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The relation between resting heart rate and cancer incidence, cancer mortality and all-cause mortality in patients with manifest vascular disease

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ABSTRACT

Background: Previous studies suggest that elevated resting heart rate (RHR) is related to an increased risk of cancer mortality. The aim of this study was to evaluate the relation between RHR and cancer incidence and mortality in patients with vascular disease.
Methods: Patients with manifest vascular disease (n = 6007) were prospectively followed-up for cancer incidence and mortality. At baseline, RHR was obtained from an electrocardiogram. The relation between RHR and cancer incidence, cancer mortality and total mortality was assessed using competing risks models.
Results: During a median follow-up of 6.0 years (interquartile range: 3.1–9.3) 491 patients (8%) were diagnosed with cancer and 907 (15%) patients died, 248 (27%) died from cancer. After adjustment for potential confounders, the hazard ratio (HR) for incident cancer per 10 beats/min increase in RHR was 1.00 (95% confidence interval [CI]: 0.93–1.07). There was a trend toward an increased risk of colorectal cancer in patients with higher RHR (HR 1.15, 95% CI 0.97–1.36). The risk of all-cause mortality was increased in patients in the highest quartile of RHR compared to the lowest quartile (HR 1.86, 95% CI 1.53–2.27), but no effect of RHR on cancer mortality was observed (HR 1.01, 95% CI 0.70–1.46).
Conclusions: In patients with manifest vascular disease, elevated RHR was related to a higher risk of premature all-cause mortality, but this was not due to increased cancer mortality. RHR was not related to risk of overall cancer incidence, although a relation between elevated RHR and incident colorectal cancer risk could not be ruled out.

1. Introduction

Measuring heart rate is one of the oldest forms of physical examination and is still commonly done in routine clinical practice. Being a simple and inexpensive procedure, it can provide physicians and patients with important prognostic information. Resting heart rate (RHR) reflects sympathetic nerve activity and is often elevated in severe disease, such as heart failure [1]. Previous studies have identified elevated resting heart rate as an independent risk factor for cardiovascular mortality in the general population and patients with vascular disease [2–6]. Although the focus of these studies was mainly on cardiovascular mortality, several studies also observed a significantly higher risk of non-cardiovascular mortality, particularly cancer mortality, in individuals with elevated RHR [4,6,7]. A recent study among healthy middle-aged men in the Paris Prospective Study-1 showed a consistent and graded association between RHR and exercise heart rate and cancer mortality, with a hazard ratio (HR) of 2.4 (95% confidence interval [CI]: 1.9–2.9) for the highest quartile of RHR compared with the lowest quartile [7]. The mechanisms underlying this possible relation are not well understood, but insulin resistance, systemic low-grade inflammation and physical fitness

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may play a role, since these factors are related to both elevated RHR and cancer risk [7–11]. Moreover, direct effects of increased sympathetic activation might also be important, as beta-adrenergic signaling has been found to regulate multiple cellular processes that contribute to the initiation and progression of cancer, including inflammation, angiogenesis, tissue invasion, epithelial–mesenchymal transition and impaired cellular immune response [12]. To date, however, evidence for the relation between RHR and cancer is inconsistent [2,4,5,7,13], and it remains unclear whether elevated RHR is a risk marker for developing cancer, or a reflection of poor physical condition in patients with cancer and thus related to mortality [7].

Previous studies investigating the relation between RHR and cancer mortality were performed in the general population and were generally confined to men [4–7]. We previously showed that the risk of incident cancer and cancer mortality in patients with vascular disease is higher compared to the general population and that RHR is an important risk factor for vascular and all-cause mortality in this population [3,14–16]. Information about the effects of RHR on cancer could be valuable to help stratify these patients in terms of cancer risk. Thus far, however, studies evaluating this relation in patients with vascular disease are lacking. In the present study, we therefore evaluated the effects of RHR on cancer incidence, cancer mortality and all-cause mortality in a prospective cohort of patients with clinically manifest vascular disease.

2. Methods

2.1. Study population

Patients originated from the Second Manifestations of ARTerial disease (SMART)-study, an ongoing prospective cohort study at the University Medical Center Utrecht in the Netherlands. The central aims of the SMART study are to determine prevalence of concomitant atherosclerotic disease and of risk factors for atherosclerotic disease and to study the incidence of future cardiovascular events and its predictors. A detailed description of the SMART-study has been published previously [16]. In short, newly referred patients, aged 18–80 years with a recent history of manifest atherosclerotic disease (coronary artery disease [CAD], cerebrovascular disease [CVD], peripheral artery disease [PAD] or abdominal aorta aneurysm [AAA]) or traditional cardiovascular risk factors (hypertension, dyslipidemia and diabetes mellitus) are included in the SMART-study. The qualifying diagnosis was confirmed by the referring physician. CAD was defined as a recent diagnosis of angina pectoris with a confirmed stenosis on a coronary angiogram, myocardial infarction or coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention). Patients with CVD include those with a recent diagnosis of ischemic stroke, transient ischemic attack or amaurosis fugax. PAD was defined as a clinical diagnosis of PAD (Fontaine stage 2–4), which was confirmed by either an ankle-brachial index of $\leq$0.90 in rest or decrease in ABI of at least 20% after exercise, whereas AAA was defined as a distal aortic anteroposterior diameter of $\geq$3 cm, as measured with ultrasonography. Patients who had a terminal malignancy at baseline, patients dependent in daily activities and/or patients not sufficiently fluent in the Dutch language were not included. The institutional ethics committee approved the SMART-study and all participants gave their written informed consent. For the present study, data of patients with clinically manifest vascular disease included between September 1996 and March 2012, who had sinus rhythm and did not have a history of cancer, were used (Fig. 1). Since information on cancer incidence was unavailable for patients who were included after 2010, this group was excluded from the analyses for cancer incidence (n = 408).

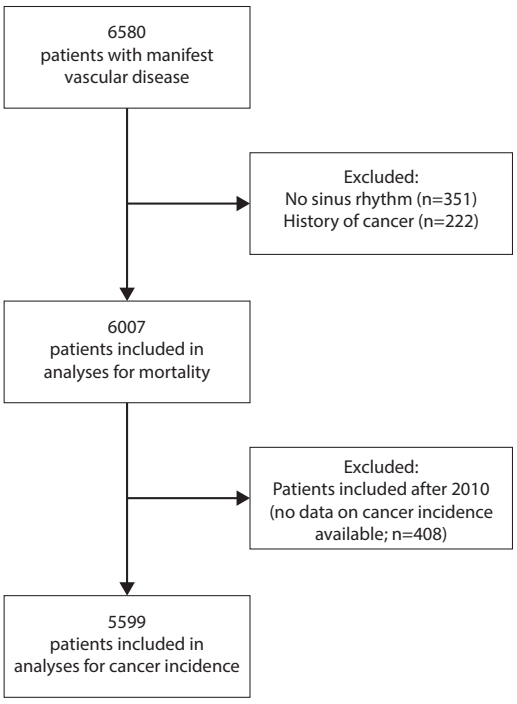

Fig. 1. Study flow diagram.

2.2. Baseline measurements

At inclusion, patients underwent a standardized cardiovascular screening program including a questionnaire covering medical history, symptoms and lifestyle, including smoking habits and physical activity. Assessment of physical activity included questions on patients' usual pattern of physical activity during a normal week in the past year. In order to quantify the intensity of each activity, a specific metabolic equivalent (MET) value was assigned to each reported activity [17]. Furthermore, physical examination (height, weight and blood pressure) and laboratory tests (metabolic markers, fasting serum glucose and lipid levels) were done. Height and weight were measured while patients wore indoor clothes and no shoes. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). In addition, non-invasive imaging techniques were used to detect the presence of additional (sub)clinical atherosclerosis [16].

A 12-lead electrocardiogram (ECG) was recorded from all patients in the morning, after resting for 5 min in supine position. The RHR was calculated using the digitally stored 12-lead 10-second data, by dividing the number of R–R intervals by the time difference between the first and last beat, and the result was converted to beats per minute (bpm). This calculation was performed using the Marquette-12SL analysis program (General Electric Healthcare, Hoevelaken, The Netherlands).

2.3. Follow-up

Patients were biannually asked to complete a questionnaire on hospitalization and outpatient clinic visits for follow-up. The main endpoints of interest of the present study were all-cause mortality, cancer mortality, total incident cancer, which was defined as the first primary invasive neoplasm, excluding non-melanoma skin cancer, and the three most common cancers in men and women (i.e. colorectal, lung, prostate and breast cancer, respectively). Deaths of participants were reported by relatives of the participant,