



Editorial

Could coronary calcification identified at non-gated chest CT be a predictor for cardiovascular events in breast cancer patients?



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With the advance of cancer therapy, the survival rate of breast cancer patients has become higher. Cardiac events might become a significant prognostic factor in these patients [1]. In the current issue of the *International Journal of Cardiology*, Phillips et al. [2] investigated the relationship between the coronary artery calcification (CAC) at non-gated chest CT of breast cancer patients and the future cardiac events. They retrospectively included 256 breast cancer patients who underwent non-gated chest CT as part of cancer staging. CAC was semi-quantitatively analyzed using a scoring system ranging from 0 to 12 [3]. The primary end point was a composite of all-cause mortality and cardiac events (non-fatal myocardial infarction, coronary revascularization, new atrial fibrillation or heart failure episode requiring hospitalization). They compared the CAC and Framingham risk score (FRS) to predict the primary endpoint. During a median follow-up of 6.5 years, primary endpoint occurred in 112 patients (43.8%). The primary end point was more commonly seen in patients with CAC than those without (35.2% vs 17.9%, $p < 0.001$). The association of primary end point and CAC maintained after adjusting with cancer stage, but FRS was no longer a significant factor in multivariate analysis. This study is important in that it clearly showed that not a small proportion of patients with breast cancers suffer from cardiovascular events and that these events could be predicted using a routinely performed non-gated chest CT scan.

However, this study warrants several comments. The non-gated CT scan was performed using various CT scanners ranging from 16 to 320 rows, and the reconstruction thickness ranged from 1.0 to 5.0 mm. Because image noise increases with thinner slices, too thin images might misinterpret noise as CAC [4]. A previous study by Azour

et al. [3] used a thickness between 2.5 and 5.0 mm to evaluate CAC in a non-gated scan. CAC evaluation should be performed with an optimal image quality. Secondly, although zero-calcium guarantees an excellent prognosis, this does not exclude the presence of high-risk coronary plaques including thin-cap fibroatheroma. Patients with diabetes mellitus or dyslipidemia have a higher risk of possessing these plaques [5] and these patients deserve preventive therapies including statin intake to prevent future cardiovascular events.

The timing to evaluate the chest CT scan is also an important issue. The patients in the study by Phillips et al. [2] were evaluated for chest CT at a median of 1 year from the initial visit and the time interval until the first CT ranged up to 3 years. Ideally, CAC evaluation should be performed before cancer therapy and a further prospective study is necessary to investigate this point. Also, it is important that most of the mortality (81 out of 83 total deaths, 98%) was non-cardiac in nature, probably oncology-related deaths. The study did not show that the presence of CAC could predict hard cardiovascular events. Although CAC might still be a significant predictor for non-fatal endpoints, such as revascularization and hospitalization for heart failure, it needs to be highlighted that this cohort was derived from a cardio-oncology clinic, such that the prevalence of heart failure might be higher than the general breast cancer population.

The influence of cardio-protective medication is important to prevent future cardiovascular events. Especially, appropriate statin therapy would reduce coronary plaque volume [6] and result in lower cardiac mortality [7]. The results of the study by Phillips et al. [2] did not show relationship between cardio-protective medication and reduction of future events. One reason might be that more than 30% of patients with a high FRS ($\geq 10\%$) were not under statin treatment. It would be of interest whether appropriate medication strategy would improve the event-free survival of breast cancer patients.

The predictive power of CAC outperformed FRS to stratify the risk of breast cancer patients in the study by Phillips et al. [2]. Similar approach using CAC was also investigated in a lung cancer population of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort [8]. The study showed that the discrimination of cardiovascular events improved using a model with CAC than MESA-based risk model alone which included cardiovascular risk factors similar to the FRS. Another study by Hadamitzky et al. [9] showed that coronary plaque or significant stenosis at proximal segments detected by coronary CT had an additive value over the FRS to predict mortality. These studies as well as the results in the study by Phillips et al. [2] emphasizes the importance of image-

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guided risk stratification in that it would have an incremental value to predict the patient prognosis. The study by Hadamitzky et al. [9] resulted that patients with severe coronary artery disease had a worse prognosis than patients with mild disease. The study by Phillips et al. [2] showed that increasing CAC severity was associated with cardiac events (hazard ratio 1.214, 95% confidence interval, 1.077–1.444, $p = 0.003$). However, the sample size was small to calculate the individual risk for cardiovascular events in each CAC category. To show how to manage patients with various cardiovascular risk would be the next steps. Patients with low risk should receive optimal medical therapy, while patients with high risk should go on to further investigation such as nuclear exam, cardiac CT, or catheter exam. The therapeutic strategy when a significant stenosis is present would be a troublesome issue in cancer patients because anti-platelet therapy after stent placement might be a problem for pre-operative patients. Studies to investigate the treatment strategies in cancer patients should be performed in the future.

In conclusion, Phillips et al. [2] showed that CAC detected on non-gated chest CT could predict future cardiovascular events better than FRS in breast cancer patients. Further study is necessary to stratify the risk with the severity of CAC and to propose an optimal therapeutic strategy in patients with breast cancer.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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