NEW PERSPECTIVES IN COMPUTED TOMOGRAPHY BASED CARDIOVASCULAR RISK ASSESSMENT

PhD thesis (short version)

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1 Introduction

Cardiovascular disease (CVD) and cancer continue to be the leading cause of death in the developed countries. Cancer and CVD commonly co-exist, and these two conditions share many cumulative risk factors. In 2021, with more cancer survivors than ever before, the overlap of cancer survivors and patients with CVD is on the rise. In addition, cancer survivors are at increased CVD risk not only due to the overlap of risk factors but also due to the wide range of received cardiotoxic cancer therapies. As cancer survivors live longer, modifiable risk factors that affect both cancer and CVD must gain more attention. Identifying those at risk for CVD is at utmost importance to target effective dietary, lifestyle, and drug interventions. Whether the presence of a risk factor is determined by genetic or environmental factors, is modifiable or not modifiable, has a significant part in finding the appropriate preventative approaches.

Several risk prediction models have been developed to identify those asymptomatic subjects at higher CVD risk. However, the accuracy of these risk prediction models is not perfect, and neither is their generalizability. Moreover, in CVD risk scores, cancer therapies are usually not included. The risk prediction

systems could be improved by adding nontraditional risk factors such as more metabolic, anthropometric, imaging-based, or genetic data.

Coronary Computed Tomography (CT) Angiography is a robust diagnostic tool suitable for the non-invasive visualization of coronary vessels and quantification of coronary artery plaques. Moreover, ectopic fat depots, such as hepatic and pancreatic lipid accumulations, can also be assessed and measured on CT images. Data is lacking on the heritability of coronary artery plaques, pancreatic lipid accumulation, and hepatic lipid accumulation.

As regards patients with cancer, in recent years, immunotherapy has revolutionized cancer treatment. Immune checkpoint inhibitors (ICI) are a type of immunotherapy. The role of inflammation and immune modulation in CVD is well established. Immune cells are an important part of the atheroma, and animal studies have demonstrated that these immune checkpoints are critical negative regulators of atherosclerosis. Therefore, cancer patients receiving ICI therapy may be at increased risk for atherosclerotic plaque progression and CVD.

2 Objectives

The goal of my doctoral studies was to assess new perspectives in CT-based cardiovascular risk assessment with a special focus on cancer patients undergoing immunotherapy.

In a classic twin study design, we aimed to evaluate the heritability of non-calcified and calcified coronary plaque volumes. Using the same twin study design, we also aimed to evaluate the heritability of ectopic fat depots, such as hepatic and pancreatic lipid accumulations.

Leveraging a retrospective database of individuals treated with an ICI, an imaging study was performed to evaluate the effect of ICI therapy on atherosclerotic plaque progression. Furthermore, we also aimed to evaluate the effect of ICI therapy on clinical cardiovascular events.

3 Methods

Similarly to the thesis, methods already published with my authorship are briefly described or excluded from this thesis, following the general rules of the Doctoral School.

To assess the heritability of coronary plaque volumes, hepatic, and pancreatic lipid accumulation a prospective, single center, classical twin study was performed under the name of BUDAPEST-GLOBAL (Burden of Atherosclerotic Plaques Study in Twins - Genetic Loci and the Burden of Atherosclerotic Lesions). To assess the heritability of coronary plaque volumes, Falconer based heritability index (H^2) was calculated using the correlation values among the monozygotic (r_{MZ}) and dizygotic (r_{DZ}) twins. To assess the heritability of hepatic and pancreatic lipid accumulations, genetic structural equation models were built.

To assess the effect of ICI therapy on atherosclerotic plaque progression, patients with cancer who received ICI therapy and had at least three CT scans available were selected. Plaque volumes were measured, and progression over time was calculated. To assess the effect of ICI therapy on cardiovascular events, a matched cohort study was performed. The primary outcome was the occurrence of a cardiovascular event, defined as a composite of myocardial infarction, coronary revascularization, and ischemic stroke. These events were chart reviewed and blindly adjudicated. Cox proportional hazard

regression analysis was performed to calculate hazard ratios (HR) with 95% Confidence Interval (CI)s, counting only the first cardiovascular event.

4 Results

4.1 Heritability of coronary plaque volumes

A total of 196 twin subjects had adequate image quality to participate in the coronary plaque sub-study. Subjects in the monozygotic group were older than the dizygotic group (54 ± 10 vs. 58 ± 8 years, $P = 0.005$). 16.8% (33/196) of the participants were on primary preventive statin therapy. The 10-year Atherosclerotic Cardiovascular Disease Risk Score was 7.9 ± 7.7 for the total cohort. Calcified plaque volume showed a strong correlation between both the MZ and DZ twin pairs with an r_{MZ} of 0.96 and an r_{DZ} of 0.87. However, non-calcified plaque volume showed stronger correlations between the monozygotic as compared to the dizygotic twins (r_{MZ}=0.73 and r_{DZ}=0.44). Based on these correlation values, the broad heritability of calcified plaque volume was moderate (H^2=0.59), whereas the heritability of non-calcified plaque volume was found to be weak, yielding an H^2 of 0.17.

4.2 Heritability of hepatic and pancreatic lipid accumulations

A total of 182 twin subjects had sufficient data to measure hepatic lipid accumulation, and 136 twin subjects had sufficient data to measure pancreatic lipid accumulation. Using the structural equation model, a greater unique environmental influence (62% [95% CI 15-58%]) and a moderate additive genetic dependence (38% [95% CI 5-58%]) was found for hepatic lipid accumulation. Similarly, for pancreatic lipid accumulation, a greater unique environmental influence (54% [95% CI 19-66%]) and a moderate additive genetic dependence (46% [95% CI 34-81%]) was found.

4.3 Atherosclerotic plaque progression after Immune Checkpoint Inhibitor therapy

In the imaging sub-study of patients receiving ICI therapy (n=40), the mean age was 67 ± 7 years, with 55% male subjects. Patients received ICI monotherapy in most of the cases (87.5%), and the median number of ICI cycles received was 8.5 (4.5–23.5). The clinical characteristics of the patients in the imaging study remained constant over time. There was an increase in the total calcified plaque volume throughout the three CT scans (median [IQR] total plaque volume at baseline 1438 [703–2690] mm^3 to 1567 [703–2676] mm^3 at ICI start to 2183 [923–4150] mm^3 during follow up). Similarly, there was an increase in the non-calcified plaque volume throughout the three scans (median

[IQR] non-calcified plaque volume at baseline 1285 [643–2193] mm^3 to 1130 [592–1986] mm^3 at ICI start to 1725 [733–3584] mm^3 during follow up). The progression rate, adjusted for the study interval, was greater in the period after ICI as compared with prior, for both total (13.8 [-240-122] mm^3 vs. 103 [0-511] mm^3, P=0.02) and non-calcified plaque (-18.2 [-274-57] mm^3 vs. 53 [0-382] mm^3, P = 0.02). Specifically, the total plaque volume progression rate increased 3-fold from 2.1% per year pre- to 6.7% per year post-ICI.

4.4 Cardiovascular events after Immune Checkpoint Inhibitor therapy

Overall, cases and controls were not different with respect to type of cancer and a history of any cardiovascular event. Non-small cell lung cancer (28.8%) and melanoma (27.9%) were the most common type of cancer. Controls were more likely to be female (46.9 vs. 42.6%, P = 0.001) and had higher rates of hypertension (53.5 vs. 49.2%, P = 0.001) and diabetes mellitus (18.2 vs. 15.7%, P = 0.014). Among patients receiving ICI therapy, a median of five cycles of ICI were administered.

In univariable Cox proportional hazard model, the use of an ICI was associated with a >4-fold increase in the risk for a composite cardiovascular event, and for the individual outcomes, similar results were found (Figure 1).

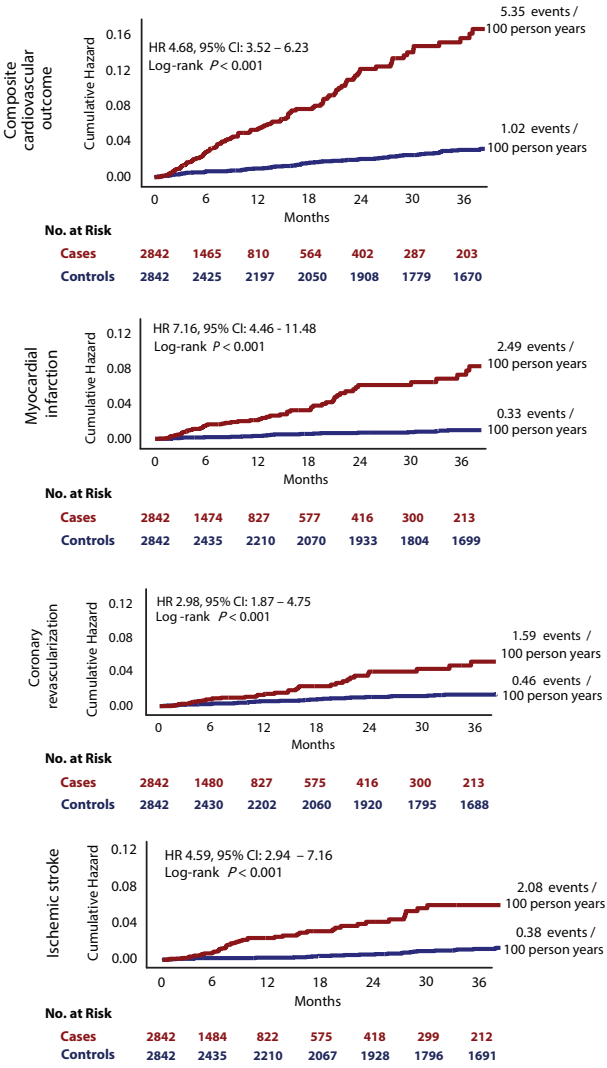

Figure 1. *Kaplan-Meier curves of the cumulative hazard in cases (red) and controls (blue) of the composite and individual component outcomes and the event rates at three years.*

In a parsimonious multivariable model, which included known cardiovascular risk factors (male sex, age, body mass index, hypertension, diabetes mellitus, chronic kidney disease, smoking, prior history of a cardiovascular event, statin use, aspirin use, hemoglobin, and low-density lipoprotein), the use of an ICI was associated with a 3-fold increase in the risk for a composite cardiovascular event (multivariable HR, 3.3 [95% CI 2.0-5.5]; $P < 0.001$).

5 Conclusion

In conclusion, we have observed that non-calcified plaque volume is less determined by genetic factors, predominantly determined by environmental factors, while calcified plaque volume is influenced mainly by genetics. These findings suggest that lifestyle may have an important role in the initiation of CAD since non-calcified plaques were more determined by environmental factors, and genetic factors showed a more substantial effect on the presence of calcified plaque. We have also found that unique environmental influences outweighed additive genetic effects on the phenotypic appearance of both hepatic and pancreatic lipid accumulations.

In a retrospective study of patients receiving ICI therapy, an increased atherosclerotic plaque progression was found after

starting the therapy. Moreover, as compared to cancer patients who did not receive ICI therapy, there was a higher rate of cardiovascular events associated with ICI therapy.

Our results underline the importance of optimal cardiovascular risk factor management early in life and prior to therapy with ICIs. Favorable changes of modifiable environmental factors are of great importance in preventing and treating non-calcified coronary plaques and ectopic fat depots such as hepatic and pancreatic fat accumulations. ICI therapy should be considered as a modifier of cardiovascular risk. Patients eligible for ICI therapy should undergo a comprehensive cardiovascular risk evaluation and optimization of preventive measures with close monitoring after that.

6 Publications

6.1 Publications directly related to this thesis

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