Metabolic syndrome and risk of subsequent colorectal cancer

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Abstract
The metabolic syndrome and visceral obesity have an increasing prevalence and incidence in the general population. The actual prevalence of the metabolic syndrome is 24% in US population and between 24.6% and 30.9% in Europe. As demonstrated by many clinical trials (NAHANES III, INTERHART) the metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease. In addition to cardiovascular disease, individual components of the metabolic syndrome have been linked to the development of cancer, particularly to colorectal cancer. Colorectal cancer is an important public health problem; in the year 2000 there was an estimated total of 944,717 incident cases of colorectal cancer diagnosed world-wide. This association is sustained by many epidemiological studies. Recent reports suggest that individuals with metabolic syndrome have a higher risk of colon or rectal cancer. Moreover, the clusters of metabolic syndrome components increase the risk of associated cancer. The physiopathological mechanism that links metabolic syndrome and colorectal cancer is mostly related to abdominal obesity and insulin resistance. Population and experimental studies demonstrated that hyperinsulinemia, elevated C-peptide, elevated body mass index, high levels of insulin growth factor-1, low levels of insulin growth factor binding protein-3, high leptin levels and low adiponectin levels are all involved in carcinogenesis. Understanding the pathological mechanism that links metabolic syndrome and its components to carcinogenesis has a major clinical significance and may have profound health benefits on a number of diseases including cancer, which represents a major cause of mortality and morbidity in our societies.

INTRODUCTION
The concept of metabolic syndrome has existed for at least 80 years and was first described by Kylin[1], a Swedish physician, as a clustering of hypertension, hyperglycemia and gout, and later on by Vague[2] who added to the previous description the presence of abdominal obesity.

While the concept of metabolic syndrome has been accepted for a long time, there was no largely recognized international definition until 1998.

The first proposal came in 1998 from a consultation group for the definition of diabetes for World Health Organisation. This definition was then modified by the European Group for Study of Insulin Resistance in 1999, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) in 2001 and revised in 2005, and the International Diabetes Foundation (IDF) in 2005. These definitions agree on the different components of metabolic syndrome but differ in details (Table 1)[3].

More recently, the use of the term of “metabolic syndrome” has been questioned by the American...
Diabetes Association and the European Association for the Study of Diabetes for several reasons: (1) Criteria are ambiguous or incomplete (for example it is unclear if the blood pressure definition is systolic blood pressure ≥ 130 mmHg and diastolic ≥ 85 mmHg or whether it is either ≥ 130 mmHg or > 85 mmHg); (2) The value of including diabetes in the definition is questionable and the role of insulin resistance as unifying etiology is uncertain. Furthermore it is still unclear the extent to which an elevated cardiovascular (CVD) risk is due to insulin resistance itself vs isolated hyperinsulinemia; (3) There is no clear basis for including/excluding other CVD risk factors; the CVD risk associated with the syndrome appears to be no greater than the sum of its parts; (4) The treatment of the syndrome is not different from the treatment for each of its components.

A recent review of the ATP III definition broadened the etiological basis of the syndrome from insulin resistance alone to include “obesity and disorders of adipose tissue”[10].

The actual prevalence of obesity is 30.5% and that of associated metabolic syndrome is 24% in the US population[19].

In Europe, the age- and sex-adjusted prevalence of metabolic syndrome was 24.6% using the 2005 ATP III definition and 30.9% using the International Diabetes Federation definition, according to the MADRIC study (MADrid Risgo Cardiovascular Study) performed on 1344 participants[8]. In this study, the authors found a good overall agreement between the ATP III and IDF definitions, much closer in women than in men (κ = 0.92 ± 0.07; κ = 0.66 ± 0.06). The prevalence of metabolic syndrome was greater according to the IDF definition than according to ATP III, because the former definition has a lower threshold of abdominal obesity.

A cross-sectional analysis of 10206 participants aged 20-89 years in the Nord-Trøndelag Health Study 1995-97 (HUNT 2) in Norway, found a prevalence of IDF-defined metabolic syndrome of 29.6%, compared to 25.9% using the 2005 ATP III criteria[15].

In a meta-analysis, Cameron et al[9] found a variable prevalence of metabolic syndrome in urban populations from 8% (India) to 24% (USA) in men, and from 7% (France) to 43% (Iran) in women.

It is well known that the metabolic syndrome is associated with an increased risk of both diabetes and cardiovascular disease.

Many clinical studies outlined the interrelation between the metabolic syndrome and cardiovascular risk[16].

Applying the ATP III criteria to 10537 NHANES III participants resulted in a significant association between the metabolic syndrome with prevalent myocardial infarction and stroke in a multivariate analysis: myocardial infarction [OR: 2.01, 95% confidence intervals (CI): 1.53-2.64], stroke (OR: 2.16, 95% CI: 1.48-3.16), and myocardial infarction/stroke (OR: 2.05, 95% CI: 1.64-2.57)[17]. The INTERHART study performed on 15152 cases and 14820 controls in nearly 52 countries found a significant association between abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity and the risk of myocardial infarction. Collectively, these nine risk factors accounted for 90% of the population risks in men and 94% in women[11].

In addition to CVD, individual components of the metabolic syndrome have been linked to the development of cancer[12].

Colorectal cancer is an important health problem since one million new cases are diagnosed world-wide each year with half million related deaths[13]. The incidence rate of colon cancer according to Five Continents cancer registries varies from 3% in Africa (Algeria) up to 40% in North America. In Europe the incidence of colon cancer ranges from 12.1% in Belarus up to 30.5% in Italy[14].

There is evidence that body composition and hormonal factors contribute to colorectal cancer etiology. In this paper we will highlight this association supported by epidemiological data and pathophysiological mechanisms arising from prospective human research studies.

**EPIDEMIOLOGY**

In an analysis of nearly 58 000 individuals who participated in the National Health Interview Survey (2002-2003), Garow et al[15] identified 1200 individuals with metabolic syndrome, 350 of them being diagnosed with colorectal cancer. After controlling for age, race, gender, obesity, smoking and alcohol use the individuals with metabolic syndrome had a 75% increased risk for colon or rectal cancer.

In a large prospective study of more than 900 000 US adults (404 576 men and 495 477 women) conducted by Calle et al[19], there were 57 145 deaths from cancer during a follow up period of 16 years. The authors also studied the relationship between the relative risk (RR) of death and body mass index (BMI). For all cancer there was a trend in increasing death rate with BMI. For colorectal cancer the RR of death varied from 1.34 (95% CI: 0.94-1.34) for a BMI of 25-29.9, to 1.90 (95% CI: 1.46-2.47) and 4.52 (95% CI: 2.94-6.94) for an BMI between 30.0-34.9 and 35.0-39.9, respectively[19].

Recent studies also provide information concerning the association between colorectal cancer incidence and the number of metabolic syndrome components, especially BMI, waist circumference (WC), lipid levels, plasma glucose and glycosylated hemoglobin (HbA1c). In an analysis of 14109 participants from the ARIC study (Atherosclerosis Risk in Communities), 194 incident colorectal cancers were identified. In this study baseline metabolic syndrome (≥ 3 components vs 0 components) had a positive association with age-adjusted and gender-adjusted colorectal cancer incidence (RR: 1.49, 95% CI: 1.0-2.4). There was a dose-response association between colorectal cancer incidence and the number of metabolic syndrome components present at baseline (P for trend = 0.006) after multivariate adjustment[17].

In another study, Trevisan et al[18] used information
from the Risk Factors and Life Expectancy study, which pooled data from nine epidemiological studies conducted in Italy between 1978 and 1987, including 21,311 men and 15,991 women. In this study, low high density lipoprotein (HDL) and high triglyceride levels, hypertension and plasma glucose levels were also analyzed as individual components of the metabolic syndrome. For the presence of the cluster of metabolic abnormalities, the calculated hazard ratios and 95% CIs were 2.99 (1.27-7.01) when both sexes were combined. When analyzing the individual components, only glucose level was associated with an increased risk of death from colorectal cancer, and only in men and women combined (RR: 1.8, 95% CI: 1.05-3.09). The results of this study suggest that the effects of the individual components of metabolic syndrome are additive, because the RR of death from colorectal cancer was increased in cluster analysis compared with glucose alone.

The association between plasma glucose levels reflected by HbA1c and the incidence of colorectal cancer was outlined in a prospective analysis from the European Prospective Investigation into Cancer and Nutrition (EPIC) study[20]. Among 9,605 participants in this study, aged between 45 and 79 years, there were 67 incident colorectal cancers. In this study population, the RR of colorectal cancer for a WC of > 99 cm in women and 101 cm in men; the risk increased linearly with increasing WC[23]. One Japanese study[24] of 51 consecutive patients aged ≥ 40 years, suggests that visceral adipose tissue rather than whole body adipose tissue correlates better with the risk of colorectal adenoma. Furthermore, in this study, low adiponectin level is a factor associated with the development of colorectal adenoma. It is known that adiponectin levels decrease in obesity, especially abdominal obesity in association with insulin resistance; thus, the results of this study offer an insight to understanding the relationship of colorectal carcinogenesis with abdominal obesity and insulin resistance which will be discussed later on this paper.

The fact that the metabolic syndrome is a risk factor for both CVD and colorectal cancer raised the question if there is any association between CVD and colorectal cancer. This correlation was found to be positive in several studies. In a pilot study of 63 patients with colorectal cancer, Hamoudi and Dumitrascu demonstrated a statistical association between CVD and colorectal cancer in men[25].

The relationship between individual components of metabolic syndrome and the risk of colorectal cancer was also separately analyzed by several studies. Colangelo et al[23] found a 35% increased risk of colorectal cancer associated with high blood pressure. The results were confirmed by another study[17]. Both studies also underlined that the clustering of metabolic syndrome components significantly increased the risk of associated colorectal cancer.

High circulating triacylglycerols were associated in a large prospective study with a non-significant two-
fold elevation in risk of colorectal cancer in men, but no clear association was observed in women\[37\]. In another prospective study, there was a 40% increased risk of colorectal cancer for men and women in the top quartile of triacylglycerol levels, although this association was not significant\[37\].

The association between C-peptide levels as a marker of hyperinsulinemia and colorectal cancer risk was also examined by several studies. In a case control study in the Physicians’ Health Study, an increased concentration of plasma C-peptide was statistically significantly associated with an increased risk of colorectal cancer in men (RR for the highest vs lowest quintile of plasma C-peptide = 2.7, 95% CI: 1.2-6.2, \(P\) trend = 0.047), after adjusting for age, smoking status, fasting, BMI and alcohol consumption. The results of this study also suggest that elevated insulin production, as reflected by elevated concentrations of plasma C-peptide, may predict the risk of developing colorectal cancer, independently of BMI, factors related to insulin resistance, or levels of insulin growth factor (IGF)-1 and insulin growth factor binding protein (IGFBP)-3\[28\]. The interrelation between a high concentration of plasma C-peptide and colorectal adenoma was also demonstrated in women in a series of 380 patients with a multivariable relative risk (MVRR) top vs bottom quartile, 1.63, 95% CI: 1.01-2.66, \(P\) = 0.01, even after including BMI and physical activity in the statistical model\[29\].

The findings of all these studies suggest that the clusters of the metabolic syndrome components may be predictors for developing colorectal cancer and for colorectal cancer mortality. The understanding of the underlying physiopathology that links the metabolic syndrome and cancer may play a key role in developing new strategies for prevention and treatment.

**PHYSIOPATHOLOGICAL LINKS BETWEEN METABOLIC SYNDROME AND COLORECTAL CANCER**

**Obesity, insulin resistance and insulin growth factors and binding proteins**

It has been hypothesized that insulin resistance is the most important underlying mechanism of the metabolic syndrome in close relationship to abdominal obesity. Insulin has been shown to affect growth of normal and neoplastic epithelial cells and to have mitogenic actions in vitro and in experimental models, either directly or indirectly through IGF-1\[17\]. At high concentrations, insulin can bind to IGF-1 receptors (IGF1Rs) or can act directly to promote IGF-1 biosynthesis, enhancing IGF-1 bioavailability and inhibiting the production of IGFBP-1, IGFBP-2 and IGFBP-3\[18\].

IGF-1 is an important mitogen required for the progression through the cell cycle and has autocrine, paracrine and endocrine actions on cell proliferation and apoptosis\[19\], increasing the risk of cellular transformation by enhancing cell turnover. In addition, IGF-1 increases the production of vascular endothelial growth factor (VEGF), an angiogenic factor that can support cancer growth\[15\].

It has been shown that normal colorectal epithelia and colon cancer cells have both insulin and IGF1Rs\[16\]. Tissue homeostasis in the normal colonic crypt relies on a balance between proliferation, differentiation and apoptosis, with apoptosis occurring at the top of the colonic crypt as the culmination of a differentiation pathway. The link between IGF-1 and IGFBP-3 levels and the increased risk of colorectal adenoma and cancer came first to attention in acromegalic patients, characterized by chronically elevated growth hormone (GH) levels. GH excess leads to hepatic and peripheral insulin resistance and thus to hyperinsulinemia, a common feature of acromegaly and metabolic syndrome, that causes IGF-1 hypersecretion and low IGFBP-3 levels\[19\].

The relationship between IGF-1 and IGFBP-3 levels and colorectal cancer was examined by Giovannucci et al\[20\] on 32826 women from Nurses’ Health Study. Controlling for IGFBP-3 level, relative to women in the lowest tertile of IGF-1, those in the highest tertile were at elevated risk of intermediate/late-stage colorectal neoplasmia adenoma (MVRR: 2.78, 95% CI: 0.76-9.76) and cancer (RR: 2.18, 95% CI: 0.94-5.08). Controlling for IGF-1 level, relative to women in the lowest tertile of IGFBP-3, women in the highest tertile of IGFBP-3 were at lower risk of intermediate/late-stage colorectal adenoma (RR: 0.28, 95% CI: 0.09-0.85) and cancer (RR: 0.28, 95% CI: 0.10-0.83). Neither IGF-1 nor IGFBP-3 had any appreciable relation with early-stage adenoma. These analyses indicate that high levels of circulating IGF-1 and particularly low levels of IGFBP-3 are associated independently with an elevated risk of large or tubulo-villous/villous colorectal adenoma and cancer. These results are concordant with those obtained previously in Physicians’ Health Study\[21\].

The role of IGFBP-3 in colorectal cancer was independently analyzed by Williams et al\[22\]. IGFBP-3 has been shown to enhance p53-dependent apoptosis after DNA damage. Therefore, loss of IGFBP-3 could contribute to the development of colonic adenomas that retain wild-type p53 function through suppression of p53-dependent apoptotic signals, allowing aberrant cell survival and tumor formation. Furthermore there is disruption in both adenoma and carcinoma tissue. This pattern is similar to that of TGF-β distribution in normal, adenoma and carcinoma tissue\[17\]. Because it is known that TGF-β is a potent growth inhibitor for colonic epithelium\[23\], this similarity suggests that IGFBP-3 may have an important role in the regulation of differentiation and apoptosis in human colonic epithelium\[24\].

The role of insulin resistance and hyperinsulinemia in colorectal cancer was directly assessed by Schoen et al\[25\] in a study performed on 5849 participants in the Cardiovascular Health Study cohort. The authors identified 102 cases of colorectal cancer. Fasting insulin was not related to an increased risk (RR = 1.2), whereas 2 h insulin was related to a significantly increased risk (RR = 2.0).

Giovannucci et al\[20\] found that BMI was not significantly
associated with an increased risk of distal colon adenoma irrespective of size, while WC and waist hip ratio were strong risk factors for large distal colon adenomas with diameter $\geq 1$ cm but were unrelated to small adenomas with diameter $< 1$ cm. The association of WC with an increased risk of cancer has been reported to be slightly stronger for distal colon cancer.

There are also several studies which determined the relationship between C-peptide (an indicator of insulin production) and the risk of colorectal cancer. As mentioned before, in the Physicians’ Health Study, men with C-peptide in the top $\alpha$ the bottom quintile had a 2.7-fold significantly higher risk of colorectal cancer after control for BMI and exercise; this RR increased to 3.4 after the analysis was controlled for indicators of the metabolic syndrome$^{30}$. In a prospective study of 14,275 women in New York State, a 3-fold higher risk of colorectal cancer was observed in those in the top quintile of C-peptide, and a 4-fold higher risk was observed for colon cancer alone$^{30}$.

**Adipokines and inflammatory cytokines**

Adipose tissue is a complex endocrine organ, responsible for the secretion and synthesis of hormones, cytokines and other signaling proteins, collectively termed as adipokines. Adipokines are a diverse group of signaling molecules that play roles in such processes as appetite and energy balance, inflammation, insulin resistance/sensitivity; angiogenesis, lipid metabolism, cell proliferation and atherosclerosis. Many of these functions are related to either the metabolic syndrome or cancer, and they may serve as a link between these two pathologies$^{39}$. 

**Adiponectin**

Adiponectin, a 30-kDa complement C1q-related protein, is a key regulator of insulin sensitivity and inflammation and modulates several physiologic processes, such as metabolism of glucose and fatty acids. In contrast to other adipokines such as leptin, adiponectin circulating levels are decreased in obese individuals and in those with diabetes$^{41}$. Decreased plasma adiponectin concentrations are associated with insulin resistance, type 2 diabetes and atherosclerosis. In addition, it was recently shown that adiponectin may play a role in the development and progression of various types of malignancies. Accumulating evidence suggests that adiponectin is an important regulator of cell proliferation. Adiponectin may act either directly on cancer cells or indirectly by regulating whole-body insulin sensitivity$^{42}$.

**Mechanisms that may link adiponectin with carcinogenesis**

In obesity, reduced adiponectin levels lead to the development of insulin resistance and compensatory, chronic hyperinsulinaemia. Increased insulin levels results in increased levels of bioavailable IGF-1. Insulin and IGF-1 signal through the insulin receptors and IGF1R, promote cellular proliferation and inhibit apoptosis in many tissue types up-regulating the secretion of VEGF, contributing thus to carcinogenesis$^{49}$. Adiponectin has also been shown to inhibit both the production of TNF-α in macrophages and its action in endothelial cells, thus promoting carcinogenesis through the altered effect of TNF-α on tumor cell proliferation and angiogenesis$^{45}$. Adiponectin can also protect from carcinogenesis through more direct effects.

Specifically, adiponectin has been found to be an important negative regulator of hematopoiesis and the immune system. Moreover, adiponectin may inhibit activation of nuclear factor-κB (NF-κB), a transcription factor that upregulates VEGF$^{40}$. Several signalling molecules such as 50-AMP-activated protein kinase (AMPK), NF-κB, peroxisome proliferators activated receptor (PPAR)-α and p38 mitogen-activated protein kinase are known to mediate adiponectin-induced metabolic effects. AMPK might inhibit the growth and/or survival of cancer cells$^{45}$. Finally, adiponectin may also regulate angiogenesis negatively (independently of AMPK) through induction of apoptosis in vascular endothelial cells by activating the caspase cascade, a group of apoptotic enzymes$^{46}$. The relationship between circulating adiponectin levels and colorectal cancer was demonstrated by several clinical and experimental studies.

Ferroni et al$^{47}$ demonstrated in a study involving 60 patients with non metastatic colorectal cancer that low adiponectin levels are inversely correlated with increases in tumor stage and were independent predictors of recurrent disease. Low adiponectin levels were found in 52% of relapsing patients, compared with 26% of non-relapsing patients$^{47}$. Similar results were obtained by Wei et al$^{48}$ in a prospective case-control study of 18,225 men enrolled in the Health Professional Follow-up Study. Over the approximately 8 years of follow-up, the authors noted 25 cases of colorectal cancer in the 3,645 men in the highest category of adiponectin compared with 54 cases of colorectal cancer in the 3,645 men in the lowest quintile of adiponectin.

**Leptin**

Leptin is a 16 kDa glycoprotein which is expressed almost exclusively (> 95%) by adipocytes. Initial interest in leptin focused on its role in obesity but recently leptin, has been associated with the inflammatory response, insulin signaling, and carcinogenesis. Insulin and leptin interact at multiple levels within a complex network of adipose tissue signaling pathways, providing several mechanisms that could link leptin to colon cancer. Of particular importance for cancer is the influence of leptin on suppressors of cytokine signaling 1 and 3 which in turn limits insulin signaling$^{49}$. Although data directly linking leptin to colon cancer are limited, some studies have shown increased risk of colon and colorectal cancer with high serum leptin levels.

Data from a cohort study in Norway detected an almost 3-fold increased risk of colon cancer among people with high leptin levels, independently of BMI$^{50}$. 

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Another study found that men in the highest tertile of leptin concentrations had a 3.3-fold (95% CI: 1.2-8.7) increased adenoma risk compared with those in the lowest tertile. The association between leptin concentration and colorectal cancer was also evaluated in women, in a case-control study conducted in Japan, suggesting that leptin increases substantially the risk of female colorectal cancer, independent of BMI.

**Inflammatory cytokines and colorectal cancer**

Accumulating evidence suggests that systemic inflammation might be a plausible mechanism for colon carcinogenesis. Studies have shown that genetic variations in inflammation-related genes, such as interleukin (IL)-6, IL-8, and IL-10, are associated with susceptibility to colorectal cancer and adenomas.

IL-6 appears to enhance tumorigenesis by a paracrine and autocrine mechanism, to stimulate cell growth and inhibit apoptosis. Also IL-6 concentrations reflected disease status and were commonly associated with metastatic disease.

TNF-α activates NF-κB (by phosphorylation of its inhibitor IκB), which increases production of NO, a substrate for reactive oxygen species (ROS) formation, and stimulates other inflammatory cytokines. With respect to cancer, ROS can damage DNA by several processes including DNA base modification, deletions, frame shifts, strand breaks, DNA-protein cross-links, and chromosomal rearrangements. DNA damage can occur in genes that are important in cell proliferation (such as ras), or cell survival (such as p53), which can then trigger cancer progression.

There are several studies which demonstrated the correlation between high levels of IL-6, TNF-α, C-reactive proteins (CRP) and colorectal carcinogenesis. Moreover, a Greek study demonstrated that high levels of serum IL-6, TNF-α and CRP were correlated with larger tumor size. The relation to tumor size could be related to the fact, that larger tumors may trigger a more potent immunological response manifested by the circulation of proinflammatory cytokines such as TNF-α.

**PPAR-γ**

PPAR-γ, a ligand-activated transcription factor, is a key regulator of adipogenic differentiation and glucose homeostasis. PPAR-γ ligands have recently been demonstrated to affect proliferation and differentiation in cancer cell lines. A gradually increasing number of studies demonstrated the association between PPAR-γ and colorectal cancer.

A recent study demonstrated a positive PPAR-γ immunostaining in 48 of 86 cases of colon cancer (56%). No association was found for PPAR-γ positivity with different Dukes’ stages, histological grade of differentiation, tumor location, presence of lymph node and liver metastasis, venous invasion, or tumor cell proliferating capacity assessed as Ki-67 overexpression. On the contrary, PPAR-γ expression was statistically significant correlated with the expression of cell cycle-related molecules.

Another recent study demonstrated that PPAR-γ agonists have inhibitory effects on the proliferation of colon cancer cell lines associated with G1 cell cycle arrest and invasive activity. The latter effect is demonstrated in certain cell lines through the down-regulation of metalloproteinase-7 synthesis.

**CONCLUSION**

The association between metabolic syndrome and colorectal cancer is now supported by a large number of epidemiological studies. The components of metabolic syndrome appear to have an additive effect on colon cancer development acting through different pathophysiological pathways. This evidence is based on studies of determinants of the metabolic syndrome (obesity, abdominal distribution of adiposity, physical inactivity), clinical consequences (type 2 diabetes, hypertension) of this syndrome, plasma or serum components of the definition of metabolic syndrome (hypertriglyceridemia, hyperglycemia, low HDL cholesterol), markers of hyperinsulinemia or insulin resistance (insulin, C-peptide), and serum inflammatory cytokines levels in relation to colon cancer or adenoma risk. High insulin and insulin resistance are common features of industrialized societies characterized by a large prevalence of overweight individuals and obesity, a diet rich in energy intake, and a lifestyle characterized by low calorie expenditure. Understanding the pathological mechanism that links metabolic syndrome and its components to carcinogenesis has a very important clinical significance. Controlling even one or two of the components of the metabolic syndrome may result in a longer, healthier and cancer-free life. Public health efforts aimed at reducing lifestyle patterns and dietary habits associated with this imbalance on insulin metabolism may have profound health benefits on a number of diseases including cancer, that represent major causes of mortality and morbidity in our societies.

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