Association Between Obesity and Cancer Mortality: An Internal Medicine Outpatient Clinic Perspective

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Abstract

Background: Obesity is one of the leading preventable causes of cancer that has a causal relationship with cancers of esophagus, breast and colon. Paradoxically, there are studies demonstrating that obesity is associated with improved survival in cancer patients. The aim of our study was to investigate the association of obesity and cancer mortality in adult patients.

Methods: Retrospective medical record review of 784 adult patients who had a diagnosis of cancer and who were seen in our outpatient Internal Medicine Clinic between January 1, 2019 and December 31, 2019.

Results: Forty-three (5.2%) patients were cancer non-survivors and 741 (94.8%) were cancer survivors. The mean age of the cancer non-survivors group was significantly higher than that of the cancer survivors (78.7 vs. 68.0 years, respectively; P < 0.001). For every unit increase in age, there was 7.6% increased odds of cancer death (95% confidence interval (CI): 3-12%) (P = 0.001). Average body mass index (BMI) of the patients in the cancer non-survivors group was significantly lower than that of the cancer survivors group (25.0 vs. 28.1 kg/m\textsuperscript{2}; P = 0.008). Non-obese patients had 4.9 times greater odds of cancer death (95% CI: 1.51 - 15.81) (P = 0.008). The mean glycated hemoglobin (HbA1c) was significantly higher in the cancer non-survivors group compared to the cancer survivors group (7.1% vs. 6.0%; P < 0.001), and for every unit increase in HbA1c there was 1.6 times greater odds of cancer death (95% CI: 1.14 - 2.23) (P = 0.006). Patients with peripheral artery disease (PAD) had 3.5 times greater odds of cancer death compared to those without PAD (95% CI: 1.18 - 10.19) (P = 0.023).

Conclusions: Non-obese patients with cancer had higher odds of cancer death. Rising HbA1c, increasing age, and presence of PAD were associated with increased cancer mortality.

Keywords: Obesity; Cancer mortality; Obesity paradox

Introduction

Obesity is an important public health concern that currently affects 42.4\% of adults in the USA [1, 2]. The Center for Disease Control and Prevention (CDC) uses body mass index (BMI) as an indirect measure of body fatness given its correlation with other direct measurements, and defines overweight as a BMI of 25.0 - 29.9 kg/m\textsuperscript{2} and obesity as a BMI $\geq$ 30.0 kg/m\textsuperscript{2} [3]. The consequences of obesity are well known, which contribute to a wide spectrum of disease states that include diabetes mellitus, end-stage renal disease, coronary artery disease and even cancer [4]. With regard to cancer, obesity is becoming one of the leading preventable causes of cancer and it has been shown to have a causal relation in malignancies such as adenocarcinoma of the esophagus, breast cancer and colon cancer [5]. On the other hand, there has been a lack of consensus on the association between obesity and cancer mortality [4, 6, 7]. For instance, in a prospective study by Calle and associates, there was a significant association between BMI and rates of death, estimating that in the USA, obesity and overweight account for 14\% and 20\% of deaths, respectively among men and women who suffer from cancer [8]. Elevated BMI was specifically associated with death by cancer of the esophagus, pancreas and multiple myeloma [8, 9]. Schmitz and associates explained that there were no clear mechanisms for the association, but potential causes include cancer treatment toxicities that vary with obesity and growth factors that are expressed on malignant cells, and are believed to be increased in the obese subjects [8, 9].

Interestingly, there are emerging studies demonstrating that obesity is associated with improved survival in cancer patients, and this finding is termed as “obesity paradox” [7, 10]. For instance, the COMPARZ trial found that obese patients with clear cell renal cell carcinoma had a lower mortality than patients who were of normal weight [11]. This relationship has also been appreciated in other malignancies such as lung...
cancer and melanoma [10, 12]. In a review by Trestini and associates, some of the proposed mechanisms for this effect are proposed as obesity can be associated with less aggressive tumor subtypes and lower-stage disease [13]. Given the complex interaction between obesity and cancer, the American Clinical Society on Oncology (ASCO) is advocating for the increase in education and research on overweight-obesity and cancer [4]. Overall, there is lack of consensus regarding the effect of overweight and obesity on cancer mortality. The aim of our study was to investigate the association of obesity and cancer mortality in adult patients.

Materials and Methods

Study selection

This study was a retrospective study of patients with a diagnosis of cancer who were seen in our outpatient clinic between January 1, 2019 and December 31, 2019. The study was reviewed and approved by the Institutional Review Board of the Cooper University Health Care, Camden, New Jersey, USA. This study was fully compliant with the ethical standards set forth by the CUHC institutional review board. The inclusion criteria were patients aged 18 years or older who had a diagnosis of cancer.

Data collection

The data were collected by reviewing the existing electronic medical records of our patients who fulfilled the selection criteria. The following data were collected for each patient: age, gender, BMI, type of cancer (breast, colon, prostate, gynecological and other types), race (non-Hispanic, Caucasian, African American, Alaskan native, American Indian, Asian, Hispanic, Pacific islander, and other), cigarette smoking history (current or former use), alcohol use, recreational drugs use, family history (obesity, cancer and type of cancer), associated medical conditions (hypertension, diabetes mellitus (DM), hyperlipidemia, hypothyroidism, coronary artery disease (CAD), cerebral vascular disease, peripheral vascular disease, carotid artery stenosis, congestive heart failure (CHF), arthritis and other rheumatologic disorder), psychiatric conditions, glycosylated hemoglobin (HbA1c), and living status (survivor or non-survivor).

The majority of our patients received their cancer care outside our healthcare system. The details of their cancer staging and management were not linked with our electronic medical records, hence the data were not available to us. We had to rely on the scanned reports of the consultant oncologists from various healthcare systems which varied widely based on the patient-specific cancer care needs, and lacked many details, such as consistent staging, symptoms of loss of appetite, treatments other than chemotherapy, radiotherapy or surgery, as well as follow-up course. In order to mitigate the influence of such factors on the BMI, for each patient we collected the average BMI out of the preceding 5-year BMIs documented in our electronic medical record.

Statistical analysis

All of the collected data were entered into a Microsoft Excel (2016, Remond, Washington, USA) spreadsheet. Statistical analysis was done by using SPSS (Statistical Package for the Social Sciences, version 15.01, IBM, Armonk, New York, USA). We calculated an approximate sample size of 784 patients based on the calculation of the approximate number of patients with a diagnosis of cancer who visited our outpatient office during the previous 12 months.

The patients were divided into two groups: first group represented the patients with cancer who were cancer non-survivors, and the second group represented patients who were cancer survivors. Unifactorial analysis was conducted by applying independent t-tests to compare the means of continuous variables between the study groups. Chi-square tests were used to compare the categorical (dichotomous) variables between the study groups. For multifactorial analysis, we used logistic regression. The model was used to examine the relationship between the variable of interest (obesity) and the dependent variable (cancer mortality) after adjusting (or controlling) for other independent variables that may also be related to the outcome (confounding factors or covariates). In this study, significance was defined as a P < 0.05.

Results

A total of 784 patients were included in the study. These comprised of 43 patients (5.2%) who were deceased at the time of chart review hence grouped as cancer non-survivors and 741 patients (94.8%) who were cancer survivors. The age range for all patients was between 21 and 99 years. The mean age of the cancer survivors group was 68.0 years and the mean age of the cancer non-survivors patient group was 78.7 years (Table 1). The difference between both groups of patients was statistically significant (P < 0.001). Multivariate analysis revealed that for every unit increase in age, there was 7.6% increased odds of cancer death (95% confidence interval (CI): 3.1-12%) (P = 0.001) (Table 2).

In gender analysis, the difference between both cancer non-survivors and cancer survivors groups was significant (P = 0.019), with the cancer non-survivors group having more males than females (53.5% vs. 46.5%), whereas the cancer survivors group had more females than males (64.2% vs. 35.8%). However, gender did not have significant influence on mortality in our patient population (Table 2). The breakdown of races was similar between the cancer non-survivors group and the survivors group, with White race being the majority (76.7% vs. 68.7%), followed by other races (11.6% vs. 18.9%), Black race (9.3% vs. 8.5%) and Hispanic race (2.3% vs. 3.9%) (Table 1). There was no significant difference between both groups with regard to race (P = 0.606). About half of the patients in both the groups had history of cigarette smoking or alcohol use, but the differences were not statistically different (Table 1).

The breakdown of cancer types between both groups was also similar (Fig. 1). In the cancer non-survivors group, frequency of breast cancer was 11.6%, followed by colorectal
cancer 9.3%, prostate cancer 14%, gynecological cancer 2.3% and other cancers 62.8%. In the survivors group, frequency of breast cancer was 24.4%, followed by colorectal cancer 5.7%, prostate 13.2%, gynecological cancer 7.4% and other cancers 49.3%. Although the frequency of breast cancer was higher in the cancer survivors group compared to the cancer non-survivors group, the differences in the frequencies of various cancers between the two groups were not statistically significant (Table 1).

We found that the frequencies of arthritis, hypertension, hyperlipidemia, other rheumatologic disorders, hypothyroidism, depression and anxiety were greater in the cancer non-survivors group compared to the cancer survivors group, but the differences were not statistically significant (Table 1). However, for other comorbid conditions, there were statistically significant differences between the groups, but the comorbid condition did not have any effect on the cancer mortality. For instance, there was a higher frequency of cerebral vascular accidents (CVAs) in the cancer non-survivors group compared to the cancer survivors group (14% vs. 4.9%, \( P = 0.023 \)) (Table 1); however, multivariate analysis revealed that CVA did not have a significant effect on cancer mortality (Table 2). Similarly, the frequencies of association of DM, CAD and CHF were significantly higher in the cancer non-survivors group compared to the cancer survivors group (41.9% vs. 20.6%, \( P = 0.015 \); 27.9% vs. 14.3%, \( P = 0.015 \); and 20.9% vs. 5.5%, \( P = 0.001 \)), but these comorbidities had no effect on cancer mortality (Table 2). Interestingly, we found that the frequency of peripheral artery disease (PAD) was significantly higher in the cancer non-survivors group (23.3%) compared to the cancer survivors group (4.2%) (\( P < 0.001 \)) (Table 1). Multivariate analysis showed that the patients with PAD had 3.5 times greater odds of cancer death (95% CI: 1.18 - 10.19) compared to those without PAD (\( P = 0.023 \)) (Table 2).

Analysis of family history of cancers revealed that the frequencies of breast cancer, prostate cancer, gynecological cancer and other cancers were not significantly different between the two groups. For family history of colorectal cancer, we found that the cancer survivors group had a significantly higher frequency of association compared to the cancer non-survivors group (17.5% vs. 4.7%) (\( P = 0.028 \)) (Table 1); however, multivariate analysis showed that it did not have an effect on cancer mortality (Table 2).

As mentioned earlier, we found a statistically significant difference in frequency of association between DM in the cancer non-survivors group compared to the cancer survivors group. Although DM by itself had no effect on the cancer mortality (Table 2), the mean HbA1c was significantly higher in the cancer non-survivors group compared to the cancer survivors group (7.1% vs. 6.0%, \( P < 0.001 \)) (Table 1) and for every unit increase in HbA1c, there was 1.6 times greater odds of cancer death (95% CI: 1.14 - 2.23) (\( P = 0.006 \)) (Table 2).

In the assessment of overweight and obesity, we found that the average BMI of the patients in the cancer non-survivors group was significantly lower than that in the cancer survivors group (25.0 vs. 28.1 kg/m²) (\( P = 0.008 \)) (Table 1). The frequencies of patients in each BMI category also differed significantly (Fig. 2). Multivariate analysis showed that non-obese patients had 4.9 times greater odds of cancer death (95% CI: 1.51 - 15.81) (\( P = 0.008 \)) (Table 2).

**Discussion**

The major finding of our study was that the non-obese patients with cancer had higher odds of cancer death. Our findings are supported by the findings of many studies [14-20] that have documented that among patients with cancer, elevated BMI is associated with improved survival compared to the patients who had normal BMI. Hines and associates found that in patients with colon cancer, being overweight increased the risk of death; however, being overweight and obese was protective [14]. Navarro and associates studied the role of high-dose therapy with autologous hematopoietic cell transplantation in patients with lymphoma. They reported that the overall mortality was higher in the overweight group, and lower in the overweight and obese groups compared with the normal BMI group [15]. Parker and associates found that the overweight patients with renal cell carcinoma were at a reduced risk of death compared with patients with BMI in the normal range [16]. A meta-analysis of colorectal cancer survivors conducted by Schlesinger and associates concluded that patients with BMI in the underweight category were at an increased risk for all-cause mortality, whereas patients who were overweight had a lower risk, compared to the patients who were in the normal BMI range [17]. Similarly, Tsang and associates studied the association between BMI and overall survival in patients with distant metastases and who had favorable performance status. They found that the median overall survival time was 3.23 months for underweight patients, 6.08 months for normal weight patients, 7.99 months for overweight patients, and 12.49 months for obese patients. In their study they also found that compared with normal weight patients, both obese and overweight patients had a reduced risk of all-cause mortality [20].

There have been several postulations to explain this phenomenon. One such explanation is that some tumors are less aggressive in obese patients such as renal cell carcinoma, where obesity is associated with more indolent forms of tumor characteristics [21]. Another potential explanation is that obese patients have altered pharmacokinetics to treatment regimens and they respond differently to certain surgeries, both resulting in improved outcomes [22, 23]. It is also possible that obesity plays a role in having a “nutrient reserve” and patients experience a mortality benefit [7]. Although BMI has been implicated as a poor proxy for estimation of body adipose tissue and composition [24], it correlates positively with waist circumference, and negatively with mortality [25]. BMI also has an inverse association with the expression of fatty acid synthase (FASN) [20], an oncogene that is involved in the fatty acid synthesis, and found to be overexpressed in several malignancies. It has been reported that FASN is significantly downregulated in obese patients with renal cell carcinoma offering favorable effects on cancer-specific survival [21]. Additionally, muscle wasting negatively impacts BMI. It is a common feature of aging. In our study, we did find that with every unit increase
Table 1. Baseline Characteristics

| Variable                  | Cancer non-survivors (N = 43) | Cancer survivors (N = 741) | P     |
|---------------------------|-------------------------------|---------------------------|-------|
| Age, mean (SD)            | 78.7 (11.8)                   | 68.0 (13.5)               | < 0.001|
| Gender                    |                               |                           |       |
| Male (n, %)               | 23 (53)                       | 265 (35.8)                | 0.019 |
| Female (n, %)             | 20 (46)                       | 476 (64.2)                |       |
| Race                      |                               |                           |       |
| White (n, %)              | 33 (76.7)                     | 509 (68.7)                | 0.606 |
| Black (n, %)              | 4 (9.3)                       | 63 (8.5)                  |       |
| Hispanic (n, %)           | 1 (2.3)                       | 29 (3.9)                  |       |
| Other (n, %)              | 5 (11.6)                      | 140 (18.9)                |       |
| Social factors            |                               |                           |       |
| Cigarettes (n, %)         | 23 (53.5)                     | 303 (40.9)                | 0.103 |
| Alcohol (n, %)            | 21 (48.0)                     | 426 (57.5)                | 0.265 |
| Cancer type               |                               |                           |       |
| Breast cancer (n, %)      | 5 (11.6)                      | 181 (24.4)                | 0.152 |
| Colorectal cancer (n, %)  | 4 (9.3)                       | 42 (5.7)                  |       |
| Prostate cancer (n, %)    | 6 (14.0)                      | 98 (13.2)                 |       |
| Gynecological cancer (n, %)| 1 (2.3)                        | 55 (7.4)                  |       |
| Other cancer (n, %)       | 27 (62.8)                     | 365 (49.3)                |       |
| Comorbidities             |                               |                           |       |
| HTN (n, %)                | 32 (74.4)                     | 442 (59.8)                | 0.650 |
| Diabetes mellitus (n, %)  | 18 (41.9)                     | 152 (20.6)                | 0.015 |
| Hyperlipidemia (n, %)     | 29 (67.4)                     | 432 (58.3)                | 0.236 |
| Hypothyroidism (n, %)     | 10 (23.3)                     | 151 (20.4)                | 0.650 |
| CAD (n, %)                | 12 (27.9)                     | 106 (14.3)                | 0.015 |
| CVA (n, %)                | 6 (14.0)                      | 36 (4.9)                  | 0.023 |
| PAD (n, %)                | 10 (23.3)                     | 31 (4.2)                  | < 0.001|
| CAS (n, %)                | 1 (2.3)                       | 23 (3.1)                  | 1.000 |
| CHF (n, %)                | 9 (20.9)                      | 41 (5.5)                  | 0.001 |
| Arthritis (n, %)          | 15 (34.9)                     | 199 (26.9)                | 0.251 |
| Rheumatologic disease (n, %)| 5 (11.6)                   | 60 (8.1)                  | 0.391 |
| Depression (n, %)         | 8 (18.6)                      | 121 (16.3)                | 0.696 |
| Anxiety (n, %)            | 10 (23.3)                     | 158 (21.3)                | 0.794 |
| Family history            |                               |                           |       |
| Breast cancer (n, %)      | 6 (14.0)                      | 205 (27.7)                | 0.051 |
| Colorectal cancer (n, %)  | 2 (4.7)                       | 130 (17.5)                | 0.028 |
| Prostate cancer (n, %)    | 2 (4.7)                       | 78 (10.5)                 | 0.802 |
| Gynecological cancer (n, %)| 2 (4.7)                        | 66 (8.9)                  | 0.573 |
| Other cancer (n, %)       | 16 (37.2)                     | 303 (40.9)                | 0.633 |
| Other parameters          |                               |                           |       |
| BMI, mean (SD)            | 25.0 (5.0)                    | 28.1 (6.4)                | 0.008 |
| HbA1c, mean (SD)          | 7.1 (2.4)                     | 6.0 (0.9)                 | < 0.001|

SD: standard deviation; HTN: hypertension; CAD: coronary artery disease; CVA: cerebrovascular accident; PAD: peripheral artery disease; CAS: carotid artery stenosis; CHF: congestive heart failure; BMI: body mass index; HbA1c: glycosylated hemoglobin.
in age, there was 7.6% increased odds of cancer death in our patients. Muscle wasting is also associated with distant metastasis, treatment toxicities, and mortality [26-29]. Although the exact mechanism remains unclear but increased levels of pro-inflammatory interleukin 6 (IL-6) have been associated with muscle wasting and low BMI [30, 31]. Studies have shown that increased levels of IL-6 activate pro-inflammatory and angiogenic factors that drive and promote tumorigenesis [32]. Increased levels of IL-6 also trigger epithelial mesenchymal transformation in breast cancer cells, which promote distant metastasis [33]. To summarize, several studies have reported the “obesity paradox” where the mortality benefit had been seen in patients who were overweight or obese [7, 10] which further support our findings of the higher odds of cancer deaths

Table 2. Influence of Risk Factors on Cancer Mortality

| Risk factor          | B   | P    | Exp(B) | Lower | Upper |
|----------------------|-----|------|--------|-------|-------|
| Age (years)          | 0.073 | 0.001 | 1.076  | 1.030 | 1.124 |
| Gender               | 0.275 | 0.552 | 1.317  | 0.532 | 3.256 |
| Non-obese           | 1.587 | 0.008 | 4.889  | 1.511 | 15.810 |
| HbA1c               | 0.466 | 0.006 | 1.594  | 1.140 | 2.230 |
| Family history of CRC | 0.801 | 0.307 | 2.228  | 0.478 | 10.375 |
| DM                  | 0.195 | 0.711 | 1.215  | 0.434 | 3.402 |
| CAD                 | 0.089 | 0.862 | 1.093  | 0.402 | 2.973 |
| CVA                 | 0.561 | 0.397 | 1.753  | 0.479 | 6.417 |
| CHF                 | 0.601 | 0.579 | 2.651  | 0.892 | 7.866 |
| PAD                 | 1.247 | 0.023 | 3.480  | 1.188 | 10.190 |

CI: confidence interval; HbA1c: glycosylated hemoglobin; CRC: colorectal cancer; DM: diabetes mellitus; CAD: coronary artery disease; CVA: cerebrovascular accident; CHF: congestive heart failure; PAD: peripheral artery disease.

Figure 1. Frequencies of types of cancers.
Our findings contrast with the findings of several studies that have suggested that a higher BMI increases the incidence of cancers [34-36], particularly in the highest weight category (class III: BMI $\geq 40$ kg/m$^2$) [8]. Calle and associates reported an increase in mortality associated with obesity in patients with all cancers, and especially for the esophageal cancer, colorectal cancer and breast cancer [8]. It is possible that relationships between obesity and cancer mortality differ with tumor site. In our study, in the cancer non-survivors group, approximately 20% of the patients had breast cancer while the majority of patients had other cancers that included malignancies, such as lung cancer, basal cell carcinoma, melanoma, etc. Interestingly, Taghizadeh and associates found no significant association between long-term annual change in BMI and cancer mortality risk, while both short-term annual increase and decrease in BMI were associated with a lower mortality risk from any cancer [37]. They also reported a lower risk of mortality from lung cancer among overweight subjects, especially males. There are several studies that have consistently found an inverse association between BMI and cancer mortality and suggested that this association is independent of smoking and weight loss because of preclinical disease [38-41].

In our study, with each year increase in age, there was a 7.6% increase in odds of cancer death. Several studies have investigated the effect of age on specific malignancies, and the data are consistent with the fact that increasing age confers a worse prognosis. For instance, when considering breast cancer, a prospective study showed that increasing age was associated with higher cancer mortality [42]. In other studies, the same relationship was seen in liver cancer and cervical cancer [43, 44]. Furthermore, the CDC performed a study in which information was collected by the CDC’s National Center for Health Statistics which used death certificates from all 50 states in the USA [17]. The study found an upward trend in death rate (defined as deaths per 100,000 population) with the increase in the age group [45]. Our findings correlate with the findings from the CDC and by other studies. In a study by Pal and associates, there were some proposed mechanisms for these findings, such as decreased physiological reserve that include changes to renal and gastric function in elderly patients. Also, in patients who developed a malignancy in older age, the cancer characteristics could have been associated with worse outcomes [46].

Figure 2. Frequencies of patients in each BMI category. BMI: body mass index.
In our patient group, the diagnosis of diabetes was significantly higher in the cancer non-survivors group compared to the cancer survivors group. Similarly, the mean HbA1c level was significantly higher in the cancer non-survivors group compared to the cancer survivors group, and for each unit increase in HbA1c, there was 1.6 times greater odds of cancer death (95% CI: 1.14 - 2.23). Our findings correspond with the study conducted by Harding and colleagues, in which they showed that cancer patients with diabetes had a 30% higher rate of cancer mortality than non-diabetic cancer patients [47]. In another study, Currie and colleagues found that cancer mortality was increased in those with diabetes, compared with those without (hazard ratio (HR): 1.09 (95% CI: 1.06 - 1.13)). They also found that the mortality was particularly increased in patients with breast cancer (1.32 (1.17 - 1.49)) and prostate cancer (1.19 (1.08 - 1.31)). After controlling for the confounding factors, they reported that diabetes was associated with approximately 10% increase in the mortality for all cancers compared to those without diabetes. Their prognosis estimation in patients with diabetes revealed that bladder, breast, and prostate cancers were associated with significantly diminished survival [48]. Interestingly, the management of diabetes in patients with cancer can have an impact on the type of cancer and survival, as well. It has been reported that patients managed with insulin, or insulin secretagogues, were found to be more likely to develop solid cancers than those managed with metformin alone [49]. Xiu and colleagues investigated the impact of diabetes on the progression-free survival and overall survival of extensive-stage small-cell lung cancer. They reported that the mean progression-free survival of patients without diabetes was 9 months, while it was significantly reduced for patients with diabetes (5 months (P < 0.0001)). They also reported that the overall survival of patients with diabetes was significantly shorter than that of patients without diabetes (HR: 1.455; 95% CI: 1.134 - 1.868; P = 0.003) [50]. Kelkar and colleagues investigated the association between diabetes and prostate cancer-specific mortality. They found that diabetes was associated with increased risks of prostate cancer progression and mortality among obese men [51]. Similarly, Wu and colleagues reported that long-term plasma glucose fluctuation was significantly associated with the risk of cancer mortality (HR: 1.41 (95% CI: 1.04 - 1.92)), especially in the highest quartile of coefficient of variation of plasma glucose [52]. This finding aligns with our observation that with each unit increase in HbA1c there was 1.6 times greater odds of cancer death (95% CI: 1.14 - 2.23). Additional studies have also reported that the increased mortality associated with poorly managed diabetes has been particularly appreciated in specific malignancies, such as colorectal cancer and breast cancer [53, 54]. The exact relationship between diabetes and cancer mortality remains to be fully understood, but uncontrolled diabetes may have a direct effect on tumorigenesis, and indirect effects, such as influence of diabetes in medical decision making [53, 54]. Other possible mechanisms include less aggressive treatment in diabetic patients, poor response to treatment, and an increased risk of adverse events due to the treatment [55, 56].

We also found that PAD was associated with an increase in cancer mortality, with the odds of cancer death being 3.5 times higher than patients without peripheral vascular disease. A similar report was published by Fiotti and associates, in which they found that the patients with PAD had a higher long-term mortality rate, and mortality rate from cancer exceeded that of cardiovascular diseases [57]. According to Yannoutsos and colleagues, and many other studies, the epidemiological evidence confirms that PAD is a marker for the development of lung cancer, independent of age [58-63]. Similarly, Kaschwich and colleagues found that patients suffering from symptomatic PAD had a markedly higher risk for incident cancer in the long-term follow-up, especially for certain types of cancers, such as cancer of the lung, bladder, pancreas, and colon [64]. Sundboll and colleagues examined cancer risk and prognosis of cancer in patients with lower limb PAD and arterial thrombosis. They reported that the risk of any cancer was 2.5% after 6 months of follow-up, which increased to 17.9% after 20 years [65]. Since cigarette smoking happens to be the common risk factor for many cancers, such as cancer of lung, head and neck, esophagus, stomach, liver, colon, pancreas, kidney, bladder, ovary, uterine cervix and myeloid leukemia, the association of PAD can be an indirect evidence of presence of cancer and overall influence on mortality. In our study, we found no significant difference in cigarette smoking between the cancer survivors and cancer non-survivors; hence we believe that the association of PAD in increased cancer mortality is a unique finding of our study.

The major strength of our study is a relatively large sample size of patients with cancer from one office location who were followed with the same small group of healthcare providers, which allowed proper documentation of cancers, comorbid conditions, mortality and other variables in the electronic medical record. The major limitation of our study was a small sample size of the cancer non-survivors which limited further analysis of BMI class on obesity. As seen in Figure 1, there were no patients in the cancer non-survivors group in the highest BMI class, as a result, we could not study the effect of increasing BMI on cancer mortality. Additionally, our patient selection limited to a suburban outpatient population limits generalization.

**Conclusion**

We found that non-obese patients with cancer had higher odds of cancer death. We also found that rising HbA1c, increasing age, and presence of PAD were associated with increased cancer mortality.

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**Financial Disclosure**

None to declare.
Conflict of Interest

None to declare.

Informed Consent

Not applicable. Being a retrospective chart review study the Institutional Review Board waived the need for informed consent.

Author Contributions

VR and SR made substantial contributions to the study design, drafting, data acquisition and analysis, and manuscript writing. All authors contributed in data collection and manuscript writing. KH analyzed the data. SR contributed in revising the manuscript critically for improved intellectual content, and final approval for the version to be published.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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