The Impact of Obesity on Tumor Glucose Uptake in Breast and Lung Cancer

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Abstract

Obesity confers an increased incidence and poorer clinical prognosis in more than 10 cancer types. Paradoxically, obesity may provide protection from poor outcomes in lung cancer. Mechanisms for the obesity-cancer links are not fully elucidated, with altered glucose metabolism being a promising candidate. Using 18F-fluorodeoxyglucose positron-emission-tomography/computed tomography images from The Cancer Imaging Archive, we explored the relationship between body mass index (BMI) and glucose metabolism in several cancers. In 188 patients (BMI mean [SD] = 27.7 [5.1], range = 17.4–49.3 kg/m^2), higher BMI was associated with greater tumor glucose uptake in breast cancer ($r = 0.36$; $P = .02$) and with lower tumor glucose uptake in non-small cell lung cancer ($r = -0.26$; $P = .048$) using two-sided Pearson correlations. No relationship was observed in soft tissue sarcoma or squamous cell carcinoma. Harnessing the National Cancer Institute's open-access database, we demonstrate altered tumor glucose metabolism as a potential mechanism for the detrimental and protective effects of obesity on breast and lung cancer, respectively.

Obesity, currently affecting 35–40% of adults in the United States (1), is correlated with an increased incidence and poorer clinical outcomes in more than 10 different types of cancer (2). The mechanisms underlying the obesity-associated cancer risk are currently not well defined, but altered glucose metabolism is characteristic of both increased body mass index (BMI) (3) and cancer (4–7). Distinct metabolic mechanisms exist between tumor types at the cellular level (8,9). Epidemiologic data allude to differences at the population level: obesity is detrimental in many cases (10) but seemingly protective in lung cancer (11).

As a tumor's avidity for glucose underlies the use of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT), we used PET and CT images to examine tumor glucose metabolism in patients with four cancer types: head and neck squamous cell carcinoma (HNSCC) (12), soft tissue sarcoma (STS) (13), breast cancer (14,15), and non-small cell lung cancer (NSCLC) (16–21). Utilizing the National Cancer Institute-funded open-source database, The Cancer Imaging Archive (TCIA) (22), we performed a retrospective cross-sectional analysis to examine tumor glucose uptake (TGU) in patients with obesity-associated and obesity-independent cancers.

All patients with an ^{18}F-FDG PET/CT scan, sex, height, and weight available from TCIA were studied. All subjects provided informed consent in accordance with each site's institutional review board. If multiple images were available, the earliest PET and CT scan was used to minimize effects of therapy on the tumor. Power analyses for correlation ($\beta = 0.20$ and $\alpha = 0.05$) necessitated a minimum of 29 patients, thus the four tumor types with no less than 29 unique patient PET and CTs were analyzed. Clinical parameters such as tumor stage and medications were unavailable.

PET and CT images were loaded into ImageJ (NIH, Bethesda, MD, USA) with an open source PET-CT Viewer (23), and tissues were analyzed with a fixed-volume approach (24). Briefly, fixed-volume spheres were drawn to measure maximal glucose uptake in tumor, skeletal muscle (deltoid, infraspinatus, or quadriceps), liver, spleen, and subcutaneous and supraclavicular adipose tissue. Standardized uptake values (SUV) were calculated (25). Because BMI alone is related to SUV in obese patients, the Janmahastian Formula was used to calculate and correct for estimated lean body mass (LBM) (26). The primary endpoint was LBM-corrected SUV (SUL) (in g/mL) of tumors, as related to BMI (in kg/m^2). Maximal SUL was chosen to avoid issues from partial volume effects.

Two-sided Pearson correlations were used to measure BMI vs TGU. A two-way ANOVA was used with Tukey multiple comparisons test to examine differences in TGU across cancer types, between tissues, and between sexes. Data were analyzed in GraphPad Prism 7.0 (San Diego, CA, USA), and REMARK
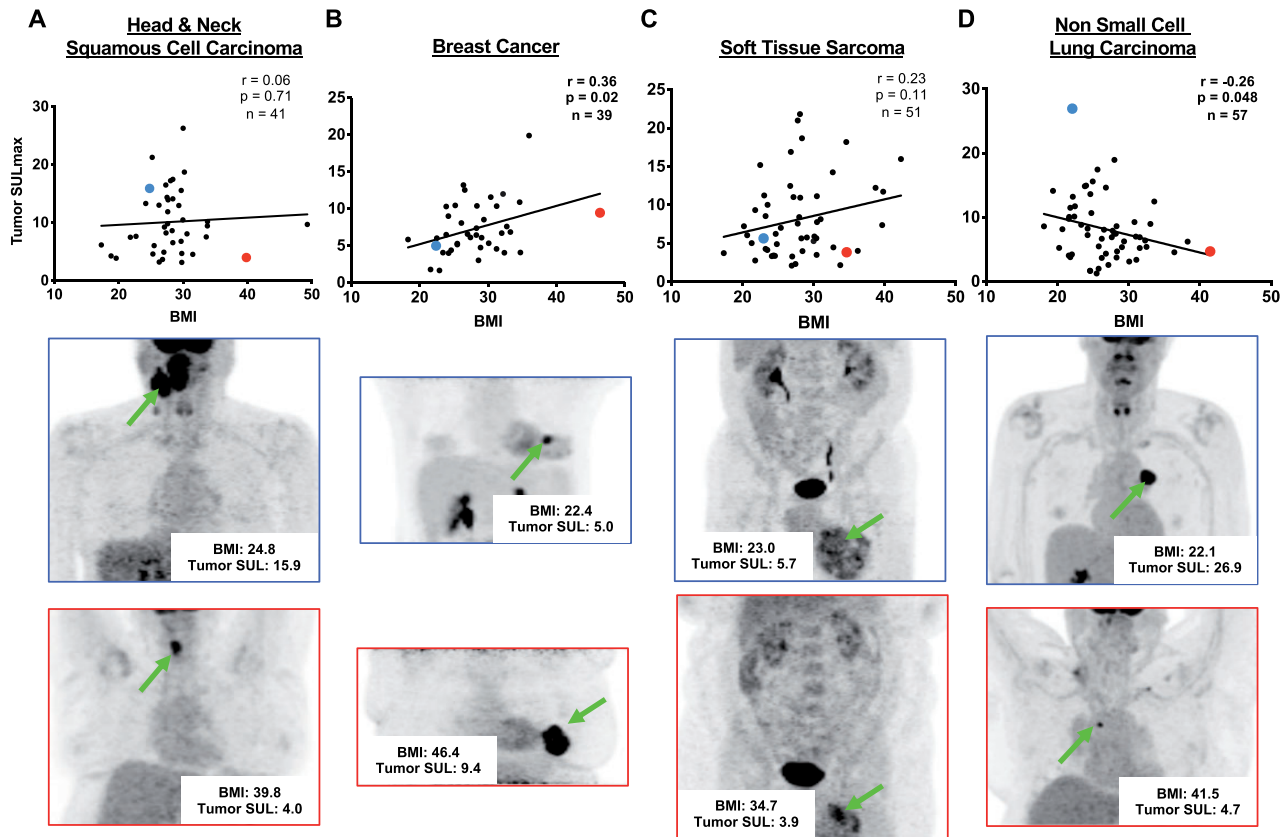
Figure 1. Body mass index vs lean body mass corrected-glucose uptake. Correlations between body mass index (BMI) and lean body mass-corrected maximized standardized uptake value (SULmax) in tumors of (**A**) head and neck squamous cell carcinoma, (**B**) breast cancer, (**C**) soft tissue sarcoma, and (**D**) non-small cell lung carcinoma. A lean representative subject is highlighted in **blue** in the scatter plot, the same subject's maximum intensity projection PET shown beneath with a **blue frame**, and a **green arrow** pointing to the tumor. An obese representative subject is highlighted in the **red** the scatter plot, with his or her maximum intensity projection PET shown beneath with a **red frame**, and a **green arrow** pointing to the tumor. A two-sided Pearson correlation was performed, and statistical significance was determined as P < .05. SUL = standardized uptake value.

reporting guidelines were used where applicable (27). Statistical significance was determined as P values less than .05.

Sex, height, weight, BMI, estimated LBM, and estimated percent body fat (%BF) were reported (Supplementary Table 1, available online). Among 97 women and 91 men, BMI ranged from 17.4% to 49.3 kg/m^2 (mean [SD] = 27.7 [5.1]) and %BF ranged from 11.1% to 55.5%. Many STS PET and CT images were taken from waist down, and some breast cancer images were taken from above L3, thus estimated %BF could not be calculated using the L3 vertebral level method (28).

PET and CT data revealed a positive correlation between BMI and TGU in breast cancer (r = 0.36; P = .02), yet a negative correlation in NSCLC (r = −0.26; P = .048) (Figure 1). In these cohorts, we calculated target to background ratio, where tumor SUV was divided by SUV in the descending aorta. Pearson correlations between target to background ratio and BMI for breast cancer (r = 0.25; P = .13) and NSCLC (r = −0.34; P < .001) were calculated. No statistically significant correlations were seen in HNSCC (r = 0.06; P = .71) or STS (r = 0.23; P = .11) (Figure 1). HNSCC TGU was higher than in breast cancer (P < .001), STS (P < .001), and NSCLC (P = .04) (Figure 2). STS TGU was higher than breast cancer TGU (P = .002) (Figure 2). This may be due to a higher proportion of men in the HNSCC group (17.1% female) and STS group (52.9% female) as compared with the 100% female breast cancer cohort, because men had higher glucose uptake in nearly all tissues (Supplementary Table 2, available online). This observation likely reflects men's higher metabolic rate (29).

Tumor SUV intensity has been used as a surrogate for breast cancer time to progression (30). In the PERCIST guidelines (31), lowered SUV in breast cancer is beneficial, whereas treatment nonresponders show no decline in SUV. Further, recent literature has demonstrated the use of the maximum SUV to predict prognosis of NSCLC, with lower pre- and posttreatment SUV showing improved outcomes (32–34). These data suggest tumor glucose metabolism as a link between obesity's detrimental and protective effects on cancer aggressiveness in breast and NSCLC, respectively.

Our results demonstrate no statistically significant correlation of BMI with TGU in STS (35), but previous reports suggest a weak link between STS severity and obesity (36,37). We detected no correlation between BMI and SUV in HNSCC, supporting a prior study that demonstrates that even in the setting of diabetes, obesity per se is not correlated with HNSCC risk (38). Although our results cannot confirm that TGU is altered by obesity, this study provides a potential explanation for obesity's role in cancer risk and progression in patients with a wide range of BMIs. Yet, the limited sample size may have reduced the power of our study.
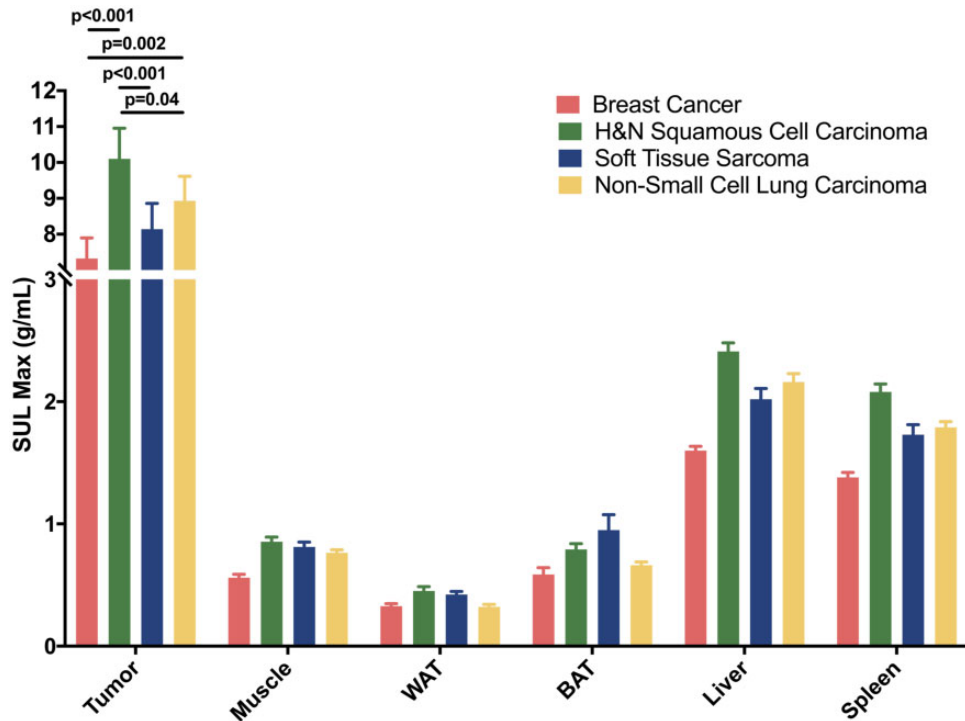
Figure 2. Lean body mass-corrected maximal standardized uptake value (SULmax) in tumor; muscle; white adipose tissue (WAT); brown adipose tissue (BAT) from the supraclavicular fat depot; liver; and spleen in all four cancer types. A two-way ANOVA was performed, with Tukey test for multiple comparisons to compare tissue glucose uptake between cancer types. All tests were two-sided, and statistical significance was determined as $P < .05$. H&N = head and neck.

The influence of health and treatment status could not be studied here. Chronic hyperglycemia, higher circulating insulin levels, increased inflammation, elevated glucocorticoids, and more related mechanisms on systemic glucose metabolism in obese patients may impact tumor progression (39). These and other obesity-related factors may reduce TGU in NSCLC and reduce risk (40) and improve survival (41) across all stages and histological subtypes of lung cancer (42). Chemotherapy can increase or decrease tumor and immune cell FDG uptake (43). Antidiabetic therapies [metformin (44) and SGLT2 inhibitors (45)] may also reduce TGU in multiple cancers.

In summary, tumor glucose metabolism was related to BMI in a detrimental and protective manner in breast and lung cancer, respectively. Publicly available PET and CT images were acquired through the National Cancer Institute's TCIA and analyzed in free open source software, demonstrating the growing utility of shared resources in oncology. Although limited by the availability of clinical information, we highlighted a putative physiological mechanism for obesity's impact on the aggressiveness of multiple tumor types. Prospective studies should be designed to include clinical parameters to better characterize dysregulated glucose metabolism.

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Notes

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