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RESEARCH ARTICLE

Metabolic Syndrome and Carcinogenesis: Epidemiology, Mechanisms, and Clinical Implications for Internal Medicine - A Narrative Review

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Abstract: ***Background***: Metabolic syndrome (MetS), characterized by central obesity, insulin resistance, dyslipidemia, and hypertension, has emerged as a major global health challenge. While traditionally associated with diabetes and cardiovascular disease, MetS is increasingly recognized as a precursor to several malignancies. ***Objective***: This review synthesizes epidemiological evidence and mechanistic insights linking MetS to carcinogenesis and highlights the implications for internal medicine practice. ***Methods***: Literature was reviewed from PubMed, Scopus, and Web of Science (2000–2025) using the terms "metabolic syndrome," "carcinogenesis," "internal medicine," and "cancer risk." Priority was given to meta-analyses, large cohort studies, and mechanistic research. ***Results***: MetS was associated with a higher incidence of colorectal, breast, hepatocellular, pancreatic, endometrial, and other cancers. The mechanistic pathways include insulin resistance and IGF-1 signaling, chronic inflammation, adipokine imbalance, oxidative stress, NAFLD/MASH progression, microbiome alterations, and hypoxia-driven angiogenesis. Preventive strategies, such as lifestyle modifications, weight loss, targeted screening, and selected pharmacological interventions (e.g., metformin, statins, GLP-1 receptor agonists, and aspirin), are promising.

Keywords: Metabolic syndrome, Carcinogenesis, Insulin Resistance, Chronic inflammation, Adipokines, Non-alcoholic fatty liver disease (NAFLD), Internal medicine, Cancer prevention.

INTRODUCTION

Metabolic syndrome (MetS) is a complex of interrelated risk factors associated with one another, including abdominal obesity, impaired glucose tolerance, diabetes, high blood pressure, and lipid alterations. Each of these abnormalities is linked to a higher risk of cardiovascular disease and type 2 diabetes; however, when these two factors work together, the synergistic effect is great, and the risk of chronic disease increases dramatically [1]. The International Diabetes Federation estimates that the prevalence of MetS worldwide is approximately 20–25 percent among adults and that most urban and industrialized communities have a higher prevalence, indicating a change in lifestyle, obesity, and aging phenomenon [2]. Although historically investigated in the framework of cardiovascular outcomes, growing evidence currently supports MetS as a precancerous condition. Epidemiological literature in the last 20 years has shown that patients with MetS are at an increased risk of developing various malignancies, such as colorectal, breast, liver, pancreatic, and endometrial cancers [3]. In addition, mechanistic research has a high level of biological plausibility and has associated insulin resistance, adipokine imbalance, oxidative stress, and chronic low-grade inflammation with tumor initiation and progression [4]. These acknowledgments have far-reaching implications for internal medical practice. Patients who present with hypertension, diabetes, or dyslipidemia are usually treated in primary care and hospital settings. Thus, internists play a leading role in the detection and prevention of oncologic risks in patients with MetS. In addition to glucose or blood pressure therapy, they are now confronted with the issues of predicting long-term cancer risk, integrating cancer preventive interventions into metabolic therapy, and proper surveillance. The objective of the present review was to integrate the existing evidence regarding the association between MetS and cancer. The first part discusses epidemiological evidence and indicates the associations between various types of cancer and geographical localities.

EPIDEMIOLOGICAL EVIDENCE

Metabolic syndrome (MetS), characterized by insulin resistance, hyperinsulinemia, obesity, dyslipidemia, hypertension, and chronic low-grade inflammation, is

consistently associated with an increased overall cancer risk, with studies showing a 12–24% higher incidence than metabolically healthy individuals. The risk increases with the number of MetS components, and type 2 diabetes and its metabolic correlates contribute significantly to the global cancer burden [5]. MetS strongly predisposes individuals to colorectal cancer (CRC), particularly men, through insulin/IGF-1–mediated epithelial proliferation and visceral fat–driven inflammation [6,7]. In postmenopausal women, MetS increases the risk of breast cancer due to adipose-derived estrogen and insulin-driven mitogenic signaling [8, 9]. Hepatocellular carcinoma (HCC) arises from NAFLD/MASH, often in non-cirrhotic livers, with obesity and diabetes conferring a 2–4-fold higher risk [10, 11]. The risk of pancreatic cancer is elevated in patients with MetS, particularly those with long-standing diabetes, reflecting chronic metabolic stress [12]. Endometrial cancer risk triples in women with MetS due to increased estrogen exposure and SHBG suppression [13], whereas MetS in men is associated with aggressive prostate cancer and higher mortality [14]. Gastrointestinal malignancies, including gastric and esophageal cancers, show site- and region-specific associations with MetS, which are largely mediated by obesity [15]. Hematologic malignancies, especially lymphoid cancers, are linked to obesity and chronic inflammation in patients with MetS [16]. These cancer risks are further compounded by systemic and hormonal disturbances in MetS, including hyperinsulinemia, IGF-1 activation, sex hormone imbalance, adipokine dysregulation, oxidative stress, lipotoxicity, hypoxia, microbiome alterations, and epigenetic changes, which collectively promote proliferative signaling, angiogenesis, apoptosis resistance, genomic instability, and metastatic potential, thereby creating a tumor-promoting environment for cancer development.

Pathophysiological Mechanisms of Carcinogenesis in Metabolic Syndrome

Insulin Resistance and Hyperinsulinemia: Insulin resistance (IR) in muscle, adipose tissue, and liver triggers compensatory hyperinsulinemia, which promotes mitogenic signaling through insulin receptor isoform A (IR-A) overexpression. Epidemiological studies have linked hyperinsulinemia in patients with diabetes to a higher risk of colorectal, breast, and pancreatic cancers, independent of hyperglycemia [17].

Insulin-Like Growth Factor (IGF) Axis: Hyperinsulinemia lowers IGFBPs, increasing free IGF-1, which activates IGF-1R and downstream PI3K-AKT, mTOR, and RAS-RAF-MEK-ERK pathways, enhancing proliferation and survival. Experimental and clinical studies have correlated high IGF-1 levels with breast, prostate, and colorectal cancer risk [18-19].

Sex Hormone Alterations: Hyperinsulinemia decreases SHBG levels, increasing circulating estrogen and androgen levels, particularly post-menopause, which contributes to breast, endometrial, and prostate cancer risk [20-22].

Adipokine Dysregulation: Expanded visceral fat alters adipokine levels. Leptin promotes angiogenesis and EMT, whereas low adiponectin levels impair AMPK signaling and increase cancer risk. The leptin/adiponectin ratio is a potential biomarker of obesity-related oncogenesis [23].

Chronic Low-Grade Inflammation: Enlarged adipocytes attract M1 macrophages, releasing TNF-α, IL-6, and IL-1β, promoting NF-κB and STAT3 activation, DNA damage and tumorigenesis. Elevated CRP and IL-6 levels are predictive of colorectal and pancreatic cancers [24].

Inflammation–Insulin Resistance Crosstalk: Cytokines inhibit IRS-1, aggravating insulin resistance, which amplifies lipolysis and inflammation, creating a self-perpetuating tumor-promoting cycle [25].

Oxidative Stress and ROS: Hyperglycemia and dyslipidemia increase ROS levels, causing DNA damage, telomere shortening, and activation of NF-κB, HIF-1α, and MAPK, promoting tumor growth. AGEs and RAGE further exacerbate this oxidative stress.

Lipotoxicity and Dyslipidemia: High triglyceride levels, low HDL levels, and lipid intermediates activate PKC, ER stress, and SREBP/FASN-mediated lipogenesis, supporting cancer cell proliferation. Epidemiological links exist between colorectal, prostate, breast, and gastric cancers [26].

NAFLD/MASH and Liver Carcinogenesis: Metabolic-associated liver disease progresses from steatosis to HCC, even without cirrhosis, and is mediated by oxidative stress, inflammation, and genetic variants (e.g., PNPLA3) [27].

Hypoxia, Angiogenesis, and ECM Remodeling: Obesity-induced hypoxia stabilizes HIF-1α, driving VEGF-mediated angiogenesis, glycolysis, and MMP-mediated ECM remodeling, thereby enhancing tumor invasiveness.

Microbiome, Endotoxemia, and Bile Acids: MetS-related gut dysbiosis increases LPS and systemic inflammation via TLR4, promoting hepatocarcinogenesis. Microbiota-mediated bile acid metabolism induces DNA damage and causes oxidative stress.

Epigenetic Alterations: Metabolic stress induces DNA methylation, histone modification, and miRNA dysregulation (e.g., miR-21 upregulation and miR-122 downregulation), impairing tumor suppressor activity and promoting carcinogenesis. Many epigenetic changes

are reversible, representing potential therapeutic interventions [28].

Convergence on Cancer Hallmarks: MetS mechanisms collectively support proliferative signaling, apoptosis resistance, genomic instability, angiogenesis, invasion, and metabolic reprogramming, predisposing tissues to malignant transformation [29].

CLINICAL IMPLICATIONS AND PHARMACOLOGICAL INTERVENTIONS

Clinical and Preventive Implications in Internal Medicine

Risk Stratification and Identification of High-Risk Patients

The importance of metabolic syndrome (MetS) as a precancerous disease makes internists shift the paradigm of cardiovascular risk evaluation and implement oncologic vigilance in routine practice. Although typical cancer screening initiatives are at the population level, patients with MetS constitute a subset in which customized approaches can be justified. Multiple large cohort studies have indicated that the cumulative burden of MetS components is a more accurate predictor of cancer prevalence than individual factors. Individuals with three or more abnormalities, including central obesity, hyperglycemia, and dyslipidemia, are at a considerably increased risk of colorectal, breast, and endometrial cancers compared to the risk associated with one abnormality [30]. The cumulative properties of these risks indicate that there is a threshold model in which oncogenic transformation is increasingly likely once a number of metabolic abnormalities are combined.

From a clinical standpoint, internists should consider a structured oncology risk score for patients with MetS that incorporates the following factors:

- **Anthropometrics:** waist circumference, waist-to-hip ratio, BMI.
- **Glycemic status:** HbA1c level, fasting insulin level, and presence/duration of type 2 diabetes.
- **Liver health:** Imaging evidence of NAFLD and elevated ALT/AST levels.
- **Family history and lifestyle factors:** diet, physical inactivity, alcohol consumption, and smoking.

While formal calculators are still being validated, a simple “red flag” system can already be applied; any patient with obesity, diabetes, and NAFLD should be considered at high oncologic risk, warranting closer surveillance and follow-up.

Cancer Screening in MetS: Adapting Current Guidelines

➢ **Colorectal Cancer**

Colorectal cancer (CRC) is strongly correlated with MetS. The general rules indicate that one should undergo colonoscopy at 45-50 years of age in case of being of average risk. Nevertheless, there is new evidence that obese, diabetic men could be helped by an earlier start or a reduction in the frequency of colonoscopies [31]. As an illustration, adenomas are more prevalent and tend to develop faster in centrally obese men who do not have good glycemic control. In reality, internists are advised to have personalized conversations with such patients; in the presence of other risk factors (family history, past adenoma, chronic smoking), colonoscopy in the early 40s can be reasonable.

➢ **Breast Cancer**

Postmenopausal women with MetS are at a risk of breast cancer almost half that of metabolically healthy women [64]. Existing mammography procedures (biennial screening from the age of 50 years) may not be suitable for this group. Screening once a year from the age of 40 or 45 years, especially in obese and diabetic women, may help in early detection. Imaging should be used alongside lifestyle counseling, as weight loss and exercise have quantifiable protective effects.

➢ **Hepatocellular Carcinoma (HCC) in NAFLD**

NAFLD is rapidly becoming a major cause of hepatocellular carcinoma (HCC) in most areas. Surveillance with ultrasound +/- AFP (every six months) is recommended in the current hepatology guidelines for patients with cirrhosis. However, this is not the case for NAFLD-HCC, which tends to develop in non-cirrhotic livers, especially among diabetics [32]. There is a dilemma among internists regarding whether all patients with NAFLD should be subjected to regular surveillance. Although cost-effectiveness studies are in progress, a pragmatic approach is to survey high-risk subgroups, such as patients with diabetes and obesity, older age, or PNPLA3 genetic variants (where available). Such patients should undergo liver ultrasound every 6-12 months even in the absence of cirrhosis.

➢ **Endometrial Cancer**

Women with obesity who are insulin resistant are at a significantly high risk of developing endometrial cancer. Practically, a low referral threshold must be set in cases of abnormal uterine bleeding, as reported by women with MetS by internists. Delays in transvaginal ultrasound and endometrial biopsy should be avoided because the early clinical manifestations of the condition are often obscured or complicated by metabolic risk factors [33].

➢ **Prostate, Gastric, and Hematologic Cancers**

The evidence of these malignancies is not as revealing but is still of clinical importance. Prostate cancer is more likely to be diagnosed at an advanced stage and is associated with a poor prognosis in men with MetS [34]. Even when PSA screening is not remarkable, internists should focus on risk factor modification. MetS has been indicated to increase the risk of gastric cancer, which is widely prevalent in Asia, by approximately 25% [35]. Therefore, diabetic or obese patients undergoing endoscopy because of dyspepsia can be of interest for close observation of premalignant lesions. Obesity and insulin resistance have also been identified as causes of

hematologic cancers, especially lymphomas; however, there are no specific screening recommendations [36].

Cancer	Standard guideline	Suggested modification in MetS patients
Colorectal	Colonoscopy age 45–50	Consider earlier and shorter intervals if obese/diabetic men
Breast	Biennial mammogram age 50+	Annual mammogram age 40–45 in postmenopausal MetS women
HCC	US ± AFP if cirrhosis	Consider NAFLD diabetics and obese non-cirrhotics for US/AFP every 6–12 mo
Endometrial	Symptom-driven	Lower threshold for biopsy in obese/diabetic women with bleeding
Prostate	PSA discussion age 50–55	Aggressive risk modification in MetS even if PSA low

Lifestyle Interventions as Cancer Prevention

➢ Weight Loss

The most effective intervention method to curb both metabolic and oncological risks is weight loss. The Diabetes Prevention Program (DPP) revealed that a small amount of weight loss (approximately 7 percent) decreased the occurrence of diabetes by half [37]. Secondary analyses provided evidence of concomitant decreases in inflammatory and insulin markers, which are pertinent to cancer biology. The Look AHEAD trial, which followed the outcomes of over 5,000 overweight diabetics, indicated sustained weight loss and cardiovascular and metabolic results accompanied by a reduction in cancer biomarkers [38]. Moreover, the bariatric surgery cohorts showed excellent findings: women who underwent bariatric surgery women had 30-40 lower cancer rates throughout the country, especially for breast and endometrial malignancies [39].

➢ Diet

The prevention of cancer relies mostly on diet quality. In meta-analyses, the Mediterranean diet, which comprises fruits, vegetables, whole grains, legumes, fish, and unsaturated fat, has been found to lower the risk of colorectal and breast cancer [40]. In contrast, Western diets that are rich in processed meat, refined carbohydrates, and saturated fats are inflammatory, insulin-resistant, and oncogenic. Internists are encouraged to recommend plant-based and high-fiber diets to patients with MetS not only for metabolic health but also as a preventive measure against cancer. Basic measures, such as substituting red meat with fish or legumes, adding more fiber, and reducing the consumption of sugar-sweetened beverages, can have a significant long-term impact.

➢ Physical Activity

It has been shown that there are various metabolic abnormalities that are countered by physical activity and decreased cancer rates. The NIH-AARP cohort of 1.4 million participants revealed that the greater the activity, the lower the incidence of 13 cancers, including colon, breast, endometrial, and liver cancer [41]. Exercise enhances insulin sensitivity, decreases visceral adiposity, alters adipokine release, and reduces systemic inflammation. Moderate activity should be performed for at least 150 min per week, with a higher benefit seen with large volumes. Exercise and weight reduction have a synergistic effect in obese individuals.

➢ Smoking and Alcohol

Smoking and alcohol consumption are synergistic with MetS in reducing the risk of cancer. For example, alcohol triggers NAFLD to HCC [42], whereas smoking triggers colorectal and pancreatic cancers. Thus, cessation counseling has become increasingly relevant for the MetS population. The inclusion of smoking cessation and alcohol moderation in metabolic care systems has revolutionized prevention strategies in oncology.

Practical Considerations for Internal Medicine Training and Practice

Although the evidence on the association between MetS and cancer is strong, there are several challenges to its application in clinical practice. In most cases, the internists do not have enough time during the consultation to discuss oncological prevention when treating diabetes, hypertension, and dyslipidemia. Embedding preventive prompts into electronic medical records (EMRs) can be useful. An example of this is the case of a patient with obesity and diabetes; when they are coded, EMR can automatically create cancer reminders to have colonoscopy, mammography tests, or liver ultrasound. Second, there is a gap in awareness. A survey indicated that most internal medicine residents are unaware of the cancer risks associated with MetS [43]. Residency training should include oncologic prevention modules so that future internists can integrate this knowledge as a routine. Third, lifestyle interventions are usually impeded by cultural and socioeconomic factors. Patients may be deprived of healthy food, suitable physical activity, or weight loss resources. Therefore, internists should collaborate with dietitians, social workers, and community health programs to develop manageable plans. Finally, the change toward treating MetS as a precancerous disease must be advocated at the policy level. National guidelines now focus on cardiovascular outcomes and seldom on oncologic risks. Modifying the recommendations to emphasize the implications of cancer may enable internists to be more authoritative in their actions.

Clinical Implications and Pharmacological Interventions

Pharmacological Interventions and Multidisciplinary Management

Metformin: cornerstone with plausible anticancer benefit

The first-line treatment for type 2 diabetes is metformin because of its effectiveness, weight neutrality, and safety in a wide population [44]. Mechanistically, it stimulates AMPK and suppresses mTOR, thereby lowering proliferative signaling. It also reduces insulin levels in circulation, thus reducing the insulin/IGF fuel of tumor growth [45]. Cancer evidence. In patients with diabetes, observational meta-analyses have consistently shown that metformin reduces the risk and improves the survival of a number of cancers (colorectal, breast, and liver); however, the magnitude of this reduction cannot be measured by confounding factors (unmeasured). There are few randomized cancer prevention trials, but perioperative and adjuvant trials are increasingly evaluating metformin as an add-on metabolic modulator in high-risk environments. It is used in internal medicine. The treatment was initiated at 500 mg/day with food and titrate after 1-2 weeks to 1500–2000 mg/day, as tolerated. eGFR should be monitored prior to starting and once yearly; the majority of guidance permits use at eGFR 30 mL/min/1.73 m 2 with dose precautions and temporary withholding in the face of acute disease or contrast exposure. Surveillance of vitamin B12 once per year in patients on long-term use and GI effects and slow titration. In cases where it is most helpful for the oncologist. Obese patients with hyperinsulinemia (high fasting insulin/HbA1c) or NAFLD are plausible beneficiaries of the greatest cancer risk modulation, as the insulin-IGF and mTOR axes are metformin-targeted.

Statins: mevalonate pathway and tumor biology

Rationale. Statins suppress HMG-CoA reductase, reducing the isoprenoid intermediates needed by prenylate RAS/RHO GTPases to blunt proliferation, migration, and survival signalling in tumor cells [46].

Cancer evidence. One large meta-analysis found that statins did not increase overall cancer in randomized trials (good news on safety) [47], whereas observational and umbrella meta-analyses indicated that statins reduced the risk of hepatocellular and colorectal cancers, predominantly in high-risk metabolic phenotypes [48].

It is used in internal medicine. High-intensity statins (atorvastatin 40 80 mg, rosuvastatin 20 40 mg) should be considered in patients at risk of atherosclerosis; these dosages are safe in NAFLD and have the potential to slow hepatic inflammation [49]. Monitor CYP3A4 interactions (e.g., macrolides and azoles). In case of intolerance, alternate day dosing or change of agents should be employed.

Who benefits most. Statins can be a rational default, except when contraindicated, as dual therapy can be received by patients with MetS, dyslipidemia, and NAFLD (and/or diabetes) and provide cardiovascular and hepatic/oncologic benefits [50].

GLP-1 receptor agonists: weight loss, insulin lowering, and safety

Rationale. GLP-1RAs (e.g., liraglutide and semaglutide) provide potent weight loss and glycemic control, decreasing insulin requirements and systemic inflammation, which, in turn, should theoretically lead to a decreased obesity-induced cancer risk [51]. Cancer evidence. Several meta-analyses have indicated no general effect of GLP-1RAs on cancer, and pancreatic and thyroid C-cell signals in animals have not been associated with any substantial human risk in clinical trials and pharmacovigilance studies [52]. Reduced incidence of cancers associated with obesity has been reported in observational datasets of users, but these are hypothesis-generating signals. It is used in internal medicine. In the case of obesity with or without diabetes, semaglutide 2.4 mg per week (following step-up titration) yields approximately 15% weight loss and strong metabolic benefits, enhancing a variety of cancer-relevant biomarkers (insulin and CRP) [53]. GI effects, risk of gallbladder disease, and avoidance counsel for MEN2/medullary thyroid carcinoma histories (class warning). Who benefits most. The strongest metabolic changes are frequently observed in patients with severe obesity, postmenopausal women with central adiposity, and NAFLD, and these groups coincide with an elevated oncologic risk [54].

SGLT2 inhibitors: organ-protective agents with neutral/possibly favorable cancer profile

Rationale. SGLT2 inhibitors decrease glucose reabsorption, decrease ambient glycemia and insulin, decrease weight and adiposity viscerosity, and have anti-inflammatory and antioxidant actions in cardio-renal tissues [55]. Cancer evidence. Revised meta-analyses indicate no overall cancer risk excess; initial concerns about bladder cancer have not been found to continue with longer follow-ups. Certain cohort signals indicate that HCC is lower in patients with diabetes and NAFLD; however, causality has not been established [56]. It is used in internal medicine. Empagliflozin, dapagliflozin, and canagliflozin were chosen to protect organs in diabetic patients with ASCVD/CKD/HF because they showed favorable organ protection. Education about euglycemic DKA (occurring during acute illness/fasting), genital mycotic infections, and volume depletion. The majority of agents may be initiated at an eGFR of 3045 or more based on the label. Who benefits most. Patients with NaFLD Diabetes CKD/HF have robust cardiorenal outcomes with at least neutral oncologic surrogates, frequently a high-value alternative to MetS.

Aspirin and NSAIDs: targeted chemoprevention vs bleeding risk

Rationale. The COX-2/PGE2-mediated signal facilitates proliferation, angiogenesis, and immune evasion in the

colorectal mucosa, and aspirin inhibits platelet-mediated tumor cell interactions and prostaglandin [57]. Cancer evidence. Daily aspirin use over the long term (510 years) lowers the incidence and mortality of colorectal cancer, and the effects become apparent after 510 years of use [58]. Nevertheless, all-cause mortality in ASPREE in older adults was higher, partly due to cancer-related death, thus underscoring the importance of carefully selecting and avoiding blanket usage in the elderly [59]. It is used in internal medicine to treat various diseases. aspirin (75100 mg/day) was used for the prevention of CRC in 5069-year-old with high cardiovascular risk and low bleeding risk after shared decision-making [60]. Risk assessment of ulcers, comorbid anticoagulants, and H. pylori (eliminated in case of positive results). Primary prevention of aspirin use in adults aged ≥ 70 years should not be routine unless there are strong reasons [61].

Other candidates: what to consider (and what to avoid)

PPAR agonists (thiazolidinedione). Although pioglitazone has been shown to enhance insulin sensitivity and NAFLD histology events, bladder cancer events have been reported, and its use in any hypothetical anticancer action is discouraged by most clinicians [62]. Vitamin D. Biologic plausibility (differentiating cells, immune modulation) is good, but the VITAL trial did not reveal any reduction in incident cancer, although cancer mortality could be reduced modestly; supplementation must be taken in response to bone-health signals and not on the basis of cancer prevention [63]. Anti-inflammatory Biologics. In CANTOS, IL-1 inhibition prevented the prevalence of post-MI lung cancer and mortality, which is indicative of inflammation as a pathogenic factor. Nevertheless, its regular use as a preventive measure against cancer is not possible because of the risk of infection and expense in the context of MetS [64].

Practical prescribing: a phenotype-based algorithm

To make choices actionable in internal medicine, drugs are mapped to the patient phenotypes and oncologic pathways.

1. **Obesity, insulin-resistant diabetes with NAFLD (ALT↑, ultrasound steatosis)**
    - Metformin backbone (AMPK/mTOR, ↓insulin) [65]
    - Statin (cardiovascular + possible HCC/CRC benefit; safe in NAFLD) [66]
    - Add GLP-1RA for weight loss (largest effect on oncologic drivers) [67]
    - Consider SGLT2i if CKD/HF or poor glycemic control (neutral/favorable cancer profile) [68]
    - Aspirin only if 50–69 yrs with low bleeding risk and CVD benefit [69]
2. **Postmenopausal women with central obesity, prediabetes, or dyslipidemia**
    - Metformin (if glucose high-risk) + statin for LDL control [70]
    - GLP-1RA if BMI ≥27–30 for weight-centric strategy (breast/endometrial risk modulated via weight loss)
    - Emphasize annual mammography and aggressive lifestyle change (see Part 3A)
3. **Elderly patients (≥70 years) with frailty and MetS**
    - Prioritize SGLT2i/statin for cardiorenal protection; be cautious with aspirin given ASPREE findings [71]
    - Use GLP-1RA selectively (GI tolerance, sarcopenia risk with rapid weight loss)
4. **CKD stage 3 diabetes with obesity**
    - **Metformin** (dose-limited by eGFR) + SGLT2i for kidney benefit [72]
    - Statin for ASCVD risk; consider GLP-1RA for weight if GI tolerance acceptable

Drug–drug interactions and safety factors

- **Statins:** monitor CYP3A4 inhibitors (macrolides/azoles); check CK levels only if symptoms are present.
- **Metformin:** Hold around contrast or acute illness; monitor B12.
- **SGLT2i:** sick-day rules; stop before major surgery to avoid euglycemic DKA.
- **GLP-1RA:** slow titration to mitigate nausea and monitor gallbladder symptoms.
- **Aspirin:** assess GI bleed risk; test/treat H. pylori when appropriate.

Multidisciplinary care models: making prevention real

Why teams matter. MetS spans endocrinology, hepatology, cardiology, oncology, and primary care. Patients at the metabolic–oncologic crossroads (e.g., diabetes + NAFLD) benefit from coordinated pathways, a model that improves adherence to surveillance (HCC ultrasound), optimizes metabolic therapy, and streamlines lifestyle services.

Clinic design.

- Metabolic liver clinics for NAFLD: Embed ultrasound reminders (q6–12 months) and standardized fibrosis risk tools (FIB-4, elastography) to triage patients who need hepatology referral and HCC surveillance under guidance, such as AASLD [73].
- Cardiometabolic-oncology prevention clinics: Statin/metformin/GLP-1RA/SGLT2i optimization with CRC and breast screening
- Dietitian-led group visits and behavioral programs to sustain weight loss (a key driver of cancer risk reduction).

EMR prompts and the quality metrics. Build clinical decision support: if "T2D + BMI ≥30 + ALT↑," prompt: "Assess NAFLD; consider HCC surveillance if high-risk; optimize GLP-1RA/SGLT2i/statin." Care-gap dashboards were added for colonoscopy, mammography, and liver ultrasound. Over time, process metrics (surveillance adherence) and outcomes (weight, HbA1c, LDL, and incident cancer) were tracked.

Equity & access. GLP-1RA and SGLT2i costs can impede uptake. Programs leveraging insurance navigation, generic statins/metformin, and community partnerships (exercise/food access) can help narrow these disparities.

Implementation playbook for internists

1. **Risk flag for every patient with MetS** (waist circumference, HbA1c, ALT, and NAFLD imaging).
2. **Map phenotype → meds** (as above) and document a **prevention plan**.
3. **Stand-up EMR reminders** for CRC, breast cancer, HCC, and endometrial red flags.
4. **Bundle counseling** (weight, diet pattern, activity, smoking, and alcohol) was provided at each visit.
5. **Referral loops** were created (hepatology for advanced fibrosis and oncology for high-risk lesions).
6. **We audited quarterly** surveillance adherence, metabolic targets, and medication persistence.
7. **Educate your team** (residents and nurses) using quick-reference cards and order sets.

Future Directions and Research Gaps

Precision Risk, Early Detection, and Systems Innovation

6.1 Precision medicine for metabolic–oncologic risk

Existing risk tools continue to rely on coarse indicators (BMI, waist circumference), despite the fact that the risk of cancer in MetS is biologically diverse and varies by sex. Risk can be refined in precision medicine by integrating co-layered genetic, metabolic, and clinical data into individualized scores [74]. Substitutions in PNPLA3, TM6SF2, and HSD17B13 may distinguish patients with NAFLD who develop advanced fibrosis and hepatocellular carcinoma, providing a genetics-based surveillance template [75]. More recent clinical definitions, such as MAFLD, have focused on positive metabolic criteria rather than alcohol exclusion and may be more reflective of the at-risk phenotype that internists actually observe [76]. In addition to genomics, metabolomics (branched-chain amino acids, acylcarnitines, and lipidomic signatures) can identify insulin resistance and inflammatory tone years before the onset of cancer, and help justify earlier intervention years before cancer appears in the patient [77]. In the long run, multi-omic risk panels can be used to screen those who warrant further investigation of colorectal, liver, or endometrial cancers as a component of routine internal medicine practice.

Liquid biopsy and blood-based early detection

Circulating tumor DNA (ctDNA) and methylation-based assays are shifting the field of oncology toward prediagnostic screening. Multi-analyte blood tests can identify cancers with clinically relevant specificity; however, sensitivity differs by stage and tissue of origin [78]. A massive methylation cfDNA experiment showed that it could detect many cancers with the prediction of tissue-of-origin, indicating a direction toward increasing site-specific screening in high-risk MetS cohorts [79]. The combination of a blood test with confirmatory imaging in a pragmatic trial demonstrated workability in population screening processes; however, cost-effectiveness and interval-cancer questions remain to be addressed [80]. In the case of internists, the near-term role is adjunctive, such as emphasizing colonoscopy or liver imaging among patients at metabolic risk until the guidelines mature.

Imaging and noninvasive fibrosis staging in NAFLD

As HCC may develop in the absence of cirrhosis in NAFLD, non-invasive fibrosis and steatosis instruments will help define surveillance trajectories. Elastography and composite serum panels (e.g., FIB-4, ELF) can be used to stratify the risk of fibrosis and may inform individuals about the need for ultrasound after 6-12 months, as opposed to those requiring less frequent reviews [81]. MRI-PDFF accurately measures liver fat and may be a pharmacodynamic biomarker in weight loss drug or insulin sensitizer prevention trials in MetS [82]. These tools can be embedded into internal medicine clinics to make opportunistic liver checks a structured, risk-based surveillance.

Artificial intelligence for prediction and care-gaps

Longitudinal vitals, labs, methods, imaging, and social determinants are incorporated into machine learning on EHRs to forecast complex outcomes with more accuracy than manual scores [83]. In cancer, AI can integrate metabolic features, imaging, and genomics to raise a red flag on CRC or HCC risk trajectories earlier than the existing triggers [84]. Nevertheless, models should be externally checked, biases assessed, and interpretable to clinicians and fair deployment, particularly in the poorly served MetS groups.

Microbiome modulation as prevention science

MetS is defined as dysbiosis (loss of diversity, bile acid metabolism) that promotes inflammation and genotoxic liver and colon [85]. Dietary fibers, polyphenols, and fermented foods reorient the microbiome toward the synthesis of short-chain fatty acids and reduce endotoxemia, providing low-risk levers for internists [86]. As demonstrated in proof-of-concept studies, fecal microbiota transfer from lean donors can have acute effects on insulin sensitivity in metabolic syndrome, implicating the microbiome as a manipulable node in the

MetS-cancer axis [87]. The next notable steps are larger, durable, and cancer endpoint trials.

Trial design: from signals to standards

Several anticancer signals in MetS (metformin, statins, and GLP-1RA) are the result of confounded observational data. Continued randomized trials, such as MA.32 (metformin in breast cancer prevention/adjuvancy), will illuminate the role of drug classes other than glucose regulation. In NAFLD, semaglutide and liraglutide have been shown to enhance NASH histology and weight, a mechanistic transition to HCC risk reduction that needs to be evaluated using hard cancer endpoints and extended follow-up. An opportunity to prospectively incorporate cancer surveillance results in MetS cohorts [88] arises when weight-loss trials report a reduction of ≥1015 percent (e.g., semaglutide). Likewise, SGLT2 inhibitors enhance hepatic steatosis and metabolic phenotypes; therefore, any connection to the incidence of HCC in randomized studies is a pending study gap.

Health-system levers and policy

Innovation at the clinic level must be coupled with policies. The drivers of NCDs that are reduced by WHO best buys (food policy, physical-activity environments, and tobacco control) are the same drivers of obesity-related cancer [89]. Sugar taxation on soft drinks decreases purchases and consumption at the population level, pushing the caloric balance in a direction that accumulates over time for cancer prevention. Dietary-risk analyses list low whole-grain and fruit consumption as one of the top mortality drivers worldwide, reinforcing the common prevention dividend of cardiometabolic diseases and cancer. These multifaceted interventions can be implemented in clinics with the assistance of implementation science frameworks.

Limits of Evidence, Practice Blueprint, and Conclusion

What we still don't know

Although it has a high degree of biological plausibility and epidemiology, much evidence on preventing MetS is observational, increasing the risks of confounding and reverse causation. For example, the reduced cancer incidence among metformin users may be due to channeling bias and not the drug effect [84]. Evidence that weight-loss drugs or SGLT2 inhibitors prevent cancer has not yet been established; most trials use surrogate endpoints (weight, NASH histology) instead of incident cancer. The screening questions are yet to be resolved: Which patients with non-cirrhotic NAFLD should be screened for HCC? How can we integrate the use of elastography, laboratories, and genetics to make this decision? With the maturity of liquid biopsy technologies, practical experiments are required to establish the underlying mortality benefits, acceptable false-positive rates, and fair access to different metabolic phenotypes[89].

A prioritized research agenda

1. Phenotype-driven RCTs. High-risk MetS phenotypes (e.g., NAFLD + diabetes + elevated fibrosis score) were randomized to GLP-1RA/SGLT2i/statin/metformin combinations with cancer endpoints (CRC adenoma burden, HCC incidence) over 5–10 years.
2. Integrated risk calculators. Combined genetics (PNPLA3/HSD17B13), elastography, and omics into validated, externally tested calculators to trigger bespoke screening intervals.
3. Liquid biopsy implementation trial. Test methylation of cfDNA as an adjunct to colonoscopy/ultrasound in MetS, measuring stage shift, and mortality.
4. Microbiome intervention trials. Diet, pre/probiotics, or FMT with durable metabolic and neoplastic endpoints (adenoma recurrence and dysplasia).
5. Equity and policy evaluation. Rigorous studies on SSB taxes, built environment changes, and reimbursement policies for anti-obesity measures on cancer outcomes in high-MetS regions are needed.

Practice blueprint for internists

Risk flag at intake. In any patient with BMI ≥30 or waist circumference above cut-off points, add a MetS–oncology flag; record HbA1c/fasting insulin, lipid panel, and NAFLD screening (ALT, FIB-4 → elastography if ≥intermediate).

Tiered surveillance.

- CRC: If the patient is male, obese, or diabetic, discuss earlier colonoscopy and tighter intervals, especially with family history.
- Breast: Annual mammography for postmenopausal women with MetS coupled with weight loss counselling.
- HCC: If NAFLD + diabetes and fibrosis risk are not trivial, consider US ± AFP every 6–12 months, even without cirrhosis, pending shared decision making
- Endometrium: Low threshold for biopsy in obese/insulin-resistant women with abnormal bleeding.

Therapeutic stack (metabolic and preventive).

- Metformin (unless contraindicated) for insulin lowering and mTOR brake.
- Statins are used for ASCVD and possible CRC/HCC reduction and are safe in NAFLD.
- Add GLP-1RA for ≥10–15% weight-loss targets; consider SGLT2i for CKD/HF or added glycemic/weight benefit [89].
- Aspirin chemoprevention is only recommended when CVD benefits outweigh bleeding risk (generally 50–69 years, low bleeding risk).

Team and tools. Building metabolic liver pathways (NAFLD → elastography → HCC surveillance), creating EHR prompts for missed colonoscopy/mammography/US, and partnering with dietitians and community programs to support behavioral change at scale [86].

Global perspective and synergy with infection control

In the Western context, obesity-related cancers prevail, whereas in Asia, NAFLD-HCC and gastric cancer continue to be the main cancers, indicating metabolic and infectious cofactors [89]. HBV vaccines have reduced childhood HCC; evidence-based prevention can alter cancer epidemiology at the population level. Likewise, metachronous gastric cancer is less likely to occur following H. pylori elimination following endoscopic resection, demonstrating how infection management is an adjunct to metabolic prevention in high-risk areas.

CONCLUSION

Metabolic syndrome is most effectively conceptualized as a pre-neoplastic field effect, which is a systemic condition that decreases the barrier to malignant changes in various organs. Population studies, mechanistic biology, and interventional science have converged to support oncological vigilance in internal medicine. What has changed in practice? Measuring central adiposity, noninvasive staging of liver disease, weight loss, prioritizing, reducing insulin exposure, and screening metabolic risk by changing the intensity of screening. Drugs that minimize cardiometabolic incidents and are likely to counteract carcinogenesis should be selected. Delivering clinics and EHR nudges that form teams to make prevention a habit and not a dream. With the rise of precision tools, liquid biopsies, and powerful metabolic therapies, the future is clear: addressing metabolic dysfunction at an early and systemic level, internists can change the cancer curves not only at the level of the individual patient but also at the level of a population.

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