Welcome to the fifth edition of the Duke Cardio-Oncology newsletter

The cardio-oncology field is moving at fast pace with many opportunities for collaborations, sharing knowledge, and investigating connections.

Two randomized, phase III trials from the Alliance for Clinical Trials in Oncology highlight the clinical overlap between breast cancer and cardiac disease (page 3).

We hope this newsletter serves you to keep you abreast of the latest cardio-oncology news.

The Global Cardio-Oncology Summit 2018

SAVE THE DATE!
September 27–28, 2018, Tampa, FL
Immune Checkpoint Inhibitors in Cancer Therapy

The use of cancer immunotherapy has become widespread in recent decades, having demonstrated promising antitumor responses and safety profiles in clinical trials of both solid and hematological malignances. T lymphocytes (or T cells) are cells of the immune system that can kill cancer cells. On their surface there are the so-called immune checkpoints, paired receptor-ligand molecules, that control the immune responses. When the immune system is activated, these checkpoints are involved in determining an inhibitory feedback loop to reduce the inflammation. Some cancer cells can turn off the immune response—they turn off the T cell bindings to the cell receptor. Immune checkpoint inhibitors targeting receptors on the T cell or tumor cell prevent the tumor cell from attaching to the T cell so that the immune system can infiltrate the cancer and stop its growth. The first immune checkpoint receptor to be characterized and found relevant to cancer therapy was the cytotoxic T lymphocyte antigen 4 (CTLA-4). Ipilimumab, the monoclonal antibody that activates the immune system by targeting CTLA-4, was approved by the FDA in 2011 to treat advanced melanoma based on long-term overall survival observed in a group of treated patients. Due to CTLA-4’s role in modulating early activation of systemic T-lymphocytes immunity, the administration of its inhibitor was associated with frequent adverse events such as rash and colitis thyroiditis, events that mimicked autoimmune disorders.

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Breast Cancer Clinical Trials Targeting Issues Important to Cardiovascular Disease and Cancer

Gretchen Kimmick, MD, MS

The first and second leading causes of death are heart disease and cancer. Together, they accounted for approximately half of all deaths in 2010. \(^{(1,2)}\) It should come as no surprise that they share common risk factors. As demonstrated in Figure 1, there is geographic clustering of cardiovascular disease and cancer in the United States. The epidemiology of the two diseases is remarkably similar and there are several shared risk factors.\(^{(3)}\) Cardiovascular risk factors, including abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, limited physical activity and consumption of fruits, vegetables, and alcohol, account for 90% and 94% of population attributable risk of myocardial infarction in men and women, respectively.\(^{(4)}\) Epidemiologic studies have also demonstrated that these same potentially modifiable risk factors are associated with development of cancer, including lung, breast, prostate, and colon cancers. Many breast cancer patients, for instance, have multiple risk factors for cardiac disease, such as cigarette smoking, diabetes, dyslipidemia, alcohol consumption, obesity, and sedentary lifestyle.\(^{(5–7)}\)

Emerging evidence suggests that inflammation might be one of the common mechanisms linking diet, obesity, tobacco use and time to

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these two seemingly disparate diseases.

Two randomized, phase III, trials from the Alliance for Clinical Trials in Oncology highlight the clinical overlap:

1. **Alliance A011502**: A Randomized Phase III Double Blinded Placebo Controlled Trial of Aspirin as Adjuvant Therapy for Node Positive HER2 Negative Breast Cancer: The ABC Trial

2. **Alliance A011401**: Randomized Phase III Trial Evaluating the Role of Weight Loss in Adjuvant Treatment of Overweight and Obese Women with Early Breast Cancer

These trials stem from epidemiologic and clinical evidence that (1) aspirin intake may decrease breast cancer risk; and (2) obesity contributes to higher breast cancer mortality.

**ASPIRIN AS POSSIBLE ADJUVANT IN EARLY STAGE BREAST CANCER**

**Background**: Inflammation is key in the pathogenesis of atherosclerosis, heart failure and cancer\(^{8–12}\) and use of nonsteroidal anti-inflammatory agents, such as aspirin which is recommended for primary and secondary prevention of CVD, \(^{13}\) may decrease the risk of breast cancer. Among 80,874 postmenopausal women in the prospective Women’s Health Initiative (WHI) study who reported no history of breast cancer or other cancers, regular (2 or more tablets/week for 10 or more years) use of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs), was associated with a 28% reduction in the incidence of breast cancer (95% CI, 0.56—0.91). \(^{14}\) Other meta-analysis of aspirin use have confirmed the reduced risk of breast cancer.\(^{15,16}\) The US Preventive Services Task Force (USPSTF), therefore, recommends that adults 50 to 69 years of age should take daily low-dose aspirin for at least 10 years to reduce their risk for cardiovascular disease (CVD) and colorectal cancer, \(^{17–20}\) but proof of the benefit in breast cancer patients is not as robust.

**Primary objective**: In order to bring aspirin into routine clinical care of women with early-stage breast cancer, investigators in the Alliance for Cancer Clinical Trials, chaired by Dr. Wendy Y. Chen, MD, MPH from Dana Farber Cancer Institute, designed a randomized, placebo-controlled trial to prove its efficacy.

**Main eligibility**: This phase III trial will accrue 2936 women, age 18 to 70 years, with early-stage, node-positive, HER2-negative breast cancer over 30 months.

**Intervention**: Participants will take 300 mg aspirin or placebo for 5 years.

**Endpoints**: With planned follow-up of 48 months, the primary endpoint of invasive disease-free survival will be compared between those taking aspirin and those taking placebo. In addition, cardiovascular endpoints continued on page 5
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will include rate of myocardial infarction, cerebrovascular events, and need for cardiovascular procedures including coronary artery bypass surgery, coronary stent placement, and angioplasty of coronary vessels.

TARGETING OBESITY: A WEIGHT LOSS INTERVENTION TO DECREASE RISK OF BREAST CANCER RECURRENCE

**Background:** Defined as a body mass index (BMI) greater than 30 kg/m², obesity is highly prevalent in developed countries\(^{21}\) and is associated with increased risk of both cardiovascular disease\(^{22,23}\) and cancer. Higher BMI has consistently been shown to increase risk of breast cancer\(^{24–28}\) and worsen breast cancer prognosis. In 1976, the association between obesity and breast cancer recurrence was first reported and, since then, there have been more than 50 studies examining the relationship between body weight and breast cancer prognosis.\(^{29–32}\)

Weight loss interventions for those who are overweight and obese have varying success, but rehabilitation programs after cardiovascular events are highly successful.

**Primary objective:** The Alliance for Cancer Clinical Trials, with study chair Jennifer Ligibel, MD from Dana-Farber Cancer Institute, is conducting a phase III randomized trial to study use of a phone-based weight-loss intervention to improve survival in overweight and obese women.

**Main eligibility:** This trial will enroll 3136 women with a BMI of 27 kg/m² or higher with HER2 negative, stage II and III breast cancer.

**Intervention:** Participants will be randomized to a 2-year health education intervention or the same with a supervised weight loss intervention. The 2-year supervised weight loss intervention will include individual weight loss, caloric restriction, and physical activity goals for each participant, administered through semi-structured phone calls delivered by trained coaches.

Participants will be followed for a maximum of 10 years, with study follow-up every 6 months for the first 3 years and then annually until 10 years from registration.

**Endpoints:** The primary endpoint is invasive disease-free survival. Other endpoints include overall survival, weight loss, body composition, insulin resistance syndrome and associated conditions including cardiovascular disease.

Potentially modifiable risk factors shared between CV disease and cancer

- Abnormal lipids
- Smoking
- Diabetes
- Obesity
- Physical inactivity
- Consumption of fruits and vegetables
- Alcohol consumption

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For those who are interested in referring someone to consider participating in one or both of these studies, please contact Gretchen Kimmick, MD, MS at Duke Cancer Institute at (919) 668-0718.

REFERENCES


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Immune Checkpoint Inhibitors (from page 2)

In the following years, attention was placed on inhibitors of the programmed cell death 1 (PD-1), an inhibitory receptor expressed on the surface of activated T cells. Its ligand (programmed death-ligand 1 [PD-L1]) that is expressed in many human cancers has also been studied. PD-1/PD-L1 interaction ensures that the immune system is activated only at the appropriate time in order to minimize the possibility of chronic autoimmune inflammation. The monoclonal antibody therapies against PD-1 and PD-L1 have shown promising results and are approved for previously treated metastatic melanoma (nivolumab, pembrolizumab) and squamous non–small-cell lung cancer (nivolumab). Due to the novelty of this class of drugs, the cardiovascular safety profile has not been characterized yet, however the review of a large safety database has shown that myocarditis may occur and is more frequent and severe after the co-administration of both ipilimumab and nivolumab. Frequency of the event is overall rare, occurring in less than 1% of the treated patients.


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From the Cardio-Oncology working group:

We are really honored to welcome Kevin C. Oeffinger, MD as our new member of the Duke cardio-oncology working group.

Dr. Oeffinger recently joined Duke after spending the last 12 years at Memorial Sloan Kettering Cancer Center. He is a family physician, Director of the Duke Supportive Care and Survivorship Center and Director of the newly established Duke Center for Onco-Primary Care. Dr. Oeffinger has a long-track record of NIH-supported research focused on cardiometabolic outcomes and second primary malignancies among cancer survivors. He has co-authored over 200 peer-reviewed manuscripts including publications in the New England Journal of Medicine, Lancet, JAMA, the Journal of Clinical Oncology, and Annals of Internal Medicine. Dr. Oeffinger also serves as an Associate Editor for the Journal of the National Cancer Institute, chairs the American Cancer Society Cancer Screening Guideline Panel, and is a member of the NCI Cancer Prevention Steering Committee.

David Bartlett, PhD is a Medical Instructor at the Duke Cancer Institute and faculty member of the Duke Molecular Physiology Institute. Dr. Bartlett received his PhD in immunology from the University of Birmingham in England where he specialized in the effects of exercise and physical activity on immune function and inflammation in older adults. Dr. Bartlett was awarded the Korenchevsky Prize from the British Society for Ageing for his work on the role cytomegalovirus plays on systemic

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Dr. Bartlett is the co-leader of the Energy Balance in Oncology Working Group. His primary research focus is on the mechanisms by which exercise and diet can improve the immune system and inflammatory imbalance and physiological fitness of cancer patients and promote improved quality of life and survival. His research spans many cancers including kidney, hematologic, brain and breast cancers. He has a particular interest in understanding the potential for exercise to influence drug interactions and toxicities in patients receiving therapies. His lab is currently assessing immunological responses in a number of research studies include assessing the interactions of acute exercise during infusional immuno-therapy and exercise training in patients receiving immuno-therapy; exercise training in breast cancer survivors; neutrophil responses to bone marrow transplantation with a home based therapy; and physical activity and disease progression in patients with CLL.

From the Cardio-Oncology working group: (from page 8)
Recent publications

CANCER, THROMBOSIS AND ANTICOAGULATION


BREAST CANCER


CHILDHOOD CANCER SURVIVORS


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Recent publications (from page 10)

**MISCELLANEOUS**


Bo Xi, Sreenivas P. Veeranki, Min Zhao, Chuanwei Ma, Yinkun Yan and Jie Mi. Relationship of Alcohol Consumption to All-Cause, Cardiovascular, and Cancer-Related Mortality in U.S. Adults. J Am Coll Cardiol 2017;70:913–22

Useful links

cardiooncologyjournal.biomedcentral.com, a new open access cardio-oncology journal

https://www.acc.org/clinical-topics/cardio-oncology

icosna.org, International Cardioncology Society, North America

cardiaconcology.ca, Canadian Cardiac Oncology Network (CCON)

MD Anderson cancer lecture series on the practice of onco-cardiology discussing important topics relevant to cancer patients with heart disease and cardiotoxicity

Recently released!

Cardio-Oncology: The Clinical Overlap of Cancer and Heart Disease

Dr. Kimmick served as chief editor of a new cardio-oncology textbook and Drs. Melloni, Harrison and Dr. Khouri were among the authors. The book was co-edited and written by an interdisciplinary team of experts in oncology and cardiology, each chapter included a cardiologist and an oncologist to ensure clinically relevant interdisciplinary coverage. The book covers different area of interest including cardiac complications in patients receiving cancer therapy; the treatment of cancer in patients with cardiovascular disease; and the treatment of cardiovascular disease in patients with cancer.

Upcoming meetings

Advancing Cardiovascular Care of the Oncology Patient

FEBRUARY 16–18TH, THE RITZ-CARLTON, WASHINGTON, DC

American College of Cardiology (ACC) Scientific Session 2018

MARCH 10–12, 2018, ORLANDO, FL

American Society of Clinical Oncology (ASCO) Annual Meeting

JUNE 1–5, 2018, CHICAGO, ILLINOIS

The Global Cardio-Oncology Summit 2018

SEPTEMBER 27–28, 2018, TAMPA, FL — SAVE THE DATE!

Contact us

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