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Establishing computed tomography–defined visceral fat area thresholds for use in obesity-related cancer research

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ABSTRACT

Excess visceral adiposity is associated with increased gastrointestinal cancer risk. Evidence suggests that the systemic inflammation and dysmetabolism observed in visceral obesity underpins this association. Along with magnetic resonance imaging, computed tomography is a gold standard for abdominal fat quantification and is routinely available for gastrointestinal cancer research. However, no gender-specific cutoff values are currently available for classifying visceral obesity in white populations. Using the metabolic syndrome (MetSyn) as an indicator of obesity-associated dysmetabolism, this study aimed to establish pathologically relevant, gender-specific cut-off values for use in obesity-associated cancer research. Total, visceral and subcutaneous fat areas were calculated between the L3 and L4 invertebral space from computed tomography scans in a cohort of 170 males and 66 females undergoing gastrointestinal resection. Receiver operating characteristics analysis was used to determine cut-off values for total, visceral and subcutaneous fat areas associated with MetSyn. Linear regression was used to correlate these values with waist circumference. Visceral fat area (VFA) strongly correlated with the presence of MetSyn ($P < .0001$). The cut-off value for VFA associated with the presence of MetSyn was 163.8 cm^2 in males (83.6% sensitivity, 62.5% specificity) and 80.1 cm^2 for females (96% sensitivity, 73.2% specificity). The waist circumference corresponding to these VFA values was 96.1 cm in males and 83.2 cm in females. This study is the first to generate gender-specific and pathologically relevant cut-off values for VFA in patients with gastrointestinal cancer. In the field of obesity-associated research, this new anthropometric measure is of paramount importance for determining the accurate pathological obesity status of cancer patients.

Abbreviations: AUC, area under curve; BMI, body mass index; CT, computed tomography; HDL-C, high density lipoprotein-C; IDF, International Diabetes Federation; MetSyn, metabolic syndrome; ROC, Receiver operating characteristics; SFA, subcutaneous fat area; TFA, total fat area; VFA, visceral fat area; WC, waist circumference; WHO, World Health Organization.

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1. Introduction

Obesity is a known risk factor for chronic diseases including cardiovascular disease and type 2 diabetes mellitus [1]. In recent years, there has been an increased acknowledgement of the impact of obesity on the incidence and mortality of a wide range of cancer types, including adenocarcinoma of the esophagus, pancreas, colorectum, breast, endometrium, and kidney [2]. What drives the association between obesity and cancer is unclear, and emerging research has targeted the study of different fat compartments, with visceral (central) fat considered to be more pro-inflammatory and pro-tumorigenic than subcutaneous fat depots [3].

Visceral adipose tissue has multiple endocrine, metabolic and immunological functions [4] and is central to the pathogenesis of the metabolic syndrome (MetSyn), a pro-inflammatory, pro-coagulant state associated with insulin resistance [5]. The multiple risk factors that commonly appear together as the MetSyn include abdominal obesity, atherogenic dyslipidemia (raised triglycerides and reduced high-density lipoprotein cholesterol), elevated fasting plasma glucose and hypertension [6]. The ratio of visceral fat area (VFA) to subcutaneous fat area (SFA) as a relative index of intra-abdominal fat accumulation has been shown to be strongly related with disorders of glucose and lipid metabolism in obese subjects [7]. These metabolic parameters have been shown to be significantly dysregulated in individuals with a greater proportion of visceral fat (VFA/SFA ratio of $\geq$0.4) compared to those with a greater proportion of subcutaneous fat (VFA/SFA ratio of <0.4) [7].

As increasing evidence points to the specific role of visceral obesity in disease, it is important to be able to identify individuals with excessive amounts of visceral adipose tissue, as opposed to increased overall mass. The widely used body mass index (BMI) criteria for overweight and obesity [8] is not suitable for determining visceral obesity as within each category of BMI there can be substantial individual variation in total and visceral adiposity [9]. Commonly used BMI cut-off values to diagnose obesity have high specificity, but low sensitivity to identify adiposity, as they fail to identify those with excess body fat [10]. Furthermore, VFA is superior to both waist circumference measurements and BMI for discriminating individuals with two or more features of dysmetabolism [11]. Hence, when researching the metabolic implications of excess adiposity, reliable methods to discriminate between visceral and subcutaneous adipose tissue depots are essential. Computed tomography (CT) imaging and magnetic resonance imaging are the gold standard for the quantification of total, visceral, and subcutaneous adipose tissue [12].

The current hypothesis in obesity-related cancer research is that visceral obesity increases cancer risk via its adverse impact on inflammation and metabolism [13]. Numerous studies have employed these gold standard techniques to quantify visceral fat area and have confirmed that an increased volume of visceral adipose tissue is deleterious to metabolic function, promotes inflammation and promotes tumorigenesis [7,14–18]. Furthermore, recent studies have suggested that CT-determined visceral fat area may influence response to therapy in obesity-associated malignancies [19,20]. However, what is not known is the acceptable threshold level of visceral adipose tissue, above which it begins to detrimentally affect metabolic and inflammatory processes, ultimately increasing cancer risk. There is a paucity of studies attempting to identify pathologically relevant and gender specific cut-off values for VFA in white populations. Studies carried out in the 1990s determined that in both men and women, a VFA above 100 cm^2 was associated with moderate disturbances in the risk profile, whereas a VFA greater than 130 cm^2 was associated with a further deterioration of metabolic variables predictive of type 2 diabetes mellitus and cardiovascular disease [21,22].

However neither of these studies took into consideration the gender difference in adipose tissue distribution [23,24] and dysmetabolism [25]. Moreover, studies that have determined separate optimal thresholds for VFA in males and females have been carried out in Asian populations who, due to ethnic differences in fat distribution and metabolism, are not representative of white populations [26–28]. Although established cut-offs exist for BMI and waist circumference, no such cut-offs exist for VFA. In the absence of a cut-off, many researchers dichotomize their cohort into those above and below the median of VFA which in turn results in a range of different quantities of visceral fat area being reported in the literature as “high” [19,29].

The absence of appropriate VFA thresholds is hampering the field of cancer research as it hinders our ability to make useful associations between visceral obesity and markers of tumorigenesis. CT scanning is generally limited to individuals under medical investigation; nevertheless, an appropriate threshold should be generated for use in obesity research when CT scanning is available. In the absence of healthy individuals, gastrointestinal cancer patients represent an appropriate cohort for the study of VFA thresholds. One of the strongest obesity-cancer links exists between gastrointestinal cancer and visceral obesity and all patients undergo a diagnostic CT scan. Thus, in this study, we focused on esophageal and colorectal adenocarcinoma cohorts and used the collective factors of the MetSyn as a pathological indicator(s) for visceral obesity.

In this study it was hypothesized that when associating total, visceral and subcutaneous fat area with the MetSyn, different CT derived cut-off values would be determined for white male and female gastrointestinal cancer patients. We generate, for the first time, pathologically relevant thresholds for VFA that associate with the MetSyn in white males and females. This new anthropometric measure is of paramount importance for determining the accurate pathological obesity status of cancer patients, a cornerstone in the study of obesity-associated cancer research.

2. Methods and materials

2.1. *Study population*

The study cohort consisted of 236 consecutively recruited subjects, 170 male and 66 females, who underwent a gastrointestinal resection for malignancy with curative intent between July 2007 and January 2011 at St James’s Hospital, Dublin, Ireland. The cohort ranged in age from 29 to 94 years, with a mean age of 65 years. Excluded from the study were individuals