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Metabolism and Target Organ Damage

Editorial

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Cancer in individuals with obesity and metabolic disorders. A preventable epidemic?

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EPIDEMIOLOGY OF OBESITY AND DIABETES

The number of people affected by obesity globally keeps increasing, and this imposes a very high toll on society, including reduced life expectancy, increased incidence of debilitating conditions, and inflated medical costs.

According to the CDC[1], the US obesity prevalence was 41.9% in 2017. "*From 1999-2000 through 2017, the obesity prevalence increased from 30.5% to 41.9%. At the same time, severe obesity increased from 4.7% to 9.2%*". "*The estimated annual medical cost of obesity in the United States was nearly $173 billion in 2019 and medical costs for adults who had obesity were $1861 higher than medical costs for people with healthy weight*"[2].

"*Of all high-income countries, the United States has the highest rates of overweight and obesity, with fully a third of the population obese-a rate projected to rise to around 50 percent by 2030*"[3].

However, this is hardly a phenomenon limited to industrialized countries, and two-thirds of obese people currently live in underdeveloped countries[4]. Globally, the percentage of obese people (i.e., individuals with a BMI of ≥ 25) went from 28.8% (95%UI: 28.4-29.3) in 1980 to 36.9% (95%UI: 36.3-37.4) in 2013 in men and from 29.8% (95%UI: 29.3-30.2) to 38.0% (95%UI: 37.5-38.5) in women. Increases were observed in both developed and developing countries[4].

Since 1980, age-standardized diabetes prevalence has nearly quadrupled globally. This increase has been more pronounced in low- and middle-income countries and is thought to be the result of a combination of dietary, genetic factors, access to early detection and therapy, rising prevalence of obesity and population ageing[5].

In the United States, the incidence of diabetes is higher among Native Americans and African Americans and is inversely correlated with education level[6]. These data further highlight the socioeconomic underpinnings of the disease.

LINK BETWEEN METABOLISM AND CANCER

From 2003, when Calle *et al.* described in a seminal paper the association between obesity and cancer in a large epidemiological cohort to date, there has been ample confirmation of the view that obesity increases the risk of multiple malignancies, including esophageal adenocarcinoma, colon, rectal, liver, pancreatic, postmenopausal breast, endometrial, and renal cell cancer[7,8]. It has also been firmly established that T2DM, atherogenic dyslipidemia (high cholesterol, low HDL, high VLDL) and the metabolic syndrome increase the risk of cancer[8].

A significant nuance that has been unveiled since the study of Calle is that the anatomical distribution of excess fat may constitute a crucial factor modulating this association. Particularly, data have shown that visceral obesity may be a more reliable and significant marker of increased cancer incidence and cancer-related mortality, in some anatomical settings, than BMI[9,10]. Hepatic accumulation of fat, reflected by the presence of NAFLD, has been shown to have a tighter association with increased incidence of cancers, particularly of the liver and gastrointestinal tract, than increased BMI[10,11]. Interestingly, the association between NAFLD and colon cancer is not present in women[10], reaffirming the importance of sex as a key factor in modulating human health and disease[12] while also highlighting the multifactorial pathogenesis of cancer.

A recent epidemiological study, including 10,568 biopsy-proven NAFLD patients, with 4388 deaths occurring over a median follow-up of 14.2 years, compared to 49,925 controls, has found that the excess mortality seen in NAFLD is primarily secondary to extrahepatic cancers, followed by cirrhosis[13]. These data point to NAFLD as a key marker of increased cancer risk.

These findings have multiple implications. First, they stress the importance of including measurements of the anatomical distribution of fat (i.e., visceral, hepatic *vs.* subcutaneous), rather than just BMI in epidemiological studies[14]. Second, they highlight the need for implementing cancer screening in patients with NAFLD[10]. From a molecular standpoint, they raise the question of whether the association between NAFLD and cancer is just secondary to its association with visceral adiposity[15,16] or reflects unique (pro-carcinogenic) biochemical profiles of intrahepatic fat[17]. Indeed, the metabolomic profiles associated with liver, visceral and peripancreatic fat show both similarities and differences[18]. Future research will hopefully shed light on this issue.

CELLULAR AND MOLECULAR BASIS OF THE ASSOCIATION ALTERED METABOLISM -

CANCER

The molecular underpinnings of this association have started to unravel, elucidating at the molecular level the crosstalk that exists between signalling pathways involved in metabolism and cancer development. Two molecules, among the many involved in this process[9], may be singled out in order to exemplify this crosstalk.

β2 spectrin has been identified as crucial in both hepatic steatogenesis and the development of Hepato Cellular Carcinoma (HCC)[19], explaining the increased incidence of HCC in patients with NAFLD (see the comprehensive review on HCC mechanisms by Lonardo *et al.* in this issue). Adiponectin, which exerts a protective effect against the development of diabetes and obesity and an inverse relation with cancer risk, is able to affect multiple signalling pathways involved not only in carcinogenesis[20], but also in atherosclerosis, insulin resistance, lipid metabolism[21] and arterial hypertension[22], thus providing some molecular basis for the frequent coexistence of these pathologies in humans.

CLINICAL SIGNIFICANCE AND CHALLENGES

A recent review found that the most important risk factors for cancer mortality and disability-adjusted life years globally were smoking, alcohol use and high BMI[23]. Therefore, there is an urgent need to take effective measures to reduce the cancer risk associated with obesity and its associated dysmetabolic conditions.

A recent epidemiological study[24] of 5000 obese patients treated with bariatric surgery and 25,000 non-surgically treated patients (the largest cohort studied so far for this association) has shown that bariatric surgery reduces this excess cancer risk (0.8 % in treated *vs.* 1.4% in non-treated patients at 10 years follow-up), confirming previous studies[25]. These data provide definitive proof of principle for the reversibility of this association and place the responsibility for alleviating it squarely on the shoulders of the medical community and society at large.

This goal can be achieved through prevention ("*an ounce of prevention is worth a pound of cure*") and/or medical control of obesity and its associated metabolic alterations. While obesity is a multifactorial disease, it is commonly regarded as being caused predominantly by acquired lifestyle habits (poor diet, excessive caloric intake, and lack of physical exercise) and is therefore largely preventable[26]. Preventive strategies[27] for reducing obesity's prevalence should be multi-pronged, including: (1) universal prevention, aimed at the entire population and started from childhood, achieved by mass education on healthy lifestyle habits[28]; (2) selective prevention, aimed at patients with a family history of obesity and/or T2DM; and (3) targeted prevention, aimed at overweight or obese patients, to reduce current weight and prevent further weight increase.

This goal is challenging and may encounter significant psychological and socioeconomic obstacles[29,30], as is the case with physicians' ongoing battle against smoking[31].

Medical intervention may also reduce the increased cancer risk conferred by obesity and its associated metabolic disturbances. One of these is the aforementioned bariatric surgery. Another approach/example is the pharmacological management of dyslipidemia achieved by statins. Yi *et al.*, by meta-analyzing six eligible prospective cohort studies (overall totaling 11, 8961 participants), found a statistically significant association between increasing statins intake and liver cancer risk reduction (OR = 0.46, 95%CI: 0.24-0.68, $P < .001$)[32]. In 2020, Jeong *et al.*, in a comprehensive review of published meta-analyses of observational studies, assessed the strength of evidence and impact of potential biases of claimed associations between

statin use and cancer mortality and survival owing to various cancer types and found convincing evidence for statin use being associated with a reduced cancer-specific mortality rate for colorectal cancer[33]. Additionally, suggestive evidence was found for reduced all-cause mortality among those with breast cancer, colorectal cancer, endocrine-related gynecological cancer, and ovarian cancer[33].

Overall, these data highlight that this epidemic may be reversed or at least curtailed.

RATIONALE OF THIS SPECIAL ISSUE

This issue builds on and expands a previous general review of the topic published in this journa[9] by providing targeted reviews of the association existing between cancer and metabolism in specific anatomical settings and cancer types: endometrial cancer (Dr. Ali), hepatocellular carcinoma (Drs. A. Lonardo and G. Francica) and colon cancer (Dr. L. Roncucci).

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The author contributed solely to the article.

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Ethical approval and consent to participate

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Consent for publication

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