JACC: CARDIOONCOLOGY VOL. 6, NO. 5, 2024


EDITORIAL COMMENT

# Epigenomics of Cardio-Oncology

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The human epigenome has been described as the link between our inherited DNA and our environment, including health behaviors and other traditional epidemiologic risk factors. This makes epigenetic modifications a natural area of focus for epidemiologists and other health researchers who seek to understand what happens at small scales within the human body to translate a risk factor into subclinical and ultimately clinical disease.[1] DNA methylation (DNAm) is the most commonly studied of these modifications in population science for its potential to directly affect gene expression (and thus mechanistically affect disease development), among other characteristics. Changes in DNAm can disrupt the normal functioning of biological processes within the human body, which could potentially lead to any number of chronic diseases.[2-4] Similarly, many health behaviors and other traditional risk factors have also been linked to various DNAm measures,[5-7] with the potential to help explain many unanswered questions in chronic disease epidemiology. However the same ubiquity of DNAm and other epigenetic mechanisms that makes them attractive from a research point of view also complicates their use from a clinical point of view. When so many things can cause epigenetic dysregulation, and it can have so many consequences for health and longevity, studies that are not equally rigorous in both exposure and outcome ascertainment in their study populations will be able to shed only limited light on these questions.

In a study reported in this issue of *JACC: CardioOncology*, Domingo-Relloso et al[8] took a broader look at DNAm in chronic disease. They combined 3 large, well-characterized, and diverse cohorts: the SHS (Strong Heart Study), the FHS (Framingham Heart Study), and the ARIC (Atherosclerosis Risk in Communities) study. Prospective cohort data are critical for studies of DNAm in disease, as DNAm is frequently altered by disease itself in addition to related exposures. Citing the overlap in risk factors (both genetic and environmental), the investigators sought to evaluate DNAm signatures common to both cardiovascular disease (CVD) and cancer using these 3 populations in a 3-stage analytical strategy. The first stage was an untargeted epigenome-wide association study of each cohort using Cox regression with an elastic-net penalty to simultaneously consider all CpG (cytosine followed by a guanine with a phosphate link) sites as independent variables in separate models of time to cancer and/or CVD. This step was used to generate a union set of all CpG sites that were found to be differentially methylated in each cohort, which was then used for a second set of models to identify CpGs associated with cancer, CVD, or both across all 3 cohorts using meta-analytical methods.

Across the 3 cohorts studied, the investigators found overlapping sets of CpGs associated with CVD and with cancer. This provides evidence for a biological mechanism for both diseases that is common across different racial/ethnic groups; in total, the investigators' cancer and CVD model revealed 2 CpGs common across all cohorts, and the CVD model (without cancer) revealed 5. A functional analysis of these revealed proteins known to be involved in molecular pathways for cancer and CVD. However, the majority of the CpGs studied were found in only some cohorts. Whether this points to an environmental basis for these epigenetic alterations or to some other effect will need to be determined in future research.

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.07.013

JACC: CARDIOONCOLOGY, VOL. 6, NO. 5, 2024
OCTOBER 2024:743–745

The investigators point out several limitations, most notably a lack of power in the cancer models. The heterogeneity of epigenetic and genetic changes across types of cancer as well as within individual cancer types exacerbates this problem from a statistical point of view, but the small number of cases for specific cancer types even in these large and well-characterized cohorts constitutes a chief limitation of this study. The investigators also note some limitations with the source data; methodological heterogeneities among the cohorts used for this study also constitute a limitation and a potential explanation for the relatively small number of CpGs identified as common to all cohorts in the cancer and CVD models. The investigators acknowledge the need to further expand this study to larger and more diverse cohorts to answer these questions.

The study by Domingo-Relloso et al[8] joins an increasing number of studies that apply bioinformatic approaches to identify epigenetic markers of human diseases.[9,10] This study adds to the literature by reinforcing common mechanisms in cancer and CVD that might also explain the overlap in some risk factors between the diseases. The investigators' other key finding is the result of their protein-protein interaction analysis, which provides a rich picture of the molecular mechanisms involved in cancer and CVD. This work provides a blueprint for future studies of epigenomics and other molecular factors in CVD and cancer development across multiple large and diverse populations, and highlights the need to complete the "omics" picture. What then are the next steps for the field?

First, gene expression data are crucial for the interpretation of DNAm studies. The investigators used numerous powerful tools and external databases to examine plausible connections between DNAm alterations and changes in gene expression, but human population studies that include gene expression data are still necessary to confirm these findings. Similarly, other epigenetic changes such as microRNAs and histone modifications (as well as their functional effects on gene expression) are necessary to complete the causal picture on a molecular level and ensure that the therapeutic targets identified in these studies can actually be used in human populations to reduce and prevent disease.[11]

Second, different forms of CVD and cancer can be associated with different DNAm modifications.[12] This may be a reflection of the reduced power in smaller, single-cohort studies or a reflection of distinct biological pathways in disease development. The investigators' decision to comingle different CVD and cancer outcomes was necessary to analyze such a large and diverse population set, with the drawback being that it makes causal inference on specific diseases more difficult. Well-powered studies of individual, clinically diagnosable diseases will help focus these findings on new ways to detect cancer and CVD early and intervene to prevent them.

Third, although DNAm and other post-transcriptional modifications hold great promise for the treatment and prevention of CVD and cancer, developing treatments on the basis of this research remains challenging. Dietary factors have been shown to affect DNAm and other epigenetic modifications, but few specific compounds have been found that can target disease-promoting methylation changes in CVD specifically.[13] It is unlikely that a single therapy will be able to target all CVD or all cancer,[14] and although some drugs exist that do target epigenetic changes (including in cancer),[10] few of these therapies have advanced past animal studies. This highlights the need for more translational research in this area before the ultimate goal of clinical trials.

Fourth, importantly, few studies have examined methylation in the context of both CVD and cancer. The overlapping methylation targets identified may be particularly useful for cancer screening in patients after CVD, or vice versa. This finding is particularly relevant to the field of cardio-oncology, and epigenetic mechanisms that stand at the intersection between CVD and cancers will be crucial to the field going forward.[15] Future studies in cardio-oncology will need to clarify the temporal relationships among CVD, cancer, and DNAm.

The wealth of epigenetic factors identified by Domingo-Relloso et al[8] coupled with the enormously complex protein map linked to these factors highlight the massive amount of data (and equal amount of promise) held by the advent of new omics technologies in clinical research. This work adds to the evidence of complex and overlapping mechanisms in the development of incident disease, particularly in cardo-oncology. The investigators' findings should serve to inspire new work to further identify and explore these complex interrelationships.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that he has no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** cancer, cardiovascular disease, DNA methylation, mortality