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CLINICAL CASE CHALLENGES

Cardiovascular Prevention in Individuals at High Risk of Developing Cancer

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Despite impressive advances in diagnosis and treatment, cancer remains a serious disease with a significant risk of recurrence and death. Although personalized and less toxic therapies have decreased the public health burden associated with many cancer types, the ideal cancer-mitigating intervention focuses on prevention through adoption of healthy lifestyle behaviors and avoidance of carcinogens. Cancer prevention strategies also include risk-modifying interventions (e.g., prophylactic mastectomy, prophylactic oophorectomy), some of which may be associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD).

The following clinical scenarios focused on cancer prevention highlight the value of systematic cardiovascular risk assessment in individuals at high risk of cancer who are treated with cancer risk-reducing therapies. Recommendations regarding the evaluation of lipid abnormalities and the role of coronary artery calcium (CAC) scan are provided, balancing existing evidence with the need for rigorous data that specifically applies to cancer populations.

CASE 1: PATIENTS AT HIGH RISK FOR OVARIAN CANCER UNDERGOING PROPHYLACTIC OOPHORECTOMY

A 45-year-old Caucasian woman with a known pathogenic BRCA1 mutation underwent bilateral prophylactic oophorectomy 1 year ago. She had not had menstrual periods since then, and is considered menopausal. She is treated with amlodipine for hypertension. She is a heavy smoker and follows a sedentary lifestyle. She does not have diabetes mellitus (hemoglobin A1C, 5.4%). Her office blood pressure is 145/95 mm Hg, weight is 187 pounds (85 kg), and body mass index is 29.3 kg/m^2. Her lipid profile is as follows: low-density lipoprotein cholesterol 105 mg/dl, total cholesterol 177 mg/dl, high-density lipoprotein cholesterol 45 mg/dl and triglyceride level 135 mg/dl. Her 10-year ASCVD risk using the pooled cohort equation is 5.3%. She is reluctant to consider statin therapy as she is already taking multiple medications.

In terms of additional potential cardiovascular risk factors, BRCA1 has been implicated in the repair of DNA double-stranded breaks, and its loss-of-function is associated with reduced cardiac performance and

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAC = coronary artery calcium

CVD = cardiovascular disease

FAP = familial adenomatous polyposis

NSAID = nonsteroidal anti-inflammatory drug

accelerated cardiomyocyte death in murine models. Human studies investigating the association between BRCA1/2 mutations and incident cardiovascular disease (CVD) have shown conflicting results, potentially due to variable sample sizes and ethnic-specific differences in the pathogenesis of CVD (1). Bilateral prophylactic oophorectomy is associated with a 96% reduction in the risk of epithelial ovarian cancer in BRCA1/2 mutation carriers. In women younger than 45 years of age, the risk of cardiovascular death after surgical oophorectomy is 44% higher than that of healthy control subjects (2). Premature menopause was shown to predict future coronary heart disease and stroke in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort and represents an important risk-enhancing factor (3).

PRACTICAL STRATEGIES

The patient has a borderline-range (5% to 7.4%) estimated ASCVD risk in the presence of a risk-enhancing factor, namely premature menopause. Given this, we would advocate for a discussion regarding initiation of moderate-intensity statin therapy. However, the patient has expressed a preference to avoid taking additional medications. In this case, a CAC scan could help refine ASCVD risk assessment (4). An Agatston score of ≥100 and/or a CAC score ≥75th percentile for the patient's age, sex, and race would suggest a benefit to statin initiation, although there are no randomized clinical trial data supporting the use of CAC in treatment decisions. A CAC score of 300 would increase this patient's 10-year coronary heart disease risk to 10% using the MESA risk score calculator, and would further support the use of lipid-lowering therapy. Nicotine cessation should be a primary strategy to reduce CVD risk in this patient, while the importance of healthy lifestyle habits, normal-range blood pressure and lipid profile, weight loss, and glycemic control should also be emphasized.

CASE 2: PATIENTS AT HIGH RISK FOR COLORECTAL CANCER RECEIVING CELECOXIB

A 53-year-old Caucasian man with familial adenomatous polyposis (FAP) underwent prophylactic total colectomy 3 months prior and was subsequently started on sulindac to delay the development of adenomas in the upper gastrointestinal tract and in the retained rectum. The patient has a history of hypertension controlled with hydrochlorothiazide and diet-controlled diabetes mellitus. He is a nonsmoker and maintains a physically active lifestyle. His family history is significant for a brother who experienced ST-segment elevation myocardial infarction at the age of 49 years. His office blood pressure is 125/75 mm Hg, body weight 160 pounds (68 kg), and body mass index 22 kg/m^2. His lipid profile is as follows: low-density lipoprotein cholesterol 145 mg/dl, total cholesterol 198 mg/dl, high-density lipoprotein cholesterol 37 mg/dl, and triglyceride level 80 mg/dl. His 10-year ASCVD risk using the pooled cohort equation is 13%.

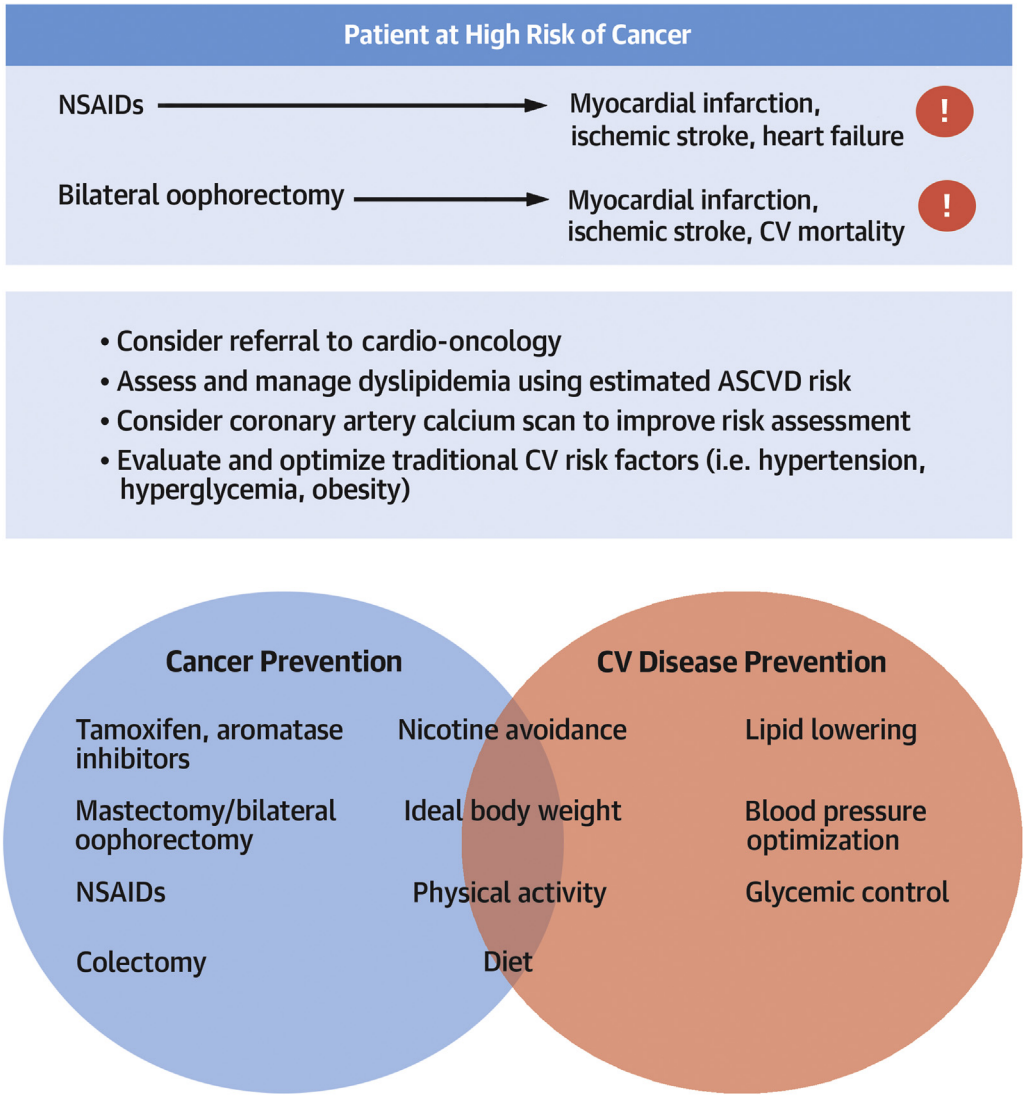
Aspirin and sulindac are commonly used, contemporary pharmacoprophylactic therapies in patients who are at high risk of colorectal cancer, with the former being the preferred drug for individuals with sporadic adenomas and the latter for those with FAP. In the late 1990s, celecoxib was approved for use in patients with FAP. The risk-reduction benefit appeared to be significant with a 31% lower colorectal polyp burden rate in FAP patients treated with celecoxib and a 15% lower incidence of duodenal polyps. However, in a large study of colorectal adenoma prevention, long-term use of celecoxib (200 or 400 mg twice daily) was associated with a 3.4-fold increased risk of death from CVD, myocardial infarction, stroke, or heart failure (5).

In addition, a meta-analysis of randomized controlled trials showed that celecoxib use was associated with a 3-fold increased risk of myocardial infarction. A subsequent prospective investigation, assessing the safety of a lower dose of celecoxib (200 mg daily), did not demonstrate a statistically significant hazard; as such, the cardiovascular risk mediated by celecoxib remains incompletely understood (6). In 2004, due to high cardiovascular event rates, rofecoxib was removed from the market, and a black-box warning was issued for celecoxib the following year.

PRACTICAL STRATEGIES

This patient is in an intermediate-risk ASCVD category, but has 2 additional factors that increase his likelihood of future cardiovascular events: chronic nonsteroidal anti-inflammatory drug (NSAID) use and a strong family history of premature ASCVD. Importantly, the presence of diabetes mellitus in an individual 40 to 75 years of age is an indication for the use of moderate-intensity statins regardless of ASCVD score, and in an individual

FIGURE 1 Interactions Between Risk-Reducing Interventions in Oncology and Cardiovascular Medicine



Numerous risk-reducing interventions are utilized by cardiologists and oncologists in patients at risk of developing cardiovascular disease or cancer. Some therapies used to lower the incidence of cancer in individuals at increased risk for malignancy (e.g., prophylactic bilateral oophorectomy in carriers of BRCA1/2 mutations, sulindac in patients with familial adenomatous polyposis) may potentially increase the risk of cardiovascular disease. Consideration of such interventions, particularly in individuals with coexisting cardiovascular risk factors or comorbidities, should prompt referral to cardiology for careful risk assessment and modification that integrates traditional risk factors and the effects of cancer risk-reducing therapies. ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; NSAID = nonsteroidal anti-inflammatory drug.

with multiple ASCVD risk factors, high-intensity statin therapy should be considered. NSAID use and family history are not incorporated into the pooled cohort equation, but represent established potentiators of CVD.

It is important to understand that patients with FAP who are treated with preventive total colectomy have favorable long-term survival outcomes. The notion that CVD represents an important competing risk to cancer mortality should be conveyed and serve as a motivating factor to introduce lifestyle changes and consideration of pharmacological therapies. Consideration of chronic NSAID initiation in this patient, especially in the context of conventional cardiovascular risk factors, should prompt referral to an internist or cardiologist.

Importantly, decisions regarding long-term NSAID therapy should balance the reduced polyp and potential colorectal cancer rate with the increased CVD risk.

Attainment of optimal blood pressure and glycemic control should be targeted. In addition, a CAC scan could be considered. If highly abnormal, it could be used to counsel and motivate this patient to further modify his lifestyle (4). It would also be reasonable to check a lipoprotein(a) level given the strong family history of premature atherosclerosis. Due to the expected long-term use of sulindac, statin therapy and improved lifestyle habits would be appropriate risk-reduction interventions in this case.

CONCLUSIONS

Cardiovascular risk assessment in individuals who are deemed to be at high risk for cancer is distinct from that in patients with an established cancer. Specific therapies aimed at reducing the risk of cancer may augment cardiovascular risk and deserve careful consideration. Two important tenets of cardiovascular risk assessment include evaluation of lipid abnormalities and understanding the role of CAC imaging in refining ASCVD risk stratification in this unique population.

Although more research is needed regarding the value of CAC burden in patients with cancer, available evidence suggests that elevated CAC scores are predictive of both future cardiovascular events and cancer. In a recent study, CAC >300, when compared with a score of 0, was associated with a 3.7-fold increase in the risk of CV death and a 30% increase in the risk of cancer death (7). The most common cause of death among individuals with 0 CAC was cancer (50%), whereas patients with CAC >300 experienced most of the mortality due to CVD.

In a study of 464 patients with locally-advanced nonsmall-cell lung cancer treated with thoracic radiation therapy, an increased CAC score, measured from planning radiation therapy computed tomography, was associated with an elevated risk of all-cause mortality (hazard ratio: 1.29; confidence interval: 1.0 to 1.6; $p = 0.027$) (8). In a separate analysis of breast cancer patients who had received radiation therapy, higher pre-RT CAC scores were associated with a higher likelihood of acute coronary syndrome at 9 years of follow-up (hazard ratio: 1.42; confidence interval: 0.49 to 4.17; $p = 0.519$) (9). Coronary calcification is therefore a predictor of CVD in the cancer population and further research is needed to better characterize the contribution of cause-specific mortality and cardiovascular events in cancer patients according to CAC levels (10). Last, breast arterial calcifications detected on screening mammogram are an independent marker for the presence of coronary artery disease and may help identify women at higher risk of ASCVD.

Lipid-lowering therapies should be considered in patients with cardiovascular risk factors or disease, as per the standard ASCVD risk score. Particular medical interventions to decrease the risk of cancer, such as prophylactic oophorectomy or long-term nonsteroidal anti-inflammatory drugs, may increase the risk of ASCVD and should be regarded as deleterious factors.

In the coming decade, cardio-oncologists may be asked to assess and manage cardiovascular toxicities in individuals who receive cancer risk-reducing interventions but who are free of cancer. Given the increasing data supporting an overlap between the molecular and clinical underpinnings of cancer and heart disease, oncologists should consider involving their cardiovascular medicine colleagues for risk assessment and preemptive management. In addition, longitudinal cardiovascular safety evaluations of specific patient subgroups in whom prophylactic anticancer therapies are considered should be performed to provide an evidence-based understanding of the risks and benefits of such therapies.

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