low levels of physical activity have a pro-inflammatory effect on the body (102-112). These factors have also have been shown to exert an effect on colorectal carcinogenesis through inflammation-related pathways (113-121). Thus, it is important to understand this aspect of association.

Purpose and Objectives

Several studies have examined the association between CRC and diabetes (3, 28-44, 61, 76). Most of these studies have been conducted in developed countries, where the CRC rates are higher. Not many studies have been conducted in developing countries especially in a country such as India, which is currently experiencing dramatic demographic, economic, epidemiologic and nutrition transitions (5, 8, 9, 13-15, 122, 123). Besides this, none of the studies have checked for the role of inflammation through diet in this association. Studies including diet as a confounder have focused only on a few dietary items such as fruits and vegetables, coffee intake, dairy products, whole grains

and red meat consumption.(3, 29, 37, 38, 42, 44, 124, 125) There are dietary items that also have been shown to be associated with CRC via its inflammatory effect. Therefore, it is important to study this effect, too. Secondly, many previous studies have mentioned the possibility of diagnostic bias existing in this association. Through our study, we will try to address these gaps in this association.

With our first objective, we will determine the association between diabetes (T2DM) and all cancer incidence in an Indian database (MCS. India is a diverse country in terms of religion, culture, and lifestyle behaviors. Currently, diabetes is increasing at an alarmingly rate in India (48-50). Although, compared to Western countries, the cancer rates are lower in India; they are still high and are on an increasing trend. Additionally, with the current ominous changes in above-mentioned lifestyle factors, it is likely that cancer rates will increase. Thus, it becomes important to determine the association between diabetes and cancer incidence in India.

Besides changes in lifestyle factors leading to the increase in chronic disease rates the Indian population is more susceptible to metabolic syndrome (126-131). Metabolic syndrome is characterized by higher blood pressure, abdominal obesity, abnormal cholesterol levels, higher blood sugar, pro-inflammatory state (132). Worldwide, the Indian population is shown to be prone to metabolic syndrome and having a higher risk of developing T2DM (130). We will evaluate for the potentially confounding effect of BMI in this association. Similar to race and ethnicity in the USA, (caste) religion also can have an effect on this association as considerable differences exist by religion in the dietary, physical activity, and other lifestyle habits. Therefore we will adjust these potential confounders.

In our second objective, we will use Prostate Lung Cancer Ovarian Screening Trial – a longitudinal US database to determine the association between T2DM and CRC. We will include all of the important potential confounders – including a variety of socio-demographic variables, BMI, physical activity, and duration of T2DM. Based on the literature, it is known that diet and inflammation play an important role in this association. Most of the studies focusing on diet have included only few dietary items that do not represent a complete measure of diet. In this study, we will include DII that calculates the inflammatory score based on total dietary intake. Thereby, we will check for impact of inflammation through diet (using the DII) on the association between T2DM and CRC incidence. As seen in most of the studies, one of the important biases determined in all studies was diagnostic bias; in our project we will include screening as one of the confounders. Fortunately, the PLCO is a screening trial and thus has information on screening for 4 cancers (prostrate, lung, colorectal and ovarian cancer).

In our third objective, we will use duration of T2DM as our main exposure and examine its effect on CRC incidence, whereby the study will be restricted to participants having diabetes at baseline. We will also explore the association between T2DM duration and CRC grade and stage. For this question, we will use the PLCO database. Cancer grade is based on the ICD-O-2 (International Classification of Disease for Oncology 2nd Edition). In this part of the dissertation we will again determine effect modification caused by DII.

For all our aims involving cancer incidence and time-to-disease as the outcome, we will use Cox Proportional Hazards Models.

AIM 1: To determine the association between diabetes (T2DM) and all cancer incidence in an Indian database (MCS)

Hypothesis: Participants with T2DM have a higher risk of cancer incidence after controlling potential confounders. Religion and BMI also has an impact on this association. Additionally, diabetes is also associated with cancer subgroups.

AIM 2: To determine the association between T2DM and colorectal cancer incidence in PLCO screening trial database

Hypothesis 1: Participants with T2DM have a higher risk of CRC incidence after adjusting for potential confounders.

Hypothesis 2: DII influences the association between T2DM and CRC incidence.

Hypothesis 3: Screening modifies the association between diabetes and CRC

AIM 3: To examine the effect of duration of diabetes with colorectal cancer incidence and grades and stages of cancer.

Hypothesis 1: With an increase in the duration of T2DM there is an increased risk of CRC incidence.

Hypothesis 2: With increasing duration of diabetes, a higher stage of CRC is observed.

Significance of Research:

Our overall findings will contribute to current knowledge regarding the association between T2DM and cancer. With our first aim, we are determining this association in India, where no such studies exist. It is important to study this question in a

country such as India, because the rates of T2DM are increasing at an alarming rate and it is in an epidemiological transition phase. Findings of the study will demonstrate the importance of this association and the probable reasons that need to be studied in future studies that will inform steps that would need to be taken among diabetics to reduce the likelihood of colorectal cancer (and other inflammation -related conditions). An obvious strength of this work is that it is a prospective study conducted in Mumbai – a culturally diverse and densely populated city.

In our 2nd aim, we will be studying the association in US database – PLCO - a cohort study. This study was a screening trial; therefore, for this study; we will use information on screening. This can help in avoiding diagnostic bias that is one of the commonest biases many previous studies. Besides that, we will be using DII - a technique that quantifies the inflammatory potential of diet. As inflammation plays a vital role in this association, utilizing DII provides a new angle to the existing knowledge about diet and its role in the association. As both of these diseases have common risk factors, we will be controlling for the potential confounders.

As shown by a few of the previous studies, duration of T2DM also has an impact on CRC. As a part of my 3rd aim, we will be looking at the duration of T2DM and its impact on CRC incidence, disease grade and stage. Results from this study will help in understanding if longer duration of diabetes has an impact on the development, grading and staging of CRC. The main exposure used here; i.e., diet-related inflammation, has rarely been checked for in the previous studies. Again, in this study we will include DII score in our models. Based on the previous literature, it is known that diet has an

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influence on diabetes. This dietary effect also may be due to the inflammatory effect of diet. Therefore, it is more important to understand this association in greater detail.

Most of the previous studies have not utilized diet for their analysis and the studies including it have only used restricted groups of foods. In our study, including DII is innovative and will lead to meaningful improvements in our understanding of colorectal carcinogenesis.

Study Outline

In Chapter 2, we will provide details on the past studies conducted worldwide determining the association between diabetes and CRC. We also will briefly mention previous study results providing background and support on the association and the factors being controlled. For the Chapter 3, we will provide details on the two databases being used in our study, the data collection techniques and our selected analytical methods. In chapter 4, we will include our first manuscript based on our first aim, followed by Chapter 5 and 6, based on the manuscripts for aim 2 and 3, respectively. Chapter 7 will include information on the overall discussions and conclusions for the study. In Chapter 7, I also will discuss what I have learned in the process of conducting this dissertation research, describe the scope for further research in this area, and provide a description of my personal experience as a PhD student.

CHAPTER 2

BACKGROUND AND SIGNIFICANCE

Cancer Statistics

One of the leading causes of morbidity and mortality worldwide is cancer. The estimated number of new cases of cancer is 15 million worldwide. Regional disparities exist across different types of cancer and affect population subgroups differentially. Colorectal cancer (CRC) is one of the top four cancers seen in both males and females (4). Among all cancers, it is the 3rd most common (1, 18). It is also the fourth leading cause of cancer mortality (18). It is well-documented that quality of life is impaired in cancer patients, especially after receiving cancer treatment (133-136). Five-year mortality for CRC patients is around 40% (22). There are treatment differences based on disease stage and grade. Clearly, this affects associated costs.

5-10% of CRC cases are due to hereditary causes, but most of the other cases are due to modifiable causes (24).   While CRC incidence rates have been high in developed countries for some time, an overall increase in CRC incidence rates is observed in low- and middle-income countries (1, 7). The CRC rates are also increasing rapidly in Asia, especially in Eastern Asia, for example, in countries like China, Japan, and Singapore a two- fourfold increase has been observed in the past few years (10). Contrary to this, a decrease in the CRC incidence rates is seen in especially the previous high-risk places (New Zealand, US and Canada) due to early screening and detection of pre-cancerous

polyps(1). To develop an optimum prevention strategy, it is important to understand the risk factors and underlying pathology of the disease in further detail.

A number of CRC risk factors– modifiable and non-modifiable have been identified. For example, CRC is more commonly observed among older age groups. People with a personal history of inflammatory bowel disease, diabetes and a family history of CRC and or adenomatous polyps are at a higher risk of developing CRC. However, there are many risk factors that can be changed to reduce the risk of CRC. These include diet, physical activity, smoking, alcohol use and obesity. These risk factors are also common for type 2 diabetes.

Risk factors in relation to Colorectal Cancer

Physical Activity and Colorectal Cancer

Many studies have examined this association. It was found that physical inactivity is related to increased risk of CRC (61, 74, 118, 119, 137, 138). These results are consistent with what is observed worldwide. Sedentary lifestyle also is associated with obesity, which is another risk factor for CRC (38, 73, 139, 140). Besides this, physical activity also protects against inflammation and insulin resistance (101-103, 105, 114, 141), both of which also are linked with T2DM (103). Most of these studies included self reported questionnaire data on physical activity. These questionnaires include information on the intensity, duration of physical activity (25, 61, 74, 138).

Diet and Colorectal cancer

Diet is one of the important factors linked with CRC. Different dietary components have differential effects. Inconsistent results have been have been seen between red meat intake and risk of CRC (142-144). However, most of these studies have observed an increased risk of CRC with increased intake of red meat (145-147). Studies determining effect of fish consumption on CRC also showed mixed results; however, most of these studies demonstrated beneficial effects of fish consumption on CRC risk (44, 145, 146, 148-150). Dietary fiber, whole foods, and fruit and vegetable intake are associated with reduced risk of CRC (113, 117, 151, 152). Literature suggests that most of these dietary factors have an impact on CRC risk through inflammation-related pathways (107). Diets high in total calories and saturated fat and with low levels of dietary fiber leads to insulin resistance, which is associated with both T2DM and CRC (82). Several types of diets have shown to have distinct effects on risk of CRC and other chronic diseases. Western diet is associated with increased inflammation, while Mediterranean and Macrobiotic diets are associated with decreased inflammation (106, 110, 112, 153). Mediterranean diet consists of higher intake of fruits and vegetables, olive oil, nuts and seeds (106, 110, 154-158). Macrobiotic diet is based on a high intake of vegetables and beans and whole grains and low intake of sweeteners, and fruits (159, 160). These patterns include components that are linked with lower inflammation, thereby associated with reduced risk of inflammatory diseases (161-167).

Alcohol intake, Smoking and CRC risk

Alcohol intake may have either a positive or negative effect on CRC risk depending on the amount (dose) of intake (23, 27, 38, 138, 168, 169). Higher intake is associated with increased risk (38, 138, 168, 169). Most of the studies observed that smokers have a higher risk of CRC (26, 170-172).

Diabetes and CRC risk

As mentioned earlier, CRC also is considered to be one of the important risk factors for CRC. Studies have shown an increased risk of CRC among diabetics (3, 28-35, 37, 39-44, 61).

Meta-Analysis and Review Studies

A meta-analysis by De Bruijin, included 20 studies examining the association between T2DM and breast and colorectal cancer risk and mortality, of which 6 prospective studies had CRC incidence as their main outcome. Results from these studies suggest that people with diabetes are at increased risk of CRC compared to non-diabetics (31). Shikata et al. in their review study also summarized similar results regarding the association (66). People with T2DM are at increased risk of developing and dying from CRC. These results are consistent across studies conducted in different geographical regions. However not all studies produce consistent information on all the potential risk factors including, diet and physical activity. Another meta-analysis conducted by Deng, based on studies conducted from 1966 to 2011 included 24 case-control and cohort studies (32). This review demonstrated 26% higher risk of CRC among diabetics as compared to non-diabetics. On stratifying by study design, an 8% increased risk of CRC

was observed in case-control studies compared to cohort studies.. The three important confounders having a positive association in the risk between diabetes and CRC risk are BMI, physical activity and tobacco use. The review also demonstrated the importance of insulin therapy on CRC incidence. The results of another meta-analysis consisting of 25 studies suggested a strong positive association (37). No significant difference in this association was observed between males and females. Higher incidence rates were observed among case-control studies than in cohort studies. Besides these reviews and meta-analysis, there have been various case-control and cohort studies conducted worldwide.

European Studies / Australian:

The European studies also suggest an increased risk of CRC among diabetics as compared to non-diabetics (29, 37, 76). Some of the studies evaluated the association separately for colon and rectal cancer. Most of these studies showed an increased risk of colon cancer associated with diabetes; however, mixed results were observed with rectal cancer (29, 37, 62, 76). One study, conducted in Scotland, found an increased association with colon cancer but detected no association with rectal cancer (62). Some of the studies showed an increase risk in both colon and rectal cancer. Physical activity, one of the important risk factors, was evaluated by most of these studies and some of these results were consistent with the previous literature showing a higher risk associated with low physical activity (37, 61). The study by La Vecchia et al. suggested no association with leisure-time physical activity (29). Total energy intake, dietary fiber and fat intake were some of the important dietary factors considered in the Italian study, and the results did not show any effect modification by diet in this association (29). However, not all studies

included information on some of the important confounders. Dietary data were lacking in most of these studies except for the study by La Vecchia (29). The retrospective cohort study conducted by Yang et al. focused only on insulin therapy (30). Only one study has been conducted in Australia that showed an increased risk of colon cancer, higher among males compared to females (60).

American Studies:

Many studies evaluating this association have been conducted in the US (3, 34, 44, 84, 124). Although the rates are decreasing, the US still ranks high in sex-specific, lung, pancreatic and colorectal cancer rates. Western populations are at a higher risk for different cancers especially due to unhealthy lifestyle behaviors. Red meat intake, alcohol consumption, low physical activity, and higher smoking rates are some of the factors strongly linked with CRC , majorly contributing towards the increase in risk (37, 38, 44, 61, 74, 113, 118, 119, 137, 138, 145-147, 170-173). However, recent trends suggest decrease in the incidence and mortality of CRC (18, 174). This is attributed to the improved and timely implementation of screening techniques leading to early detection of risk factors and thereby early treatment (59, 125, 175-177).

Based on our literature search, all US studies have suggested an increased risk of CRC in association with T2DM. Studies focusing only on women found results similar to those seen in general population; i.e., an increased risk of CRC among diabetics as compared to non-diabetics (33, 34, 39). However, some of the studies comparing the association between the two sexes, showed a higher risk among males as compared to females (39, 41, 42, 57). However, a study by Diaz Algorri et al. no association was

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detected among men. Subsite specific risk also showed no association in men; however, among women it demonstrated a higher risk of proximal colon cancer compared to controls (124). Physical activity was controlled in most of the studies (3, 28, 33, 34, 37, 38, 42, 44). As obesity is one of the important confounders, most of the studies adjusted for BMI. Many studies adjusted for diet. However, fruits and vegetables were the only items adjusted consistently in most of these studies (28, 33, 37, 38, 44, 84, 124). Some of these studies also adjusted for red meat consumption, which is linked with higher risk of CRC (28, 33, 34, 44, 124).

Some studies also considered duration of diabetes and examined its association with CRC risk. There was no specific trend observed in the association. Few of the studies suggested a stronger association among subjects with increased duration of diabetes, while one study showed participants in the intermediate duration of diabetes had a stronger association compared to the longest duration and minimum duration diabetics (28, 29, 34).

Asian Studies:

There are very few Asian studies assessing the association between T2DM and CRC. Most of these studies have been conducted in Japan and China and between the years 1988-2003. However, all of these studies showed an increased risk of colon cancer among diabetics as compared to non-diabetics. Both studies conducted in Japan were cohort designs. The study by M.Inoue consisted information on medical history of major diseases, smoking and alcohol habits, BMI, physical activity and food intake frequency while the study by Khan et al. included information on history of diabetes, BMI, smoking

and drinking habits and other demographic variables only (57, 65). An ecological study based on data from 170 countries and a population-based risk analysis was conducted in China by X.Ren (41). In this study, a higher risk of colon cancer was observed among diabetics. However, no association was found with rectal cancer. An increased risk of colon cancer was observed among both males and females in the prospective study conducted by Seow et al.(42). This association remained consistent among individuals with high calorie intake and low physical activity. Using stratified analysis, they also found an association between diabetes and CRC among people with lower BMI levels compared to Western population. In another study conducted in Japanese population by Kiyonori et al, strong increased risk of cancer of pancreas among men and stomach, colorectum and corpus uteri among females was observed among diabetics (58). Family history of diabetes also was associated with an increased cancer risk. High rates were observed for colorectal cancer among both men and women. However, due to the case-control study design, it was difficult to determine the causality in the association.

Purpose of the study

As mentioned previously, both T2DM and CRC have common risk factors. In evaluating the association between T2DM and CRC, it is important to understand the role of, and account for these risk factors that may function as potential confounders. Besides obesity, the majority of previous studies have been unable to account for some of the important confounders. Diet (dietary factors) and physical activity were controlled for in very few studies. Through our study, we want to overcome this limitation and include all the available potential confounders and/or effect modifiers important in this association.

Addressing the existing gaps

<u>Diet:</u> Studies examining dietary factors included individual food items and/or dietary ingredients. The major dietary factors included in these studies were fruits and vegetable and total calorie intake (3, 28, 33, 34, 37, 38, 42, 44, 84, 124). Red meat and dietary fat intake also was studied by the authors and it was found to be associated with increased risk of CRC in some of these studies (28, 33, 34, 37, 124). However, not all studies included important dietary covariates. Most of these dietary factors are associated with cancer due to its inflammatory effect on body.

It is important to understand that overall diet can have differential impact on health as compared to individual dietary ingredients. We know that diet, through inflammatory pathways, is associated with cancer (115, 116, 120, 165). Inflammation also is known to be associated with T2DM (87, 88). Besides this, unhealthy dietary habits i.e. diets high in fat, sugar intake and overall consisting of higher pro-inflammatory components also are related to obesity which is one of the risk factors for both T2DM and cancer. Diet plays a major role in the development and progression of T2DM, too.

Therefore, in our study we will be utilizing the dietary inflammatory index (DII) - a unique tool developed to calculate the overall inflammatory potential of diet. DII scores are based on up to 45 food parameters. The index has been validated using different methods of dietary data collection (24-hour recalls and 7DDR) (115). Various studies using DII have found that higher pro-inflammatory scores are associated with higher risk of colorectal cancer (115, 116, 120) The current ongoing research also has shown that it is associated with T2DM (108)

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Diagnostic Bias: Diagnostic bias was one of the concerns raised in most of the above-mentioned studies (30, 34, 60). People with diabetes might have a higher probability of visiting doctor's clinic, thereby getting screened for other diseases too. A lot of these studies were unable to resolve this bias. For this part of our project, we are using data from the Prostate Lung Colorectal Ovarian Cancer Screening Trial (PLCO), a screening trial. The PLCO study was conducted to determine if screening tests reduces mortality from prostate, lung, colorectal, and ovarian cancer. At the beginning of the study the participants were randomized on screening tests for each cancer. We can utilize this information on screening and try to address the problem of diagnostic bias.

Indian Study: Based on the past research conducted in this area, it was observed that no studies have been conducted in India. India is a culturally diverse country with lot of variations in their overall dietary and lifestyle behavior (14, 178). More than 60% of diabetics worldwide are in Asia, of which around 50% are in India and China combined. Recent trends have shown an increasing prevalence of diabetes in India (6, 46, 49). With the ongoing nutrition and lifestyle transition, there is higher probability of developing chronic diseases, as observed in Western countries. Besides complications, T2DM also is associated with increased risk of colorectal cancer. With the recent trend, there is probability of increase in rates of colorectal cancer.

CHAPTER 3

METHODS

Introduction

For all analyses, we will be using either the Mumbai Cohort Study (MCS) and Prostate Lung Colorectal or the Ovarian Cancer Screening Trial (PLCO) databases. <u>AIM 1:</u> To determine the association between diabetes (T2DM) and all cancer incidence in an Indian database (MCS). We will also determine the association between diabetes and cancer subtypes. <u>AIM 2:</u> To determine the association between T2DM and colorectal cancer incidence in PLCO screening trial database. <u>AIM 3</u> To examine the effect of duration of diabetes with colorectal cancer incidence and grades and stages of cancer. The details are mentioned below.

Databases Used:

Mumbai Cohort Study (MCS)

MCS was conducted in Mumbai (formerly known as Bombay) in Maharashtra. Mumbai is a densely populated city that is divided into three parts: the main city, suburbs, and extended suburbs. The recruitment of participants was conducted from 1991-1997 and follow-up was done from 1997-2003. The study was restricted to the main city and recruited individuals over 35 years of age. The voters list was used as the sampling frame and it provided information on age, sex, and address of individuals' ≥ 18

years. The apartments serving the upper-middle class and upper-class housing complexes were gated communities and were not easily accessible to the interviewers, therefore they were excluded from the study (179). Only people located in the study area were eligible to be recruited into the study. The interviewers conducted face-face interviews in the participant's home using structured questionnaires. Handheld computers (electronic diaries) were utilized for this purpose. All the interviews were conducted in local languages (e.g., Marathi, Hindi) but the information was recorded in English. All the procedures regarding participant recruitment and ethical treatment of human subjects were approved by the Indian Council of Medical Research (ICMR) (179-181).

Follow-up: A house-to-house follow-up was conducted on average of 5.5 years after the initial survey. A list of names and addresses of the participants was provided to the field investigators for re-interviewing the participant. If the participant was dead, information regarding the date and place of death was recorded with utmost care and accuracy. Participants who permanently migrated to another place were considered as withdrawn from the study and the date of migration was noted. Participants not available at the particular time and/or not available for re-interview after multiple visits, were censored at the date of revisit. Re-interviews were conducted during 1997-2003 (181).

Prostate Lung Colorectal Ovarian Cancer Screening Trial (PLCO)

The PLCO is a multicenter cancer screening trial (182). It was a randomized trial conducted with the main aim to determine if screening examinations can reduce the mortality of prostate, lung, colorectal, and ovarian cancer. Participants were enrolled and randomized in the years 1993-2001 from 10 different centers to different screening

procedures (for colorectal cancer – flexible sigmoidoscopy). . Participants were aged 55

years to 74 years. The exclusion criteria included history of prostate, lung, colorectal or

ovarian cancer, ongoing cancer treatment for any cancer except basal-cell or squamous–

cell cancer. People who had surgical removal of their entire prostate, entire colon or one

lung were ineligible. People participating in other cancer screening or prevention trials

also were excluded. Eligible participants were required to provide signed informed

consent. All participants completed a baseline questionnaire, including information of the

demographics, medical history, personal/family and past and history. Other information

included screening data, dietary data, health status, collection of blood samples. An

additional supplemental questionnaire was administered in 2006. This questionnaire

consisted of similar information as collected in the baseline questionnaire with few

additions (183).

**Aim 1: To determine the association between diabetes (T2DM) and all cancer
incidence in an Indian database (MCS)**

Question 1: To determine the association between diabetes and cancer incidence

adjusting for potential confounders like BMI and religion

Question 2: To determine the association between diabetes and cancer subtypes

Study Population: The manuscript will be based on the information collected from the

MCS. As mentioned earlier, this study was conducted in Mumbai.

Main Independent variable: Our main independent variable was T2DM. The

information on diabetes mellitus was collected at baseline using the baseline survey. The

question determining this information was an open-ended question 'Do/ did you suffer

from any major disease in the past years (Y/N)___ If 'Y' then, disease name. Although it is a self-reported questionnaire, the information was collected and entered by the interviewer.

Dependent variable:

Cancer incidence is defined as the occurrence of any new cases of cancer in the defined population during that specified time period. Cancers registered and first diagnosed between 1st January and 31st December of that particular year were considered incident cases for that year. Cancer cases also were selected if information was available only through death certificate.

The Population Based Cancer Registry (PBCR) of Mumbai established in June 1963 was the first such registry in India. Information was collected from cancer patients who were registered in 150 government hospitals/ institutions and private hospitals or nursing homes in Mumbai under the care of specialists. Cases were excluded if they came under code '0' = benign or '1'= uncertain if benign or malignant borderline malignancy or '2'=*carcinoma in situ*. Besides this, patients in whom cancer was ruled out or was not diagnosed were also removed. The World Health Organization coding system with the code number C00-97 as published in manual of the International Classification of Diseases, Injuries, and Cause of Death was used (184) .According to a paper published by International Agency for Research Cancer, the data collected by PBCR Mumbai meets the standards for completeness and reliability (185).

The data from the Mumbai Cohort Study and PBCR were combined using the variables- Name, Sex, Age, Postal pincode, Religion, and Mother tongue. Information on

all the newly developed cancer cases ≥35 years developed from 1991-2003 was abstracted from PBCR.

Covariates:

We will check for all available covariates including age, sex, education, employment, marital status, body mass index, smoking status in the association. We will check for any interaction for BMI or religion.

Inclusion/ Exclusion Criteria:

Participants with missing information on diabetes and positive history of cancer at baseline will be excluded from the study.

Statistical Analysis:

Based on the aforementioned criteria, our analytic sample consists of 95,220 MCS participants. Descriptive statistics were calculated using chi-sq test for the categorical variables and t-test for the continuous variables. For our main analysis, we used Cox proportional hazards model examining cancer incidence among diabetics and non-diabetics. Follow-up/Person years were calculated using the date of recruitment through 31st December 2003 until the date of re-interview, death, migration or cancer incidence. We checked for proportional hazards assumptions using both; graphical, and Schoenfeld residual method (186, 187). Based on this we conducted sequential modeling with first model representing the crude model; second model stratified by BMI (strata variable), the third model including BMI in the final model to check if BMI also has an impact on cancer incidence.

We adjusted for age, gender, native speech (including North Indian and South Indian languages), education (secondary/ college, primary/middle, uneducated), employment (employed, retired, unemployed, unknown), tobacco use (current user, past-user, never-user), BMI (overweight/obese, normal, underweight) and religion (Hindu, Muslim, others).

We grouped the diagnosed cancers into sub-categories 'lip, oral-cavity and pharynx' (C00-C14), 'digestive organs cancers' (C15-C26), 'respiratory tract cancer' (C30-C39), 'breast, cervical, uterine, prostrate cancer' (C50,C51-C55, C61), and others based on the ICD10 coding. For the initial analysis, we conducted a chi-sq test for each of these cancer subtypes (cancer subtype/ no cancer) by diabetes (yes/no) using the overall dataset. Following this, we conducted matching based on age, gender and person-time for each for these four cancer groups. The ratio used for matching was 1:4 for the 'lip, oral-cavity and pharynx' (N=1230), 'digestive organ cancer' (N=1692) and 'respiratory tract cancer' (N=875) and 1:3 for 'breast, cervical, uterine, prostrate cancer' (N=1106). We conducted conditional logistic regression to determine the association between diabetes mellitus and cancer subtypes.

Aim 2: To determine the association between T2DM **and colorectal cancer incidence in PLCO screening trial database**

Question 1: To evaluate the association between diabetes and CRC incidence adjusting for potential confounders

Question 2: Check if BMI, screening modify the relationship between diabetes and cancer incidence

Study Population:

We will use the Prostate Lung Colorectal Ovarian Cancer Screening Trial data for this project.

Main Independent Variable:

In this study, information on diabetes and 16 others diseases was collected using the baseline questionnaire and also via supplemental questionnaire that was one of the follow-up questionnaires. For this project we will use the baseline data. The question used to collect this information – 'Has a doctor ever told you that you have any of the following conditions'. It is a binary variable (yes/no).

Main Dependent Variable:

Colorectal cancer incidence is our main outcome. These data were collected using mailed annual study update (ASU) questionnaire that was mailed yearly around each anniversary of the participant's randomization date. The ASU questionnaire consisted information on type and date of diagnosed cancer in the past year. Non-respondents were contacted again by the study staff via mail and telephone. Information on cancer incidence was verified using medical records.

Covariates**:**

The baseline questionnaire consisted of information on socio-demographic, anthropometric, and personal medical history. Dietary data were collected twice throughout the course of the study. At baseline the data was collected only in the intervention arm and it was administered again from 1998-2001 in both the intervention

and control arms. We used the dietary inflammatory index (DII[TM]), a tool used for calculating the inflammatory level of food. DII was determined using the diet history questionnaire (DHQ) administered to both the screening arms Around 118,804 participants have information on diet. The DII is based on 45 food parameters (188). In our study it was calculated based on the 37 parameters available in the DHQ.

Inclusion/ Exclusion Criteria:

Participants with missing data on diabetes status at baseline will be excluded.

Statistical Analysis:

Figure1 provides the information used for creating the final analytic dataset. Baseline characteristics were estimated by diabetes status. Person-time (in days) were calculated from the baseline date to the date of cancer incidence or the latest completion date of ASU, death, or 13 year of cut off, whichever occurred first. We adjusted for sex, age (<60 years, 60-70 years, >70 years), BMI (<25, 25–29.9, and 30 kg/m^2 and unknown), education (≥college, post high school/some college, <high school), family history of cancer (yes, no, missing), aspirin intake (>2/day,1/day, 1-4/week, <4/month and none), cigarette smoking (current, former, non smoker), DII in tertiles (<-2.74, <-0.39, >=-0.39). For all our analytical models using Cox proportional hazards model, we checked for the proportional hazards (PH) assumption. Once satisfied, we fit these models estimate hazards ratios and 95% confidence intervals controlling for important covariates.

For our initial analysis, we did not include the diet information as a covariate. For the overall sample size (N= 145,642) BMI was included as a strata variable as it did not

satisfy the PH assumption. For our further analysis, participants with a person-time of 0 were deleted from the study. Also, only participants with a confirmed cancer status (yes/no) were included in the study.

Separate analyses were conducted by stratifying the models by the intervention arm and BMI to check if screening and BMI modified the association between diabetes and CRC. BMI was re-categorized into (normal/underweight, overweight and obese) for stratified analysis. While checking for BMI, we conducted the analysis, initially with the overall data (N=145,642) and again in the dataset with dietary data (N=114,017), as shown in Figure1. Physical activity was collected using the baseline dietary and the supplemental questionnaire (SQX). However the baseline information was collected only in the intervention arm. We also performed sensitivity analysis, removing people with missing physical activity data (as per the SQX administered in 2006). Sensitivity analysis was also conducted restricting to participants with person-time of more than1 year and 2 years with sample sizes of (N=113,689) and (N=113480) respectively.

Aim 3: To examine the effect of duration of diabetes with colorectal cancer incidence and grades and stages of cancer

Question 1: To assess the association between duration of diabetes associated with colorectal cancer incidence adjusting for the potential confounders

Question 2: To check if duration of diabetes is related to cancer aggressiveness (cancer stage and grade)

Study Population: We will use the Prostate Lung Colorectal Ovarian Cancer Screening Trial data for this project.

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Main Independent Variable: Duration of diabetes

The baseline (BQX) and supplemental (SQX) questionnaires were used to determine this variable. The BQX and SQX were administered at baseline and years 2006-2008 respectively. BQX included the question "Did the participant ever have diabetes?" and the SQX used the question "Were you ever diagnosed with diabetes?" The SQX also included information on the age at diagnosis of diabetes with 4 categories (<50 years, 50-59years, 60-69years and >70years).

Participants with missing information on diabetes in both BQX and SQX were deleted. The overall sample with a valid SQX consists of 103,758 participants. For the estimation of duration of diabetes variable, we included participants who mentioned yes for diabetes in the SQX. Among the participants who mentioned yes for diabetes in the SQX (N=13,675), 12,927 participants answered the question regarding the age at diagnosis. For the final calculation, we subtracted the mean of the range for the 50-59 years (i.e., 54.5 years) and 60-69 years (i.e., 64.5 years) from the age of the participant when the SQX was answered. For the last category (>70 years), we will use the mean of 70 years and the highest age of the participant during the SQX i.e. (87 years) (i.e. 78.5) and subtract it from the age of participant. Using this method, we get negative values for some of the participants for the calculated variable. As duration of diabetes cannot be less than 0, we convert these numbers to 1 (minimum possible value). Figure1 gives the distribution of the participants used for determining the diabetes status. Based on this information the variable diabetes duration was categorized into 'no diabetes', '<=10years', and '>10years'.

Main Dependent Variable**:** Colorectal Cancer (CRC) incidence, stage, and grade

CRC incidence data were collected using Annual Study Update Questionnaire (ASU) administered annually. The incidence, stage and grade of CRC were confirmed using medical records. For the final analysis, participants with confirmed status of CRC (yes/no) were included. CRC grades I and II were combined and considered low grade while grade III and IV were grouped together as high grade. For determining CRC stage, we used information combining the clinical and pathologic stage of CRC and similar to grade, stage I and II were combined and stage III and IV were combined. Accordingly, the sample size was 1032 and 1073 for CRC grade and CRC stage as outcomes respectively.

Statistical Analysis:

Descriptive statistics (chi-sq for categorical and t-test for continuous variables) were calculated for participants by their diabetes duration. For CRC incidence, the following exclusion criteria were used. Participants with missing data on the variable 'age at diagnosis' in the SQX, missing information on education, an invalid SQX were deleted. Person-years were calculated from the day of entry in the trial to CRC diagnosis, or last day of remaining free from cancer and/or death of the participant. Cox proportional hazard model was used to estimate hazards ratio and 95% Confidence interval (CI) of CRC incidence by diabetes duration.

We adjusted for age (when SQX was answered), race (non-Hispanic white, non-Hispanic black and others), screening arm (intervention, control group), BMI (<25, 25–29.9, and 30 kg/m^2 and unknown), gender, employment status (employed, unemployed,

retired and others), education (graduate and more, high school/some college, and less than high school), aspirin intake in past 12 months (≤1/week, ≥2/week, none, unknown), smoking status (current smoker, past smoker, non-smoker and unknown), family history of colorectal cancer (yes, no, missing) and DII (dietary inflammatory index) score, physical activity (active –yes, no, missing).DII is a tool measuring the inflammatory level of food. It is calculated using up to 45 food parameters, and based on availability of these parameters. In our study it was based on 37 parameters, which is at the upper end of what is available from structured questionnaires such as food frequency questionnaires (FFQ). The details regarding DII have been provided elsewhere (188). We checked the proportional hazards (PH)-assumptions for diabetes duration and other covariates. As BMI did not satisfy the PH-assumption, we conducted stratified analysis. Figure 2 provides the final sample used for analysis (N= 83,904).

For CRC stage and grade as the outcomes, the data were restricted to participants with information on stage and grade, respectively. Further, the people with missing data on aspirin intake and cigarette smoking were deleted. Logistic regression was used to estimate odds ratio (OR) and 95% confidence interval (CI) for CRC stage and grade by duration of diabetes.

Sensitivity analysis was conducted, deleting participants with diagnosis of CRC before the detection of diabetes based on the age at diagnosis of diabetes.

Strengths: Through our first aim we will be determining the association in India using a longitudinal database, where the question has not yet been studied. The study design will also help in determining the temporal sequence of the association.

In our Aim 2 and Aim 3, we are using a US national database (PLCO trial). In the PLCO data, we have information on screening for colorectal cancer. Most of the previous studies have diagnostic bias as one of the main limitations. Through this study, we will try to address this problem. We will also be looking at the impact of duration of diabetes with cancer incidence and aggressiveness. We will include DII – a new concept especially in this association. In the existing literature it was observed that only few dietary ingredients were included in the models, while in our study, the dietary component included, is based on the total dietary intake.

Limitations: In both the study databases, diabetes is self-reported. In the MCS, although the data for self-reported, it was entered by the interviewer and in the PLCO database, one of the follow-up questionnaires includes data on diabetes and its duration. We will validate the data using these two questionnaires. For our MCS study, we do not have information on a lot of covariates like diet and physical activity

CHAPTER 4

ASSOCIATION BETWEEN DIABETES MELLITUS AND CANCER AND CANCER SUBTYPES IN INDIAN POPULATION

Abstract

Background: There is growing evidence of association between diabetes and cancer. No studies have been conducted in India evaluating this association. With the current epidemiologic, nutritional and economic transition in India, it becomes extremely important to examine this association in an Indian population.

Method: We used Mumbai Cohort Study- a longitudinal study for this purpose. Diabetes information was collected at baseline and cancer information was received via follow-up questionnaire and confirmed using cancer registry. We also evaluated the association between diabetes and cancer subtypes after creating matched datasets for each cancer subtype. We used Cox Proportional model for cancer incidence and conditional logistic regression for cancer subtypes.

Results: We did not observe any significant associations between diabetes and all cancer incidence and cancer subgroups. However the association was in the expected direction. The hazard of all cancer incidence was 1.06 (95%CI=0.75, 1.62) among persons with diabetes as compared to people without diabetes.. Among cancer subtypes, there was an increased risk of 'lip/oral/pharyngeal cancer' (OR=1.83; 95%CI=0.86, 3.86) and

‘respiratory tract cancer’ among people with diabetes (OR=1.28; 95%CI=0.53,3.13)

respectively. Inverse direction was observed for ‘digestive organ cancer and

‘breast/prostate/uterine/cervical cancer’ among people with diabetes compared to people

without diabetes (OR=0.59; 95%CI=0.27, 1.32) and (OR=0.66; 95%CI=0.24, 1.84)

respectively, but none of these associations reached statistical significance.

Conclusion: Our findings appear to show a higher hazards of all cancer incidence,

lip/oral/pharyngeal and respiratory tract cancer among people with diabetes compared to

people without diabetes. They direction of the association is consistent with previous

study results. However the association is not significant. Future studies needed to explore

this association in detail.

Introduction

Apart from the diabetic complications like diabetic foot, diabetic ketoacidosis, diabetes has also been linked with other chronic diseases like hypertension, other cardiovascular diseases (189-192). Several studies have shown an association between diabetes mellitus and cancer. Literature suggests an increased risk of colorectal cancer (28-40, 42, 61, 76, 124), breast cancer (31, 193-195), liver cancer (196, 197), and pancreatic cancer (198-200) among people with diabetes. On the other hand people with diabetes are associated with a lower risk of prostate cancer (59, 201, 202). Besides sites-specific mechanisms for certain cancers like pancreatic and liver cancer, hyperinsulinemia, chronic inflammation and hyperglycemia are the suggested pathways in this association (28, 31-33, 43, 58, 95, 193, 194, 196, 198).

To date, most of these studies determining the association between diabetes mellitus and cancer are in the Western nations (29, 30, 33, 37, 39, 40, 57, 61-64, 66, 193, 194, 202-207). None of these studies are conducted in India, which is currently experiencing dramatic demographic, economic, epidemiologic and nutrition transitions (5, 8, 9, 13-15, 122, 123) and diabetes is developing the status of an epidemic. India is also a diverse country in terms of religion and culture and people in different religions have a different dietary and lifestyle habit that have also linked with these diseases. Globally the Indian population is more prone to metabolic syndrome (128-130). Indians are also at a higher risk of diabetes mellitus, CVD, dyslipidemia, even at a lower or normal BMI (208-210). Similar results are seen among Asian Indians worldwide. Although, compared to Western countries, the cancer rates are lower in India; they are still on increasing trend (211-214). Additionally, with the current ominous changes in

above-mentioned lifestyle factors, it is likely that cancer rates will increase. Thus, it becomes important to study this association in India. In our study, we will assess the association between diabetes mellitus and cancer incidence and cancer sub-types in an Indian population.

Methods

Study Design

Baseline: The Mumbai Cohort Study (MCS) was conducted in Mumbai (previously known as Bombay) in Maharashtra. The participants were recruited from 1991-1997 and the follow-up was conducted from 1997-2003. The study was restricted to the main city and recruited individuals over 35 years of age. The voters' list was used as the sampling frame and it provided information on age, sex, and address of individuals who are ≥ 18 years. The apartments serving the upper-middle class and upper-class housing complexes were essentially gated communities and were not easily accessible to the interviewers, therefore they were excluded from the study (179). Footpath dwellers, who did not have a permanent residence also were excluded because they are not generally included in the electoral rolls; hence they would be very difficult to follow-up (180, 184, 215-218). Of all of the major cancer cohorts in the world, the MCS is the more diverse in terms of income and socioeconomic status more generally. Only people located in the study area were eligible to be recruited into the study. Face-to-face interviews were conducted using structured questionnaires in handheld computers (electronic diaries) by interviewers in the participant's home. All of the interviews were conducted in local languages (e.g., Marathi, Hindi) but the information was recorded in

English. All the procedures regarding participant recruitment and ethical treatment of human subjects were approved by the Indian Council of Medical Research (ICMR) (179-181).

Follow-up: A list of names and addresses of the participants were provided to the field investigators for re-interviewing the participants. A house-to-house follow-up interview was conducted on an average of 5.5 years after the initial survey. If the participant had died, information regarding the date and place of death was accurately recorded. For the participants who permanently migrated to another place their date of migration was noted. (181).

Main Independent variable:

Our main independent variable was T2DM. The information on diabetes mellitus was collected at baseline using the baseline survey. The question determining this information was an open-ended question 'Do/ did you suffer from any major disease in the past years (Y/N)___ If 'Y' then, disease name.' Although it is a self-reported questionnaire, the information was collected and entered by the interviewer.

Dependent variable:

Cancer incidence was defined as the occurrence of any new cases of cancer in the defined population during that specified time period. Cancers registered and first diagnosed between the 1st January and the 31st December of that particular year were considered incident cases for that year. Cancer cases also were selected if information was available only through death certificate. The cancer information (status and date of diagnosis) was confirmed using the population-based cancer registry (PBCR). The PBCR

in Mumbai was the first registry to be established in India, in June 1963. Information was collected from cancer patients who were registered in 150 government hospitals/ institutions and private hospitals or nursing homes in Mumbai under the care of specialists. Cases were excluded if they came under code '0' = benign or '1'= uncertain if benign or malignant borderline malignancy or '2'=*carcinoma in situ*. The World Health Organization coding system with the code number C00-97 as published in manual of the International Classification of Diseases, Injuries, and Cause of Death was used (184). According to a paper published by the International Agency for Research on Cancer, the data collected by PBCR Mumbai met the standards for completeness and reliability (185). The data from the Mumbai Cohort Study and PBCR were combined using these variables: Name, Sex, Age, Postal pin code, Religion, and Mother tongue. Information on all the newly diagnosed cancer cases ≥35 years developed from 1991-2003 was abstracted from PBCR.

Inclusion/ Exclusion Criteria: The overall sample size at baseline is 148,173. Participants with missing information on diabetes mellitus and a person-time of ≤0 were excluded from the study. Participants with a past history of cancer also were deleted. For further analysis, participants with missing information on employment status, mother-tongue and with a follow-up status of 'unknown' and 'other' were removed from our analysis. Based on the aforementioned criteria, our analytic sample consists of 95,220 MCS participants.

Statistical Analysis:

Descriptive statistics were calculated using chi-sq test for the categorical variables and t-test for the continuous variables. For our main analysis, we used Cox proportional hazards model examining cancer incidence among people with diabetes and people without diabetes. Follow-up/Person years were calculated using the date of recruitment through 31ˢᵗ December 2003 until the date of re-interview, death, migration or cancer incidence. We checked for proportional hazards assumptions using both; graphical, and Schoenfeld residual method (186, 187). Based on this we conducted sequential modeling with first model representing the crude model; second model stratified by BMI (strata variable), the third model including BMI in the final model to check if BMI also has an impact on cancer incidence.

We adjusted for age, gender, native speech (including North Indian and South Indian languages), education (secondary/ college, primary/middle, uneducated), employment (employed, retired, unemployed, unknown), tobacco use (current user, past-user, never-user), BMI (overweight/obese, normal, underweight) and religion (Hindu, Muslim, others). Additionally, we also considered native speech and religion. These factors could also act as potential confounders considering the fact that diet and other factors change significantly among these religions and language.

We grouped the diagnosed cancers into sub-categories 'lip, oral-cavity and pharynx' (C00-C14), 'digestive organs cancers' (C15-C26), 'respiratory tract cancer' (C30-C39), 'breast, cervical, uterine, prostate cancer' (C50,C51-C55, C61), and others based on the ICD10 coding. For the initial analysis, we conducted a chi-sq test for each of

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these cancer subtypes (cancer subtype/ no cancer) by diabetes (yes/no) using the overall dataset. Following this, we conducted matching based on age, gender and person-time for each for these four cancer groups. The ratio used for matching was 1:4 for the 'lip, oral-cavity and pharynx' (N=1230), 'digestive organ cancer' (N=1692) and 'respiratory tract cancer' (N=875) and 1:3 for 'breast, cervical, uterine, prostate cancer' (N=1106). We conducted conditional logistic regression to determine the association between diabetes mellitus and cancer subtypes.

Results:

Descriptive characteristics of the participants, in relation to their diabetes mellitus status are summarized in Table 4.1. People with diabetes were comparatively older with a mean age of 59.2 years. Across the two groups, males (79.8% vs 66.2%), and participants of Muslim and other religion (17.3% vs. 13.9% & 8.2% vs 6.2% respectively) were more common among people with diabetes compared to those without diabetes. Participants speaking languages of Dravidian origin (South Indian languages including Tamil, Kannada, Telugu and Malayalam) were more common among people with diabetes than people without diabetes (16.2% vs. 9.7%). Around 60% of participants in both the groups had at least primary/ middle level of education. People with diabetes had a higher percent of participants with secondary school or college education (23.9% vs. 12.5%), and were more obese/overweight (37.5% vs. 23.4%).

Similar to the crude model, in our final adjusted model the hazards of cancer incidence appeared to be higher among people with diabetes compared to those without diabetes although it did not reach the statistical significance (crude model- HR=1.11;

95%CI=0.78, 1.58, adjusted model-HR=1.06; 95%CI=0.75, 1.52) (Table 4.2). Among the other covariates, gender, religion, tobacco use had a significant effect.

Table 5.3 represents the difference in the proportion of cancer subgroups as compared to people without cancer by their diabetes status. The 'lip/oral cavity/pharynx' cancer group was significantly different between people with diabetes as compared people without diabetes (p-value=0.0192). None of the other cancer subgroups showed any significant difference. Table 5.4 provides the conditional odds ratio for the different cancer subgroups. Both, the crude and adjusted model did not produce significant results. We adjusted for age, religion, native speech, education, BMI and overall tobacco intake. In the adjusted model, people with diabetes appeared to show a higher odds of lips/oral/pharynx cancer (OR=1.83; 95%CI=0.86, 3.86) and respiratory tract cancer (OR=1.28; 95%CI=0.53, 3.13) as compared to those without diabetes. Opposite results were observed for digestive and hormone related cancers i.e. the odds of cancer were lower among people with diabetes compared people without diabetes (OR=0.63; 95%CI=0.28, 1.44) (OR=0.66, 95%CI=0.24, 1.84) respectively.

Discussion

In our study we examined the association between diabetes and the risk of developing cancer using a longitudinal study conducted in India. The results were not significant, however the estimates were in the expected direction i.e. the risk of all cancer incidence was higher among people with diabetes.

Existing literature assessing the relation between diabetes and all cancer incidence have inconsistent results. Zhang et al. in their retrospective cohort study in China,

suggested an increased incidence ratio of overall cancer risk in both men and women among people with diabetes (SIR=1.33; 95%CI=1.14, 1.52 and SIR=1.74; 95%CI= 1.48, 2.00 respectively) (204). Another study from Denmark demonstrated similar results and found a 10% increased risk of cancer among people with diabetes. As opposed to the above results, one of the studies conducted in Scotland, suggested no significant association between diabetes and overall cancer incidence (62).

We regrouped cancer in different subtypes based on ICD10 categories. Our results showed increased odds of 'lip/oral cavity and pharynx', and 'respiratory tract' cancer among people with diabetes compared to those without diabetes, however the results were not significant. A retrospective study in Hungary showed that participants with oral cancer had 14.6% people with diabetes, which was higher than people without oral cancer (219). Wideroff et al. in his study demonstrated a higher risk of oral/pharyngeal and esophageal cancer in people with diabetes under the age of 50 years (220). With regards to lung cancer, most of the previous studies did not show significant association with diabetes (204, 220). For digestive tract cancer, we observed an inverse relation i.e. people with diabetes had a decreased odds of digestive tract cancer compared to those without diabetes contrary to the results found by Wideroff et al. that showed an elevated risk of digestive tract cancer (including esophageal, stomach, small intestine, colon, rectum, liver, biliary tract and pancreatic cancer) among people with diabetes (220). In this study the digestive tract cancers included esophagus, stomach, colon and liver & intrahepatic bile duct cancer while the people without diabetes had a number of other cancers included in this group. Similar to digestive tract cancer, we found an inverse direction for hormone-related cancers. The probable reason could be the higher number

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(four of five) of prostate cancer cases among people with diabetes and only one participant with breast cancer. Although the results were insignificant, the direction is consistent with most of the previous studies showing an inverse association in relation to prostate cancer (59, 203, 207). Two meta-analysis also showed similar results (201, 202).

Hyperinsulinemia is suggested to be one of the major connecting links in the association between diabetes and cancer suggesting an increased level of insulin and insulin-like growth factor. Both, insulin and IGF-I are involved in cell growth initiation and progression by proliferation and IGF-I also act as an inhibitor of apoptosis. Additionally obesity is considered to be a predisposing factor for both diabetes and cancer. Especially abdominal adiposity (visceral obesity) is more strongly associated with these chronic diseases (221, 222). Asian population is more prone to abdominal obesity and other chronic diseases even at a lower BMI. Furthermore, chronic inflammation is associated with insulin-resistance thereby considered to be one of the links between diabetes, obesity and cancer. All these factors, individually or in connection with each other lead to an increased risk of cancer.

One of the major limitations of our study is the study population which is not representative of the entire population as the upper –middle-class and upper class housing complex could not be included during the recruitment due to security issues. We had a lot of missing data for our main independent variable i.e. diabetes. In our study, the results were directed towards null, which could be probably due to the data not missing at random. We could not adjust for potential confounders like diet and physical activity due to lack of information. Despite the limitations this study has several strengths. MCS is a

longitudinal study conducted with a very diverse population and has a large sample size. Although the diabetes status was self-report it was hand entered by the interviewer.

This is the first study evaluating the association between diabetes and cancer in an Indian population. Studies are required determining this association in further details especially in an Indian population where the diabetes rates are increasing at an alarming rate (223). In these studies we need to consider all the factors that can act as potential confounders as a lot of studies lack this information. Furthermore, differences also exist in the socio-demographic characteristics (like education, tobacco use) among the Indian population as compared to the other western population. Assessment of these risk factors could help in better understanding of the association. Additionally, better registries are needed throughout India, to be successful in capturing important data.

Table 4.1: Descriptive Statistics for the overall population by diabetes mellitus status, Mumbai Cohort Study, Mumbai Maharashtra, 1991-2003.

Variables		Diabetes mellitus		p-value
		Yes (N=2143)	No (N=93077)	
		Mean(±std)		
Age		59.2 (±9.8)	51.6 (±11.1)	<.0001
		% (N)		
Gender	Male	79.8 (1,710)	66.2 (61,606)	<.0001
	Female	20.2 (433)	33.8 (31,471)	
Religion	Hindu	74.5 (1596)	79.9 (74,354)	<.0001
	Muslim	17.3 (370)	13.9 (12,910)	
	Others	8.2 (177)	6.2 (5,813)	
Primary language	Aryan	83.8 (1,796)	90.3 (84,056)	<.0001
	Dravidian	16.2 (347)	9.7 (9,021)	
Education	Secondary school/ college	23.9 (511)	12.5 (11,616)	<.0001
	Primary / middle school	59.6 (1,278)	63.1 (58,782)	
	Uneducated	16.5 (354)	24.4 (22,679)	
Employment	Employed	38.3 (822)	46.8 (43,593)	<.0001
	Unemployed	15.5 (332)	30.7 (28,584)	
	Retired	41.5 (889)	19.7 (18,332)	
	Unknown	4.7 (100)	2.8 (2,568)	
Tobacco Use	Current user	51.7 (11.7)	58.1 (54,072)	<.0001
	Past user	12.1 (259)	4.9 (4,518)	
	Non-user	36.3 (777)	37.0 (34,487)	
BMI (kg/m^2)	Obese/ overweight	37.5 (804)	23.4 (21,774)	<.0001
	Underweight	5.5 (117)	18.3 (17,073)	
	Normal	57.0 (1,222)	58.3 (54,230)	

Table 4.2: Unadjusted model - HR (95%CI) for all cancer incidence by diabetes mellitus, Mumbai Cohort Study, Mumbai Maharashtra, 1991-2003

	All cancer incidence	
Reported Regression Estimate	HR (95% CI)	P-value
Unadjusted		
Diabetes (yes/no)	1.11 (0.78,1.58)	0.55
Adjusted model with BMI as a strata variable		
Diabetes (yes/no)	1.06 (0.75-1.52)	0.75

Table 4.3: Distribution of cancer subtypes across four categories of cancer, Mumbai Cohort Study, Mumbai Maharashtra, 1991-2003.

Table of Cancer type by diabetes			
CANCERTYPE	Diabetes % (N)		
	yes	No	p-value
Lip/oralcavity/pharynx Cancer	0.51% (11)	0.25% (235)	0.0192
Digestive organ Cancer	0.33% (7)	0.36% (332)	0.8179
Respiratory tract Cancer	0.33% (7)	0.18% (168)	0.1193
Breast/Cervical/uterus/prostate Cancer	0.23% (5)	0.30% (281)	0.5672
No Cancer	98.6% (2111)	98.9% (91684)	

Table 4.4: Conditional OR (95%CI) for cancer subtypes in relation to diabetes mellitus, Mumbai Cohort Study, Mumbai Maharashtra, 1991-2003

	Cancer Sub-categories			
	Lip/ Oral/ Pharynx Cancer	**Digestive Organ Cancer**	**Respiratory Tract Cancer**	**Breast/ Uterine/ Cervical/ Prostate Cancer**
Reported Regression Estimate	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted Diabetes (yes/no)	1.39 (0.69, 2.81)	0.59 (0.27,1.32)	1.12 (0.48, 2.59)	0.75 (0.28, 2.00)
Adjusted model Diabetes (yes/no)	1.83 (0.86,3.86)	0.63 (0.28,1.44)	1.28 (0.53,3.13)	0.66 (0.24,1.84)

CHAPTER 5

ASSOCIATION BETWEEN DIABETES AND COLORECTAL CANCER INCIDENCE- A LONGITUDINAL STUDY IN THE US POPULATION

Abstract

Background: Research has shown that diabetes is associated with an increased risk of colorectal cancer. However most of these studies suggest detection bias to be one of the probable reasons for this association. Additionally, the common risk factors shared by both these conditions are considered to one of the reasons in the association.

Objective: In this study, we examine the association between diabetes and CRC, accounting for important potential confounders and also check for detection bias.

Methods: We used the Prostate Lung Colorectal Ovarian (PLCO) Cancer screening trial. The diabetes information was self-report data and collected at baseline. The cancer information was collected using annual survey questionnaire (ASU) administered every year and confirmed using medical records. For our final analysis we use cox proportional hazards model. To evaluate the notion of detection bias, we conducted stratified analysis.

Results: We observed a 33% higher risk of CRC among people with diabetes as compared to people without diabetes. After stratifying the results by screening arm, we still found a higher risk among both the screening arms, (HR=1.41, 95%CI=1.13, 1.76)

among the control arm (HR=1.22, 95%CI=0.94, 1.58). After stratifying by BMI, the risk was still high among people with diabetes in all the groups.

Conclusion: Our findings showed an association between diabetes and increased risk of colorectal cancer. Detection might not be the reason for this association. Further studies should include information on other factors like diabetic medications.

Introduction

Type 2 Diabetes Mellitus (T2DM) and cancer are both among the top 10 leading causes of mortality worldwide (1-3). Apart from the established diabetic complications, existing literature suggests an increasing risk of cancer among people with diabetes. Evidence shows that people with diabetes have an increased risk of colorectal cancer (CRC) (28-40, 42, 59, 61, 76, 124). Hyperinsulinemia is suggested to one of the mechanisms in this association. Both insulin and IGF-I act as a growth stimulator and inhibitor of apoptosis, thereby promoting carcinogenesis within the colonic epithelium (31, 32, 43, 224).

In addition to this, both these diseases have a lot of common risk factors like lack of physical activity, obesity and unhealthy dietary habits. As seen from literature, diet high in total energy, fat, red meat, and carbohydrates and low in fruits and vegetables elevate the risk of CRC through inflammatory pathways (44, 142-150). Diets high in total calories and saturated fat and low levels of dietary fiber also lead to insulin resistance, which in turn is associated with both T2DM and CRC (82). Inflammatory pathways are also suggested as one of the mechanisms underlying the association between T2DM and CRC risk (34-36, 43, 224). Therefore diets with an inflammatory potential can also play a role in this association.

Although there is a lot of existing literature, most of the previous studies mention detection bias as one the probable reasons leading to this association. People with diabetes are more likely to visit their physicians and thereby have a higher probability of being diagnosed by other diseases (29-35, 37, 39, 76, 205). Apart from detection bias BMI is also considered to be the driving force in this association as it one of the common

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risk factors for both these diseases. Majority of the studies assessing the role of diet in the association have just focused on specific dietary components. Diet, as a whole can altogether have a different effect on these diseases..

There is a global increase in the T2DM rates and even though the rates of CRC are decreasing, the incidence and prevalence of CRC is still high among the US population. It still remains one of the top 3 causes of cancer deaths in both men and women (20). Diabetes and cancer affect the health and economy at both; individual and national level.

Considering the facts and gaps in literature, in our study we aim to address those questions. We will evaluate if there is any association between T2DM and CRC incidence accounting for the possibility of detection bias. We will also check if BMI and dietary inflammatory index (DII) modify this association. DII is a unique tool measuring the overall inflammatory potential of a diet that will help in understanding the role of diet on this association

Materials and methods

Study population

This study is conducted using data from the Prostate Lung Colorectal Ovarian (PLCO) Cancer Screening Trial. The PLCO is a multicenter screening trial conducted with the aim of understanding the importance of screening examinations on reduction of mortality rates of cancers of the prostate, lung, colorectal and ovarian. Participants were enrolled from 10 different centers and randomized in the years 1993-2001. Around 154,900 participants were recruited at the beginning of the study and approximately

77,000 of these individuals were randomized to both study arms. A series of questionnaires were administered throughout the course of the study. The demographic, anthropometric and medical history information was collected from baseline and supplemental questionnaires. Diet information was collected twice during the course of the study- at baseline from the intervention arm and from 1998 to 2001 from both the screening arms that include the intervention and the control arm, using a food frequency questionnaire.

For our study, we used the following exclusion criteria; a) participants with baseline colorectal cancer, b) People with no information on diabetes. We excluded participants with missing information on the following covariates; employment, education, family history of colorectal cancer, aspirin intake and cigarette smoking. The final sample size consisted of 146,918 participants. Other details regarding the study design and methods have been summarized elsewhere (183).

Main Dependent Variable: Colorectal Cancer Incidence

The cancer incidence data were collected using the annual study update questionnaire (ASU), administered every year to each participant on the date of randomization. The ASU collected information on the type and date of diagnosed cancer in the past year. This information was confirmed through medical records. Non-respondents were contacted again by the study staff via mail and telephone.

Independent variables

The baseline questionnaire included information on diabetes and other 19 medical conditions. Although the diabetes data were self reported, studies have shown these results to be accurate, especially for diseases like diabetes and hypertension (225-229).

Covariates:

The baseline questionnaire consisted of information on socio-demographic, anthropometric, and personal medical history. Dietary data were collected twice throughout the course of the study using food frequency questionnaire. At baseline the data was collected only in the intervention arm and it was administered again from 1998-2001 in both the intervention and control arms. We used the dietary inflammatory index (DII^{TM}), a tool used for calculating the inflammatory potential of diet. DII was determined using the diet history questionnaire (DHQ) administered to both the screening arms. Around 118,804 participants have information on diet. The DII is based on 45 food parameters (188). In our study it was calculated based on the 37 parameters available in the DHQ. A higher DII score indicates a pro-inflammatory diet.

Statistical Analysis:

Based on the inclusion/ exclusion criteria, we determined the final analytic dataset as provided in Figure1. Baseline characteristics were estimated by diabetes status. For the categorical variables, we used chi-sq test and t-test for the continuous variables. Person-time (in days) was calculated from the baseline date to the date of cancer incidence or the latest completion date of ASU, death, or 13 year of cut off, whichever occurred first. We adjusted for sex, age (<60 years, 60-70 years, >70 years), BMI (<25, 25–29.9, and

30 kg/m^2 and unknown), education (≥college, post high school/some college, <high school), family history of cancer (yes, no, missing), aspirin intake (>2/day,1/day, 1-4/week, <4/month and none), cigarette smoking (current, former, non-smoker), DII in tertiles (<-2.74, <-0.39, >=-0.39). For all our analytical models using Cox proportional hazards model, we checked for the proportional hazards (PH) assumption. Once the ph-assumption was satisfied, we fit these models and estimated the hazards ratios and 95% confidence intervals, controlling for important covariates.

For our initial analysis, we did not include the diet information as a covariate. For the overall sample size (N= 145,642) BMI was included as a strata variable as it did not satisfy the PH assumption. For our further analysis, participants with a person-time of 0 were deleted from the study. Also, only participants with a confirmed cancer status (yes/no) were included in the study.

Separate analyses were conducted by stratifying the models by the intervention arm and BMI to check if screening and BMI modified the association between diabetes and CRC. BMI was re-categorized into three strata (normal/underweight, overweight and obese). For analysis, with BMI, we used two sample sizes i.e. initially with the overall data (N=145,642) and again with dataset including the dietary data (N=114,017), as shown in Figure1. Physical activity was collected using the baseline dietary and the supplemental questionnaire (SQX). However the baseline information was collected only in the intervention arm. We also performed sensitivity analysis, removing people with missing physical activity data (as per the SQX administered in 2006). A sensitivity analysis was conducted by restricting to participants with person-time of more than1 year and 2 years with sample sizes of (N=113,689) and (N=113480) respectively.

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Results

The distribution of socio-demographic, lifestyle characteristics of participants by their diabetes status in the PLCO study is provided in Table 5.1 (N=114,017). The sample size was significantly different across the two groups. Compared to people without diabetes, people with diabetes had a higher proportion of male (57% vs. 47.5%), Non-Hispanic Blacks (8.7% vs. 3.2%) and other group (9.6% vs. 5.5%) participants, tended to be older age group (73.5% vs 65.9% in >60years group). Also, people with diabetes had a higher percent of obese (44.5% vs 21.8%) compared to those without diabetes. However, people without diabetes had a relatively higher proportion of overweight (i.e., $25 \leq BMI < 30 kg/m^2$) participants (42.4% vs. 37.7%). In both the groups fewer than 10% of participants were current smokers (8% people with diabetes vs. 9.6% people without diabetes). However the sample was almost similarly distributed for the intervention and control arm across the two groups. Around 87% of participants had no family history of colorectal cancer in both the groups. More than 50% of participants had some intake of aspirin in the people with diabetes as compared to people without diabetes, where the aspirin intake was less than 50%.

During the follow-up of 13 years, 1622 cases of CRC were detected. Table 5.2 provides the results for the crude model (Table 5.2), the adjusted model (Table 5.3) in the overall sample size (figure1 (a)) and the final sample including the diet data (figure1 (b)) (Table 5.4). In the crude model, the hazards of CRC incidence was significantly higher among people with diabetes (HR-1.56; 95%CI, 1.33- 1.84) compared to people without diabetes. After adjusting for the potential confounders, the risk was higher among people with diabetes; however, it was slightly attenuated in both the models with a hazard ratio

of 1.40 (95%CI, 1.22-1.61) in the overall model and hazards ratio of 1.32 (95%CI, 1.12-1.57) in the final analytical sample size.

When stratified by the screening arm, the hazard ratios were higher among people with diabetes in both the intervention and control group. It was significant in the control group (HR-1.42; 95%CI, 1.14-1.77), unlike in the intervention group (HR-1.22; 95%CI, 0.94-1.58) as seen in Table 5.5. However, the interaction term was not significant (p-value=0.08). In stratified analysis by BMI, the hazards were similar across the three categories (i.e. normal/underweight, overweight, obese); (HR-1.37; 95%CI, 0.98-1.93 for the normal/underweight group, HR-1.27; 95%CI, 1.02-1.58 for the overweight group and HR-1.34; 95%CI, 1.07-1.67) (Table 5.6). Similar results were seen when analyzed with the sample including dietary data (Table 5.7). Sensitivity analysis done after removal of participants with a person-time of a) ≤1 year, and b) ≤2years, did not suggest any change in the hazards ratio (HR-1.30, 1.31 respectively). Similarly, the sensitivity analysis conducted for physical activity suggested no changes in the estimates.

Discussion

In our study we found an elevated risk of CRC among people with diabetes compared to people without diabetes. After adjusting for screening, gender, race, employment, education, age, family history of CRC, aspirin intake and cigarette smoking the risk of CRC was 40% higher among people with diabetes. Additionally adjusting for DII and physical activity, the risk was 33% higher. The results are consistent with the previous studies conducted in US and elsewhere (28-40, 42, 61, 76).

Most of the past literature suggests a positive association between diabetes and CRC. However some of studies investigating the all-site cancer risk and cancer subtypes, found no significant association between CRC and diabetes (206). Previous studies have shown inconsistency in results between males and females.. Studies by Diaz et al., J He et al. and Nilsen et al. show a higher risk among females (61, 124, 205). Diaz et al. in his study among a Hispanic population also showed that women had a higher risk of colon cancer (CC) while no significant association between T2DM and CC were found. In their study, Magliano et al. found a 36% increased risk of CRC among men (60). The estimates are also similar across most of these studies (ranging from 1.3-1.5). However, a lot of the studies could not adjust for some important confounders (only adjusted for age, BMI) (28-40, 42, 61, 76, 206) .

As mentioned earlier hyperinsulinemia is one of major mechanisms in the association between diabetes and CRC. The simultaneous existence of common risk factors like unhealthy dietary habits, lack of physical activity, obesity, contributes towards insulin resistance and hyperinsulinemia. These factors lead to activation of IGF-I promoting carcinogenesis (28, 75, 82-84).

As detection bias is suggested to be one of the explanations for the positive association between diabetes and colorectal cancer, we checked the association including screening as one of the covariates. After adjusting for screening, the association still existed. Besides that on stratification by the screening arm, an elevated risk was detected in both groups; however the association was only significant in the control group. Additionally, the distribution of screening was similar across the people with diabetes and people without diabetes.

We adjusted for all the available potential confounders. From the crude model, the estimates were slightly attenuated, however he important covariates; there was an increased risk of CRC among people with diabetes. As a measurement of diet and inflammation through diet, we adjusted for DII. We observed a little difference between the model with and without DII. Most of the previous studies have adjusted for BMI. In our adjusted model, BMI showed no significance with CRC risk, in consistence with some of the some of the previous studies (42, 61).

Obesity is considered one of the major risk factors in this association; we also conducted a stratified analysis by BMI. Irrespective of the BMI group, people with diabetes still had a higher risk of CRC. Significant elevated risk were seen in normal/underweight and obese group. Our findings suggest that BMI might not be the only driving force in the association between diabetes and CRC. The results are similar to the study conducted by Seow et al. among Chinese population residing in Singapore (42).

We conducted sensitivity analysis, excluding participants detected with CRC within two years of recruitment in the study. We still found the same results as in the final adjusted models.

There are a few limitations to our study. Diabetes was self-reported which might lead to misclassification. However past literature suggests that self-report data regarding the chronic diseases is mostly accurate (228, 229). We could not account for diabetes medication due to lack of data. Apart from this, it is a longitudinal study with a large database. It had information on a lot of potential confounders that we considered in our analysis. We tried to address the problem of detection bias and also tried to figure out the

impact of BMI on the association between diabetes and CRC. This is the first study to include DII while determining this important association, as inflammation is one of the suggested pathways in the association.

Our study strengthens the existing results on the association between diabetes and CRC. However in addition to hyperinsulinemia, other mechanisms need to be explored in further details. Future studies can also include additional information on diabetic medications.

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│   N=154,897      │
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         ▼◄────────│ 5874 with missing diabetes information –│
         │         │ deleted                                 │
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         │         │ 2075 participants with missing          │
         ▼◄────────│ employment, education, F/H, cigarette   │
         │         │ smoking, aspirin intake were deleted    │
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│   N=146,918      │
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         │         │ 576 and 700 participants were deleted   │
         ▼◄────────│ with unconfirmed cancer status and      │
         │         │ person-time= 0 respectively             │
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         ▼◄────────│ 31,625 participants with missing diet   │
         │         │ information - deleted                    │
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│ N=114,017└───┘
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Figure 5.1: Consort diagram for the final analytic dataset

Table 5.1: Descriptive statistics of the PLCO population by diabetes status

	Diabetes Status		
	Yes (%) N= 7,898	No (%) N=106119	p-values
Sex			
Male	57.0	47.5	<.0001
Female	43.0	52.5	
Randomization Arm			
Intervention	50.8	51.4	0.2782
Control	49.2	48.6	
Race			
Non- Hispanic White	81.7	91.3	
Non- Hispanic Black	8.7	3.2	<.0001
Others	9.6	5.5	
Age group			
70-80 years	16.6	12.6	
60-70 years	56.9	53.3	<.0001
less then 60 years	26.5	34.1	
Education			
college grad and more	28.8	36.2	
post high school, some college	36.1	34.4	<.0001
less than high school	35.1	29.4	
Employment			
Employed	29.4	40.2	
Retired	52.2	43.1	<.0001
Unemployed	11.0	12.8	
Others	7.3	3.9	
Body Mass Index (kg/m^2)			
Obese	44.5	21.8	
Overweight	37.7	42.4	
Normal	16.0	33.8	<.0001
Underweight	0.3	0.7	
Unknown	1.5	1.2	
Cigarette Smoking Status			
Current Cigarette Smoker	8.0	9.6	
Former Cigarette Smoker	48.9	42.6	<.0001
Never Smoked Cigarettes	43.1	47.8	
Family History of Colorectal Cancer			
Yes, Immediate Family Member	9.6	10.3	
Possibly - Relative Or Cancer Type Not Clear	3.3	2.5	<.0001
No	87.1	87.3	

| | Diabetes Status | | p-values |
	Yes (%) N= 7,898	No (%) N=106119	
Aspirin Intake			
2+/day	6.1	5.2	
1/day	32.0	19.9	
1-4/month	9.4	13.4	<.0001
<4/month	8.1	9.8	
None	44.4	51.7	

Table 5.2: Unadjusted HR (95%CI) for CRC by diabetes

	HR	(95% CI)
Diabetes (Yes)	1.56	(1.33,1.84)
(No)	1	

Table 5.3: Adjusted model with HR (95%CI) for CRC by diabetes

	HR (95% CI)	
Diabetes (yes vs no)	1.40	(1.22,1.61)
Randomization Arm (intervention vs control)	1.29	(1.19,1.41)
Sex (female vs male)	0.69	(0.62,0.76)
Race (non-Hispanic black vs non-Hispanic white)	1.22	(1.02,1.45)
Race (others vs non-Hispanic white)	0.85	(0.71,1.02)
Employment (others vs employed)	1.04	(0.84,1.29)
Employment (retired vs employed)	1.06	(0.96,1.18)
Employment (unknown vs employed)	1.10	(0.94,1.29)
Education (college and more vs less than high school)	0.82	(0.73,0.91)
Education (post high school/some college vs less than high school)	0.90	(0.82,1.00)
Age group (60-70 years vs <60 years)	1.74	(1.55,1.95)
Age group (70-80 years vs <60 years)	2.41	(2.07,2.79)
Family history (possibly vs no)	1.41	(1.14,1.75)
Family history (yes vs no)	1.30	(1.14,1.48)
Aspirin intake (1-4/week vs none)	0.79	(0.69,0.91)
Aspirin intake (1/day vs none)	0.82	(0.73,0.92)
Aspirin intake (>2/day vs none)	0.81	(0.66,0.99)
Aspirin intake (<4/month vs none)	1.04	(0.91,1.20)
Cigarette smoking (current smoker vs non-smoker)	1.43	(1.24,1.64)
Cigarette smoking (past smoker vs non-smoker)	1.13	(1.03,1.23)

In overall sample size without diet and physical activity data (Sample size in fig1a)

Table 5.4: Adjusted model with HR (95%CI) for CRC by diabetes

	HR	95%CI
Diabetes (yes vs no)	1.33	(1.12,1.57)
Gender (female vs male)	0.73	(0.65,0.81)
BMI (unknown vs normal)	1.49	(1.04,2.13)
BMI (obese vs normal)	1.10	(0.96,1.27)
BMI (overweight vs normal)	1.06	(0.95,1.20)
BMI (underweight vs normal)	0.73	(0.34,1.53)
Screening Arm (Intervention vs control)	1.34	(1.22,1.48)
Race (non-Hispanic black vs non-Hispanic white)	1.23	(0.97,1.55)
Race (others vs non-Hispanic white)	0.83	(0.67,1.04)
Education (college and more vs less than high school)	0.86	(0.76,0.97)
Education (post high school/some college vs less than high school)	0.98	(0.87,1.10)
Family history (possibly vs no)	1.43	(1.11,1.83)
Family history (yes vs no)	1.28	(1.10,1.48)
Aspirin intake (1-4/week vs none)	0.83	(0.71,0.97)
Aspirin intake (1/day vs none)	0.84	(0.74,0.96)
Aspirin intake (>2/day vs none)	0.77	(0.60,0.97)
Aspirin intake (<4/month vs none)	1.08	(0.92,1.27)
Cigarette smoking (current smoker vs non-smoker)	1.25	(1.06,1.49)
Cigarette smoking (past smoker vs non-smoker)	1.09	(0.98,1.21)
Physical Activity (yes vs no)	0.772	(0.64,0.92)
Physical Activity (unknown vs no)	1.248	(1.04,1.50)
Dietary Inflammatory Index (tertile 1 vs tertile 0)	1.05	(0.96,1.18)
Dietary Inflammatory Index (tertile 2 vs tertile 0)	1.092	(0.96,1.24)

In overall sample size without diet and physical activity data (Sample size in fig1b)

Table 5.5: HR (95% CI) for CRC in relation to diabetes stratified by screening arm

	HR (95% CI)			
	Intervention		Control	
Diabetes (yes vs no)	1.22	(0.94,1.58)	1.41	(1.13,1.76)
Gender (female vs male)	0.80	(0.68,0.94)	0.67	(0.58,0.78)
BMI (unknown vs normal)	1.60	(0.89,2.87)	1.43	(0.91,2.26)
BMI (obese vs normal)	1.06	(0.87,1.31)	1.13	(0.94,1.36)
BMI (overweight vs normal)	1.03	(0.87,1.24)	1.09	(0.93,1.28)
BMI (underweight vs normal)	0.45	(0.11,1.82)	0.95	(0.39,2.31)
Race (non-Hispanic black vs non-Hispanic white)	1.55	(1.13,2.12)	0.97	(0.69,1.38)
Race (others vs non-Hispanic white)	0.83	(0.58,1.17)	0.84	(0.63,1.12)
Education (college and more vs less than high school)	0.84	(0.70,1.02)	0.87	(0.73,1.03)
Education (post high school/some college vs less than high school)	0.98	(0.82,1.17)	0.97	(0.83,1.14)
Family history (possibly vs no)	1.17	(0.78,1.75)	1.66	(1.21,2.28)
Family history (yes vs no)	1.23	(0.98,1.54)	1.31	(1.08,1.60)
Aspirin intake (1-4/week vs none)	0.93	(0.73,1.17)	0.76	(0.61,0.95)
Aspirin intake (1/day vs none)	1.00	(0.83,1.21)	0.72	(0.61,0.87)
Aspirin intake (>2/day vs none)	0.85	(0.60,1.21)	0.70	(0.51,0.98)
Aspirin intake (<4/month vs none)	1.07	(0.82,1.38)	1.09	(0.88,1.34)
Cigarette smoking (current smoker vs non-smoker)	1.24	(0.96,1.61)	1.27	(1.01,1.59)
Cigarette smoking (past smoker vs non-smoker)	1.10	(0.93,1.29)	1.09	(0.94,1.25)
Physical Activity (yes vs no)	0.75	(0.57,0.98)	0.79	(0.62,1.01)
Physical Activity (unknown vs no)	1.35	(1.02,1.77)	1.18	(0.92,1.50)
Dietary Inflammatory Index (pro-inflammatory vs anti-inflammatory)	1.04	(0.90,1.21)	1.09	(0.95,1.25)

#age does not satisfy the ph-assumption therefore used as strata variable

Table 5.6: Adjusted model with HR (95%CI), stratified by BMI

VARIABLES	NORMAL / UNDERWEIGHT		OVERWEIGHT		OBESE	
Diabetes (yes vs no)	1.38	(0.98,1.93)	1.27	(1.02,1.58)	1.34	(1.07,1.67)
Gender (female vs male)	0.72	(0.62,0.85)	0.71	(0.62,0.82)	0.69	(0.57,0.82)
Randomization Arm (intervention vs control)	1.28	(1.09,1.49)	1.35	(1.18,1.53)	1.19	(1.01,1.41)
Race (non-Hispanic black vs non-Hispanic white)	1.04	(0.71,1.53)	1.15	(0.87,1.52)	1.02	(0.75,1.39)
Race (others vs non-Hispanic white)	0.72	(0.53,0.97)	0.90	(0.68,1.18)	0.77	(0.48,1.23)
Education (college and more vs less than high school)	0.73	(0.60,0.89)	0.94	(0.80,1.10)	0.96	(0.77,1.20)
Education (post high school/some college vs less than high school)	0.91	(0.76,1.10)	0.88	(0.75,1.03)	1.02	(0.84,1.24)
Family history (possibly vs no)	1.71	(1.18,2.48)	1.17	(0.83,1.65)	1.41	(0.92,2.14)
Family history (yes vs no)	1.06	(0.82,1.37)	1.34	(1.10,1.62)	1.53	(1.20,1.95)
Aspirin intake (1-4/week vs none)	0.84	(0.65,1.07)	0.76	(0.62,0.94)	0.89	(0.67,1.19)
Aspirin intake (1/day vs none)	0.71	(0.57,0.89)	0.80	(0.68,0.95)	0.89	(0.71,1.1)
Aspirin intake (>2/day vs none)	0.76	(0.51,1.13)	0.82	(0.61,1.12)	0.82	(0.57,1.18)
Aspirin intake (<4/month vs none)	1.16	(0.90,1.48)	0.93	(0.75,1.16)	1.15	(0.87,1.52)
Cigarette smoking (current smoker vs non-smoker)	1.36	(1.08,1.72)	1.17	(0.93,1.47)	1.53	(1.13,2.07)
Cigarette smoking (past smoker vs non-smoker)	1.14	(0.96,1.36)	1.11	(0.96,1.27)	1.16	(0.96,1.39)
Physical Activity (yes vs no)	0.82	(0.58,1.16)	0.77	(0.59,1.00)	0.65	(0.49,0.85)
Physical Activity (unknown vs no)	1.47	(1.05,2.08)	1.36	(1.04,1.76)	1.03	(0.79,1.35)
Age group (60-70 years vs <60 years)	1.80	(1.46,2.22)	1.69	(1.43,2.00)	1.75	(1.43,2.15)
Age group (70-80 years vs <60 years)	2.42	(1.88,3.11)	2.19	(1.77,2.69)	2.26	(1.70,2.99)

Table 5.7: Adjusted model with HR (95%CI), stratified by BMI including diet data

	N=37915		N= 47962		N=26716	
	NORMAL/ UNDERWEIGHT		OVERWEIGHT		OBESE	
Diabetes (yes vs no)	1.74	(1.20,2.53)	1.25	(0.95,1.64)	1.44	(1.11,1.87)
Gender (female vs male)	0.83	(0.69,1.01)	0.77	(0.65,0.90)	0.71	(0.57,0.88)
Randomization Arm (intervention vs control)	1.30	(1.09,1.56)	1.39	(1.20,1.61)	1.38	(1.13,1.69)
Race (non-Hispanic black vs non-Hispanic white)	1.85	(1.19,2.88)	1.44	(1.00,2.07)	0.99	(0.63,1.54)
Race (others vs non-Hispanic white)	0.83	(0.58,1.19)	1.00	(0.72,1.39)	0.85	(0.48,1.50)
Family history (possibly vs no)	1.69	(1.08,2.66)	1.43	(0.98,2.09)	1.45	(0.88,2.40)
Family history (yes vs no)	1.06	(0.79,1.41)	1.31	(1.05,1.64)	1.47	(1.10,1.96)
Cigarette smoking (current smoker vs non-smoker)	1.24	(0.93,1.65)	1.26	(0.97,1.64)	1.72	(1.20,2.47)
Cigarette smoking (past smoker vs non-smoker)	1.19	(0.98,1.44)	1.05	(0.90,1.23)	1.12	(0.90,1.38)
Age group (60-70 years vs <60 years)	1.89	(1.48,2.40)	1.76	(1.46,2.13)	1.92	(1.51,2.45)
Age group (70-80 years vs <60 years)	2.57	(1.93,3.42)	2.35	(1.85,2.98)	2.58	(1.85,3.60)
DII (tertile 2 vs tertile 1)	0.96	(0.77,1.20)	1.06	(0.88,1.28)	1.28	(0.99,1.66)
DII (tertile 3 vs tertile 1)	1.22	(0.97,1.54)	1.18	(0.97,1.43)	1.13	(0.86,1.48)

additionally deleted participants with missing BMI data.

CHAPTER 6

DURATION OF DIABETES AND COLORECTAL CANCER INCIDENCE – IN A LONGITUDINAL STUDY

Abstract

Background: Diabetes has been shown to increase the risk of colorectal cancer (CRC). However, very few studies have assessed the association between duration of diabetes and either CRC risk or disease aggressiveness. Even more rarely have studies confirmed the status of type 2 diabetes mellitus (T2DM) while determining the diabetes-CRC association.

Objective: We evaluated the association between duration of diabetes and cancer risk and cancer aggressiveness measured in terms of cancer grades and stage.

Methods: Using data from the Prostate Lung Colorectal Ovarian Cancer Screening Trial (PLCO), we examined the impact of T2DM and diabetes duration on CRC risk, as well as grade and stage at diagnosis. Diabetes duration was calculated using information on age at diabetes diagnosis. CRC information was derived using annually administered questionnaires and confirmed using medical records. We fit a Cox proportional hazards model for cancer incidence and conducted logistic regression analysis for cancer grade and stage.

Results: Participants with >10 years of diabetes had a higher risk (HR=1.37; 95%CI: 1.06, 1.77) of CRC incidence compared people without diabetes. An apparently smaller effect was observed among people with <10 years of diabetes duration (HR=1.13; 95%CI: 0.89, 1.43); however, it was not significant. We did not find significant results in the association between cancer aggressiveness and diabetes.

Conclusion: CRC risk was higher among people with longer duration of diabetes, even after accounting for the potential confounders.

Introduction

Type 2 Diabetes Mellitus (T2DM) and cancer are both among the top 10 leading causes of mortality (1-3). Though to differing extents, both of these diseases can be prevented and controlled by appropriate healthy lifestyle and behavioral changes. These diseases also pose a problem towards the individual and nations' health and economic burden (22, 52, 135).

Apart from the commonly observed diabetic complications, T2DM has also been linked with several chronic diseases like cardiovascular diseases, cancer (60, 62, 63, 66, 206, 220). Site/organ specific cancers have different associations with diabetes. Past literature suggest an increased risk of colorectal, liver, pancreatic and breast cancer among people with diabetes as compared to people without diabetes (29, 34, 36, 37, 39, 42, 59, 61, 62, 64, 66, 193-196, 198, 203, 204, 220). In contrast, an inverse association is observed with prostate cancer risk (59, 201, 203, 207). Among these cancers, CRC has shown to be strongly associated with T2DM as evidenced in most of the past studies (28, 29, 33, 34, 36, 37, 39, 42, 61, 76, 205). However very few studies have used information on diabetes duration when investigating the association between T2DM and CRC (33, 34, 39, 77, 230). The existing results are inconsistent.

With hyperinsulinemia, being considered to be one of the major underlying mechanisms, it becomes important to further investigate the association between duration of diabetes and CRC. Hyperinsulinemia mainly occurs in the initial stages of T2DM that might be followed by hypoinsulinemia due to destruction of the β cells of pancreas that leads to the reduction in insulin production. In addition to this both the diseases have a lot

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of common risk factors like diet, physical activity and obesity. Over time, with longer duration of diabetes, there might be a change in these lifestyle factors.

There is growing evidence of association between T2DM and CRC but lack of data on duration of diabetes. Considering the above factors, in our study, we will determine the association between T2DM duration and CRC incidence and CRC aggressiveness (cancer grade and stage) considering important potential confounders like diet (using dietary inflammatory index), physical activity and BMI.

Methods

For our third aim, we evaluated the association between duration of diabetes and colorectal cancer risk and colorectal cancer aggressiveness. We used the PLCO database for this purpose. The PLCO trial was conducted with the aim of understanding the impact of screening on early detection of cancer (182, 183). The overall sample consisted of 154,897 participants and approximately 75,000 participants were in the intervention arm and control randomized on if they received screening or not. After applying the exclusion criteria, the final analytic dataset included 94,921 participants. A series of questionnaires were administered throughout the course of the study. The demographic, anthropometric and medical history information was collected from baseline and supplemental questionnaires. Diet information was collected twice during the course of the study- at baseline from the intervention arm and from 1998-2001 from both the screening arms. The enrollment was conducted from 1993-2001. The follow-up began in 2009 with a median follow-up time of 12.4 years. The main exclusion criteria considered were history of prostate, lung, colorectal or ovarian cancer; and ongoing treatment for any cancer

besides basal-cell or squamous–cell skin cancer. Details of the study design and other criteria have been mentioned earlier (183).

Main independent variable: Duration of diabetes

The baseline (BQX) and supplemental (SQX) questionnaires were used to determine this variable. The BQX and SQX were administered at baseline and years 2006-2008 respectively. BQX included the question "Did the participant ever have diabetes?" and the SQX used the question "Were you ever diagnosed with diabetes?" The SQX also included information on the age at diagnosis of diabetes with 4 categories (<50 years, 50-59years, 60-69years and >70years).

Participants with missing information on diabetes in both BQX and SQX were deleted. The overall sample with a valid SQX consists of 103,758 participants. For the estimation of duration of diabetes variable, we included participants who mentioned yes for diabetes in the SQX. Among the participants who mentioned yes for diabetes in the SQX (N=13,675), 12,927 participants answered the question regarding the age at diagnosis. For the final calculation, we subtracted the mean of the range for the 50-59 years (i.e., 54.5 years) and 60-69 years (i.e., 64.5 years) from the age of the participant when the SQX was answered. For the last category (>70 years), we will use the mean of 70 years and the highest age of the participant during the SQX i.e. (87 years) (i.e. 78.5) and subtract it from the age of participant. Using this method, we get negative values for some of the participants for the calculated variable. As duration of diabetes cannot be less than 0, we convert these numbers to 1 (minimum possible value). Figure1 gives the distribution of the participants used for determining the diabetes status. Based on this

information the variable diabetes duration was categorized into 'no diabetes', '<=10years', and '>10years'.

Main Dependent Variable: Colorectal Cancer (CRC) incidence, stage, and grade

CRC incidence data were collected using Annual Study Update Questionnaire (ASU) administered annually. The incidence, stage and grade of CRC were confirmed using medical records. For the final analysis, participants with confirmed status of CRC (yes/no) were included. CRC grades I and II were combined and considered low grade while grade III and IV were grouped together as high grade. For determining CRC stage, we used information combining the clinical and pathologic stage of CRC and similar to grade, stage I and II were combined and stage III and IV were combined. Accordingly, the sample size was 1032 and 1073 for CRC grade and CRC stage as outcomes respectively.

Statistical Analysis:

Descriptive statistics (chi-sq for categorical and t-test for continuous variables) were calculated for participants by their diabetes duration. For CRC incidence, the following exclusion criteria were used. Participants with missing data on the variable 'age at diagnosis' in the SQX, missing information on education, an invalid SQX were deleted. Person-years were calculated from the day of entry in the trial to CRC diagnosis, or last day of remaining free from cancer and/or death of the participant. Cox proportional hazard model was used to estimate hazards ratio and 95% Confidence interval (CI) of CRC incidence by diabetes duration.

We adjusted for age (when SQX was answered), race (non-Hispanic white, non-Hispanic black and others), screening arm (intervention, control group), BMI (<25, 25–29.9, and 30 kg/m^2 and unknown), gender, employment status (employed, unemployed, retired and others), education (graduate and more, high school/some college, and less than high school), aspirin intake in past 12 months (≤1/week, ≥2/week, none, unknown), smoking status (current smoker, past smoker, non-smoker and unknown), family history of colorectal cancer (yes, no, missing) and DII (dietary inflammatory index) score, physical activity (active –yes, no, missing).DII is a tool measuring the inflammatory level of food. It is calculated using up to 45 food parameters, and based on availability of these parameters. In our study it was based on 37 parameters, which is at the upper end of what is available from structured questionnaires such as food frequency questionnaires (FFQ). The details regarding DII have been provided elsewhere (188). We checked the proportional hazards (PH)-assumptions for diabetes duration and other covariates. As BMI did not satisfy the PH-assumption, we conducted stratified analysis. Figure 2 provides the final sample used for analysis (N= 83,904).

For CRC stage and grade as the outcomes, the data were restricted to participants with information on stage and grade, respectively. Further, the people with missing data on aspirin intake and cigarette smoking were deleted. Logistic regression was used to estimate odds ratio (OR) and 95% confidence interval (CI) for CRC stage and grade by duration of diabetes.

Sensitivity analysis was conducted, deleting participants with diagnosis of CRC before the detection of diabetes based on the age at diagnosis of diabetes.

Results:

The participants in the diabetes (including both groups with diabetes i.e. >10 and <=10 years duration) group are significantly different in their characteristics from those without diabetes. More than 50% of participants in the diabetic group are males. Compared to people without diabetes, people with diabetes had a lower proportion of Non-Hispanic Whites (92% vs. 88% and 85.6%). More than 75% of diabetic participants are either obese or overweight. A majority of the participants were retired. Around 5% of participants were current smokers and more than 75% of participants did not have a family history of CRC. However, the distribution of the screening arm was similar across the diabetic and non diabetic groups (Table 6.1).

The crude model estimated higher hazards of CRC among both the diabetic groups compared to people without diabetes (HR=1.69; 95%CI=1.34, 2.13 among the > 10 years of duration and HR=1.27, 95%CI=1.03, 1.56 among ≤10years of duration). The adjusted HR was 1.37 (95%CI=1.06, 1.77) among participants with >10 years of diabetes and 1.13 (95%CI=0.89, 1.42) with diabetes ≤10 years of diabetes compared to people without diabetes. Males had a higher risk of CRC compared to females (HR=1.45; 95%CI=1.25, 1.69) (Table 6.2).

The results of the adjusted model for cancer aggressiveness (grade and stage) are shown in Table 6.3. No significant association was detected between diabetes duration and cancer aggressiveness. In the adjusted model, the hazards of higher cancer stage (III and IV) was 0.79 (95%CI=0.45, 1.38) among people with >10 years of diabetes and 1.12 (95%CI=0.71, 1.78) in ≤10 years of diabetes duration (Table 6.3). Similar results were

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seen for cancer grades (Table 6.4). The results remained same, after conducting sensitivity analysis.

Discussion

In our study, we evaluated the association between duration of diabetes and colorectal cancer incidence and cancer stage and grade. Our findings suggest an increased risk of CRC among participants with longest duration compared to people without diabetes. Participants with >10 years of diabetes duration had a 37% higher risk while participants with <=10 years of diabetes duration appeared to have a 13% higher risk compared to participants without diabetes. We found contrasting results in our study compared to previous study results; however the duration ranges are different across studies (34).

Substantial evidence exists assessing the association between diabetes and CRC and have demonstrated an increased risk among people with diabetes. However, very few studies have checked the role of diabetes duration in in this regards. Currie et al. and Yang et al. in their studies, adjusted for diabetes duration when evaluating the association between diabetes and cancer. These studies lacked information on diet and physical activity (77, 230). In a Swedish study, a 39% elevated incidence of colon cancer was observed among people with diabetes, unaffected by duration of diabetes, age or gender. In the study conducted by Flood et al, in the US, the results showed that participants with moderate duration had a higher risk and people with longer duration had a lower risk as compared to participants without diabetes. Participants with diabetes diagnosis between 4-8 years had a risk of 2.36, while those with a diabetes diagnosis from 8-12 years and >

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12 years had a lower non-significant association with CRC risk (33). Hu et al. in their study also showed similar result among participants with moderate duration of diabetes (11-15 years) having a higher risk of colorectal cancer compared to people without diabetes. While those with duration of >15years had a lower risk of CRC (34).

Hyperinsulinemia is considered as the major reason leading to this association. Common risk factors like lack of physical activity, unhealthy diet and obesity contribute towards insulin resistance and hyperinsulinemia. Hyperinsulinemia leads to activation of IGF-I. As insulin and IGF-I act a growth promoter and inhibitor of apoptosis; it helps in carcinogenesis in colonic epithelium. However, in the later stages of diabetes the β cells of pancreas are unable to compensate for the insulin production leading to hypoinsulinemia. However inflammation could lead to the association for longer duration of diabetes and increased risk of CRC. Persistence of unhealthy lifestyle factors and longer duration of diabetes can lead to inflammation. Apart from this, there can be a change in the intake of diabetic medications. As seen from the past literature, diabetic medications are also associated with CRC risk (43, 78, 80, 81, 84, 93, 95, 99, 230-232).

We did not find any significant association with CRC stage and grade. The direction of association was higher among people with shorter duration of diabetes as compared to those with longer duration of diabetes.

However our study did not have information on diabetic medication. The sample size for cancer grade and stage was reduced because of the missing data. With all the limitations, our study, we could determine and confirm the T2DM diabetes status for the participants based on the baseline and supplemental questionnaire. It is still based on self-

report questionnaire data. These self-report data regarding chronic diseases are usually accurate (225-227). Except for medication data, we adjusted for physical activity, obesity, family history of CRC and others that can affect the association between diabetes and CRC. Thus our results are strengthened by adjusting for these confounders. Ours is the first study to adjust for inflammation caused due to diet that has been related to cancer and diabetes. No changes were observed in sensitivity analysis.

To conclude, in our study, we detected an association between duration of diabetes and CRC incidence. For future studies, we can replicate these studies with data consisting information on diabetic medications. It is also important to check the severity of diabetes in addition to duration of diabetes.

BQX (154,897)	SQX	(N=103,758)	Age of diagnosis	(N=12,927 after excluding the missing values)	
Yes (11,529)	Yes	5355	<50 years	1315	Deleted
			50-59 years	2186	
			60-69 years	1364	Used for calculation of duration
	No	300	>70 years	195	
	Missing	191	Missing	295	
No (137494)	Yes	7948	<50 years	143	Deleted
			50-59 years	1214	
			60-69 years	3977	Used for calculation of duration
	No	83,533	>70 years	2180	
	Missing	3940	Missing	434	
Missing (5874)	Yes	372	<50 years	43	Deleted
			50-59 years	86	
			60-69 years	170	Used for calculation of duration
	No	2119	>70 years	54	
	Missing	0	Missing	19	

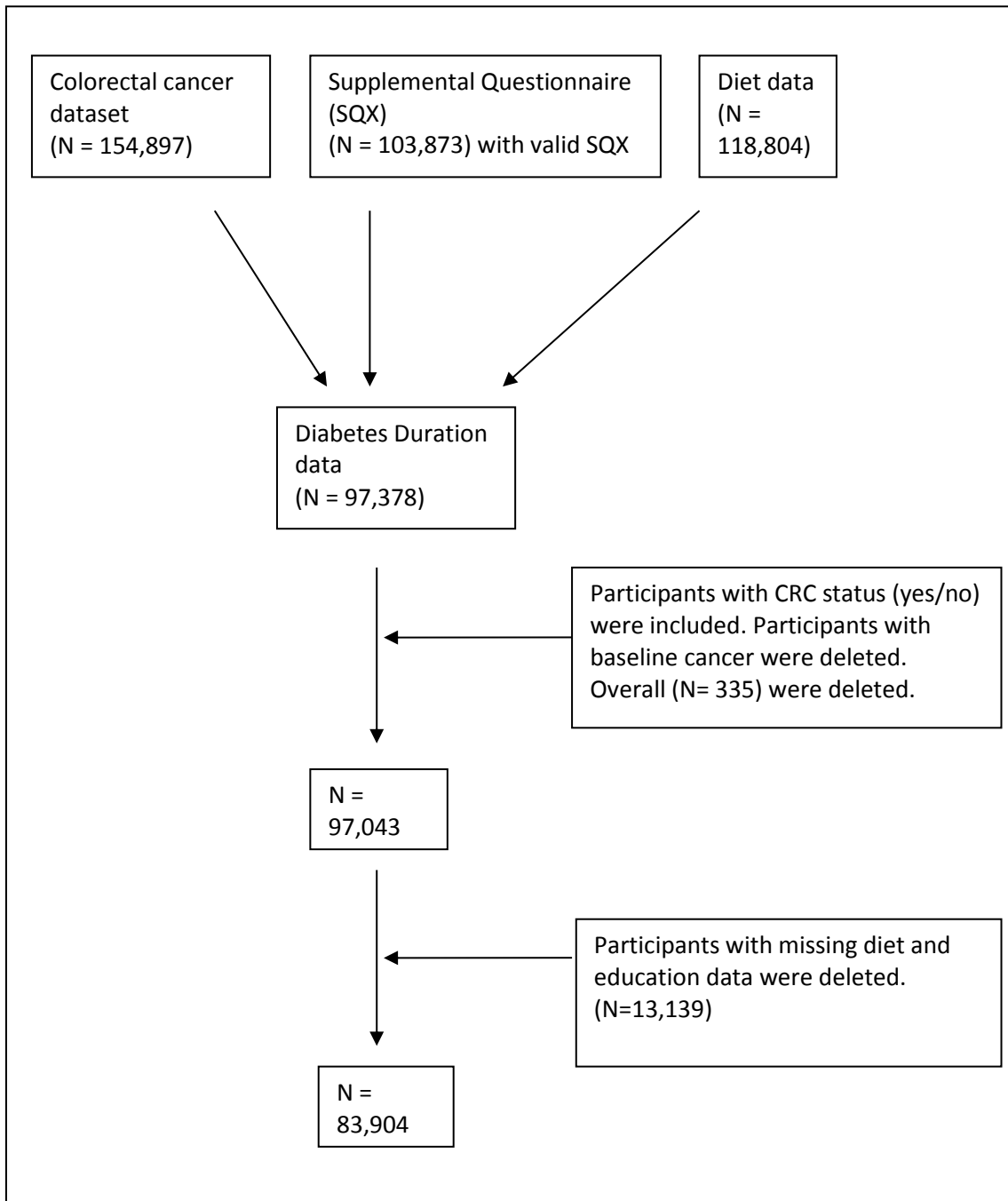Figure 6.1: Sample size used for calculating the diabetes duration

Figure 6.2: Consort diagram for final analytic dataset, PLCO, 1993 to 2009

Table 6.1: Descriptive statistics by diabetes duration, PLCO, 1993 to 2009

	Diabetes duration			
	no diabetes (N=83819)	0-10 years (N=7050)	>10years (N=4052)	p-values
Sex				
Male	45.5	54.9	62.2	<.0001
Female	54.5	45.1	37.8	
Randomization Arm				
Intervention	51.2	51.8	52.4	0.23
Control	48.8	48.2	47.6	
Race				
Non- Hispanic White	92.3	88.0	85.6	
Non- Hispanic Black	2.6	5.2	6.2	<.0001
Others	5.1	6.8	8.2	
Education				
college grad and more	39.4	32.0	32.0	
post high school, some college	34.0	37.0	34.8	<.0001
less than high school	26.6	31.0	33.2	
Employment				
Employed	17.8	15.2	9.5	
Retired	62.2	65.1	73.9	
Unemployed	8.8	7.0	6.2	<.0001
Others	1.7	2.9	1.3	
Missing	9.5	9.8	9.1	
Body Mass Index (kg/m^2)				
Obese	20.5	43.8	42.4	
Overweight	40.6	36.2	36.6	
Normal	33.9	15.0	15.9	<.0001
Underweight	1.0	0.4	0.4	
Unknown	4.0	4.6	4.7	
Cigarette Smoking Status				
Current Cigarette Smoker	6.5	6.1	5.3	
Former Cigarette Smoker	45.4	50.8	51.5	<.0001
Never Smoked Cigarettes	46.7	41.7	41.5	
Missing	1.4	1.4	1.7	

	Diabetes duration		
	no diabetes (N=83819)	0-10 years (N=7050)	>10years (N=4052)	p-values
Family History of Colorectal Cancer				
Yes	10.5	10.6	9.0	
No	77.3	76.5	77.4	<.001
Missing	12.2	12.9	13.6	
Aspirin Intake (at least 1/week)				
More than 20 years	6.6	8.1	8.1	
Less than 20 years	47.2	59.2	61.3	
Less than 1/week	21.7	14.0	12.9	<.0001
None	22.4	16.7	15.1	
Missing	2.0	2.0	2.6	
	**Mean (±std)**		
Age (years)	71.1 (±5.9)	70.9 (±5.8)	73.5 (±5.3)	<.0001
DII	-1.3 (±2.3)	-1.0 (±2.3)	-1.4 (±2.2)	<.0001

Table 6.2: HR (95%CI) for CRC incidence by diabetes duration, PLCO, 1993 to 2009

CRUDE MODEL		HR	95%CI
diabetes duration	> 10 years vs no diabetes	1.69	(1.34, 2.13)
	<=10 years vs no diabetes	1.27	(1.03,1.56)
ADJUSTED MODEL			
diabetes duration	>10 years vs no diabetes	1.37	(1.06,1.77)
	<=10 years vs no diabetes	1.13	(0.89,1.42)

adjusted for gender, age, screening arm, employment status, race, education, aspirin use, smoking status, family history of CRC, DII and physical activity

Table 6.3: OR (95%CI) for cancer aggressiveness – stage by duration of diabetes

		OR	95% CI
Diabetes duration	> 10 YEARS vs no diabetes	0.79	(0.46,1.38)
	<= 10 YEARS vs no diabetes	1.12	(0.71,1.78)

Table 6.4: OR (95%CI) for cancer aggressiveness – grade by duration of diabetes

		OR	95% CI
Diabetes duration	> 10 YEARS vs no diabetes	0.73	(0.37,1.46)
	<= 10 YEARS vs no diabetes	0.94	(0.54,1.70)

Models adjusted for gender, intervention arm, race, education, BMI, age, aspirin-intake, and smoking status and physical activity

CHAPTER 7

SUMMARY

We conducted this study with the aim of understanding the association between diabetes and cancer. A lot of previous studies have evaluated this association. However most of these studies are conducted in the western world (developed world). None of these studies were conducted in India. Therefore we began studying this association in an Indian population. Diabetes is fast gaining the status of an epidemic in India. Additionally, with the current stage of economic, nutritional and epidemiologic transition phase, it becomes even more important to understand this association in India. Besides this, the existing literature in the developed countries has mentioned a probability of detection bias as being one of the reasons in the association. Through our second question we evaluated this association in a longitudinal screening trial conducted in the US population, considering all the important available potential confounders. With our third aim we tried to determine the association between diabetes duration and CRC cancer incidence and aggressiveness.

Process of working on dissertation

To begin the dissertation process, my advisor Dr. Hebert, guided and suggested me to use the Mumbai Cohort Study. This study was started in Mumbai in 1993 and Dr. Hebert was one of the Co-PIs. We initially aimed as assessing the role of diabetes and

CRC incidence in MCS. However, due to the extremely small sample size of the incident cases, we decided to change the question and determine the association with cancer incidence. For the US study we used the Prostate Lung Colorectal Ovarian screening trial (PLCO). The PLCO questionnaires included all the important covariates and medical history information that we needed for our analysis. It also included information on the age at diagnosis of diabetes in of the questionnaires that would be helpful for our third analysis.

Problems faced and things learnt along the way

Although both these databases are longitudinal studies with a huge overall sample sizes, there were some common data cleaning problems that we faced in the process of getting the final datasets ready for our analysis. The MCS had a lot of missing data for our main exposure variable i.e. diabetes. Besides this, it took some time to come to a conclusion regarding variable coding, addressing missing data etc. However while going through this process, all my committee members helped me in coming to the correct decision for our study. Additionally as the missing diabetes data was a lot, we thought of conducting some data manipulation for this data separately and performing a separate analysis for that particular data. Following a committee meeting, we decided to utilize this data in another way by using predicted probabilities method as suggested by Dr. Zhang and agreed by the committee.

Following this, I started working on the PLCO data. We had similar questions for this study regarding the missing data and fixing the inclusion/ exclusion criteria. Following this the most difficult part of the third question was the calculation of the

diabetes duration variable. We had information on the age at diabetes diagnosis, however it was a (range) categorical variable. Some of the data did not add up to the final numbers. With Dr. Liese and Dr. Hebert's ideas and suggestions, we were finally able to derive the variable duration of diabetes.

We also aimed at understanding the role of dietary inflammatory index in this association as inflammation is one of suggested underlying process leading to the association between diabetes and cancer. However this data was only available in the PLCO data. To utilize the DII data more appropriately, we need to conduct further detailed analysis and determine its role in the association. This will be one of the questions I would like to address in details for future analysis. Additionally, we will replicate the data using other databases consisting of the medical history data too. Using the available information we finally completed our analysis.

Things learnt

Initially, I had a lot of anxiety in meeting with my committee members. Slowly, I developed confidence in my work and started having regular meeting with my professors. In my weekly meeting with Dr. Hebert, again slowly but eventually, I learnt new things and got new ideas regarding not only my PhD process but my future goals too. One thing that I worked on and am still in the process of working on is being assertive and managing time properly as guided by Dr. Hebert.

In my experience every time I had problem with the data or with the analysis, it took me time to restart the process. Therefore it is very important to stay encouraged, as it is very simple to get discouraged that's slows down the process.

PhD is a learning process and it also needs a lot of patience and that is definitely one of the other things I have developed over time. I have started being less anxious and stressed out and being more focused and positive about the work I do. My advisor helped me in thinking clearly and supported me throughout the process. Additionally my other committee members also encouraged me throughout my dissertation work.

In my opinion, staying positive is one of the keys to finishing things on time.

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