

ON THE CROSSROADS OF CARDIOVASCULAR DISEASE AND CANCER

Shared risk factors and treatment strategies

Rob C.M. van Kruijsdijk

On the crossroads of cardiovascular disease and cancer
Shared risk factors and treatment strategies

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On the crossroads of cardiovascular disease and cancer

Shared risk factors and treatment strategies

Op het raakvlak van hart- en vaatziekten en kanker

Gemeenschappelijke risicofactoren en behandelingsstrategieën

(Met een samenvatting in het Nederlands)

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Robertus Cornelis Maria van Kruijsdijk

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Promotores

Prof. dr. F.L.J. Visseren

Prof. dr. Y. van der Graaf

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CHAPTER 1

GENERAL INTRODUCTION

PART I

CARDIOVASCULAR DISEASE AND CANCER

“We’re not so different you and I”

This idiom, widely used by movie villains, might also apply to the main ‘villains’ in public health: cancer and cardiovascular disease. These two foremost non-communicable diseases together account for 46% of global mortality and even for 55-59% of mortality in high-income countries¹⁻⁴. In the past decades, the fatality rates for acute ischemic events, such as myocardial infarction and ischemic stroke, have decreased notably due to advances in acute medical care and due preventive treatment for cardiovascular disease⁴⁻⁶. In some countries this has resulted in cancer surpassing cardiovascular disease as leading cause of death³ (*Figure 1*).

Despite the decrease in cardiovascular mortality, the number of patients in a chronic phase of cardiovascular disease is still growing. The burden of this on public health is illustrated by recent estimates that cardiovascular disease is prevalent in more than one third of American adults⁶. Although there is a lack of high quality and comparable incidence data from across European countries, it is clear that cardiovascular disease also causes a substantial burden of morbidity in Europe, with hospital discharge rates for cardiovascular disease of over 2,500 per 100,000 population in 2010⁵. Recent estimates in the Netherlands indicate that the total count of Dutch individuals with some manifestation of cardiovascular disease are over one million (>8% of adult population)^{7,8}.

Cardiovascular disease shares several important modifiable risk factors with cancer, including smoking and obesity. The atherogenic and carcinogenic effects of smoking, as well as the increased risk of vascular disease in persons with excess body weight are well-established⁹⁻¹¹. The relation between excess bodyweight and increased cancer risk, however, has only recently been acknowledged¹²⁻¹⁴. Underlying mechanisms are not fully clear, but adipose tissue dysfunction may play an important role. Adipose tissue dysfunction induces insulin resistance, inflammation and changes in serum levels of adipokines (e.g. leptin and adiponectin) and sex steroids which leads to promotion of cell proliferation and -survival, invasive growth, metastasis and angiogenesis^{15,16}. In addition, physical inactivity and increased sympathetic activity have been related to both increased cardiovascular and cancer risk¹⁷⁻¹⁹. Taken together, it was estimated that these modifiable risk factors account for 42.7% of all cancers and for 70.2% of cardiovascular disease in the United Kingdom and United States^{20,21}. All these risk factors are highly prevalent in patients with chronic vascular disease who survived an initial manifestation of vascular disease (e.g. myocardial infarction or stroke)²⁰. Hence, this ever-growing population might not only be at increased risk of recurrent vascular events, but also of cancer. Especially considering the increased life expectancy in these patients by the reduction in cardiovascular mortality⁶, the effects

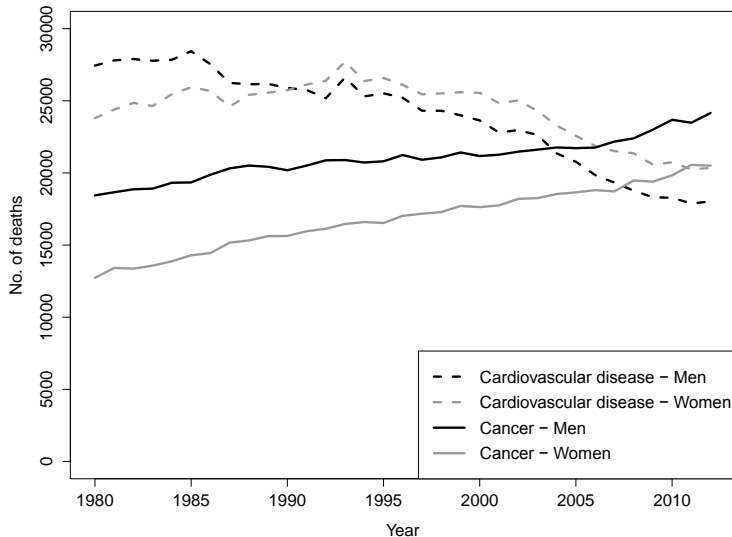


Figure 1. Absolute number of deaths by cardiovascular disease and cancer per year for men and women in the Netherlands from 1980 to 2012 (data from: CBS - Statistics Netherlands).

of lifestyle factors may lead to more non-vascular morbidity and mortality. These non-vascular diseases not only include cancer, but also other non-communicable diseases, such as diabetes and renal diseases^{22,23}. Reducing these risk factors and providing treatments that target pathways that are important in the development of both cardiovascular disease and cancer, might lower the risk of both diseases^{22,23}. Knowledge about cancer risk and its determinants in patients with vascular disease could therefore be important to guide preventative strategies.

Thus, although cardiovascular disease and cancer might appear to encompass very different entities, there is important overlap in the factors causing these diseases. More knowledge and awareness of the shared etiology of cancer and cardiovascular diseases in research and prevention programs, as well as in clinical practice, might help to reduce the global burden of disease.

PART II

PREDICTING TREATMENT EFFECT FOR INDIVIDUAL PATIENTS

Evaluating the efficacy of clinical interventions in randomized trials is a cornerstone of present-day evidence-based medicine. To provide optimal patient care, clinicians need to translate scientific evidence to the treatment of individual patients. In general, results from clinical trials are reported as average relative treatment effect estimates (such as a relative risk or hazard ratio) on a group level. Typically, if – on average – a specific intervention resulted in a better outcome than the control during the trial, it will be recommended for all patients, whereas when no beneficial effect or even harm was observed, treatment is recommended to none. Implicitly, this approach considers that all patients are at average risk and have an average response to therapy^{24,25}. Clinicians intuitively know that this is an oversimplified approach, as patients can vary greatly in risk and their response to specific treatments. In efforts to further stratify patients in terms of response to treatment subgroup analyses are often performed in trial data. However, this type of analysis has some well-known limitations, including low statistical power²⁵. Moreover, in subgroup analyses only one patient characteristic is evaluated at the time and are usually reported as relative, rather than absolute effects.

Since the response to treatment of individual patients may be determined by a combination of patient characteristics, predicting the absolute treatment effects using multivariable prediction models could provide a comprehensive approach to identify which patients will benefit from treatment^{24,26-28}. Rather than treating all, none or a certain subgroup of patients, this approach would allow clinicians to calculate the expected absolute treatment effects for each individual patient and use this information to decide together with the patient whether to start treatment or not.

Aspirin for primary prevention exemplifies a case in which individualized treatment effect prediction could provide a way to improve the overall clinical outcome. Since aspirin, on average, only modestly affects cardiovascular risk in patient without vascular disease, while increasing the risk of bleeding²⁹, it would be preferable to reserve aspirin prophylaxis for only those persons who are expected to benefit and have limited risk of adverse events, rather than recommending aspirin prophylaxis to all. Furthermore, there is recent evidence that aspirin, besides its benefit with regard to cardiovascular disease, modestly reduces the risk of cancer, particularly colorectal cancer³⁰⁻³². This additional benefit could potentially tip the balance in favour of aspirin^{31,33}, and should thus be taken into account when determining the value of aspirin prophylaxis for primary prevention. Individualized treatment effect prediction for all relevant outcomes related to aspirin, *i.e.* cardiovascular disease, cancer and bleeding, may provide a comprehensive approach to identify patients who benefit from aspirin prophylaxis. Rather than a single effect of a specific treatment on a

single outcome, this approach of obtaining individualized treatment predictions for all relevant outcomes would allow clinicians to make patient-tailored treatment decisions, taking into account how important the patient deems each separate outcome.

Dr. Arthur L. Bloomfield (1888-1962) once noted that “there are some patients whom we cannot help; there are none whom we cannot harm”. This assertion underscores the importance of well-informed treatment decisions for individual patients. Preferably, only those patients who actually benefit are treated, while withholding therapy from those who will have no benefit or may even be harmed. Besides beneficial effects of medication, individualized treatment effect prediction could also be used to estimate the risk of important adverse effects. This could be particularly valuable in the field of palliative oncology, as patients being treated for cancer frequently experience serious adverse effects.

Despite the intuitive advantages of prediction-based treatment, it is plausible that some models fail to adequately predict the actual treatment effects. Therefore, it remains important to compare selecting patients for treatment based on individualized treatment effect predictions to other treatment strategies in order to assess which strategy would lead to the optimal clinical outcome^{24,27,28}.

OBJECTIVES OF THIS THESIS

Part I

- To review the role of dysfunction of adipose tissue in the relation between obesity and cancer (**chapter 2**).
- To determine the risk of incident cancer and its determinants in patients with manifest vascular disease (**chapter 3**).
- To evaluate the causes of death and years of life lost in patients with manifest vascular disease, focusing not only on vascular, but also non-vascular causes, including cancer (**chapter 4**).
- To determine whether attainment of treatment goals for the shared risk factors of cardiovascular disease and cancer affects cancer risk in patients with manifest vascular disease (**chapter 5**).
- To evaluate whether increased sympathetic activation, as measured by resting heart rate, is related to cancer incidence in patients with manifest vascular disease (**chapter 6**).

Part II

- To predict the effects of aspirin on all relevant outcomes for individual women and to determine which aspirin treatment strategy would result in the most favourable clinical outcome in a primary prevention setting (**chapter 7**).
- To determine the value of individualized treatment effect prediction in the field of oncology

by predicting the response to chemotherapy on survival and adverse effects in pretreated patients with advanced non-small cell lung cancer (**chapter 8**).

OUTLINE OF THIS THESIS

Part I of this thesis focuses on the risk of cancer in patients with manifest vascular disease. Furthermore, it focuses on risk factors (and underlying pathophysiology) that are shared by cardiovascular disease and cancer. In **chapter 2**, the complex relation between obesity and cancer is reviewed. Obesity is strongly related to changes in the physiological function of adipose tissue, leading to insulin resistance, chronic inflammation and altered secretion of adipokines. Several of these factors are also involved in carcinogenesis and cancer progression. Here, an overview of the epidemiological evidence regarding the relation between excess bodyweight and cancer is provided along with a review of the mechanisms that could underlie this relation, focusing on adipose tissue dysfunction as an unifying causal factor.

Although in clinical practice the focus in patients with established vascular disease is on recurrence of vascular events, these patients might also be at increased risk of cancer, given the shared risk factors of cardiovascular disease and cancer. Therefore, **chapter 3** describes a study in which the risk of cancer in patients with manifest vascular disease, as compared to the general population, is assessed. Furthermore, the effects of several determinants for cancer risk, including smoking, obesity and metabolic syndrome, are evaluated. In **chapter 4**, cause-specific mortality in patients with different manifestations of vascular disease is evaluated. In addition, the excess years of life lost due to cardiovascular disease, cancer and other causes of death, compared to the general population, are provided. Given the overlap between risk factors and pathophysiology of cardiovascular disease and cancer, we hypothesized that secondary cardiovascular prevention could also reduce the risk of cancer in vascular patients. This hypothesis was tested in **chapter 5**, by evaluating the relation between the number of attained treatment goals (defined by American Heart Association/American College of Cardiology) for shared risk factors and cancer incidence. Increased sympathetic activity has been linked to carcinogenesis through beta-adrenergic signaling, inflammation and insulin resistance. The impact of increased sympathetic activation, as measured by increased resting heart rate, on cancer risk in patients with manifest vascular disease is assessed in **chapter 6**.

Part II of this thesis focuses on prediction of treatment effects for individual patients. First, in **chapter 7**, the value of aspirin in primary prevention is explored. Rather than evaluating only the effect on cardiovascular disease, all relevant outcomes, including incident cancer and major gastro-intestinal bleeding, are taken into account. Using data of the Women's Health Study, a randomized trial of alternate-day low-dose aspirin compared to placebo in healthy women, multivariable models for the prediction of the response to aspirin with

regard to each outcome are developed. The strategy of using treatment effect predictions is compared to treating none, treating all and treating only women of 65 years and older. In **chapter 8**, the value of individualized treatment effect prediction in the field of oncology is explored. This is done using data from randomized phase 2 trials of pemetrexed plus carboplatin versus pemetrexed alone in patients with advanced non-small cell lung cancer. Models for the prediction of the effect of adding carboplatin to pemetrexed on overall survival, progression-free survival and toxicity and serious adverse events, are developed and validated. The net benefit of using these models to identify patients who will benefit from carboplatin is compared to treating all with pemetrexed and carboplatin and treating all with pemetrexed alone.

The main findings of the above studies are discussed in **chapter 9**. Finally, a summary of the results presented in this thesis is provided in **chapter 10**.

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PART ONE

CANCER RISK IN PATIENTS WITH MANIFEST VASCULAR DISEASE

Rob C.M. van Kruijsdijk
Elsken van der Wall
Frank L.J. Visseren

CHAPTER 2

OBESITY AND CANCER THE ROLE OF DYSFUNCTIONAL ADIPOSE TISSUE REVIEW

Cancer Epidemiology Biomarkers & Prevention 2009; 18 (10): 2569-78

ABSTRACT

Overweight and obesity are health problems of epidemic proportions, increasing the risk not only of cardiovascular disease and type 2 diabetes mellitus but also of various types of cancer. Obesity is strongly associated with changes in the physiological function of adipose tissue, leading to insulin resistance, chronic inflammation, and altered secretion of adipokines. Several of these factors, such as insulin resistance, increased levels of leptin, plasminogen activator inhibitor-1, and endogenous sex steroids, decreased levels of adiponectin, and chronic inflammation, are involved in carcinogenesis and cancer progression. This article reviews these mechanisms, focusing on adipose tissue dysfunction as a unifying causal factor. Although understanding of the link between obesity and cancer might provide therapeutic targets, preventing overweight and obesity still remains number one priority.

INTRODUCTION

Excess body weight is a health problem of epidemic proportions that is not restricted to the developed countries¹⁻³, but affects people worldwide³. Overweight and obesity increase the risk of cardiovascular disease and type 2 diabetes mellitus⁴⁻⁶ and account for a substantial proportion of global morbidity and mortality^{3, 4, 7}. Moreover, overweight and obesity are now established risk factors for cancer and cancer-related mortality⁸⁻¹¹. It is thought that the metabolic changes associated with obesity, particularly abdominal obesity, and changes in adipocyte function underlie this increased risk. Knowledge of the pathophysiological mechanisms underlying the association between obesity and malignancy may be important for the development of preventive and therapeutic strategies for cancer. The purpose of this overview is to evaluate the association between obesity and the occurrence of various cancers and to review the pathophysiological mechanisms involved. We propose that adipose tissue dysfunction has a prominent role in cancer pathogenesis and progression.

Obesity and Cancer Epidemiology

Overweight (defined as a body mass index [BMI] of 25 to 29.9 kg/m²) and obesity (BMI \geq 30 kg/m²) are associated with an increased all-cause mortality^{4, 7}, and cancer accounts for a substantial proportion of obesity-related deaths^{7, 10, 12}. In 2003, it was estimated that overweight and obesity were responsible for 14% of all cancer deaths in men and 20% of those in women in the United States¹², which is consistent with the poorer outcome of cancer in overweight and obese subjects¹⁰. Excess bodyweight is not only associated with cancer mortality but is also associated with an increased incidence of several types of cancer. Recent meta-analyses^{10, 13, 14} have shown that an increased BMI is associated with an increased incidence of endometrial, colorectal, and postmenopausal breast cancer (*Table 1*). In addition, obesity has recently been shown to be associated with an increased risk of esophageal adenocarcinoma, thyroid cancer, renal cancer, multiple myeloma, gallbladder cancer in women, leukemia, pancreatic cancer, non-Hodgkin lymphoma, and ovarian cancer^{10, 11, 15}. However, data on the association between obesity and prostate cancer are ambiguous, with a high BMI being associated with a higher risk of high-grade prostate cancer but with a lower risk of low-grade prostate cancer¹⁶.

The obesity epidemic is not limited to adults but affects children and adolescents. In 2003-2004, 17.1% of American children and adolescents aged 2 to 19 years were overweight or obese¹. A recent study has shown that excess bodyweight in adolescence carries an increased risk of colon cancer mortality in adulthood in men (relative risk [RR], 2.1; 95% confidence interval [CI], 1.1-4.1) and women (RR, 2.0; 95% CI, 1.2-3.5; ref. 17). These results underline the necessity of preventing childhood obesity.

Dysfunctional Adipose Tissue

In addition to its lipid-storing capacity, adipose tissue is a highly active endocrine and metabolic organ. Adipose tissue, which is made up of various cell types, such as adipocytes,

pre-adipocytes, fibroblasts, macrophages, and blood vessels, produces numerous adipokines, such as leptin, adiponectin, plasminogen activator inhibitor (PAI)-1, vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF- α), and interleukin (IL)-6. As adipose tissue expands, adipocytes enlarge and the adipose tissue starts to produce chemotactic factors, such as monocyte chemoattractant protein (MCP)-1, that attract monocytes/macrophages into adipose tissue¹⁸. The subsequent increased production of adipokines and inflammatory cytokines and the decreased production of adiponectin¹⁹, in combination with the inability of adipose tissue to store the surplus free fatty acids (FFAs; ref. 20), can be considered to reflect adipose tissue dysfunction (*Figure 1*). These obesity-associated disturbances of adipose tissue function are believed to play a crucial role in the

Table 1. Body Mass Index and Risk of Several Cancer Types

Type of Cancer	Men RR (95% CI)*	Women RR (95% CI)*	Reference
Endometrial	-	2.89 (2.62-3.18)	Reeves (2007) ^{10,†}
	-	1.59 (1.50-1.68)	Renehan (2008) ^{11,‡}
Esophageal adenocarcinoma	1.52 (1.33-1.74)	1.51 (1.31-1.74)	Renehan (2008) ^{11,‡}
Postmenopausal breast	-	1.40 (1.31-1.49)	Reeves (2007) ^{10,†}
	-	1.12 (1.08-1.16)	Renehan (2008) ^{11,‡}
Colon	1.30 (1.25-1.35)	1.12 (1.07-1.18)	Larsson (2007) ^{12,‡}
	1.53 (1.33-1.75)	1.09 (0.93-1.28)	Moghaddam (2007) ^{13,¥}
	1.24 (1.20-1.28)	1.09 (1.05-1.13)	Renehan (2008) ^{11,‡}
Rectal	1.12 (1.09-1.16)	1.03 (0.99-1.08)	Larsson (2007) ^{12,‡}
	1.27 (1.17-1.37)	1.02 (0.85-1.22)	Moghaddam (2007) ^{13,¥}
	1.09 (1.06-1.12)	1.02 (1.00-1.05)	Renehan (2008) ^{11,‡}
Thyroid	1.33 (1.04-1.70)	1.14 (1.06-1.23)	Renehan (2008) ^{11,‡}
Renal	1.24 (1.15-1.34)	1.34 (1.25-1.43)	Renehan (2008) ^{11,‡}
Pancreatic	1.16 (1.05-1.28)	1.10 (1.02-1.09)	Larsson (2007) ^{14,‡}
	1.07 (0.93-1.23)	1.12 (1.02-1.22)	Renehan (2008) ^{11,‡}
Ovarian	-	1.14 (1.03-1.27)	Reeves (2007) ^{10,†}
	-	1.03 (0.99-1.08)	Renehan (2008) ^{11,‡}
Multiple myeloma	1.11 (1.05-1.18)	1.11 (1.07-1.15)	Renehan (2008) ^{11,‡}
Gallbladder	1.09 (0.99-1.21)	1.59 (1.02-2.47)	Renehan (2008) ^{11,‡}
Leukemia	1.08 (1.02-1.14)	1.17 (1.04-1.32)	Renehan (2008) ^{11,‡}
Non-Hodgkin lymphoma	1.06 (1.03-1.09)	1.07 (1.00-1.14)	Renehan (2008) ^{11,‡}
Prostate high-grade	1.25 (1.06-1.49)	-	Hsing (2007) ^{15,‡}
Prostate low-grade	0.85 (0.77-0.93)	-	

*Relative risk (RR) and 95% confidence interval (CI). †Estimated trends in the RR associated with every 10 kg/m² increase in Body Mass Index (BMI). ‡RR associated with every 5 kg/m² increase in BMI. ¥RR with BMI \geq 30 kg/m² compared to BMI <25 kg/m²

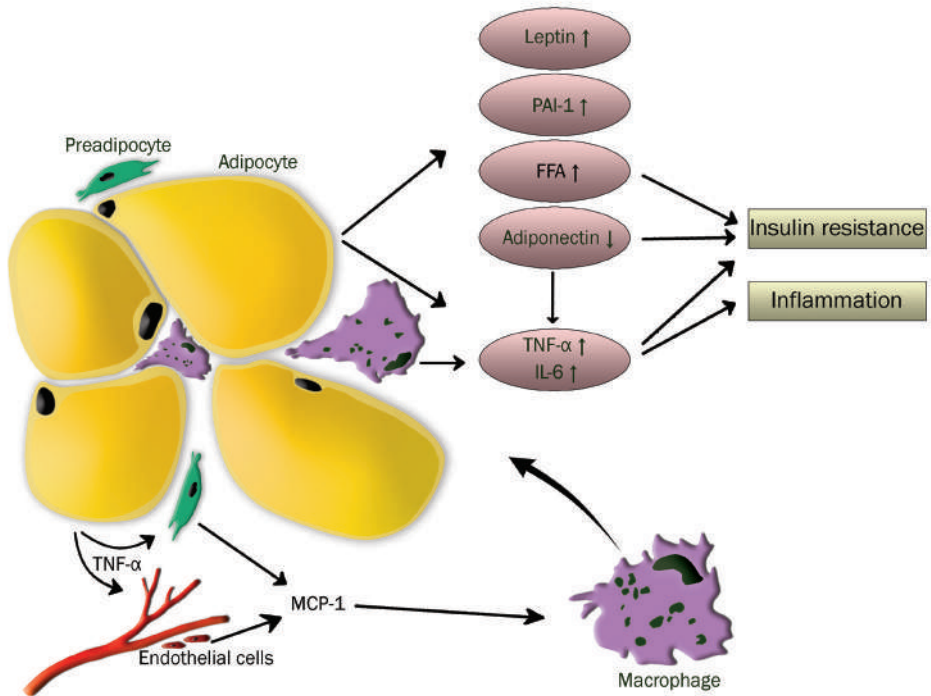


Figure 1. Dysfunctional adipose tissue in obesity. FFA, free fatty acids; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein; PAI-1, plasminogen activator inhibitor-1; TNF- α , tumor necrosis factor- α .

development of insulin resistance, type 2 diabetes, and obesity-related cardiovascular disease²¹⁻²⁴.

Despite being extensively studied, the pathogenesis of insulin resistance in obesity is still not completely understood. High levels of FFAs, as seen in obesity, reduce insulin-mediated glucose uptake by the GLUT4 transporter and inhibit the insulin receptor-mediated tyrosine phosphorylation of the insulin receptor substrate (IRS)-1²⁵. TNF- α induces insulin resistance in a similar way. By stimulating the serine phosphorylation of IRS-1 and converting IRS-1 into an inhibitor of insulin receptor tyrosine kinase activity, TNF- α attenuates the insulin signaling cascade²⁶. In turn, the suppression of lipolysis by insulin is inhibited in insulin resistance, resulting in an increased release of FFAs, thereby setting up a vicious cycle of events^{25, 26}. Under normal conditions, adiponectin increases insulin sensitivity directly, by stimulating tyrosine phosphorylation of the insulin receptor. Adiponectin may also indirectly protect against the development of insulin resistance by activating 5'-AMP-activated protein kinase (AMPK), leading to increased fatty acid oxidation and decreased influx of FFAs into the liver, which contributes to reduced hepatic glucose production and VLDL synthesis²⁷. Conceivably, the paradoxical decrease in adiponectin levels in obesity²⁸ may play an important role in the development of insulin resistance.

Obesity is thought to induce a state of chronic lowgrade inflammation^{29,30} and is associated with an increased number of macrophages in adipose tissue³¹. The exact trigger for the chronic inflammatory response of adipose tissue is not known but may be hypoxia. It is proposed that as adipose tissue enlarges, individual cells are further from blood vessels and become poorly oxygenated³². This state of relative hypoxia activates hypoxia-inducible factor (HIF) -1 α , a key regulator of oxygen homeostasis. The subsequent increased expression of IL-6 and leptin³³, the decreased production of adiponectin³⁴, and the HIF-1 α -mediated attraction of macrophages into adipose tissue³⁵ may initiate the inflammatory response in adipose tissue. Moreover, the increased production of TNF- α by adipocytes stimulates the production of MCP-1 by preadipocytes and endothelial cells¹⁸, with the result that macrophages are attracted to adipose tissue. Additional chemotactic factors, including leptin³⁶, may also contribute to the accumulation of macrophages in dysfunctional adipose tissue. It has been shown that the number of macrophages in adipose tissue decreases significantly after obese individuals undergo bariatric surgery and that this decrease is associated with changes in the expression of genes of the stroma vascular fraction of adipose tissue, which are involved in macrophage attraction³⁵. Adipose tissue macrophages are largely responsible for TNF- α expression and, to a lesser degree, IL-6 expression in adipose tissue³¹.

Distribution of adipose tissue is important in the metabolic complications of obesity. Abdominal adipose tissue, which is strategically located to the liver, is especially associated with an abnormal metabolic profile³⁷. Elevated macrophage infiltration in omental versus subcutaneous adipose tissue and increased concentrations of IL-6 in the portal circulation in obese subjects contribute to systemic inflammation as seen in abdominal obesity^{38, 39}. Furthermore, serum levels of IL-6, associated with visceral adipose tissue, influence insulin levels⁴⁰.

Obesity and Cancer: Pathophysiological Mechanisms

Although BMI is an adequate indicator of overweight and obesity in clinical studies, it does not reflect the obesity-induced metabolic changes that may be involved in carcinogenesis. The presence of metabolic syndrome (defined as a cluster of abdominal obesity, hypertension, hypertriglyceridaemia, low HDL-cholesterol, and hyperglycemia ref. 41), might be a better qualitative indicator of the carcinogenic potential of obesity⁴². Various pathophysiological mechanisms linking obesity to cancer have been postulated. We propose that dysfunctional adipose tissue is a unifying causal factor.

Insulin Resistance

The relationship between insulin resistance and adipose tissue dysfunction is complicated, as both can be caused by the other. Insulin resistance and the insulin-like growth factor (IGF) -1 system may explain in part the link between obesity and cancer. In a state of insulin resistance, which is frequently seen in obesity⁴³, serum insulin levels increase to avert hyperglycemia. Insulin upregulates growth hormone (GH) receptors in the liver, which stimulates the hepatic production of IGF-1⁴⁴. Thus, serum IGF-1 levels would be expected

to be correlated with BMI, but levels of IGF-1 are normal or low in obese subjects⁴⁵. This fact might be explained by the inhibitory effect of high levels of insulin on the secretion of IGF binding protein (IGFBP) -1 and 2. The subsequent increase in the levels of free IGF-1 leads to increased negative feedback on GH secretion, which ultimately leads to lower plasma levels of IGF-1^{46, 47}. In obese subjects, free IGF-1 levels do not respond to insulin administration and tend to be higher than in lean subjects⁴⁸. Both insulin and IGF-1 are believed to play a role in cancer development through binding to the insulin receptor (IR) and IGF-1 receptor (IGF-1R). IGF-1 can inhibit apoptosis and stimulate cell proliferation through several downstream signaling networks, including the phosphatidylinositol 3-kinase (PI3-K) -AKT system and the Ras/Raf/mitogen-activated-protein-kinase (MAPK) systems, respectively⁴⁹. Interestingly, the expression of IGF-1 receptor is increased in some tumors, which suggests that these neoplasms may be stimulated by systemic levels of IGF-1^{50, 51}. In addition, IGF-1 mediates cell migration and invasion in human pancreatic carcinoma cells, most likely by inducing the expression of urokinase-type plasminogen activator (uPA) and its receptor (uPAR) (ref. 52). Besides regulating glucose transport, insulin has mitogenic and anti-apoptotic properties mediated through pathways to some extent similar to those of IGF-1^{53, 54}. This mitogenic, anti-apoptotic environment caused by increased serum levels of insulin and IGF-1 accelerates the stepwise accumulation of genetic mutations and thereby favors carcinogenesis⁴⁹. Clinical studies have shown that patients with high levels of IGF-1 have an increased risk of several types of cancer, including colorectal, prostate, and postmenopausal breast cancer⁴⁹. Hyperinsulinaemia is also an independent risk factor for breast cancer in postmenopausal women⁵⁵ and increases the risk of colorectal and endometrial cancer; however, these results are ambiguous^{56, 57}. In addition, diabetes mellitus, a disease characterized by insulin resistance, is associated with an increased risk of breast, colorectal, pancreatic, and bladder cancer⁵⁸⁻⁶¹. Insulin resistance is likely to play a prominent role in carcinogenesis, and it appears to be one of the major mechanisms involved in the obesity-cancer link.

Adipokines

Adipose tissue produces a variety of hormones and cytokines, known as adipokines. Adipose tissue dysfunction results in altered serum levels of adipokines, which may be directly involved in obesity-related carcinogenesis.

Adiponectin

Adiponectin, an adipokine that is exclusively derived from adipocytes, has significant anti-inflammatory and insulin-sensitizing effects^{62, 63}. Plasma concentrations of adiponectin are reduced in obesity²⁸, and clinical studies point toward there being an inverse relation between serum levels of adiponectin and the risk of breast, endometrial, prostate, colorectal, and kidney cancer⁶⁴⁻⁶⁸. The role of adiponectin in cancer etiology is not yet fully understood. Although it is possible that adiponectin provides indirect protection against carcinogenesis, by affecting insulin sensitivity and the inflammatory state, it has direct anti-carcinogenic effects, many of which are mediated through the AMP-activated protein

kinase (AMPK) system via two receptors, AdipoR1 and R2. Activated AMPK plays an important role in the regulation of growth arrest and apoptosis by stimulating p53 and p21⁶⁹. Moreover, phosphorylation of the tumor suppressor, tuberous sclerosis complex (TSC)-2, by activated AMPK⁷⁰ and the subsequent inhibition of mammalian target of rapamycin may be an important downstream signaling pathway by which adiponectin counteracts carcinogenesis. Independent of AMPK activation, adiponectin decreases the production of reactive oxygen species (ROS; ref. 71), which may result in decreased activation of MAPK⁷² and thereby inhibition of cell proliferation. In vitro, adiponectin inhibits the growth of several breast cancer cell lines⁷³ and induces apoptosis of myelomonocytic (leukemia) lineage cells⁷⁴. Adiponectin also has been shown to inhibit tumor angiogenesis in in vitro experiments⁷⁵. These effects appear to be partially mediated through the activation of a cascade of apoptosis executor proteins, caspase-8,-9, and -3, leading to apoptosis in vascular endothelial cells. A number of studies with fatless A-ZIP/F-1 transgenic mice have suggested that insulin resistance and inflammation have a greater role than adipokines (76). A-ZIP/F-1 mice, which are diabetic and display a state of inflammation but do not have detectable levels of adipokines, are more susceptible to carcinogen-induced tumor formation and growth than are wild-type mice⁷⁷. The accelerated tumor formation in mice without detectable adipokine levels suggests that adiponectin may protect against carcinogenesis. Thus, the decreased plasma levels of adiponectin in obesity²⁸ may be associated with the increased risk of cancer in obesity.

Leptin

The 16-kDa protein hormone leptin, which is secreted by adipocytes, plays a pivotal role in regulating the energy balance, by decreasing appetite and increasing metabolism. Levels of leptin are raised in obese subjects, which suggests that obesity is associated with leptin resistance⁷⁸. The findings of clinical studies of the relationship between systemic leptin levels and breast or prostate cancer are inconsistent^{16, 79, 80}, but an association has been reported for colorectal cancer⁸¹⁻⁸³ and for endometrial cancer^{84, 85}. Interestingly, many colorectal, breast, and endometrial cancers overexpress the leptin receptor ObR⁸⁶⁻⁸⁸. Experimental studies have shown that leptin has mitogenic effects in cancer cell lines, depending on the type of cancer: it stimulates the growth of breast, esophagus, and prostate cancer, but inhibits the growth of pancreatic cancer cells⁸⁹. Mitogenic and anti-apoptotic effects of leptin have been described in both colon and prostate cancer cell lines. Inhibition of MAPK and PI3-K inhibited these effects, indicating that these pathways underlie the growth-promoting effect of leptin^{90, 91}. Although leptin appears to favor cancer cell growth locally, more studies are required to assess the clinical significance of elevated levels of this pleiotropic hormone in relation to the link between obesity and cancer.

PAI-1

PAI-1 is a serine protease inhibitor produced by adipocytes, endothelial cells, and stromal cells in visceral adipose tissue⁹². PAI-1 is not only produced by adipose tissue, but also affects adipocyte differentiation and insulin signaling⁹³. Moreover, PAI-1 inhibits uPA, which

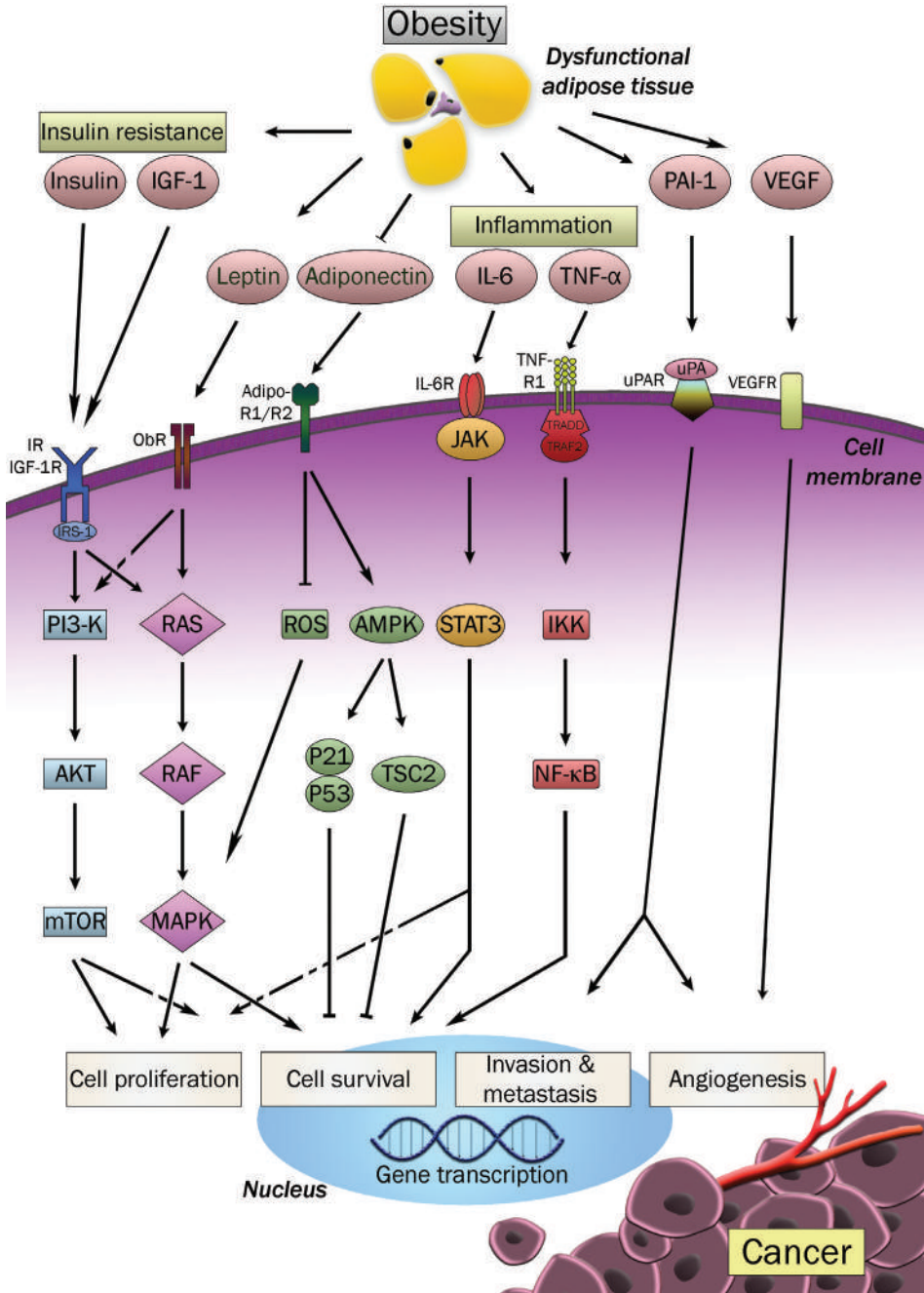
acts as an inducer of fibrinolysis and extracellular matrix degradation, and is associated with tumor cell invasion and metastasis. Paradoxically, PAI-1 is involved in tumor growth, invasion, metastasis, and angiogenesis by interacting with vitronectin, integrins, and other components of the uPA system and by affecting the extracellular matrix⁹⁴⁻⁹⁶.

Overexpression of PAI-1 has been found in many obesity-related types of cancer and is associated with the progression of breast, endometrial, colorectal, thyroid, renal, and prostate cancer⁹⁷⁻¹⁰². In addition to autocrine production by tumor cells, systemic levels of PAI-1 (e.g., produced by immune cells or adipocytes in obesity) appear to be essential for its tumor-promoting effects, though level dependent¹⁰³. Inhibition of PAI-1 might be a potential target in cancer therapy. Indeed, treatment with PAI-1 inhibitor of Min mice, which have a defect in the adenomatous polyposis coli (Apc) gene, suppressed intestinal polyp formation¹⁰⁴. It has been hypothesized recently that, as a consequence of metabolic syndrome, the up-regulation of PAI-1 expression predisposes breast cancer to more aggressive stages¹⁰⁵. This hypothesis supports the role of PAI-1 in promoting cell migration and tumor angiogenesis¹⁰⁶. Although the amount of studies of PAI-1 in obesity induced carcinogenesis is modest, results so far make PAI-1 a plausible culprit for the increased risk of cancer mortality in obesity.

Inflammation

It is well recognized that inflammation is involved in the promotion and progression of cancer^{107, 108}. For example, local chronic inflammation is seen in inflammatory bowel disease and Barrett's esophagus, disorders that carry an increased risk of colorectal cancer and esophageal adenocarcinoma, respectively¹⁰⁰⁻¹¹¹. In fact, (pre-) malignant lesions could be referred to as inflamed, because the tumor microenvironment contains a variety of leukocytes and inflammatory factors¹⁰⁷. The precise role of these inflammatory components in carcinogenesis is not completely understood and therefore continues to be an appealing avenue of research.

Obesity-induced inflammation, a key feature of adipose tissue dysfunction, is thought to be an important link between obesity and cancer. Obesity reflects a state of low-grade systemic inflammation. Serum levels of CRP, an inflammatory marker, are increased in individuals with a higher BMI¹¹², and weight loss leads to a decrease in CRP concentration, whereas weight gain leads to an increase in CRP concentrations¹¹³. Raised serum levels of CRP are correlated with an increased risk of cancer¹¹⁴. Although the causes of inflammation in obesity are not fully understood, the consequences are more evident, with increased systemic levels of proinflammatory cytokines, such as TNF- α and IL-6, which are secreted in large quantities by dysfunctional adipose tissue²⁹. Several of the proinflammatory factors in obesity are believed to be involved in carcinogenesis (*Figure 2*). As a member of the TNF superfamily, TNF- α plays a vital role in adaptive responses of the immune system and other organ systems¹¹⁵. When TNF was identified as a macrophage-derived factor that could induce necrosis in tumor cells¹¹⁶, hopes were raised that the cytokine would be a powerful anticancer agent. However, in recent years, the role of TNF- α in malignancy is being reconsidered, and it is now suggested that TNF- α is involved in



carcinogenesis and cancer progression¹¹⁷⁻¹¹⁹. These contradictory effects of TNF- α can partly be explained by its role in the regulation of apoptosis. When TNF- α binds to its primary receptor, TNF-R1, a downstream signaling cascade leads to activation of nuclear factor (NF)- κ B¹²⁰. This in turn leads to the up-regulation of several negative regulators of apoptosis, such as c-FLIP and cIAP1, which promote cell survival¹²¹. TNF- α has been reported to have tumor-promoting activity in various experimental cancers¹²², and a variety of tumor cells produce TNF- α ¹⁰⁸. TNF- α produced by ovarian cancer cells was recently found to stimulate a constitutive network of factors, including VEGF and chemokines CXCR4 and CXCL12, that promote tumor progression¹¹⁷. Whether increased systemic levels of TNF- α , as seen in obesity²⁹, act through the same signaling network to promote tumor development and progression is not fully clear; however, increased TNF- α serum levels are correlated with an increased risk of cancer-related death and, to a lesser degree, with overall cancer events¹²³. Systemic TNF- α might also be involved in the early development of some tumors, as a recent study showed elevated TNF- α levels to be associated with an increased risk of colorectal adenomas¹²⁴.

Under physiological conditions, IL-6 has an essential role in the acute inflammatory response and affects the maturation of B cells. Recent findings, however, suggest that this essential cytokine is associated with several disease processes, including chronic inflammatory diseases and cancer¹²⁵. Systemic levels of IL-6 are elevated in obesity²⁹ and, akin to TNF- α , systemic levels of IL-6 are correlated with overall cancer death and increased risk of cancer precursor lesions^{123, 124}. In addition, levels of the IL-6 promoter genotype have been associated with several hematological cancers¹²⁶. Effects of IL-6 on cell proliferation and cell survival are likely to be mediated through the Janus kinase (JAK)/signal transducer and activator of transcription (STAT)3 pathway¹²⁷.

Figure 2. Potential pathways directly linking obesity with cancer. AdipoR1/R2, adiponectin receptor 1/2; AMPK, 5'-AMP-activated protein kinase; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; IKK, I κ Bkinase; IL-6, interleukin-6; IL-6R, interleukin-6 receptor; IR, insulin receptor; IRS-1, insulin receptor substrate-1; JAK, Janus kinase; MAPK, mitogen-activated-protein-kinase; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor- κ B; ObR, leptin receptor; PAI-1, plasminogen activator inhibitor-1; PI3-K, phosphatidylinositol 3-kinase; ROS, Reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF- α , tumor necrosis factor- α ; TNF-R1, tumor necrosis factor-receptor 1; TRADD, TNFRSF1A-associated via death domain; TRAF2, TNF receptor-associated factor 2; TSC2, tuberous sclerosis complex 2; uPA, urokinase-type plasminogen activator; uPAR, urokinase-type plasminogen activator receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Obesity-induced inflammation involves other inflammatory components that could contribute to the development of cancer. These components include matrix metalloproteinases (MMPs), which are associated with cancer-cell invasion and metastasis¹²⁸. Strongly induced mRNA levels of several MMPs in obesity, as well as their role in adipocyte differentiation, might represent a potential molecular link between obesity and cancer^{129, 130}. Oxidative stress, as part of chronic inflammation, may also create a microenvironment favorable to tumor development in obesity¹³¹.

Sex Steroids

The impact of adiposity on the synthesis and bioavailability of endogenous sex steroids is of substantial importance in understanding the increased risk of postmenopausal breast and endometrial cancer in obese women. Peripheral conversion of androgenic precursors to estradiol by aromatase in adipose tissue is increased in obesity, leading to increased serum levels of estradiol, which, in turn, are insufficiently counterbalanced by levels of progesterone^{47, 132}. Furthermore, increased serum levels of insulin, as a result of adipose tissue dysfunction, can result in both increased ovarian androgen synthesis and reduced hepatic synthesis of sex-hormone-binding globulin (SHBG)⁴⁷. Recent findings of increased plasma concentrations of bioavailable estradiol and testosterone and decreased plasma concentration of SHBG in obese postmenopausal women are compatible with these mechanisms¹³².

The role of endogenous sex steroids in the development and progression of breast and endometrial cancer is well established. Prospective studies show that levels of endogenous sex steroids are strongly associated with postmenopausal breast and endometrial cancer risk¹³³⁻¹³⁶. The proliferative effect of estrogen on epithelial tissue of both breast and endometrium is believed to be the underlying mechanism^{134, 137}.

Many tumors have increased levels of obesity-related factors, both adipokines and inflammatory components, in their microenvironment, and in some cases it is these tumors that are more aggressive^{87, 94, 108, 117}. Thus, the role of local obesity-related factors should be better determined in comparison to systemic levels. These local factors could be crucial in carcinogenesis and the role of peritumoural adipose tissue herein is yet to be established. Although the above-mentioned and several other potential pathophysiological mechanisms have been proposed, their significance in the obesity-cancer link needs further exploration. It is possible that in obese individuals these mechanisms act synergistically to promote a multifactorial tumor-promoting environment. The significance of these mechanisms probably differs by tumor type, and so research should focus on the role of obesity in one particular cancer type at a time.

Concluding Remarks

Adipose tissue dysfunction, as a consequence of obesity, is likely to play a role in carcinogenesis, by affecting insulin resistance and the production of several adipokines and inflammatory cytokines. Though the precise mechanisms may differ between different types of cancer, it is plausible that these mechanisms synergistically contribute to the

increased cancer risk. While understanding the link between obesity and cancer might provide therapeutic targets, lifestyle improvement remains the most important component in preventing obesity-related morbidity and mortality. This needs to be addressed in intervention studies.

Search Strategy and Selection Criteria

We searched for papers in PubMed and the Cochrane database, using search terms including "obesity," "overweight," "cancer," "adipose tissue dysfunction," "insulin resistance," and "inflammation." Bibliographies of included papers were scanned for other relevant papers. References were selected on the basis of relevance, importance, and novelty. Papers published in peer-reviewed journals as well as papers published in the past 3 years were preferentially treated.

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Rob C.M. van Kruijsdijk
Yolanda van der Graaf
Petra H.M. Peeters
Frank L.J. Visseren

on behalf of the Second Manifestations of ARterial disease (SMART) study group.

CHAPTER 3

CANCER RISK IN PATIENTS WITH MANIFEST VASCULAR DISEASE: EFFECTS OF SMOKING, OBESITY AND METABOLIC SYNDROME

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ABSTRACT

Background

Patients with vascular disease may be at increased risk of cancer due to shared risk factors and common pathogenesis.

Methods

Patients with vascular disease ($n=6,172$) were prospectively followed for cancer incidence. Standardized incidence ratios (SIRs) were calculated to compare the cancer incidence of the study population with that of the general population. Multivariable-adjusted hazard ratios (HRs) of cancer were estimated for smoking status, pack-years, BMI, waist circumference and visceral adipose tissue [VAT] and MetS.

Results

During a median follow-up of 5.5 years, 563 patients were diagnosed with cancer. Patients with vascular disease were at increased risk of cancer (SIR 1.19, 95% CI 1.10–1.29). Specifically, risk of lung cancer (SIR 1.56, 95% CI 1.31–1.83), as well as bladder cancer (SIR 1.60, 95% CI 1.11–2.24) and cancer of the lip, oral cavity or pharynx in men (SIR 1.51, 95% CI 0.89–2.39), and colorectal (SIR 1.71, 95% CI 1.11–2.53) and kidney cancer (SIR 2.92, 95% CI 1.05–6.38) in women was increased. A relation between smoking and cancer risk was observed (HR for current smokers: 1.37, 95% CI 1.05–1.73), whereas an increase in VAT was associated with higher breast cancer risk in women (HR 1.42, 95% CI 1.03–1.96). No relation between MetS and cancer risk was found.

Conclusions

Patients with vascular disease have a 19% higher cancer risk compared to the general population. Smoking increased cancer risk and abdominal obesity is a risk factor for breast cancer in female patients with vascular disease.

Impact

These results call for awareness of the increased cancer risk in patients with vascular disease among physicians and underline the necessity of lifestyle improvement not only for reducing cardiovascular risk.

INTRODUCTION

Cardiovascular disease and cancer constitute a major burden on global health and share several important modifiable risk factors, including tobacco smoking and excess bodyweight¹⁻⁴. Over recent decades, survival of cardiovascular events has substantially improved, whereas the number of patients with prevalent cardiovascular disease is ever growing^{3,4}. Although secondary prevention in clinical practice focuses on the recurrence of vascular events^{5,6}, these patients might also be at increased risk of cancer as there are shared risk factors for both cardiovascular disease and cancer.

The atherogenic and carcinogenic effects of smoking, as well as the increased risk of vascular disease in persons with excess body weight are well established⁷⁻⁹. The relation between excess bodyweight and increased cancer risk, however, has now also been established¹⁰⁻¹³. Increased body mass index (BMI) is related with both an increased incidence and mortality of various cancer types, including endometrial, colorectal and postmenopausal breast cancer as well as several other common cancers^{10,13}. Underlying mechanisms are not fully clear, but it is assumed that adipose tissue dysfunction plays an important role by inducing insulin resistance, inflammation and changes in serum levels of adipokines (e.g. leptin and adiponectin) and sex steroids, and thereby promoting cell proliferation and survival, as well as invasive growth, metastasis and angiogenesis¹⁴. An indicator of the metabolic changes associated with obesity, is the presence of metabolic syndrome (MetS), which is a cluster of metabolic risk factors including abdominal obesity, hypertension, dyslipidemia and hyperglycemia¹⁵. Individual MetS components as well as MetS as an entity are related to the occurrence of several types of cancer in the general population¹⁶⁻¹⁸. MetS, as well as other established risk factors for cancer such as obesity and smoking, are highly prevalent in patients with vascular disease¹⁹. To date, however, knowledge about cancer incidence and the effect of these various risk factors in patients with vascular disease is limited. Therefore, we assessed cancer incidence in patients with clinical manifest vascular disease and evaluated the effects of smoking, obesity and MetS on cancer risk in a prospective cohort study.

METHODS

Study population, data collection and follow-up

Patients originated from the Second Manifestations of ARterial disease (SMART)-study²⁰, an ongoing prospective cohort study at the University Medical Center Utrecht (UMCU) in the Netherlands. Patients aged 18-80 newly referred to the UMCU with clinically manifest cerebrovascular disease (CVD), coronary heart disease (CHD), peripheral arterial disease (PAD), abdominal aortic aneurysm (AAA) or a marked cardiovascular risk factor (hypertension, dyslipidemia or diabetes mellitus) are included in the SMART study. The central aims of the SMART study are to determine the prevalence of concomitant arterial disease and of risk factors for arterial disease in a high-risk population and to study the incidence of future

cardiovascular events. A detailed description of the study has been published previously²⁰. In short, patients underwent baseline examinations, including a questionnaire covering medical history, symptoms of and risk factors for cardiovascular disease, menopausal status for female patients²¹ and current medication use. Furthermore, a standardized diagnostic protocol was performed including physical examination (height, weight, systolic and diastolic blood pressure) and laboratory tests to determine metabolic markers fasting serum glucose and lipid levels. Since January 1999 additional measurements of waist circumference and visceral adipose tissue (VAT) have been done. Waist circumference was measured halfway between the lower rib and iliac crest. VAT was estimated by ultrasonography. A detailed description of this procedure has been published previously²². Patients were biannually asked to complete a questionnaire on hospitalization and outpatient clinic visits for follow-up. Information on cancer diagnosis was obtained by linking the SMART-database with the Netherlands Cancer Registry. Age- and gender-specific cancer incidence rates in the Netherlands in the period of 1997-2010 were also acquired from the Cancer Registry²³, whereas mortality rates were obtained from Statistics Netherlands²⁴. The local ethics committee approved the study and all participants gave their written informed consent. For the present study, data of patients with manifest vascular disease included between September 1996 and March 2011 ($n=6,172$) were used. Two hundred fifty-eight patients (4.2%) were lost to follow-up because of migration or withdrawal from the study.

Definitions

MetS was defined according to the revised National Cholesterol Education Program (NCEP-R) criteria¹⁵. Participants were diagnosed with MetS when complying with three or more of the following abnormalities:

1. Abdominal obesity: waist circumference ≥ 102 cm in men or ≥ 88 cm in women.
2. Hypertension: blood pressure ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic or use of blood pressure-lowering agents.
3. Hypertriglyceridemia: serum triglycerides ≥ 1.70 mmol/l (150 mg/dl).
4. Reduced HDL-cholesterol: serum HDL-cholesterol < 1.03 mmol/l (40 mg/dl) in men or < 1.3 mmol/l (50 mg/dl) in women.
5. Elevated fasting glucose: fasting serum glucose ≥ 5.6 mmol/l (100 mg/dl) or use of glucose-lowering agents.

If waist circumference was not available ($n=863$), a BMI higher than 30 kg/m² was used as determinant for abdominal obesity²⁵. This method was evaluated in the subset of patients of whom waist circumference was available, which resulted in a positive predictive value of 91% (95% CI: 89%-93%) and a negative predictive value of 74% (95% CI: 73%-76%). Pack-years of smoking were calculated with the formula: (number of years smoked \times mean number of cigarettes smoked per day)/20. Cancer incidence data were coded according to the tenth revision of the International Classification of Diseases (ICD-10)²⁶. The main endpoint of interest was defined as the first primary invasive neoplasm, excluding non-

melanoma skin cancer. For women who were premenopausal at baseline, age 50 years was used as proxy for menopause in order to determine menopausal status at time of cancer diagnosis²⁷.

Data analyses

Standardized incidence ratios (SIRs), adjusted for age (5-year age groups), sex (when not stratified by) and calendar year were calculated for all observed cancers. Corresponding 95% confidence intervals (CIs) were computed assuming a Poisson distribution. To compare cancer incidence with the incidence of recurrent vascular events (*i.e.* myocardial infarction, ischemic stroke, or vascular death), cumulative incidences, as functions of years since study enrollment, were estimated accounting for competing risk of death by causes other than the endpoint under study.

Patients who had a history of cancer prior to enrollment ($n=232$), were excluded from further analysis. Missing data for smoking status ($n=28$; 0.5%), pack years of smoking ($n=23$; 0.4%), BMI ($n=10$; 0.2%) and alcohol use ($n=28$; 0.5%) were singly imputed by weighted probability matching on the basis of multivariable regression using covariate and outcome data (using the `aregImpute`-function in R, `Hmisc`-package)²⁸. Proportional subdistribution hazards regression models^{29,30} were fitted to estimate hazard ratios (HRs) with corresponding 95% CIs of incident cancer associated with (1) smoking status (never [reference], past, current) and pack years of smoking (0 [reference], 1 to <30 and ≥ 30); (2) BMI, waist circumference and VAT per SD increment; (3) presence of MetS and number of MetS components (categorized into three groups, *i.e.* 0-1 [reference], 2-3 and 4-5 components). Death was treated as competing event. Relations between the determinants and total incident cancer as well as the three most common male and female cancer sites (*i.e.* cancer of the colon/rectum, lower respiratory tract, breast and prostate) were examined. Two models were fitted: a crude model and a model adjusted for age, sex (when not stratified by) and additional adjustments depending on the association examined: (1) BMI (continuous) and alcohol drinking status (never, past or current alcohol use) for the association between smoking and cancer incidence; (2) smoking status, pack-years of smoking and alcohol drinking status for the association between measures of adiposity and cancer incidence and (3) smoking status, pack-years of smoking and alcohol drinking status for the association between MetS/number of MetS components and cancer incidence. The proportionality assumption for all models was checked graphically by plotting the scaled Schoenfeld residuals against failure time, but no violations were observed. For the adiposity measures, the linearity assumption was evaluated by adding these determinants to the respective models as a restricted cubic spline function. Subsequently, the presence of non-linearity was formally assessed using a Wald test. No significant non-linearity was detected (p -values > 0.05). Potential effect modification by age, sex and smoking status was tested for by adding multiplicative interaction terms to the models. No effect modification was found (p -values for interaction >0.05). Furthermore, analyses were repeated after exclusion of patients who were diagnosed with cancer within one year after inclusion ($n = 84$) to evaluate the presence of reverse causality. This procedure

did not result in substantial changes of HRs, thus final analyses were performed retaining these patients. Statistical analyses were performed in Microsoft Excel 2003 and in R, version 2.15.1 (R Development Core Team, Vienna, Austria; packages: 'cmprsk', 'rms' and 'Hmisc').

RESULTS

A total of 6,172 patients with manifest vascular disease were included in this study, of whom 1,589 (26%) were female. Baseline characteristics according to sex are shown in *Table 1*. A majority of the study population consisted of smokers (84% ever and 32% current smokers among men and 70% ever and 36% current smokers among women). Mean BMI was 26.9 kg/m² in men and 26.8 kg/m² in women. MetS was present in 53% of men and in 55% of women. Coronary artery disease was the most common vascular disease in both men (66%) and women (44%). Four percent of the participants had a history of cancer.

Cancer incidence

During a total follow-up of 36,461 person-years (median follow-up 5.5 years, interquartile range 2.9 – 8.6 years), 429 men (8.5%) and 134 women (7.9%) were diagnosed with cancer. Compared with the general Dutch population, a higher cancer incidence was observed in patients with manifest vascular disease (SIR 1.19, 95% CI 1.10–1.29), particularly in women (SIR 1.48, 95% CI 1.25–1.75) (*Table 2*). In both men and women, incidence of cancer of the lower respiratory tract (SIR 1.38, 95% CI 1.13–1.66 and 2.86, 95% CI 1.94–4.05) was increased. Men also had an excess risk of bladder cancer (SIR 1.60, 95% CI 1.11–2.24) and cancer of the lip, oral cavity or pharynx (SIR 1.76, 95% CI 1.04–2.78), whereas women had a higher risk of colorectal cancer (SIR 1.71, 95% CI 1.11–2.53) and kidney cancer (SIR 2.92, 95% CI 1.05–6.38). In addition, the incidence of melanoma of the skin was significantly higher in men and women combined (SIR 1.61, 95% CI 1.04–2.38), but not in men or women separately. *Figure 1* displays the observed and expected cumulative incidence curves for cancer and the observed recurrent vascular events in men and women.

Smoking and incident cancer risk

Table 3 shows the hazard ratios for incident cancer by smoking status and pack-years of smoking in patients with manifest vascular disease without a history of cancer at baseline. Both former and current smokers had a higher risk of incident cancer compared to never smokers (HR 1.33 95% CI 1.03–1.73 and 1.37, 95% CI 1.05–1.80, respectively). Compared to never smokers, the risk of cancer of the lower respiratory tract in former smokers was 2-fold higher (HR 2.65, 95% CI 1.22–5.78) and was 4-fold higher in current smokers (HR 4.60, 95% CI 2.13–9.92). An increase in risk for cancer of the lower respiratory tract was observed for number of pack-years (for 1 to <30 pack-years: HR 2.41, 95% CI 1.11–5.22; for ≥30 pack-years: HR 5.14, 95% CI 2.37–11.14).

Table 1. Baseline characteristics

	Men (n = 4,583)	Women (n = 1,589)
Age (y)	60 (10)	59 (12)
Smoking, current	1477 (32)	564 (36)
Smoking, ever	3688 (84)	1111 (70)
Pack years of smoking ^a	20 (6 - 35)	12 (0 - 29)
Alcohol consumption, current	2428 (53)	643 (41)
Body mass index (kg/m ²)	27 (4)	27 (5)
Visceral adipose tissue (cm)	10 (3)	8 (2)
Metabolic syndrome components		
Waist circumference (cm)	98 (11)	89 (13)
Systolic blood pressure (mmHg)	141 (20)	143 (21)
Diastolic blood pressure (mmHg)	80 (10)	78 (10)
Serum triglycerides (mmol/l)	1.4 (1.0 - 2.1)	1.4 (1.0 - 1.9)
High density lipoprotein (mmol/l)	1.2 (0.3)	1.4 (0.4)
Fasting serum glucose (mmol/l)	5.8 (5.4 - 6.5)	5.6 (5.2 - 6.4)
Metabolic syndrome ^b	2434 (53)	867 (55)
Number of components:		
0-1	762 (17)	338 (21)
2-3	2626 (57)	772 (49)
4-5	1194 (26)	477 (30)
Medical history		
Coronary artery disease	3022 (66)	699 (44)
Cerebrovascular disease	1155 (25)	616 (39)
Peripheral arterial disease	841 (18)	403 (25)
Abdominal aortic aneurysm	459 (10)	86 (5)
Cancer (excluding non-melanoma skin cancer)	171 (4)	61 (4)
Diabetes mellitus	799 (17)	269 (18)

Data are mean (standard deviation), percentage of group or median (interquartile range)

^a Only for ever smokers; ^b According to NCEP-R criteria

Measures of adiposity and incident cancer risk

The risk of incident cancer per SD increase in BMI, waist circumference and VAT is shown in *Table 4*. Among men, BMI, waist circumference and VAT were inversely related to overall cancer risk, with HRs of 0.86 (95% CI 0.77–0.97), 0.87 (95% CI 0.77–0.99) and 0.89 (95% CI 0.77–1.02) per SD increase respectively. An inverse relation was also seen between the different measures of adiposity and cancers of the lower respiratory tract and prostate, but

Table 2. Standardized incidence ratios for incident cancer in patients with manifest vascular disease

Cancer site (ICD-10 code)	Men (n= 4583)				Women (n= 1588)				Total (n= 6172)	
	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	Observed	Expected	SIR (95% CI)	
	Lip, oral cavity, pharynx (C00-C14)	18	10.2	1.76 (1.04 - 2.78)	0	1.7	-	18	11.9	1.51 (0.89 - 2.39)
Esophagus (C15)	14	16.2	0.87 (0.47 - 1.45)	1	1.6	0.63 (0 - 3.58)	15	17.8	0.84 (0.47 - 1.39)	
Stomach (C16)	15	8.9	1.69 (0.95 - 2.80)	2	1.6	1.27 (0.12 - 4.64)	17	10.4	1.63 (0.95 - 2.61)	
Colon, rectum (C18-C20)	58	62.1	0.93 (0.71 - 1.21)	25	14.6	1.71 (1.11 - 2.53)	83	76.7	1.08 (0.86 - 1.34)	
Pancreas (C25)	10	9.4	1.07 (0.51 - 1.96)	4	2.6	1.54 (0.40 - 3.97)	14	12.0	1.17 (0.64 - 1.96)	
Larynx, trachea/bronchus/lung (C32 -C34)	110	79.8	1.38 (1.13 - 1.66)	31	10.9	2.86 (1.94 - 4.05)	141	90.6	1.56 (1.31 - 1.83)	
Melanoma of skin (C43)	19	11.7	1.62 (0.97 - 2.53)	6	3.8	1.59 (0.57 - 3.47)	25	15.5	1.61 (1.04 - 2.38)	
Breast (C50)	-	-	-	31	28.5	1.09 (0.74 - 1.54)	31	28.5	1.09 (0.74 - 1.54)	
Corpus uteri (C54)	-	-	-	9	5.1	1.76 (0.80 - 3.35)	9	5.1	1.76 (0.80 - 3.35)	
Ovary (C56)	-	-	-	3	3.4	0.88 (0.17 - 2.60)	3	3.4	0.88 (0.17 - 2.60)	
Prostate (C61)	91	104.5	0.87 (0.70 - 1.07)	-	-	-	91	104.5	0.87 (0.70 - 1.07)	
Kidney (C64)	18	11.1	1.62 (0.96 - 2.56)	6	2.1	2.92 (1.05 - 6.38)	24	13.2	1.82 (1.17 - 2.71)	
Bladder (C67)	34	21.2	1.60 (1.11 - 2.24)	1	1.7	0.58 (0 - 3.29)	35	22.9	1.53 (1.06 - 2.12)	
Lymph/haematopoietic tissue (C81-C96)	30	33.3	0.90 (0.61 - 1.29)	10	7.5	1.34 (0.64 - 2.47)	40	40.8	0.98 (0.70 - 1.34)	
Other	44	40.4	1.09 (0.79 - 1.46)	12	18.6	0.64 (0.33 - 1.13)	56	59.1	0.95 (0.72 - 1.23)	
All (excluding non-melanoma skin cancer [C44])	461	408.8	1.13 (1.03 - 1.24)	141	95.1	1.48 (1.25 - 1.75)	602	503.9	1.19 (1.10 - 1.29)	

SIR: Standardized incidence ratio (quotient of observed and expected numbers of incident cancer cases); CI: Confidence interval. Presented SIRs are adjusted for age (5-year age groups), sex (when not stratified by) and calendar year. The sum of the number of expected cancer cases in men and women might differ from the total number of expected cancer cases because of rounding. The observed and expected number of cancers include multiple separate cases of incident cancer in individual patients.

only the inverse relation between BMI and prostate cancer was statistically significant (HR 0.79, 95% CI 0.64–0.97). Increase in VAT significantly increased the risk of breast cancer in women (HR 1.42, 95% CI 1.03–1.96). Ninety-two percent of women diagnosed with breast cancer were postmenopausal at time of diagnosis.

Metabolic syndrome and incident cancer risk

No significant association between MetS and cancer risk was observed in men (HR 0.92, 95% CI 0.76–1.13) or women (HR 0.96, 95% CI 0.66–1.40) (*Table 5*). In addition, the number of metabolic syndrome components did not significantly affect overall cancer risk.

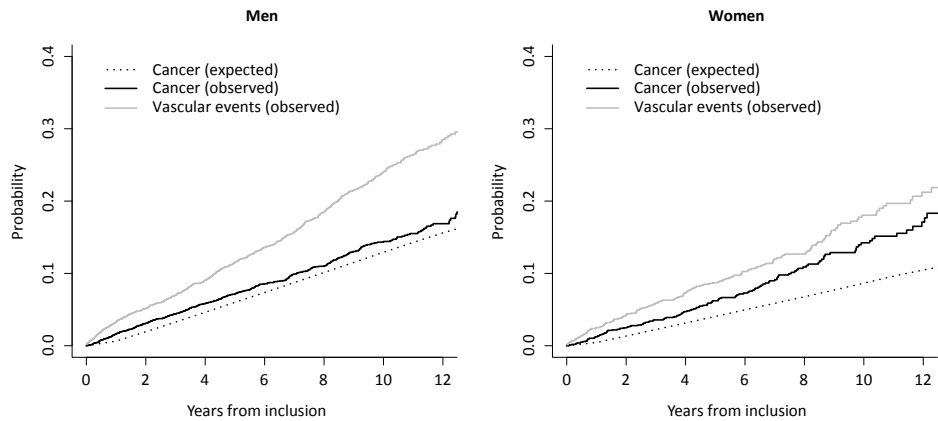


Figure 1. Cumulative incidence of cancer and recurrent vascular events in patients with manifest vascular disease.

Table 3. Hazard ratios with 95% Confidence Intervals for smoking status and pack-years of smoking for risk of incident cancer in patients with manifest vascular disease without a history of cancer at baseline

Cancer site (ICD-10 code)	Smoking status			Pack-years of smoking		
	Never	Former	Current	0	1 to <30	≥30
All (excluding non-melanoma skin cancer [C44])						
Men						
No. of patients	729	2252	1431	729	2308	1375
No. of events	46	210	135	46	185	160
Crude model	1.00 (reference)	1.41 (1.03 - 1.94)	1.29 (0.92 - 1.80)	1.00 (reference)	1.18 (0.85 - 1.63)	1.65 (1.19 - 2.30)
Adjusted model ^a	1.00 (reference)	1.25 (0.91 - 1.72)	1.41 (1.00 - 1.98)	1.00 (reference)	1.15 (0.83 - 1.59)	1.56 (1.12 - 2.16)
Women						
No. of patients	464	520	544	464	726	338
No. of events	34	49	42	34	57	34
Crude model	1.00 (reference)	1.35 (0.87 - 2.10)	0.93 (0.59 - 1.46)	1.00 (reference)	1.04 (0.68 - 1.59)	1.27 (0.79 - 2.05)
Adjusted model ^a	1.00 (reference)	1.49 (0.95 - 2.32)	1.14 (0.72 - 1.82)	1.00 (reference)	1.25 (0.81 - 1.91)	1.46 (0.90 - 2.37)
Men and women						
No. of patients	1193	2772	1975	1193	3034	1713
No. of events	80	259	177	80	242	194
Crude model	1.00 (reference)	1.36 (1.06 - 1.75)	1.16 (0.89 - 1.51)	1.00 (reference)	1.12 (0.87 - 1.44)	1.53 (1.18 - 1.99)
Adjusted model ^a	1.00 (reference)	1.33 (1.03 - 1.73)	1.37 (1.05 - 1.80)	1.00 (reference)	1.21 (0.93 - 1.56)	1.59 (1.22 - 2.07)
Colon, rectum (C18-C20)						
Men and women						
No. of patients	1193	2772	1975	1193	3034	1713
No. of events	11	39	21	11	34	26
Crude model	1.00 (reference)	1.49 (0.76 - 2.92)	1.00 (0.48 - 2.09)	1.00 (reference)	1.15 (0.58 - 2.26)	1.50 (0.74 - 3.03)
Adjusted model ^a	1.00 (reference)	1.66 (0.82 - 3.39)	1.37 (0.64 - 2.94)	1.00 (reference)	1.42 (0.70 - 2.88)	1.77 (0.84 - 3.73)

table 3 continued

Larynx, trachea/bronchus/lung (C32 - C34)										
Men and women										
No. of patients	1193	2772	1975	1193	3034	1713				
No. of events	8	51	59	8	48	62				
Crude model	1.00 (reference)	2.69 (1.28 - 5.65)	3.91 (1.87 - 8.18)	1.00 (reference)	2.23 (1.05 - 4.71)	4.95 (2.37 - 10.32)				
Adjusted model ^a	1.00 (reference)	2.65 (1.22 - 5.78)	4.60 (2.13 - 9.92)	1.00 (reference)	2.41 (1.11 - 5.22)	5.14 (2.37 - 11.14)				
Breast (C50)										
Women										
No. of patients	464	520	544	464	726	338				
No. of events	7	11	7	7	16	2				
Crude model	1.00 (reference)	1.49 (0.59 - 3.81)	0.73 (0.25 - 2.08)	1.00 (reference)	1.41 (0.58 - 3.41)	0.36 (0.07 - 1.71)				
Adjusted model ^a	1.00 (reference)	1.41 (0.52 - 3.83)	0.64 (0.21 - 1.91)	1.00 (reference)	1.34 (0.50 - 3.54)	0.35 (0.07 - 1.69)				
Prostate (C61)										
Men										
No. of patients	729	2252	1431	729	2308	1375				
No. of events	9	41	29	9	39	31				
Crude model	1.00 (reference)	1.41 (0.68 - 2.89)	1.43 (0.68 - 3.02)	1.00 (reference)	1.27 (0.62 - 2.62)	1.65 (0.79 - 3.47)				
Adjusted model ^a	1.00 (reference)	1.21 (0.58 - 2.50)	1.64 (0.77 - 3.51)	1.00 (reference)	1.23 (0.59 - 2.54)	1.55 (0.74 - 3.26)				

^a Model adjusted for age, sex (when not stratified by), body mass index and alcohol use

Table 4. Hazard ratios with 95% confidence intervals for incident cancer per standard deviation increase in body mass index, waist circumference and visceral adipose tissue in patients with manifest vascular disease without history of cancer at baseline

Cancer site (ICD-10 code)	BMI (kg/m ²)	Waist circumference (cm)	VAT (cm)
All (excluding non-melanoma skin cancer [C44])			
Men			
No. of patients	4412	3904	3496
No. of events	391	303	244
1 SD	3.6	10.6	2.4
Crude model	0.83 (0.74 - 0.93)	0.91 (0.81 - 1.02)	0.94 (0.83 - 1.08)
Adjusted model ^a	0.86 (0.77 - 0.97)	0.87 (0.77 - 0.99)	0.89 (0.77 - 1.02)
Women			
No. of patients	1528	1356	1221
No. of events	125	95	77
1 SD	4.8	12.8	2.4
Crude model	1.01 (0.85 - 1.20)	1.10 (0.91 - 1.33)	1.08 (0.89 - 1.30)
Adjusted model ^a	0.97 (0.80 - 1.18)	1.05 (0.84 - 1.31)	1.00 (0.80 - 1.24)
Men and women			
No. of patients	5940	5260	4717
No. of events	516	398	321
1 SD	4.0	11.9	2.6
Crude model	0.88 (0.80 - 0.97)	0.97 (0.88 - 1.07)	0.98 (0.88 - 1.10)
Adjusted model ^a	0.89 (0.81 - 0.99)	0.91 (0.81 - 1.02)	0.90 (0.80 - 1.02)
Colon, rectum (C18-C20)			
Men and women			
No. of patients	5940	5260	4717
No. of events	71	57	46
1 SD	4.0	11.9	2.6
Crude model	0.95 (0.76 - 1.19)	0.91 (0.70 - 1.18)	0.88 (0.68 - 1.15)
Adjusted model ^a	0.96 (0.76 - 1.22)	0.87 (0.65 - 1.17)	0.80 (0.60 - 1.09)
Larynx, trachea/bronchus/lung (C32 -C34)			
Men and women			
No. of patients	5940	5260	4717
No. of events	118	82	62
1 SD	4.0	11.9	2.6
Crude model	0.83 (0.66 - 1.03)	1.03 (0.82 - 1.30)	1.02 (0.79 - 1.30)
Adjusted model ^a	0.85 (0.68 - 1.07)	0.94 (0.70 - 1.25)	0.89 (0.66 - 1.21)

Table 4 continued

Cancer site (ICD-10 code)	BMI (kg/m ²)	Waist circumference (cm)	VAT (cm)
Breast (C50)			
Women			
No. of patients	1528	1356	1221
No. of events	25	17	14
1 SD	4.8	12.8	2.4
Crude model	0.88 (0.63 - 1.23)	1.03 (0.65 - 1.62)	1.31 (0.96 - 1.79)
Adjusted model ^a	0.88 (0.62 - 1.25)	1.14 (0.67 - 1.96)	1.42 (1.03 - 1.96)
Prostate (C61)			
Men			
No. of patients	4412	3904	3496
No. of events	79	57	51
1 SD	3.6	10.6	2.4
Crude model	0.73 (0.60 - 0.88)	0.90 (0.73 - 1.11)	0.89 (0.65 - 1.21)
Adjusted model ^a	0.79 (0.64 - 0.97)	0.87 (0.69 - 1.10)	0.85 (0.62 - 1.17)

BMI: body mass index; VAT: visceral adipose tissue; SD: standard deviation. ^a Model adjusted for age, sex (when not stratified by), smoking status, pack-years of smoking and alcohol use

Table 5. Hazard ratios with 95% confidence interval for incident cancer according to metabolic syndrome in patients with manifest vascular disease without a history of cancer at baseline

Cancer site (ICD-10)	Number of metabolic syndrome components ^a				Metabolic syndrome	
	0-1	2-3	4-5	No	Yes	
All (excluding non-melanoma skin cancer [C44])						
Men						
No. of patients	734	2531	1146	2064	2347	
No. of events	69	224	98	188	203	
Crude model	1.00 (reference)	0.91 (0.69 - 1.19)	0.87 (0.64 - 1.18)	1.00 (reference)	0.93 (0.76 - 1.13)	
Adjusted model ^b	1.00 (reference)	0.84 (0.64 - 1.10)	0.83 (0.61 - 1.13)	1.00 (reference)	0.92 (0.76 - 1.13)	
Women						
No. of patients	323	742	461	694	832	
No. of events	24	57	44	53	72	
Crude model	1.00 (reference)	1.13 (0.70 - 1.80)	1.23 (0.75 - 2.02)	1.00 (reference)	1.07 (0.75 - 1.52)	
Adjusted model ^b	1.00 (reference)	0.99 (0.61 - 1.60)	1.05 (0.63 - 1.75)	1.00 (reference)	0.96 (0.66 - 1.40)	
Men and women						
No. of patients	1057	3273	1607	2758	3179	
No. of events	93	281	142	241	275	
Crude model	1.00 (reference)	0.97 (0.77 - 1.23)	0.96 (0.74 - 1.25)	1.00 (reference)	0.96 (0.81 - 1.14)	
Adjusted model ^b	1.00 (reference)	0.87 (0.68 - 1.10)	0.88 (0.67 - 1.14)	1.00 (reference)	0.92 (0.77 - 1.10)	
Colon, rectum (C18-C20)						
Men and women						
No. of patients	1057	3273	1607	2758	3179	
No. of events	8	46	17	32	39	
Crude model	1.00 (reference)	1.84 (0.87 - 3.90)	1.33 (0.57 - 3.09)	1.00 (reference)	1.02 (0.64 - 1.63)	
Adjusted model ^b	1.00 (reference)	1.66 (0.79 - 3.51)	1.16 (0.51 - 2.67)	1.00 (reference)	0.95 (0.59 - 1.52)	

table 5 continued

Larynx, trachea/bronchus/ lung (C32 -C34)						
Men and women						
No. of patients	1057	3273	1607	2758	3179	
No. of events	17	64	37	51	67	
Crude model	1.00 (reference)	1.21 (0.71 - 2.07)	1.38 (0.78 - 2.46)	1.00 (reference)	1.11 (0.77 - 1.60)	
Adjusted model ^b	1.00 (reference)	1.04 (0.60 - 1.78)	1.14 (0.63 - 2.05)	1.00 (reference)	1.00 (0.68 - 1.46)	
Breast (C50)						
Women						
No. of patients	323	742	461	694	832	
No. of events	7	11	7	13	12	
Crude model	1.00 (reference)	0.75 (0.29 - 1.93)	0.65 (0.22 - 1.88)	1.00 (reference)	0.70 (0.32 - 1.56)	
Adjusted model ^b	1.00 (reference)	0.80 (0.30 - 2.09)	0.68 (0.22 - 2.04)	1.00 (reference)	0.73 (0.31 - 1.76)	
Prostate (C61)						
Men						
No. of patients	734	2531	1146	2064	2347	
No. of events	17	46	16	45	34	
Crude model	1.00 (reference)	0.76 (0.44 - 1.33)	0.58 (0.29 - 1.15)	1.00 (reference)	0.65 (0.42 - 1.02)	
Adjusted model ^b	1.00 (reference)	0.70 (0.40 - 1.24)	0.58 (0.30 - 1.15)	1.00 (reference)	0.68 (0.44 - 1.07)	

^a According to NCEP-R criteria; abdominal obesity: waist circumference > 102 cm in men or > 88 cm in women; Hypertension: ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic; Hypertriglyceridemia: serum triglycerides ≥ 1.70 mmol/l (150 mg/dl); Low HDL-cholesterol: serum HDL-cholesterol < 1.04 mmol/l (40 mg/dl) in men or < 1.29 mmol/l (50 mg/dl) in women; High fasting glucose: fasting serum glucose ≥ 5.6 mmol/l (100 mg/dl).

^b Model adjusted for age, sex (when not stratified by), smoking status, pack-years of smoking and alcohol use

DISCUSSION

In patients with manifest vascular disease, cancer incidence was 19% higher than expected based on cancer incidence in the general population. Specifically, risk of cancer of the lower respiratory tract, as well as cancer of the bladder and lip, oral cavity or pharynx in men and colorectal and kidney cancer in women was higher compared to the general population. Our results indicate that smoking is a strong risk factor for cancer risk in these patients. Adiposity was associated with a lower risk of overall incident cancer, but with a higher risk of breast cancer in women, whereas there was no relation between MetS and cancer risk. These findings are in line with observations of an increased risk of smoking-related cancers in patients with vascular disease in previous hospital discharge register studies³¹⁻³³. However, inconsistent results have been reported for cancers that are not known to be related to smoking, such as colorectal and prostate cancer^{1,32,34-36}. For colorectal neoplasms, several studies found an increased risk in patients with coronary artery disease^{1,32}, whereas other studies found no relation^{35,36}. Observations in this study of a higher incidence of colorectal cancer, but also of melanoma of the skin, compared to the general population, indicate that other factors besides tobacco smoking may also have a role. In contrast to previous studies, the design of this study allowed to prospectively evaluate and quantify the effects of possible explanatory factors for the observed increased cancer risk. Twenty-six per cent of the study population were female, which is similar to the percentage of women among patients with vascular disease of the same age category in the general population.

Although obesity is a known risk factor for colorectal cancer in the general population^{13,37}, no association between any of the adiposity measures and colorectal cancer risk was observed in our study population. Meta-analyses of population-based studies indicate that, in addition to colorectal cancer, increase in BMI is associated with a higher risk of esophageal adenocarcinoma, endometrial, postmenopausal breast and high-grade prostate cancer, as well as several less common cancers^{12,13,38}. Conversely, inverse associations with BMI have been reported for lung and low-grade prostate cancer^{12,13,38}. The modestly lower overall cancer risk with increasing BMI observed in the present study might have been caused by the relatively large number of lung and prostate cancer cases (38% of total cases). Indeed, inverse associations of BMI with prostate and lung cancer were found, although the latter was not statistically significant.

Insulin resistance and chronic low-grade inflammation are considered as culprits in the relation between obesity and cancer¹⁴. Especially abdominal obesity is associated with a state of insulin resistance and low-grade inflammation^{39,40} and VAT might therefore be a better determinant for certain cancers than BMI or waist circumference, as the latter measures are known to misclassify individuals in terms of VAT and metabolic risk⁴¹. Correspondingly, we observed that an increase in VAT was related to an increased risk for breast cancer risk, whereas BMI and waist circumference were not.

To our knowledge, this is the first prospective study investigating the effect of MetS on cancer risk in patients with vascular disease. This study confirms previous findings from

population-based cohorts that MetS is not related to overall cancer risk^{42,43}, or risk of cancers of the lung or prostate¹⁷. However, in contrast to the present findings in patients with vascular disease, MetS has been linked to an increased risk of colorectal and postmenopausal breast cancer in the general population, as was recently confirmed in a meta-analysis¹⁷. Furthermore, in a cross-sectional study among patients undergoing coronary angiography, a relation was observed between coronary artery disease and advanced colonic lesions which was stronger in persons with MetS¹. The lack of a relation between BMI or MetS and colorectal cancer risk in the present study warrants further research to determine which factors are responsible for this difference between patients with vascular disease and the general population.

The increased risk of cancer in patients with vascular disease warrants awareness among clinicians. Pharmaceutical treatment and lifestyle modifications of shared risk factors, such as smoking cessation, are likely to reduce both (recurrent) vascular events and cancer in these patients. Whilst targeting (abdominal) obesity may decrease breast cancer risk, the inverse relation between BMI and prostate and lung cancer risk suggests that lowering BMI might not be favourable for the risk of these cancers. The net benefit of such interventions should be determined in studies that consider both cancer and vascular disease concurrently. In addition to shared risk factors, a possible common pathogenesis, such as chronic inflammation in both atherosclerosis and colorectal carcinogenesis, may also have a role in the relation between vascular disease and cancer risk⁴⁴. A better understanding of such mechanisms might provide novel therapeutic strategies targeting both vascular disease and cancer.

Several potential limitations of our study should be considered. Relative cancer risk in patients with vascular disease might have been underestimated by using the general Dutch population – in which vascular disease is highly prevalent – as reference group to calculate SIRs. Despite the substantial number of possible confounders that was adjusted for in the models, information on other possible confounders for some specific cancer sites, such as physical activity, genetic and dietary factors, was not available. In addition, due to the relatively small number of cases the study might have been underpowered to detect significant relations with several site-specific cancers. Furthermore, the limited number of cases did not allow stratification by cancer specific features (e.g. low-/high-grade prostate cancer) in analyses of individual cancer types, hereby reducing comparability with previous studies.

Notable strengths of our study include the prospective design and the completeness of cancer diagnoses, attained through a linkage of the SMART-cohort with the Netherlands Cancer Registry, which is considered to have a near complete coverage⁴⁵. The proportion of study participants who were lost to follow-up was low, reducing the risk of bias. Furthermore, the study population is at high risk of vascular death, which is a competing event for incident cancer and may therefore complicate the interpretability of the risk estimates. We addressed this problem by using competing risk models²⁹. Hence, the HRs that are presented can be directly interpreted in terms of risk.

In conclusion, patients with vascular disease have a 19% higher cancer risk compared to the general population in a median follow-up of 5.5 years. Smoking is a risk factor for cancer in men and women, and abdominal obesity increased the risk of breast cancer in female patients with clinical manifest vascular disease.

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Rob C.M. van Kruijsdijk
Yolanda van der Graaf
Hendrik Koffijberg
Gert Jan de Borst
Hendrik M. Nathoe
L. Jaap Kappelle
Frank L.J. Visseren

on behalf of the Second Manifestations of ARterial disease (SMART) study group.

CHAPTER 4

CAUSE-SPECIFIC MORTALITY AND YEARS
OF LIFE LOST IN PATIENTS WITH DIFFERENT
MANIFESTATIONS OF VASCULAR DISEASE

Submitted

ABSTRACT

Background

Patients with cardiovascular disease might be at increased risk of non-vascular mortality due to shared risk factors. Our aim was to evaluate causes of death and years of life lost in patients with different manifestations of vascular disease.

Design

Prospective cohort study

Methods

5911 Patients with stable coronary artery disease, cerebrovascular disease, peripheral artery disease (PAD), abdominal aortic aneurysm or polyvascular disease were followed-up for mortality. Cause-specific standardized mortality ratios (SMRs) and years of life lost (YLL), compared to the Dutch population, were estimated. Determinants for cause-specific mortality were evaluated using competing risks models.

Results

During a median follow-up of 6.0 years (interquartile range: 3.1-9.2), 958 (16.2%) patients died. All-cause mortality was increased compared to the general population (SMR: 1.26, 95% CI: 1.18-1.34). Patients with PAD and polyvascular disease were at highest risk, especially for ischemic heart disease (SMR: 2.52, 95% CI: 1.70-3.60 and SMR: 3.97, 95% CI: 3.18-4.90, respectively). Patients with PAD were at increased risk of dying from cancer (SMR: 1.67, 95% CI: 1.25-2.17). On average, patients with vascular disease died 5.5 years younger than the general population, with 80% of the excess YLL attributable to cardiovascular disease. In middle-aged patients the excess YLL were about 10 years, of which 24% were lost due to cancer. Important determinants for mortality were male gender, smoking, physical inactivity, BMI < 20 kg/m², impaired renal function and polyvascular disease.

Conclusions

Patients with manifest vascular disease are at increased risk of both cardiovascular and cancer mortality, particularly middle-aged patients and those with PAD. On average, patients with vascular disease die 5.5 years younger compared to the general population.

INTRODUCTION

Advances in the treatment and prevention of cardiovascular disease have led to a significant decrease in cardiovascular-related mortality in developed countries in the last decades¹⁻³. The prevalence of patients in a chronic phase of cardiovascular disease, however, is still growing. Recent estimates of prevalent cardiovascular disease in more than one third of American adults highlight the great burden of this chronic disease on public health². Although there is a lack of high quality and comparable incidence data across Europe, it is clear that cardiovascular disease also causes a very substantial burden of morbidity in Europe, with hospital discharge rates for cardiovascular disease of over 2,500 per 100,000 population in 2010³. Atherosclerosis, the major cause of cardiovascular disease, is characterized by a progressive systemic nature and frequently manifests as coronary artery disease (CAD), cerebrovascular disease (CVD), peripheral artery disease (PAD) or an abdominal aortic aneurysm (AAA), but often multiple vascular locations are affected⁴. Patients with atherosclerotic disease have 18.3% (95% confidence interval [CI]: 17.4%-19.1%) 4-year risk of new cardiovascular events, including cardiovascular death, especially those patients with manifestations of atherosclerotic disease in different vascular territories (polyvascular disease vs risk factors only hazard ratio [HR]: 1.99, 95% CI: 1.78-2.24)⁵. Furthermore, several observational studies indicate that the risk of non-vascular causes of death, such as cancer, may be increased as well⁶⁻¹⁰. Compared to the general population, patients with manifest vascular disease have a 19% higher 5-year risk of developing cancer, including cancers of the lung, kidney and bladder¹⁰, possibly as a result of shared risk factors, such as smoking and obesity^{10,11}. Detailed information on cause-specific mortality may guide preventive measures in the growing group of patients with chronic cardiovascular disease. Thus far, however, studies on mortality and risk factors for cause-specific mortality were generally confined to a particular cardiovascular patient group, such as CAD or stroke patients or do not consider non-vascular mortality^{5-7,9}.

In the present prospective cohort study in patients with different manifestations of vascular disease (*i.e.* CAD, CVD, PAD, AAA or polyvascular disease), cause-specific mortality and years of life lost were assessed and compared to the general population. Furthermore, important determinants for specific causes of death were evaluated.

METHODS

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 study has been published previously¹². In short, all newly referred patients, aged 18

to 80 years with a recent history of manifest atherosclerotic disease or traditional cardiovascular risk factors (hypertension, dyslipidemia and diabetes mellitus) are asked to participate in the SMART study. The participation rate was approximately 80%¹². CAD was defined as a recent diagnosis of angina pectoris with a confirmed stenosis on a coronary angiogram, myocardial infarction (MI) 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 (ABI) 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 ≥ 3 cm, as measured with ultrasonography. Polyvascular disease was defined as having two or more of the aforementioned clinical manifestations of vascular disease, either as qualifying event or in the medical history. Exclusion criteria were a terminal malignancy, dependency in daily activities or not sufficiently fluent in the Dutch language. At inclusion, patients underwent a standardized cardiovascular screening program, including a questionnaire on cardiovascular history, assessment of risk factors, ABI, and ultrasonography of the carotid arteries and abdominal aorta to detect any additional (sub)clinical atherosclerosis. The local ethics committee approved the study and all patients gave their written informed consent. For the present study, data of 5,911 patients with a recent diagnosis of either CAD, CVD, PAD, AAA or polyvascular disease between September 1996 and March 2012 were used.

Follow-up and death ascertainment

Patients were biannually asked to complete a questionnaire on hospitalization and outpatient clinic visits for follow up. Deaths of patients were reported by relatives of the patient, the general practitioner or specialist. Further information on cause of death was collected by retrieving hospital discharge letters and/or contacting the general practitioner of the patient. Physicians of an endpoint committee independently audited all events on the basis of the available clinical information. Of the present study population, 215 patients (4%) were lost to follow-up. Primary causes of death, coded according to the tenth edition of the International Classification of Diseases (ICD-10)¹³, were grouped into ischemic heart disease, cerebrovascular disease, cancer, infection, and the combination of accidents and suicides (*Appendix 1*). National cause-specific mortality rates and life-expectancy data of the general Dutch population were retrieved from Statistics Netherlands¹⁴.

Data analyses

Cause-specific standardized mortality ratios (SMRs), adjusted for 5-year age groups, sex and calendar year, were calculated using cause-specific national mortality rates. Corresponding 95% CIs were computed assuming a Poisson distribution. Cumulative cause-specific mortality, as a function of years since study inclusion, was estimated while taking deaths by causes other than the one under study into account as competing risks¹⁵. Expected all-cause cumulative mortality was estimated based on national mortality data. The distribution of causes of death for different strata of vascular disease at inclusion was

evaluated using cumulative mortality estimates at 5 and 10 years. Observed and expected years of life lost (YLL) were calculated to evaluate the average years a patient would have lived if he or she had not died prematurely¹⁶. Average excess YLL due to cardiovascular, cancer and other deaths were plotted against age after fitting a cubic smoothing spline. Age-standardized YLL rates for specific causes of death were calculated to facilitate comparison to other populations. Potential determinants for cause-specific mortality, including gender, smoking status (never, former and current), alcohol consumption status (never, former and current), physical activity as measured by hours*metabolic equivalent of task (MET) per week, BMI, metabolic syndrome (according to the revised National Cholesterol Education Program [NCEP] definition¹⁷), diabetes mellitus, eGFR as estimated by the Modification of Diet in Renal Diseases (MDRD)-formula, number of localizations of atherosclerotic disease (1, 2 or more) and years since first vascular event were evaluated with proportional subdistribution hazards regression models¹⁸, accounting for competing risk of death by causes other than the one under study. All models included adjustment for potential confounding by sex, age, smoking status, pack-years of smoking, alcohol consumption, BMI and physical activity. Furthermore, multivariable-adjusted HRs of Fontaine stage II and stage III-IV vs. CAD as well of Fontaine stage II vs. stage III-IV were computed for all-cause mortality to differentiate between PAD patients. Statistical analyses were performed in R, version 2.15.3 (www.r-project.org; packages: 'Hmisc', 'RiskRegression', 'cmprsk').

RESULTS

Baseline characteristics

Baseline characteristics of the study population according to localization of vascular disease at inclusion are shown in *Table 1*. Overall, the mean age was 60.3 years (SD: 10.2 years) and 75% of the patients were men. The most common localization of vascular disease at inclusion was CAD (48%), whereas 21% of patients had CVD, 12% of patients had PAD, 3% of patients had an AAA and 16% of patients had vascular disease at more than one location. Mean age and number of ever smokers, as well as several metabolic parameters, such as total cholesterol and C-reactive protein, tended to be higher among patients included with PAD or AAA. In most strata, the majority of patients were treated with blood pressure-lowering and lipid-lowering medication, as well as with antithrombotic therapy, particularly patients with CAD. Most patients had their first vascular event <1 year before enrollment, except for patients with polyvascular disease, of whom 80% had their first vascular event \geq 2 years before enrollment.

Cause-specific mortality

During a median follow-up of 6.0 years (interquartile range: 3.1-9.2 years), 958 patients (13%) had died. All-cause mortality was higher in the total study population as 939 deaths were observed during the period from 1997-2011, whereas 748 deaths were expected based on mortality rates from the general Dutch population (SMR: 1.26, 95% CI: 1.18-1.34;

Table 1. Baseline characteristics of Study Population According to Localization of Vascular Disease at Inclusion

	Coronary artery disease (n = 2,842)	Cerebrovascular disease (n = 1,224)	Peripheral artery disease (n = 724)	Abdominal aorta aneurysm (n = 191)	Polyvascular disease (n = 930)
Age (y)	60 (10)	59 (11)	58 (11)	67 (7)	64 (9)
Male gender %	81	59	63	93	82
Smoking, current %	24	35	64	41	35
Smoking, past %	52	42	27	49	54
Pack-years of smoking ^a	21 [9 - 34]	22 [10 - 35]	29 [17 - 42]	31 [16 - 45]	26 [13 - 41]
Current alcohol consumption %	15	19	30	32	24
Physical activity (hours*MET per week)	39 [19 - 69]	33 [14 - 57]	22 [5 - 48]	25 [7 - 48]	23 [6 - 48]
Body Mass Index (kg/m ²)	27 (4)	26 (4)	26 (4)	26 (3)	27 (4)
Waist circumference (cm)	97 (11)	92 (12)	93 (12)	97 (11)	97 (12)
Visceral adipose tissue (cm)	9 (3)	8 (2)	9 (2)	9 (2)	10 (3)
Systolic blood pressure (mmHg)	137 (20)	142 (21)	146 (21)	144 (19)	144 (21)
Diastolic blood pressure (mmHg)	80 (11)	82 (11)	82 (11)	85 (11)	80 (12)
Metabolic parameters					
eGFR (ml/min/1,73 m ²)	77 (16)	78 (17)	79 (19)	72 (19)	71 (18)
Total cholesterol (mmol/l)	4.6 (1.1)	5.0 (1.2)	5.6 (1.2)	5.4 (1.1)	5.0 (1.2)
Low density lipoprotein (mmol/l)	1.2 (0.3)	1.4 (0.4)	1.3 (0.4)	1.2 (0.3)	1.2 (0.4)
High density lipoprotein (mmol/l)	2.6 (0.9)	3.0 (1.1)	3.5 (1.1)	3.5 (1.0)	3.0 (1.0)
Serum triglycerides (mmol/l)	1.4 (1.0)	1.2 (0.9)	1.5 (1.1)	1.4 (1.1)	1.5 (1.1)
C-reactive protein (mg/l)	1.6 [0.8 - 3.4]	1.8 [0.8 - 4.1]	3.2 [1.5 - 6.4]	3.9 [1.8 - 8.0]	3.0 [1.4 - 6.0]
Fasting serum glucose (mmol/l)	5.8 [5.4 - 6.5]	5.6 [5.2 - 6.1]	5.7 [5.3 - 6.4]	5.7 [5.3 - 6.3]	5.9 [5.4 - 6.7]
Metabolic syndrome ^b %	56	41	49	52	59
Medical history					
Coronary artery disease %	100	0	0	0	80
Cerebrovascular disease %	0	100	0	0	51
Peripheral arterial disease %	0	0	100	0	51
Abdominal aortic aneurysm %	0	0	0	100	32
Years since first vascular event					
< 1 year before enrollment %	67	80	90	64	11
1-2 years before enrollment %	9	12	3	15	8
≥ 2 years before enrollment %	24	9	7	20	80
Diabetes mellitus %	16	12	15	8	22
Cancer %	3	4	6	9	5
Medication					
Blood pressure-lowering medication %	92	49	37	48	78
Glucose-lowering medication %	13	9	10	5	16
Lipid-lowering medication %	81	51	34	28	67
Platelet inhibitor medication %	89	74	44	33	77
Oral anticoagulants %	11	7	8	7	19

All data are expressed as percentage, mean (S.D.) or median [interquartile range]. Percentages may not add up to 100% because of rounding. MET: Metabolic equivalent of task; eGFR: Glomerular filtration rate estimated by the Modification of Diet in Renal Diseases (MDRD)-formula. ^aFor ever smokers only; ^bAccording to the revised National Cholesterol Education Program definition.

Table 2). Particularly cardiovascular death was higher (SMR: 2.10, 95% CI: 1.92-2.29), including death due to ischemic heart disease (SMR: 2.02, 95% CI: 1.75-2.32) and cerebrovascular disease (SMR: 1.37, 95% CI: 1.05-1.75). The highest mortality was observed in patients with polyvascular disease, particularly for mortality due to ischemic heart disease (SMR: 3.97, 95% CI: 3.18-4.90). Total and cancer mortality was significantly lower in patients with CAD compared to the general population (SMR: 0.72, 95% CI: 0.63-0.82 and 0.73, 95% CI: 0.58-0.90 respectively), whereas no clear differences were seen with regard to cardiovascular mortality, including deaths due to ischemic heart disease (SMR: 1.07, 95% CI: 0.77-1.46). In the total study population, mortality due to cancer, infectious disease and accidents and suicide were not higher compared to the general population. However, risk of cancer death was markedly higher in PAD patients (SMR: 1.67, 95% CI: 1.25-2.17) compared to the general population.

Cumulative mortality

Observed and expected cumulative mortality for the different strata of vascular disease are shown in *Figure 1*. In accordance with the SMRs, observed all-cause mortality was lower than expected in patients with CAD over the entire follow-up. The most important causes of death in this group, cardiovascular disease (42.7% and 46.8% of total deaths at 5 and 10 years, respectively) and cancer (42.7% and 35.4% of total deaths at 5 and 10 years, respectively), occurred at a constant rate over follow-up (*Appendix 3, 4 and 5*). Patients with CVD were more likely to die from cardiovascular disease, with a 5 and 10-year probability of 4.0% (95% CI: 2.9-5.4%) and 11.2% (8.7-14.%), respectively. A high mortality was observed in patients with PAD (5-year probability: 9%, 95% CI: 7-12%), AAA (5-year probability: 21%, 95% CI: 15-27%) and polyvascular disease (5-year probability: 21%, 95% CI: 18-24%). Although cardiovascular disease was the most frequent cause of death (49.7% of total deaths at 5 year), cancer was also responsible for an important share of mortality (36.4%) in patients with PAD. Of the patients with AAA or polyvascular disease who died during follow-up, more than half died of cardiovascular disease. Other causes of death, including infectious diseases and accidents or suicide were relatively often seen in patients with AAA (10.0% and 2.9% of deaths after 10 years, respectively).

Years of life lost

Average excess YLL compared to the general population are shown in *Figure 2*. On average, patients with vascular disease died 5.5 years younger than individuals in the general population. The excess of YLL was highest between the ages of 55-65 years as patients dying in this age range deceased about 10 years earlier than expected. About 80% of the excess of YLL was caused by premature cardiovascular deaths. In patients between the ages of 50 and 60 years non-vascular causes were more important, with 24% of the total excess of YLL being attributable to death due to cancer. The age-standardized YLL rate of the study population was 18,762 per 100,000 person-years for cardiovascular causes, 4,131 per 100,000 person-years for cancer and 3,053 per 100,000 person-years for other causes of death. No distinct trends in the distribution of YLL over time were observed (*Appendix 6*).

Table 2. Cause-specific standardized mortality ratios in patients with manifest vascular disease

Localization of vascular disease	Cause of death							All causes
	Infection	Cancer	Cardiovascular disease (total)	Ischemic heart disease	Cerebrovascular disease	Accidents and suicide		
Coronary artery disease								
Observed	11	84	91	40	12	3	209	
Expected	14.3	115.8	85.0	37.3	16.0	8.4	290.5	
SMR (95% CI)	0.77 (0.38 - 1.38)	0.73 (0.58 - 0.90)	1.07 (0.86 - 1.31)	1.07 (0.77 - 1.46)	0.75 (0.39 - 1.31)	0.36 (0.07 - 1.04)	0.72 (0.63 - 0.82)	
Cerebrovascular disease								
Observed	7	58	80	32	22	3	174	
Expected	8.9	57.3	50.6	21.2	10.4	4.2	160.1	
SMR (95% CI)	0.79 (0.32 - 1.62)	1.01 (0.77 - 1.31)	1.58 (1.25 - 1.97)	1.51 (1.03 - 2.13)	2.12 (1.33 - 3.20)	0.71 (0.15 - 2.09)	1.09 (0.93 - 1.26)	
Peripheral artery disease								
Observed	7	54	72	30	9	3	161	
Expected	4.8	32.4	28.0	11.9	5.9	2.5	89.7	
SMR (95% CI)	1.46 (0.59 - 3.00)	1.67 (1.25 - 2.17)	2.57 (2.01 - 3.24)	2.52 (1.70 - 3.60)	1.53 (0.70 - 2.90)	1.20 (0.25 - 3.51)	1.79 (1.53 - 2.09)	
Abdominal aorta aneurysm								
Observed	6	17	42	12	4	2	76	
Expected	3.0	17.0	17.0	7.2	3.5	1.1	50.8	
SMR (95% CI)	2.00 (0.73 - 4.35)	1.00 (0.58 - 1.60)	2.47 (1.78 - 3.34)	1.67 (0.86 - 2.91)	1.14 (0.31 - 2.93)	1.82 (0.22 - 6.57)	1.50 (1.18 - 1.87)	
Polyvascular disease								
Observed	13	66	200	87	16	2	319	
Expected	8.6	55.9	50.6	21.9	10.2	3.7	156.5	
SMR (95% CI)	1.51 (0.80 - 2.58)	1.18 (0.91 - 1.50)	3.95 (3.42 - 4.54)	3.97 (3.18 - 4.90)	1.57 (0.90 - 2.55)	0.54 (0.07 - 1.95)	2.04 (1.82 - 2.27)	
Total								
Observed	44	279	485	201	63	13	939	
Expected	39.6	278.5	231.1	99.6	46.0	20.0	747.6	
SMR (95% CI)	1.11 (0.81 - 1.49)	1.00 (0.89 - 1.13)	2.10 (1.92 - 2.29)	2.02 (1.75 - 2.32)	1.37 (1.05 - 1.75)	0.65 (0.35 - 1.11)	1.26 (1.18 - 1.34)	

Presented standardized mortality ratios represent the quotient of observed and expected mortality and are adjusted for age (5-year age groups), sex and calendar year. SMR: Standardized mortality ratio ; CI: Confidence interval

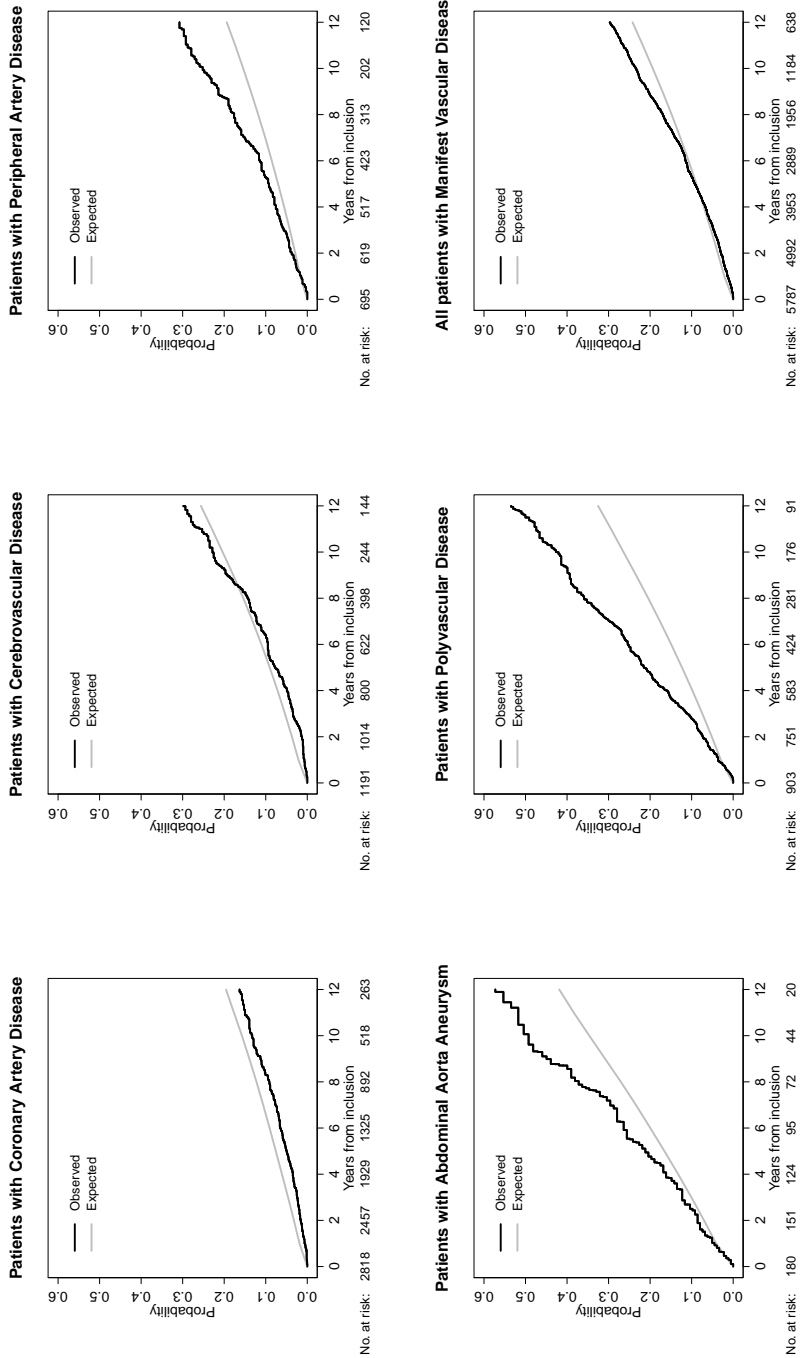


Figure 1. Observed and expected cumulative mortality of patients with different manifestations of vascular disease.

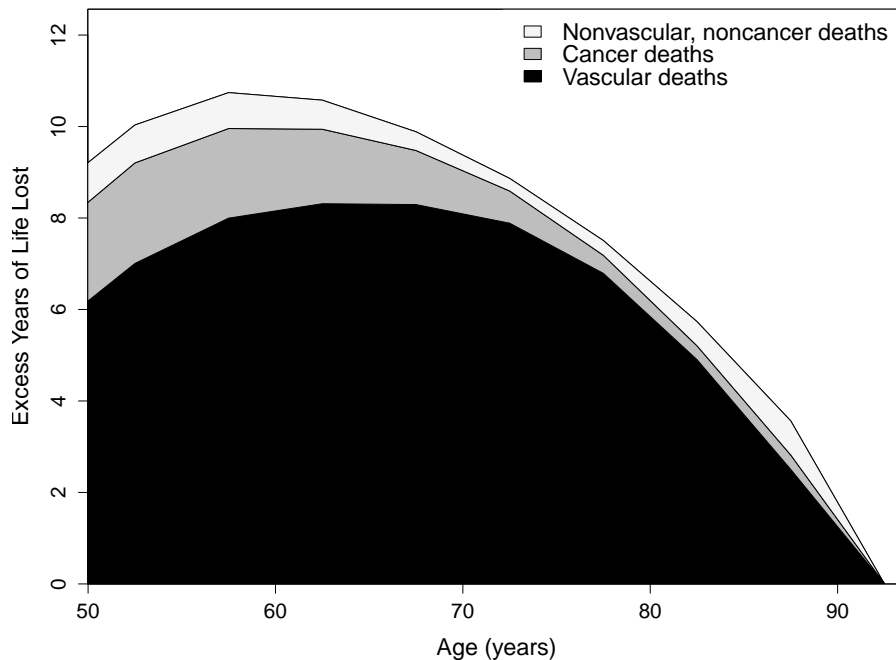


Figure 2. Average excess years of life lost due to vascular disease, cancer and other causes in patients with manifest vascular disease

Determinants for cause-specific mortality

Male gender, smoking, BMI $<20 \text{ kg/m}^2$ and eGFR $<30 \text{ mL/min/1.73m}^2$ were important determinants for all-cause mortality (Figure 3). Important risk factors for vascular death included male gender (HR: 1.50, 95% CI: 1.17-1.91), current smoking (HR: 2.36, 95% CI: 1.78-3.15), metabolic syndrome (HR: 1.33, 95% CI: 1.11-1.59), diabetes (HR: 1.49, 95% CI: 1.20-1.86), eGFR $<30 \text{ mL/min/1.73m}^2$ (HR: 5.86, 95% CI: 3.60-9.53), PAD (HR: 2.01, 95% CI: 1.48-2.74), AAA (HR: 2.46, 95% CI: 1.66-3.63), polyvascular disease (HR: 3.71, 95% CI: 2.88-4.78) and >2 years since first vascular event (HR: 1.77, 95% CI: 1.47-2.14). Higher physical activity was associated with a lower risk of vascular death (HR for 19-50 h*MET/week: 0.71, 95% CI: 0.57-0.87 and HR for $>50 \text{ h*MET/week}$: 0.54, 95% CI: 0.41-0.70). Current smoking and a BMI $<20 \text{ kg/m}^2$ were related to higher risk of cancer mortality and other non-vascular causes of death. Furthermore, patients with PAD were at higher risk of cancer death compared to CAD patients (HR: 1.77, 95% CI: 1.47-2.14). Similar to vascular death, higher physical activity was related to a lower risk of non-cancer non-vascular death ($>50 \text{ h*MET/week}$: HR: 0.60, 95% CI: 0.38-0.95). Patients with PAD Fontaine stage III-IV (n=54) were at increased risk of premature death compared to patients with Fontaine stage II (n=670; HR: 1.85, 95% CI: 1.17-2.94). Compared to patients with CAD, the HR for PAD Fontaine stage II was 1.84 (95% CI: 1.47-2.30) whereas the HR for Fontaine stage III-IV was 3.44 (95% CI 2.20-5.38).

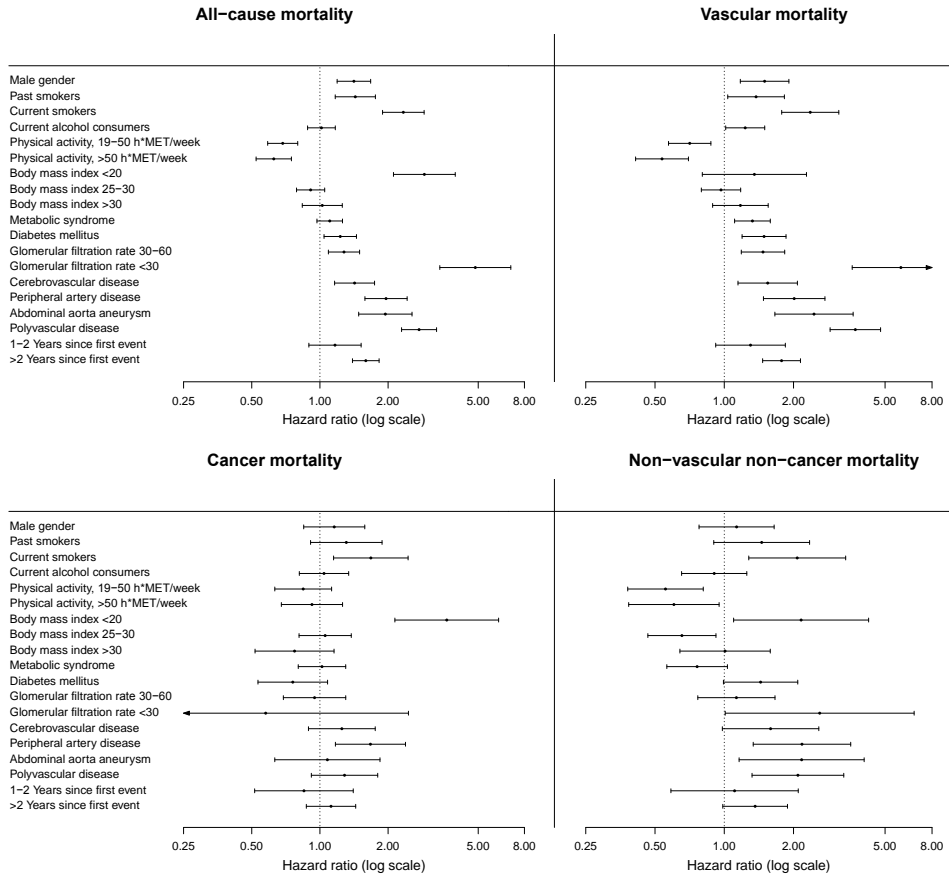


Figure 3. Hazard ratio's for determinants of cause-specific mortality. MET: metabolic equivalent of task per week; BMI: Body Mass Index; eGFR: Estimated glomerular filtration rate. Reference categories: female gender for gender, never for smoking status, never for alcohol drinking status, ≤ 19 hours*MET per week for physical activity, 20–25 kg/m² [reference category] for BMI; no diabetes for diabetes mellitus, ≥ 60 mL/min/1.73 m² for eGFR, coronary artery disease for localization of vascular disease and 1 year for years since first vascular event.

DISCUSSION

In this hospital-based cohort of patients with stable vascular disease, all-cause mortality was higher compared to the general population. On average, patients with vascular disease die 5.5 years younger than the general population, whereas the reduction in life expectancy in middle-aged patients is about 10 years. Although cardiovascular disease is the most important cause of death in these patients, over 20% of the excess of premature deaths was attributable to non-vascular causes, with cancer being the most important. Patients with CAD had a lower risk than the general population, whereas a twofold increased

mortality was observed in patients with PAD or polyvascular disease. Most important determinants for vascular mortality were male gender, smoking, BMI <20 kg/m², impaired renal function, polyvascular disease and time since first vascular event. Low physical activity and presence of PAD were related to a higher risk of vascular and non-vascular mortality. In accordance with results from the Reduction of Atherothrombosis for Continued Health (REACH)-study^{5, 19}, an international registry of outpatients either with vascular disease or at high risk for developing vascular disease, we observed that patients with PAD, in particular those with Fontaine III-IV, and polyvascular disease were at highest risk of premature death. Although, similar to the REACH-study⁵, the majority of deaths in these patient groups were caused by cardiovascular disease, we showed that cancer mortality was higher as well compared to the general population, particularly in patients with PAD. Remarkably, mortality in patients with CAD was lower than expected based on general population data. This finding may be explained by the fact that this group consists of patients who survived their initial ischemic event, underwent coronary revascularization and received optimal secondary prevention advice and treatment. Furthermore, patients with a terminal malignancy were not included in the present cohort, while these patients were likely to be present in the reference group and thus contribute to a higher risk. Hence, caution should be exerted when extrapolating these results to CAD patients in general. The comparison among the strata of vascular disease, however, is not subject to the aforementioned limitations. Mortality was significantly higher in patients with CVD, PAD, AAA, or polyvascular disease compared to CAD patients, adjusted for age, sex, smoking, pack-years, alcohol, BMI and physical activity. As expected, patients with CAD were most likely to die from ischemic heart disease. Although patients with CVD had a higher risk of dying from recurrent CVD compared to the general population, ischemic heart disease was the most common vascular cause of death in these patients as well. In contrast to death by ischemic heart disease, CVD mortality was high during first years and decreased during follow-up. This finding corresponds with results from the Danish MONICA-study in 4,162 patients after a first stroke, which included the acute phase after a stroke in the follow-up⁶. In this study, CVD accounted for 32.1% and ischemic heart disease for 22.7% of deaths. In contrast to the present results, a significant 26% increase in risk of dying from cancer was observed in stroke patients in the MONICA-population. PAD or AAA patients were also at high risk of dying from ischemic heart disease, but in these groups other vascular causes of death, as well as non-vascular causes were also important. In line with results of the present study, several studies have showed a high cancer prevalence (ranging from 9-16%) and increased cancer mortality in patients with PAD^{9, 20}. Although important, the high prevalence of smokers in PAD patients is unlikely to be the only explanation for the high cancer mortality risk since PAD patients were at significantly higher risk of dying from cancer compared to CAD patients even when adjusted for smoking status and pack-years. The reduction in life expectancy was particularly prominent in middle-aged patients with vascular disease, with an average of 10 excess life-years lost. Also considering that 24% of the excess of YLL was attributable to cancer deaths, these results underline the need for intensive risk factor treatment in these patients, not only for cardiovascular disease,

but also for cancer. In line with findings from population-based studies²¹⁻²³, we showed that several important modifiable risk factors, including smoking, low physical activity and diabetes increase both vascular and non-vascular mortality. Generally, only the effects on the occurrence of cardiovascular events are taken into account in studies that evaluate the benefits of risk factor treatment in patients with vascular disease. Given the results of the present study, however, targeting mutual risk factors for vascular mortality and cancer mortality might be a sensible strategy to simultaneously decrease premature mortality of multiple causes.

Notable strengths of this study include the large sample size and possibility to directly compare patients with different manifestations of vascular disease. In addition, the data on cause of death was of high quality and over 96% complete. Furthermore, we used competing risk methods that allow direct interpretation of the effect estimates in terms of risk, because evaluation of time-to-event data of causes of death without accounting for competing risks could lead to bias¹⁵.

Some study limitations need to be acknowledged. First, the relative mortality risk in patients with vascular disease might have been underestimated by using the general Dutch population, in which vascular disease is highly prevalent, as reference group to calculate SMRs. Second, the SMRs for cancer mortality should be interpreted considering that the presence of a terminal malignancy served as exclusion criterion for the SMART-study. Third, multiple pre-specified determinants were tested in the regression analyses, which could have led to some false-positive findings. However, as our effect estimates were robust and generally in line with results from previous studies^{5, 21-23}, this is not likely.

Conclusions

In this contemporary cohort of patients with vascular disease, mortality was higher compared to the general population of similar age and sex. Patients with vascular disease die 5.5 years younger, not only from cardiovascular disease, but also from cancer. Particularly middle-aged patients and patients with PAD or polyvascular disease are at increased risk of premature death. These results underline the necessity to target mutual and cause-specific risk factors to prevent early death in patients with stable vascular disease.

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APPENDIX 1

Outcome definitions with corresponding ICD-10 codes	
Cardiovascular disease	Vascular dementia (F01) Diseases of the circulatory system (I00-I28, I31, I34-I37, I42-I99) Vascular disorders of the intestine (K55) Other sudden death, cause unknown (R96)
Ischaemic heart disease	Ischaemic heart diseases (I20-I25) Sudden cardiac death (I46.1) Other sudden death, cause unknown (R96)
Cerebrovascular disease	Vascular dementia (F01) Intracerebral haemorrhage (I61) Cerebral infarction (I63) Stroke, not specified as haemorrhage or infarction (I64) Sequelae of intracerebral haemorrhage (I69.1) Sequelae of cerebral infarction (I69.3) Sequelae of stroke, not specified as haemorrhage or infarction (I69.4)
Ruptured abdominal aorta aneurysm	Abdominal aortic aneurysm, ruptured (I71.3)
Infectious disease	Certain infectious and parasitic diseases (A00-B99) Infectious diseases of the heart (I30, I32-I33, I38-I41) Infectious diseases of the respiratory tract (J00-J22) Infectious diseases of the central nervous system (G00-G02, G05-G09) Diverticulitis (K57) Peritonitis (K65)
Cancer	Malignant neoplasms (C00-C97)
Accidents and suicide	External causes of mortality (V00-Y98)
All causes	All causes (A00-Y98)

ICD: International Classification of Diseases

APPENDIX 2

DETAILED DESCRIPTION OF MODELS AND MODEL ASSUMPTIONS

Prior to modeling, missing data for smoking status (0.6%), pack years of smoking (0.6%), physical activity (1.1%), body mass index (BMI; 0.2%), current alcohol use (0.7%), years since first vascular event at enrollment (0.4%) and estimated glomerular filtration rate (eGFR; 0.5%) were singly imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming that these values were missing at random¹.

Restricted cubic spline functions with four knots were used to assess the linearity assumption for continuous determinants. As the relations of physical activity, BMI, eGFR and years since first vascular event with mortality appeared to be non-linear, these determinants were modeled as categorical variables. Consequently, hazard ratios (HRs) of gender (reference category female), smoking status (never [ref], former and current), alcohol drinking status (never [reference category], former and current), categories of physical activity (≤ 19 [reference category], 19-50 and >50 hours*metabolic equivalent of task per week), categories of body mass index (BMI; <20 , 20-25 [reference category], 25-30 and ≥ 30 kg/m²) metabolic syndrome (according to the revised National Cholesterol Education Program [NCEP] definition²; no [reference category], yes), diabetes mellitus no [reference category], yes), categories of glomerular filtration rate estimated using the Modification of Diet in Renal Disease formula (eGFR; ≥ 60 [reference category], 60-30, <30 mL/min/1.73 m²), localizations of atherosclerotic disease (coronary artery disease [reference category], cerebrovascular disease, peripheral artery disease, abdominal aorta aneurysm and polyvascular disease) and years since first vascular event (<1 [reference category], 1-2, >2 years) for cardiovascular, cancer and non-vascular, non-cancer mortality were estimated using proportional subdistribution hazards regression models³, accounting for competing risk of death by causes other than the one under study. All models included adjustment for potential confounding by sex, age, smoking status, pack-years of smoking, alcohol consumption, BMI and physical activity. The models for all-cause mortality to estimate HRs for Fontaine stage III-IV vs. II [reference category] and Fontaine stage II and stage III-IV vs. CAD [reference category] were adjusted for sex, age, smoking status, pack-years, alcohol use, physical activity and body mass index. Proportionality assumptions were evaluated using scaled Schoenfeld residuals. Some non-proportionality was observed for diabetes in the respective model for all-cause and vascular mortality ($p=0.004$ and $p=0.002$, respectively), for CVD in the model for all-cause and nonvascular non-cancer mortality ($p=0.048$ and $p=0.034$, respectively), for PAD for vascular mortality ($p=0.013$), for BMI <20 kg/m² and eGFR <30 mL/min/1.73 m² in the respective models for cancer mortality ($p=0.003$ and $p=0.008$, respectively), for the highest tertile of physical activity in the models for all-cause, vascular and non-vascular non-cancer mortality (p -values <0.001), for Fontaine stage 2 vs. CAD in the model for all-cause mortality ($p=0.03$). Hence, the reported effects for

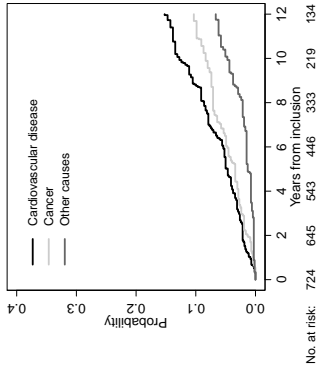
these determinants should be interpreted as the weighted average effect over follow-up⁴. Potential effect modification by age, sex and smoking status was tested for by adding multiplicative interaction terms to the models. Significant interaction ($p < 0.05$) with age was found for metabolic syndrome, diabetes and eGFR. The presented HRs for these determinants should thus be interpreted as the weighted average effect over the ages from 19-82 years.

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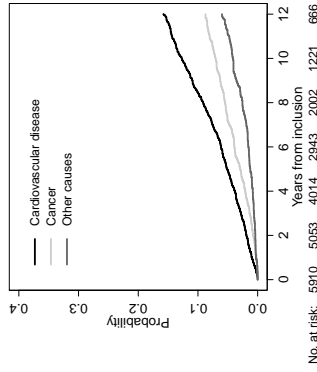
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APPENDIX 3

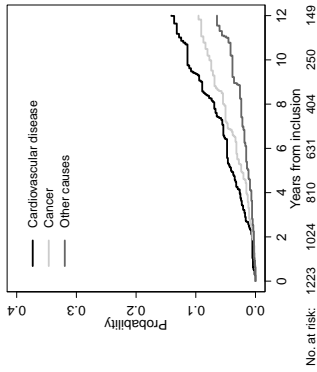
Patients with Peripheral Artery Disease



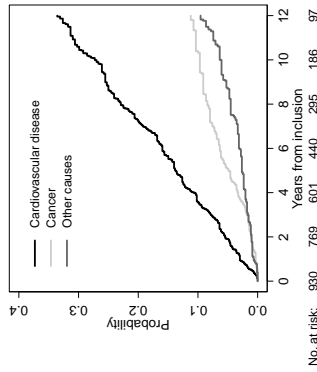
All patients with Manifest Vascular Disease



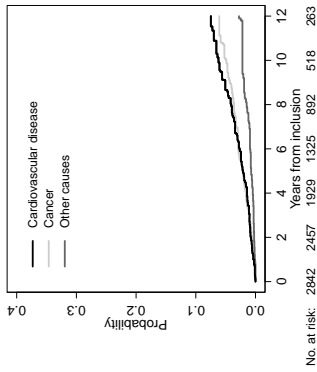
Patients with Cerebrovascular Disease



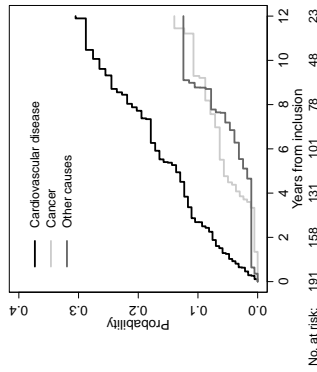
Patients with Polyvascular disease



Patients with Coronary Artery Disease



Patients with Abdominal Aorta Aneurysm



Cause-specific mortality of patients with different manifestations of vascular disease.

APPENDIX 4

Distribution of cause of death and cumulative mortality at 5 and 10 year for different strata of vascular disease at inclusion

Cause of death [ICD-10 code]	Coronary artery disease (n = 2,842)			Cerebrovascular disease (n = 1223)			
	No. of deaths	Probability in % (95% CI)	% of total probability	No. of deaths	Probability in % (95% CI)	% of total probability	
Year 5	Infectious disease [A00-B99]	6	0.3 (0.1 - 0.6)	5,3	2	0.2 (0.0 - 0.8)	3,0
	Cancer [C00-C97]	48	2.1 (1.6 - 2.8)	42,7	22	2.4 (1.5 - 3.6)	31,2
	Cardiovascular disease [I00-I99, F01, K55, R96]	48	2.1 (1.6 - 2.8)	42,7	38	4.0 (2.9 - 5.4)	52,2
	Ischemic heart disease [I20-I25, I46.1, R96]	20	0.9 (0.5 - 1.3)	17,5	14	1.4 (0.8 - 2.4)	18,5
	Cerebrovascular disease [I60-I69]	9	0.4 (0.2 - 0.7)	7,7	11	1.2 (0.6 - 2.1)	15,7
	Ruptured abdominal aorta aneurysm [I71]	0	-	0	1	0.1 (0.0 - 0.6)	1,3
	Other cardiovascular	19	0.9 (0.5 - 1.3)	17,5	12	1.3 (0.7 - 2.2)	16,8
	Accident or suicide[V00-Y99]	2	0.1 (0.0 - 0.3)	1,8	2	0.2 (0.0 - 0.7)	2,5
	Other	8	0.4 (0.2 - 0.7)	7,5	7	0.8 (0.4 - 1.6)	11,1
	Infectious disease [A00-B99]	10	0.6 (0.3 - 1.1)	4,4	2	0.2 (0.0 - 0.8)	1,0
Year 10	Cancer [C00-C97]	78	4.7 (3.6 - 5.9)	35,4	50	7.7 (5.7 - 10.1)	33,6
	Cardiovascular disease [I00-I99, F01, K55, R96]	90	6.2 (4.9 - 7.7)	46,8	73	11.2 (8.7 - 14.0)	48,6
	Ischemic heart disease [I20-I25, I46.1, R96]	41	2.9 (2.0 - 4.0)	21,9	29	4.6 (3.0 - 6.6)	20,0
	Cerebrovascular disease [I60-I69]	12	0.7 (0.4 - 1.4)	5,6	21	3.1 (1.9 - 4.8)	13,5
	Ruptured abdominal aorta aneurysm [I71]	0	-	0	2	0.2 (0.0 - 0.8)	1,0
	Other cardiovascular	37	2.6 (1.8 - 3.6)	19,3	21	3.2 (2.0 - 5.0)	14,1
	Accident or suicide[V00-Y99]	3	0.2 (0.0 - 0.5)	1,3	3	0.4 (0.1 - 1.1)	1,6
	Other	18	1.6 (1.0 - 2.5)	12,1	20	3.5 (2.2 - 5.3)	15,2

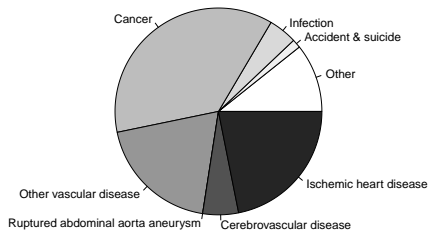
CM: Cumulative mortality; CI: Confidence interval

Appendix 4 continued

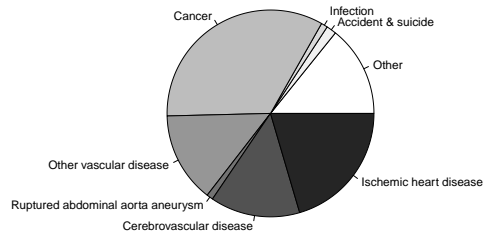
Peripheral artery disease (n = 724)			Abdominal aorta aneurysm (n = 191)			Polyvascular disease (n = 930)		
No. of deaths	Probability in % (95% CI)	% of total probability	No. of deaths	Probability in % (95% CI)	% of total probability	No. of deaths	Probability in % (95% CI)	% of total probability
3	0.5 (0.1 - 1.3)	5,2	1	0.7 (0.1 - 3.5)	3,3	4	0.5 (0.2 - 1.2)	2,3
22	3.4 (2.2 - 5.0)	36,4	9	5.7 (2.8 - 10.0)	26,9	37	4.9 (3.5 - 6.6)	22,9
30	4.6 (3.2 - 6.5)	49,7	24	13.0 (8.5 - 18.4)	61,6	110	13.7 (11.4 - 16.2)	64,1
15	2.3 (1.4 - 3.7)	24,8	7	3.9 (1.7 - 7.6)	18,7	55	6.7 (5.1 - 8.6)	31,5
3	0.5 (0.1 - 1.3)	4,8	3	1.8 (0.5 - 4.7)	8,4	9	1.1 (0.5 - 2.0)	5,0
0	-	0	3	1.6 (0.4 - 4.3)	7,6	7	0.9 (0.4 - 1.8)	4,2
12	1.9 (1.0 - 3.2)	20,0	11	5.7 (2.9 - 9.8)	26,9	39	5.0 (3.6 - 6.7)	23,3
1	0.2 (0.0 - 0.9)	2	1	0.5 (0.0 - 2.7)	2,5	2	0.2 (0.1 - 0.8)	1,1
4	0.7 (0.2 - 1.6)	7,0	1	1.2 (0.2 - 4.0)	5,8	15	2.1 (1.2 - 3.3)	9,7
7	1.5 (0.7 - 3.1)	6,0	6	4.9 (2.0 - 9.9)	10,0	9	1.6 (0.8 - 3.0)	3,7
44	8.3 (6.1 - 11.0)	32,3	15	10.7 (6.2 - 16.7)	21,6	62	9.7 (7.5 - 12.2)	22,5
63	12.4 (9.6 - 15.6)	48,1	40	25.8 (18.9 - 33.3)	52,0	176	26.9 (23.3 - 30.7)	62,6
26	4.7 (3.1 - 6.8)	18,3	12	8.0 (4.3 - 13.2)	16,1	80	11.6 (9.2 - 14.2)	26,9
8	1.9 (0.9 - 3.7)	7,3	4	2.5 (0.8 - 5.8)	5,0	12	1.6 (0.9 - 2.8)	3,8
0	-	0	5	3.3 (1.2 - 7.1)	6,6	9	1.3 (0.6 - 2.4)	3,0
29	5.8 (3.9 - 8.3)	22,5	19	12.1 (7.4 - 18.1)	24,4	75	12.5 (9.8 - 15.4)	29,0
2	0.5 (0.1 - 1.7)	2	2	1.5 (0.3 - 4.9)	2,9	2	0.2 (0.1 - 0.8)	0,6
12	3.0 (1.7 - 5.1)	11,7	8	6.7 (3.3 - 11.9)	13,5	26	4.6 (3.0 - 6.5)	10,6

APPENDIX 5

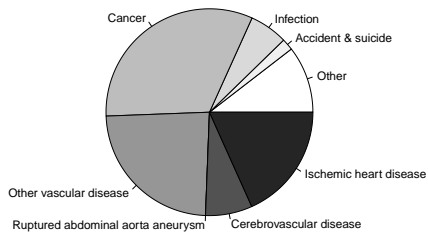
Coronary artery disease



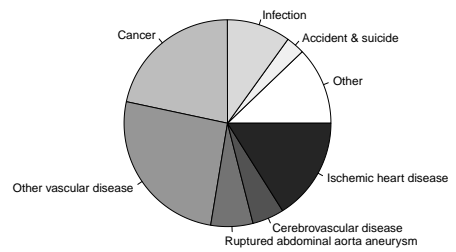
Cerebrovascular disease



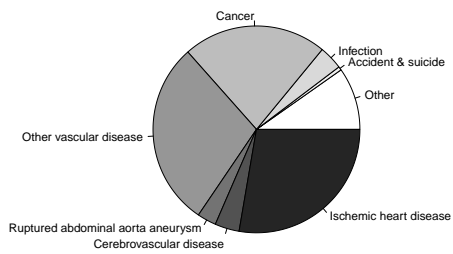
Peripheral artery disease



Abdominal aorta aneurysm

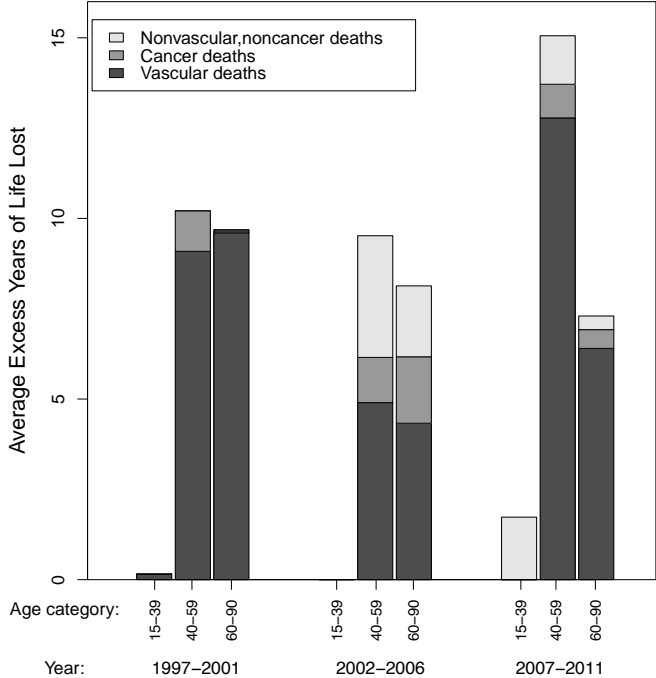


Polyvascular disease



Distribution of causes of death at 10-years of follow-up for different strata of vascular disease

APPENDIX 6



Distribution of average excess years of life lost in patients with manifest vascular disease over time and age categories.

Rob C.M. van Kruisdijk
Yolanda van der Graaf
Ale Algra
Gert Jan de Borst
Maarten J.M. Cramer
Peter D. Siersema
Frank L.J. Visseren

on behalf of the Second Manifestations of ARterial disease (SMART) study group.

CHAPTER 5

THE EFFECTS OF SECONDARY CARDIOVASCULAR
PREVENTION ON CANCER RISK IN PATIENTS WITH
MANIFEST VASCULAR DISEASE

Manuscript draft

ABSTRACT

Background

Cardiovascular disease and cancer share important risk factors and pathophysiology, including smoking, obesity, physical inactivity, insulin resistance and inflammation. These five modifiable shared risk factors have defined treatment goals by the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for secondary cardiovascular prevention. In this prospective cohort study, we evaluated the effects of meeting these treatment goals on cancer risk in patients with manifest vascular disease.

Methods and Results

Patients with stable vascular disease ($n=5,929$), enrolled in the Second Manifestations of ARterial disease (SMART) study, were followed for cancer incidence. Attainment of the AHA/ACC goals with regard to smoking, weight management, physical activity, diabetes management and antithrombotics was assessed with baseline measurements. Cox proportional hazards models were used to evaluate the relation between goal attainment and incident cancer. During a median follow-up of 5.4 years (interquartile range: 2.8-8.6 years), 516 patients were diagnosed with cancer. There was an inverse relation between number of attained goals and risk of cancer, with an adjusted hazard ratio (HR) of 0.90 (95% confidence interval [CI]: 0.82-0.98) per extra attained goal ($p_{\text{trend}}=0.02$). Patients with 5 attained goals had a 30% (95%CI: 4%-49%) lower risk compared with those with 0-2 attained goals. The association persisted after excluding smoking cessation from the attained treatment goals (HR per extra attained goal: 0.90, 95%CI: 0.81-1.00, $p_{\text{trend}}=0.04$).

Conclusion

Meeting treatment goals for shared modifiable risk factors of cardiovascular disease and cancer is related to lower risk of incident cancer in patients with manifest vascular disease.

INTRODUCTION

Although the survival of acute ischemic events has increased notably over the last decades, the number of patients in the chronic phase of clinically manifest vascular disease is ever growing^{1,2}. We recently showed that, besides an increased risk of new cardiovascular events, these patients have an increased risk of cancer incidence and mortality^{3,4}. The 5-year risk of developing cancer, including cancers of the lung, kidney and bladder, is 19% higher in patients with manifest vascular disease compared to the general population³. This increase in cancer risk might be explained by the presence of mutual risk factors, such as smoking, excess body weight and physical inactivity³⁻⁹. Furthermore, cardiovascular disease and cancer share several important pathophysiological pathways, including inflammation and insulin resistance⁵. Given these shared pathways, interventions for secondary prevention of cardiovascular disease could possibly also lower cancer risk. Recently, it was shown that ideal cardiovascular health, as defined by the American Heart Association (AHA) in health metrics for smoking status, physical activity, blood pressure, cholesterol, healthy weight and diet, is related to lower cancer incidence in participants free of cardiovascular disease at baseline¹⁰. Participants in that study with ideal levels for these health metrics had a 51% (95% confidence interval [CI]: 31%-65%) lower cancer risk than those with none of the ideal health metrics¹⁰.

Guidelines for secondary prevention in patients with established vascular disease recommend comprehensive risk factor management, including lifestyle interventions for the risk factors that are shared by cardiovascular disease and cancer, including smoking cessation, physical activity and weight management^{11,12}. In addition, several recommended pharmacological interventions for cardiovascular disease prevention, including aspirin and metformin, have been related to lower cancer risk, whereas others, including exogenous insulin, have been linked to an increased cancer risk¹³⁻¹⁵. Information about the impact of secondary cardiovascular prevention on cancer risk could be valuable to prioritize risk factors and to identify effective preventive interventions for both cardiovascular disease and cancer. Thus far, however, evidence on the effects of these shared risk factors on cancer risk in patients with established vascular disease is lacking. In the present study, we evaluated the effects of meeting treatment goals for five shared modifiable risk factors, including smoking cessation, weight management, physical activity, diabetes management and use of antithrombotics, as recommended in guidelines for secondary prevention of cardiovascular events on the risk of incident cancer in patients with manifest vascular disease.

METHODS

Design and 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 previously¹⁶. In short, newly referred patients, aged 18 to 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) have been included in the SMART-study. Patients who had a terminal malignancy at baseline, were dependent in daily activities or were not sufficiently fluent in the Dutch language were excluded. At inclusion, patients underwent a standardized cardiovascular screening program, including assessment of risk factors and non-invasive imaging techniques to detect the presence of additional (sub)clinical atherosclerosis. The local medical 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, without a history of cancer at baseline, included between September 1996 and January 2011 were used (*Appendix 1*).

Follow-up

Patients were biannually asked to complete a questionnaire on hospitalization and outpatient clinic visits for follow-up. When a possible event was reported, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Deaths were reported by relatives of the participant, the general practitioner or specialist. Based on the information from the questionnaire and/or the family, all of the events were adjudicated by 3 members of the study endpoint committee, consisting of physicians from different departments. Information on cancer incidence through 31 December 2010 was ascertained by linkage with the Dutch Cancer Registry^{3,17}. From January 2006 onwards, participants who were included for at least three years and were still alive, were invited for follow-up measurements similar to those at baseline.

Determinants

Treatment goals were based on the 2011 update of intervention recommendations by the AHA and the American College of Cardiology (ACC) for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease¹² and included interventions for the shared risk factors and pathophysiology of cardiovascular disease and cancer: smoking cessation^{18,19}, physical activity^{6,18}, weight management^{5,18}, type 2 diabetes management^{5,20} and antiplatelet agents/anticoagulants^{1,13,15} (*Box 1*). Effects of treatment goals for cardiovascular risk factors that are not related to incident cancer risk, such as hypertension and dyslipidemia, were not evaluated because no effect was expected based on available evidence or biological mechanisms²⁰⁻²². A comparison with goals for the same areas of intervention from European, international and Dutch guidelines for secondary cardiovascular prevention is provided in *Appendix 2*. The number of attained treatment

Box 1. Treatment goals as defined in secondary cardiovascular prevention guidelines for shared risk factors of cardiovascular disease and cancer

Area for intervention	Goal
Smoking	Complete cessation. No exposure to environmental tobacco smoke.
Physical activity	At least 30 minutes moderate-intensity aerobic activity, 7 days per week (minimum 5 days per week), i.e. 4.5 MET for at least 2.5h per week (11.25 MET/h/W).
Weight management	Waist circumference of <35 inches (<89 cm) in women and <40 inches (<102 cm) in men, or if waist circumference is not available, a body mass index between 18.5 and 24.9 kg/m ²
Type 2 diabetes management	If diabetic, HbA1c \leq 7%.
Antithrombotics	Use of antiplatelet agents or anticoagulant therapy

MET: Metabolic Equivalent of Task ; HbA1c: Glycated hemoglobin. Treatment goals are based on the 2011 update of the intervention recommendations by the AHA/ACCF for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease¹². The smoking goal was considered to be met if patients either never smoked or quit smoking before the baseline measurement. For non-diabetics, the treatment goal for diabetes management was considered to be met.

goals at baseline was summed for each patient, yielding a score ranging from null to five. Changes in attainment of treatment goals during follow-up were evaluated in the subset of patients of whom a follow-up measurement was available.

Outcome definitions

The main endpoint of interest was incident cancer, which was defined as the first primary invasive neoplasm, excluding non-melanoma skin cancer. The effects of attaining treatment goals on major cardiovascular events (MCVE; myocardial infarction, stroke or vascular mortality) and all-cause mortality were also evaluated in order to compare these effects to those on cancer risk.

Data analyses

Missing data for smoking status (0.4%), pack years of smoking (0.4%), physical activity (0.7%), body mass index (BMI; 0.2%), HbA1c in diabetics (1.9%), years since first vascular event at enrollment (0.4%) and history of CVD, PAD and AAA (0.1%) were imputed with bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming that these values were missing at random, because excluding patients with missing values often leads to bias and loss of statistical power²³. Hazard ratio's (HRs) for the effect of the number of attained goals on all outcomes were estimated using Cox proportional hazard models. The number of attained goals was analyzed as continuous variable and as categorical variable. Because there were only few patients with 0, 1 or 2 attained goals, these were grouped together for the analysis of number of attained goals as categorical variable and served as reference category. Models were adjusted for age and sex and additionally for year of inclusion, years since first manifestation of vascular

disease and history of diabetes, CAD, CVD, AAA, PAD. The models for MCVE and all-cause mortality included additional adjustment for use of lipid-lowering medication and hypertension. Besides the effects on total incident cancer, the effects of meeting treatment goals on the three most common cancer types, including lung, colorectal and prostate cancer, were also evaluated. Proportionality assumptions were evaluated with Schoenfeld residuals, but no non-proportionality was observed ($p>0.05$).

To assess the presence of reverse causality (i.e. yet undiagnosed cancer leads to better attainment of treatment goals at baseline, for example cancer-related weight loss), all analyses were repeated after excluding events that occurred during the first year of follow-up. Although Cox proportional cause-specific hazards models are preferred for answering etiological research questions in the presence of competing risks, the effect estimates from such models cannot be directly translated to the cumulative incidence function (i.e. absolute risk in clinical practice)²⁴. To evaluate such effects of competing risk of death by other causes, sensitivity analyses were performed for incident cancer and MCVE with proportional subdistribution hazards regression models^{24,25}. Further sensitivity analyses were performed excluding smoking cessation from the treatment goals. Analyses were performed in R, version 3.0.2 (www.r-project.org; packages: 'survival', 'Hmisc', 'RiskRegression', 'cmprsk').

RESULTS

Baseline characteristics

Baseline characteristics of the 5,929 study patients, subdivided by number of attained treatment goals, are shown in *Table 1*. Overall, mean age was 59.8 years (SD: 10.4 years) and 74% of the patients were men. Over half of the patients (64%) had had attained 4 or 5 goals at baseline. Mean age was higher in patients with more attained goals (57.9 years in 0-2 goals group vs. 61.2 years in 5 goals group). Similarly, the proportion of men increased over the groups (66% men in 0-2 goals group vs. 81% men in 5 goals group). The overall proportions of patients meeting the treatment target were highest for type 2 diabetes management (overall 93%) and antithrombotics (80%), whereas the proportions were lowest for the weight control (60%) and smoking goals (67%). On average, patients with CAD had attained most treatment goals (mean 3.9, SD:1.0) and patients with PAD attained the least goals (mean 3.2, SD:1.1).

Relation between attaining treatment goals and cancer incidence, MCVE and all-cause-mortality

During a median follow-up of 5.4 years (interquartile range: 2.8-8.6 years), 516 patients were diagnosed with cancer (incidence of 15.5 per 1,000 person-years), 830 patients experienced an MCVE (25.2 per 1,000 person-years) and 843 patients had died (24.3 per 1,000 person-years). Of the study population, 190 patients (3.2%) were lost to follow-up due to migration or withdrawal [after a median follow-up of 5.1 years].

Table 1. Baseline characteristics of the study population by number of attained treatment goals

	0-2 (n = 764)	3 (n = 1390)	4 (n = 2136)	5 (n = 1639)
Age (y)	58 (11)	59 (11)	60 (10)	61 (10)
Male sex, %	66	69	75	81
Smoking, current, %	77	55	29	0
Smoking, past, %	16	33	49	69
Pack-years of smoking ^a	28 [15 - 42]	23 [9 - 36]	23 [11 - 35]	15 [7 - 28]
Current alcohol consumption, %	53	42	27	19
Physical activity (hours*MET per week)	4 [0 - 11]	19 [6 - 44]	37 [19 - 63]	48 [29 - 75]
Body Mass Index (kg/m ²)	28 (5)	28 (4)	27 (4)	25 (2)
Waist circumference (cm)	102 (12)	99 (13)	96 (12)	90 (8)
Systolic blood pressure (mmHg)	143 (21)	142 (21)	141 (21)	140 (21)
Diastolic blood pressure (mmHg)	81 (12)	81 (11)	82 (11)	82 (11)
eGFR (ml/min/1,73 m ²)	77 (21)	77 (20)	76 (18)	75 (16)
Total cholesterol (mmol/l)	5.5 (1.3)	5.2 (1.2)	4.8 (1.2)	4.6 (1.1)
High density lipoprotein (mmol/l)	1.1 (0.4)	1.2 (0.4)	1.2 (0.4)	1.3 (0.4)
Low density lipoprotein (mmol/l)	3.4 (1.1)	3.2 (1.1)	2.9 (1.0)	2.7 (0.9)
Serum triglycerides (mmol/l)	1.9 [1.4 - 2.7]	1.6 [1.1 - 2.3]	1.4 [1.0 - 2.0]	1.2 [0.9 - 1.6]
C-reactive protein (mg/l)	3.9 [1.9 - 7.8]	2.8 [1.4 - 5.5]	2.0 [1.0 - 4.1]	1.2 [0.6 - 2.7]
Fasting serum glucose (mmol/l)	6.1 [5.4 - 8.3]	5.8 [5.4 - 6.6]	5.8 [5.4 - 6.4]	5.6 [5.3 - 6.2]
Years since first vascular event				
< 1 year before enrollment, %	60	60	59	58
1-2 years before enrollment, %	7	8	9	11
≥ 2 years before enrollment, %	32	32	32	31
Coronary artery disease, %	42	51	64	73
Cerebrovascular disease, %	24	34	29	27
Peripheral arterial disease, %	40	27	16	9
Abdominal aortic aneurysm, %	16	10	8	5
Diabetes mellitus, %	32	22	15	10
Metabolic syndrome ^b , %	75	66	57	27
Treatment goals				
Smoking cessation, %	23	45	71	100
Physical activity, %	21	60	88	100
Weight management, %	22	40	57	100
Type 2 diabetes management, %	75	88	97	100
Antiplatelet agents / anticoagulants, %	37	67	88	100

All data are expressed as mean (S.D.), percentage of group or median [interquartile range]. MET = Metabolic equivalent of task; eGFR = Estimated glomerular filtration rate; ^aFor ever smokers only; ^bAccording to the revised National Cholesterol Education Program definition.

Table 2 shows the adjusted incidence rates per 1,000 person-years and HRs per number of attained treatment goals for incident cancer, MCVE and all-cause mortality. There was a gradual and consistent inverse relation between the number of attained treatment goals and incident cancer with an adjusted HR of 0.90 (95%CI:0.82-0.98) per extra attained goal ($p_{\text{trend}}=0.019$). Patients with 5 attained goals had a 30% (95%CI: 4%-49%) lower cancer risk compared to patients who attained 0-2 goals. When evaluating the specific cancer types, an inverse relation with number of attained treatment goals was found with lung cancer (HR per extra attained goal:0.75, 95%CI:0.63-0.90), colorectal cancer (HR:0.90, 95%CI:0.71-1.15) and prostate cancer in men (HR:0.91, 95%CI:0.72-1.16), although the latter two were not statistically significant (*Appendix 3*).

The risk of MCVEs and all-cause mortality decreased notably with the number of attained treatment goals (HR for MCVEs per extra attained goal 0.83, 95%CI:0.78-0.89, $p_{\text{trend}}<0.001$ and for all-cause mortality HR:0.78, 95%CI:0.73-0.84, $p_{\text{trend}}<0.001$). Patients with 5 attained goals had the lowest relative MCVE and all-cause mortality risk (HR for MCVEs:0.54, 95%CI:0.42-0.69 and HR for all-cause mortality:0.45, 95%CI:0.35-0.58, compared with patients who met 0-2 goals), but a risk reduction was also observed in patients who met 3 or 4 goals, compared to those with 0-2 goals (for patients with 4 goals HR for MCVE:0.66, 95%CI:0.54-0.81 and HR for mortality:0.60, 95%CI:0.50-0.74 and for patients with 3 goals HR for MCVE:0.73, 95%CI:0.60-0.89 and HR for mortality:0.85, 95%CI:0.71-1.02).

Sensitivity analyses

The characteristics at baseline and during follow-up and changes in treatment goal attainment over time for those patients of whom a follow-up measurement was available in 1,392 patients are shown in *Appendix 4.1*. The mean time between baseline and follow-up measurement was 7 years (SD: 3 years). On average, patients had attained 0.2 goals (SD: 0.8) more at the follow-up measurement compared to baseline. Particularly, more patients reached the goals for smoking cessation (79% vs. 67%) and antithrombotics (94% vs.78%) during follow-up, whereas slightly less patients attained the goals for weight management (55% vs. 63%) and diabetes management (93% vs. 96%; *Appendix 4.2*).

Similar results were observed after excluding events that occurred during the first year of follow-up (*Appendix 5*) and when accounting for competing risks (*Appendix 6*). Furthermore, the inverse relation between number of attained treatment goals and cancer risk remained when smoking cessation was excluded from the sum of attained treatment goals, with a decrease of 10% (95%CI:0.6%-19%, $p_{\text{trend}}=0.042$) in cancer risk per extra attained goal (*Appendix 7*).

Table 2. Hazard ratio per number of attained treatment goals

No. of attained treatment goals	Incident cancer				Major cardiovascular event				All-cause mortality				
	n	No. of events	Incidence per 1,000 person-years	Hazard ratio (95% CI)	No. of events	Incidence per 1,000 person-years	Hazard ratio (95% CI)	No. of events	Incidence per 1,000 person-years	Hazard ratio (95% CI)	No. of events	Incidence per 1,000 person-years	Hazard ratio (95% CI)
0-2	Model I	764	94	16.8	Reference	206	38.2	Reference	221	37.8	Reference		Reference
	Model II												
3	Model I	1,390	148	17.0	0.99 (0.77 - 1.29)	236	27.3	0.67 (0.56 - 0.81)	279	30.7	0.78 (0.65 - 0.93)		0.78 (0.65 - 0.93)
	Model II				0.99 (0.76 - 1.28)			0.73 (0.60 - 0.89)			0.85 (0.71 - 1.02)		0.85 (0.71 - 1.02)
4	Model I	2,136	171	15.2	0.84 (0.65 - 1.08)	252	22.9	0.52 (0.43 - 0.62)	233	20.0	0.47 (0.39 - 0.56)		0.47 (0.39 - 0.56)
	Model II				0.83 (0.63 - 1.09)			0.66 (0.54 - 0.81)			0.60 (0.50 - 0.74)		0.60 (0.50 - 0.74)
5	Model I	1,639	103	13.1	0.71 (0.53 - 0.94)	136	17.4	0.37 (0.30 - 0.47)	110	13.6	0.31 (0.25 - 0.39)		0.31 (0.25 - 0.39)
	Model II				0.70 (0.51 - 0.96)			0.54 (0.42 - 0.69)			0.45 (0.35 - 0.58)		0.45 (0.35 - 0.58)
Per extra attained goal	Model I	5,929	516	15.5	0.90 (0.83 - 0.98)	830	25.2	0.74 (0.70 - 0.78)	843	24.3	0.70 (0.66 - 0.74)		0.70 (0.66 - 0.74)
	Model II				0.90 (0.82 - 0.98)			0.83 (0.78 - 0.89)			0.78 (0.73 - 0.84)		0.78 (0.73 - 0.84)

CI: Confidence interval; Row per extra attained goal shows the n, no. of events and incidence rate for the total study population. Model I: Adjusted for age and sex. Model II: Model I + additional adjustment for year of study inclusion, years since first manifestation of vascular disease, history of diabetes, coronary artery disease, cerebrovascular disease, abdominal aorta aneurysm, peripheral artery disease. Models for major cardiovascular events and all-cause mortality were additionally adjusted for use of lipid-lowering medication and hypertension

DISCUSSION

In this prospective cohort of patients with manifest vascular disease, meeting the AHA/ACC defined secondary cardiovascular prevention goals for smoking, weight management, physical activity, diabetes management and antithrombotics, is related to a lower risk of incident cancer as well as to a lower risk of MCVs and all-cause mortality.

Similar protective effects with regard to cancer risk have recently been shown in a general population for adherence to ideal cardiovascular health metrics defined by the AHA, which also included metrics for smoking, BMI, physical activity and fasting plasma glucose¹⁰. The HR per 1 increase in number of ideal health metrics in that study was 0.92 ($p_{\text{trend}} < 0.001$). In another study, the effects of adherence to recommendations related to diet and smoking by the American Institute for Cancer Research for individuals to reduce cancer incidence, were evaluated²⁶. With data of 29,564 postmenopausal women, it was estimated that, if all women had followed the recommendations, cancer incidence would be reduced by 31% (95%CI: 19%-37%)²⁶. In addition to the effects on cancer, following cancer prevention guidelines may also lower the risk of cardiovascular and all-cause mortality, as was shown in the Cancer Prevention Study-II with the Nutrition Cohort American Cancer Society guidelines on nutrition and physical activity²⁷. Current European national guidelines for secondary cardiovascular prevention¹¹ provide recommendations largely similar to the AHA/ACC defined goals that were evaluated in this study. Given the large overlap, it is likely that similar effects on cancer risk can be ascertained by adherence to the other guidelines for secondary cardiovascular prevention.

The observed inverse relation between the number of attained goals and cancer incidence in the present study remained after excluding the effects of the goal for smoking, indicating that effects of secondary cardiovascular prevention on cancer risk are not solely due to smoking cessation. Weight management, physical activity and diabetes management might also play an important role, primarily by reducing insulin resistance and systemic low-grade inflammation, which are related to an increased cancer risk⁵. Furthermore, 91% of the patients who met the goal for antithrombotics, used aspirin. Recently, an individual patient data meta-analysis has shown that use of aspirin for cardiovascular prevention also reduces the risk of cancer incidence and mortality (odds ratio for cancer incidence of 0.76, 95%CI:0.66-0.88 and for cancer mortality:0.85, 95%CI:0.76-0.96)¹⁵. These anticancer effects are believed to be attributable to aspirin's anti-inflammatory capacities, but an earlier detection and removal of precancerous colorectal polyps due to the increased bleeding risk related to antiplatelets/anticoagulants remains an alternative explanation²⁸. Furthermore, aspirin has been found to reduce the risk of distant metastasis¹³.

Generally, only the effects on cardiovascular disease are taken into account in studies evaluating preventive interventions in patients with vascular disease. However, given the increased risk of cancer incidence and mortality in these patients^{3,4}, as well as the shared risk factors and pathophysiology of cardiovascular disease and cancer, concurrently evaluating the effects on both cardiovascular disease and cancer seems sensible. For example, several randomized controlled trials of aspirin versus control primarily evaluating

cardiovascular outcomes, were recently reanalyzed to assess the effects of aspirin on cancer^{15,19}. In this light, following guidelines for secondary cardiovascular prevention could provide a valuable strategy to simultaneously reduce the risk of incident cancer, MCVEs and all-cause mortality in patients with vascular disease. Possibly, informing patients about the additional effects of secondary cardiovascular prevention on cancer risk could increase treatment adherence.

Strengths of this study include the prospective design, very low proportion of patients lost to follow-up and the completeness of cancer diagnoses ascertained through linkage with Netherlands Cancer Registry, which is considered to have a near complete coverage²¹. Furthermore, no important changes in the results from the sensitivity analysis for presence of reverse causality, effects of competing risks and excluding of smoking cessation from the sum of attained treatment goals resulted in important changes of HRs, indicating that the reported results are robust.

Some potential limitations of this study should be noted. First, the association between treatment goals and specific cancer types was not possible because of limited power. Furthermore, given the long period it may take for cancer to develop, the median follow-up of 5.4 years may be relatively short to observe the effects of lifestyle and pharmacological interventions. However, it is likely that (some of) the metrics have been present for a longer period before the baseline measurements. In addition, subsequent measurements were only available for a subset of patients, impeding analyses with repeated measurements over time. Given the observed changes during follow-up in the subset of patients of whom a follow-up measurement was available, the observed associations may have been biased towards the null.

In conclusion, meeting goals for shared risk factors for cardiovascular disease and cancer, as defined in the AHA/ACC guidelines for secondary cardiovascular prevention, is associated with a lower risk of incident cancer in patients with manifest vascular disease. These results underline the necessity of lifestyle and pharmacological interventions in patients with vascular disease, not only for reducing the risk of recurrent cardiovascular events, but also the risk of incident cancer.

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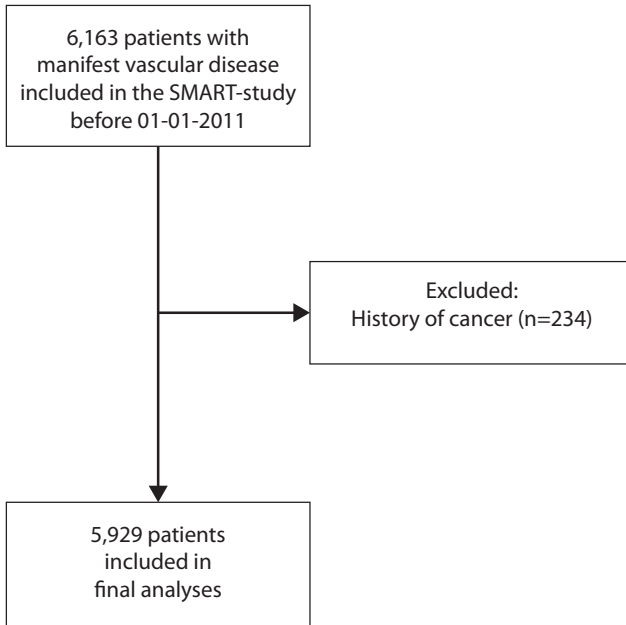
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APPENDIX 1



Study flow chart. SMART-study: Second Manifestations of ARterial Disease-study.

APPENDIX 2

Comparison of treatment goals for shared risk factors of cancer and cardiovascular disease from various current guidelines for secondary cardiovascular prevention

Shared risk factor / Area for intervention	AHA/ACCF 2011	WHO 2007	ESC 2012	CVRM 2011
Smoking	Complete cessation. No exposure to environmental tobacco smoke.	Complete cessation. No exposure to environmental tobacco smoke.	Complete cessation. No exposure to environmental tobacco smoke.	Complete cessation. No exposure to environmental tobacco smoke.
Physical activity	At least 30 minutes moderate-intensity aerobic activity, 7 days per week (minimum 5 days per week).	At least 30 minutes moderate-intensity physical activity each day.	Moderate-to-vigorous intensity aerobic exercise training ≥ 3 times a week and 30 min per session.	At least 30 minutes moderate-intensity physical activity for a minimum of 5 days per week.
Weight management	Waist circumference of <35 inches (<89 cm) in women and <40 inches (<102 cm) in men or a body mass index between 18.5 and 24.9 kg/m ² .	No specific goal for patients with vascular disease. In general: All individuals who are overweight or obese should be encouraged to lose weight through a combination of a reduced-energy diet (dietary advice) and increased physical activity.	No specific goal for patients with vascular disease. In general: weight reduction in overweight and obese people. Body mass index between 20 and 25 kg/m ² .	BMI ≤ 25 kg/m ² in persons younger than 70 years and ≤ 30 kg/m ² in those older than 70 years.
Type 2 diabetes management	If diabetic, HbA1c $\leq 7\%$.	Individuals with persistent fasting blood glucose >6 mmol/l despite diet control should be given metformin and/or insulin as appropriate.	If diabetic, HbA1c $\leq 7\%$.	If diabetic and <70 years or no glucose lowering medication or metformin monotherapy, HbA1c $\leq 7\%$. If >70 years and if time since diagnosis of diabetes is <10 years, HbA1c $\leq 7.5\%$. Else HbA1c $\leq 8\%$.
Antiplatelet agents/ anticoagulants	Use of either antiplatelet agents or anticoagulants.	Use of either antiplatelet agents or anticoagulants.	Use of either antiplatelet agents or anticoagulants.	Use of either antiplatelet agents or anticoagulants.

AHA/ACCF: American Heart Association/American College of Cardiology Foundation; 2011 update of intervention recommendations by the AHA/ACCF for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease [ref: Smith SC, Jr., et al. *Circulation*. 2011;124:2458-73]. WHO: World Health Organization; Prevention of cardiovascular disease. Guideline for assessment and management of cardiovascular risk. Geneva 2007. ESC: European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts); European Guidelines on cardiovascular disease prevention in clinical practice (version 2012) [ref: Perk J, et al. *Eur Heart J*. 2012;33:1635-701]. CVRM: Multidisciplinaire richtlijn Cardiovasculair risicomanagement, herziening 2011 (Dutch). *Presence of established cardiovascular disease plus (1) multiple major risk factors (especially diabetes), (2) severe and poorly controlled risk factors (especially continued cigarette smoking), (3) multiple risk factors of the metabolic syndrome (especially high triglycerides ≥ 200 mg/dL plus non-HDL-C ≥ 130 mg/dL with low HDL-C ≤ 40 mg/dL), and (4) patients with history of acute coronary syndrome.

APPENDIX 3

Hazard ratio per number of attained treatment goals for specific cancer types										
No. of attained treatment goals	Lung cancer			Colorectal cancer			Prostate cancer			
	n	No. of events	Hazard ratio (95% CI)	n	No. of events	Hazard ratio (95% CI)	n (men only)	No. of events	Hazard ratio (95% CI)	
0-2	Model I	764	30	Reference	764	12	Reference	501	13	Reference
	Model II									
3	Model I	1,390	42	0.86 (0.54 - 1.38)	1,390	20	1.06 (0.52 - 2.16)	957	16	0.71 (0.34 - 1.49)
	Model II			0.91 (0.56 - 1.47)			0.99 (0.48 - 2.06)			0.67 (0.32 - 1.40)
4	Model I	2,136	33	0.49 (0.30 - 0.81)	2,136	23	0.91 (0.45 - 1.84)	1,596	30	0.87 (0.45 - 1.68)
	Model II			0.58 (0.34 - 1.00)			0.78 (0.37 - 1.64)			0.80 (0.39 - 1.61)
5	Model I	1,639	13	0.26 (0.14 - 0.51)	1,639	16	0.92 (0.43 - 1.97)	1,332	20	0.74 (0.36 - 1.49)
	Model II			0.34 (0.17 - 0.71)			0.74 (0.32 - 1.72)			0.64 (0.29 - 1.42)
Per extra attained goal	Model I	5,929	118	0.70 (0.59 - 0.82)	5,929	71	0.97 (0.78 - 1.20)	4,386	79	0.95 (0.77 - 1.17)
	Model II			0.75 (0.63 - 0.90)			0.90 (0.71 - 1.15)			0.91 (0.72 - 1.16)

CI: Confidence interval; Row per extra attained goal shows the n, no. of events and incidence rate for the total study population

Model I: Adjusted for age and sex

Model II: Model I + additional adjustment for year of study inclusion, years since first manifestation of vascular disease, history of diabetes, coronary artery disease, cerebrovascular disease, abdominal aorta aneurysm, peripheral artery disease. Models for major cardiovascular events and all-cause mortality also include adjustment for use of lipid-lowering medication and hypertension

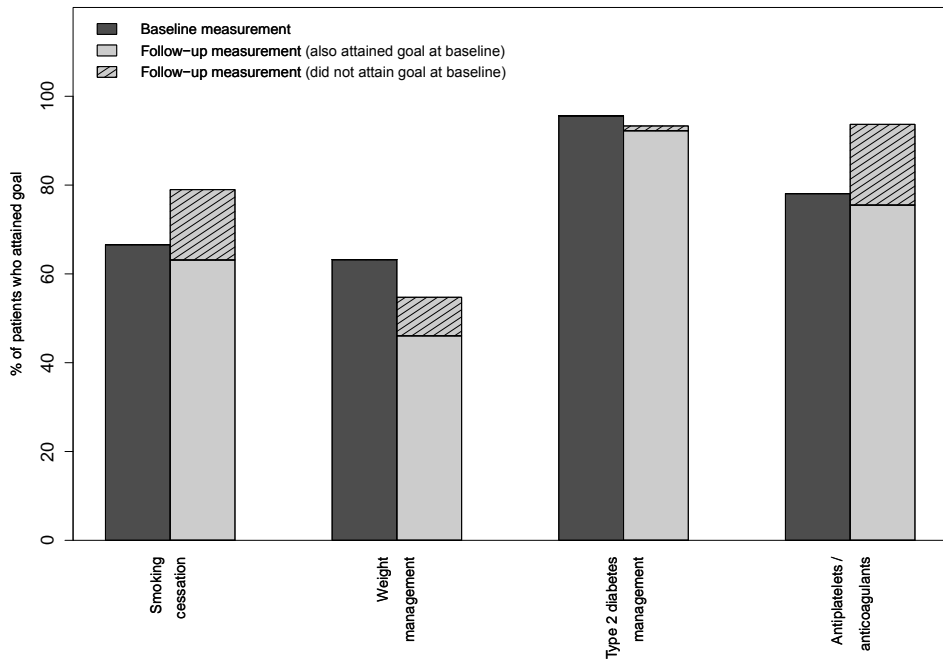
APPENDIX 4.1

Characteristics of study population at baseline and follow-up measurement

	Patients without a follow-up measurement Characteristics at baseline measurement (n = 4537)	Patients with a follow-up measurement Characteristics at baseline measurement (n = 1392)	Patients with a follow-up measurement Characteristics at follow-up measurement (n = 1392)
Time since study enrollment (y)	0	0	7 (3)
Age (y)	61 (11)	57 (9)	64 (9)
Male sex, %	72	79	79
Smoking, current %	33	33	21
Smoking, past %	46	47	62
Body Mass Index (kg/m ²)	27 (4)	27 (4)	27 (4)
Waist circumference (cm)	96 (12)	95 (11)	98 (12)
Systolic blood pressure (mmHg)	142 (22)	139 (20)	141 (18)
Diastolic blood pressure (mmHg)	82 (12)	81 (11)	81 (10)
eGFR (ml/min/1.73 m ²)	75 (19)	79 (16)	74 (17)
Total cholesterol (mmol/l)	4.9 (1.2)	5.1 (1.1)	4.5 (1.0)
High density lipoprotein (mmol/l)	1.2 (0.4)	1.2 (0.4)	1.3 (0.4)
Low density lipoprotein (mmol/l)	2.9 (1.0)	3.1 (1.0)	2.6 (0.8)
Serum triglycerides (mmol/l)	1.4 [1.0 - 2.0]	1.5 [1.1 - 2.2]	1.2 [0.8 - 1.7]
C-reactive protein (mg/l)	2.1 [1.0 - 4.6]	1.8 [0.9 - 3.8]	1.3 [0.7 - 3.0]
Fasting serum glucose (mmol/l)	5.8 [5.4 - 6.5]	5.7 [5.3 - 6.2]	5.9 [5.5 - 6.6]
Years since first vascular event			
< 1 year before enrollment, %	57	66	0
1-2 years before enrollment, %	9	8	0
≥ 2 years before enrollment, %	34	25	100
Coronary artery disease, %	60	61	65
Cerebrovascular disease, %	30	26	27
Peripheral arterial disease, %	20	19	22
Abdominal aortic aneurysm, %	9	6	8
Diabetes mellitus, %	19	12	20
Metabolic syndrome, %	54	50	52
No. of attained treatment goals*			
0 goals, %	0	0	0
1 goal, %	5	5	2
2 goals, %	22	21	14
3 goals, %	42	40	46
4 goals, %	31	34	38

All data are expressed as mean (S.D.), percentage of group or median [interquartile range]. MET = Metabolic equivalent of task; eGFR = Estimated Glomerular filtration rate; *According to the revised National Cholesterol Education Program definition. *Physical activity was not available at second measurement, so maximum number of attained treatment targets is 4 instead of 5.

APPENDIX 4.2



APPENDIX 5

Hazard ratio per number of attained treatment goals, excluding events that occurred during the first year of follow-up

No. of attained treatment goals	Incident cancer			Major cardiovascular event			All-cause mortality		
	n	No. of events	Hazard ratio (95% CI)	n	No. of events	Hazard ratio (95% CI)	n	No. of events	Hazard ratio (95% CI)
0-2	748	78	Reference	728	170	Reference	739	196	Reference
3	1,371	129	1.08 (0.81 - 1.43)	1,345	191	0.67 (0.55 - 0.83)	1,365	254	0.82 (0.68 - 0.98)
			1.05 (0.79 - 1.40)			0.73 (0.59 - 0.90)			0.88 (0.73 - 1.07)
4	2,109	144	0.91 (0.69 - 1.21)	2,082	198	0.52 (0.42 - 0.64)	2,115	212	0.50 (0.41 - 0.61)
			0.89 (0.66 - 1.20)			0.65 (0.52 - 0.81)			0.63 (0.51 - 0.77)
5	1,617	81	0.75 (0.54 - 1.02)	1,600	97	0.35 (0.27 - 0.45)	1,625	96	0.33 (0.25 - 0.42)
			0.72 (0.51 - 1.02)			0.49 (0.37 - 0.65)			0.45 (0.35 - 0.59)
Per extra attained goal	5,845	432	0.91 (0.84 - 1.00)	5,755	656	0.73 (0.68 - 0.78)	5,844	758	0.71 (0.66 - 0.75)
			0.91 (0.82 - 1.00)			0.80 (0.74 - 0.87)			0.78 (0.73 - 0.84)

CI: Confidence interval; Row per extra attained goal shows the n, no. of events and incidence rate for the total study population. Model I: Adjusted for age and sex

Model II: Model I + additional adjustment for year of study inclusion, years since first manifestation of vascular disease, history of diabetes, coronary artery disease, cerebrovascular disease, abdominal aorta aneurysm, peripheral artery disease. Models for major cardiovascular events and all-cause mortality also include adjustment for use of lipid-lowering medication and hypertension

APPENDIX 6

Competing risks analysis: Hazard ratio per number of attained treatment goals

No. of attained treatment goals	n	Incident cancer		Major cardiovascular event		All-cause mortality	
		No. of events	Hazard ratio (95% CI)	No. of events	Hazard ratio (95% CI)	No. of events	Hazard ratio (95% CI)
0-2	764	Model I	Reference	206	Reference	221	Reference
		Model II					
3	1,390	Model I	1.02 (0.79 - 1.32)	236	0.67 (0.55 - 0.80)	279	0.78 (0.65 - 0.93)
		Model II	1.01 (0.78 - 1.32)		0.72 (0.60 - 0.88)		0.85 (0.71 - 1.02)
4	2,136	Model I	0.90 (0.70 - 1.16)	252	0.52 (0.43 - 0.63)	233	0.47 (0.39 - 0.56)
		Model II	0.90 (0.69 - 1.17)		0.68 (0.55 - 0.83)		0.60 (0.50 - 0.74)
5	1,639	Model I	0.77 (0.58 - 1.03)	136	0.38 (0.31 - 0.48)	110	0.31 (0.25 - 0.39)
		Model II	0.77 (0.56 - 1.05)		0.56 (0.43 - 0.72)		0.45 (0.35 - 0.58)
Per extra attained goal	5,929	Model I	0.93 (0.86 - 1.00)	830	0.74 (0.70 - 0.79)	843	0.70 (0.66 - 0.74)
		Model II	0.93 (0.85 - 1.01)		0.84 (0.78 - 0.90)		0.78 (0.73 - 0.84)

CI: Confidence interval; Row per extra attained goal shows the n, no. of events and incidence rate for the total study population. Model I: Adjusted for age and sex. Model II: Model I + additional adjustment for year of study inclusion, years since first manifestation of vascular disease, history of diabetes, coronary artery disease, cerebrovascular disease, abdominal aorta aneurysm, peripheral artery disease. Models for major cardiovascular events and all-cause mortality also include adjustment for use of lipid-lowering medication and hypertension

APPENDIX 7

No. of attained treatment goals	Incident cancer				Major cardiovascular event		All-cause mortality	
	n	No. of events	Hazard ratio (95% CI)	No. of events	Hazard ratio (95% CI)	No. of events	Hazard ratio (95% CI)	
0-2	1,392	183	Reference	324	Reference	373	Reference	
	Model II							
3	2,270	183	0.79 (0.64 - 0.97) 0.77 (0.62 - 0.96)	296	0.69 (0.59 - 0.81) 0.85 (0.72 - 1.01)	305	0.68 (0.58 - 0.79) 0.83 (0.71 - 0.97)	
	Model II							
4	2,267	150	0.76 (0.61 - 0.95) 0.73 (0.57 - 0.93)	210	0.56 (0.47 - 0.67) 0.81 (0.66 - 0.99)	165	0.44 (0.36 - 0.53) 0.61 (0.50 - 0.75)	
	Model II							
Per extra attained goal	5,929	516	0.91 (0.83 - 1.00) 0.90 (0.81 - 1.00)	830	0.76 (0.71 - 0.82) 0.89 (0.82 - 0.97)	843	0.72 (0.67 - 0.77) 0.83 (0.77 - 0.90)	
	Model II							

CI: Confidence interval; Row per extra attained goal shows the n, no. of events and incidence rate for the total study population. Model I: Adjusted for age and sex. Model II: Model I + additional adjustment for year of study inclusion, years since first manifestation of vascular disease, history of diabetes, coronary artery disease, cerebrovascular disease, abdominal aorta aneurysm, peripheral artery disease. Models for major cardiovascular events and all-cause mortality also include adjustment for use of lipid-lowering medication and hypertension

Rob C.M. van Kruijsdijk
Yolanda van der Graaf
Remy H.H. Bemelmans
Hendrik M. Nathoe
Petra H.M. Peeters
Frank L.J. Visseren

on behalf of the Second Manifestations of ARTerial disease (SMART) study group.

CHAPTER 6

THE RELATION BETWEEN RESTING HEART RATE AND
CANCER INCIDENCE, CANCER MORTALITY AND
ALL-CAUSE MORTALITY IN PATIENTS WITH MANIFEST
VASCULAR DISEASE

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 ($n=6,007$) 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 towards 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.

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 failure¹. Previous studies have identified elevated resting heart rate as an independent risk factor for cardiovascular mortality in the general population and patients with vascular disease²⁻⁶. 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 quartile⁷. The mechanisms underlying this possible relation are not well understood, but insulin resistance, systemic low-grade inflammation and physical fitness may play a role, since these factors are related to both elevated RHR and cancer risk⁷⁻¹¹. 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 response¹². 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 mortality⁷.

Previous studies investigating the relation between RHR and cancer mortality were performed in the general population and were generally confined to men⁴⁻⁷. 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.

METHODS

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 previously¹⁶. In short, newly referred patients, aged 18 to 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 ≥ 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 (*Figure 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 ($n=408$).

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 activity¹⁷. 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 atherosclerosis¹⁶.

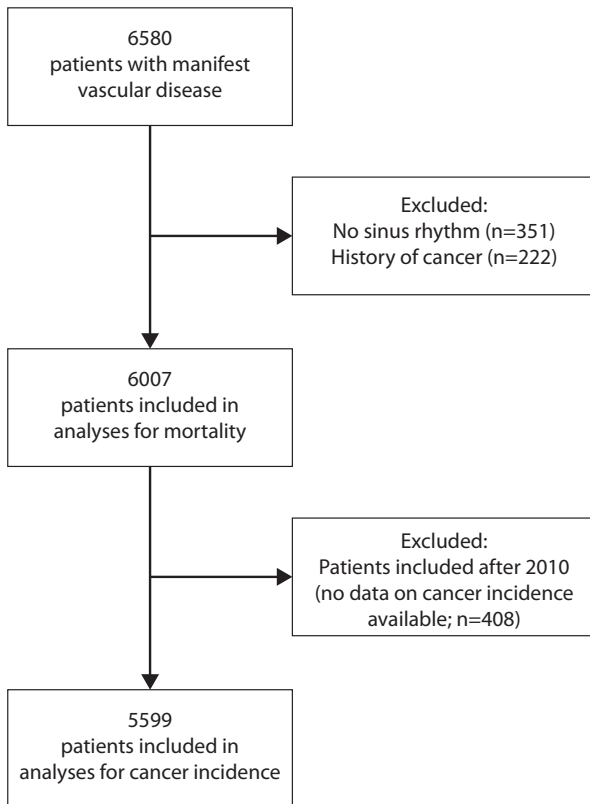


Figure 1. Study flow diagram.

A 12-lead electrocardiogram (ECG) was recorded from all patients in the morning, after resting for five minutes 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).

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, the general practitioner or specialist. Further information on cause of death was collected by retrieving hospital

discharge letters and/or contacting the general practitioner of the participant. Members of an endpoint committee, consisting of physicians from different departments, independently audited all events on the basis of the available clinical information. Information on cancer incidence through 31 December 2010 was ascertained by linkage with the Netherlands Cancer Registry^{15,18}. Follow-up time was defined as the period between date of study inclusion and date of event of interest, lost-to-follow-up, end of follow-up or death, whichever occurred first.

Data analyses

Prior to modeling, power calculations for survival analysis of epidemiological studies was performed for the cancer outcomes¹⁹ (*Appendix 1*). To avoid bias and increase power, missing data for smoking status (0.6%), pack years of smoking (0.6%), physical activity (1.1%), BMI (0.2%), current alcohol use (0.7%), RHR (4.9%), hemoglobin levels (Hb; 0.6%) and high sensitivity C-reactive protein (hsCRP; 1.4%) were singly imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming that these values were missing at random²⁰. Hazard ratio's (HRs) of RHR for all-cause mortality, cancer mortality and the incident cancer outcomes were computed using proportional subdistributions hazards models, that account for competing mortality²¹. For each outcome three models were fitted: (I) adjusted for age and sex (II) additional adjustment for current smoking, Hb and use of β/α /calcium channel-blocker or diuretic; and an explanatory model (III) with the same variables as model II, with additional adjustment for BMI, diabetes, physical activity as measured by hours*MET per week and hsCRP. Study conclusions were based on model III. In order to compare the results with previous studies, HRs were computed per quartile RHR (with quartile 1 as reference) and per 10 bpm increase in RHR. To assess the presence of reverse causality, analyses were repeated after excluding the first year of follow-up. Furthermore, HRs per 10bpm increase in RHR were calculated stratified by type of vascular disease, *i.e.* CAD, CVD, PAD or AAA and polyvascular disease (*i.e.* clinical manifestation of two or more of the aforementioned vascular diseases). To evaluate the effects of beta-blocker use and current smoking on the results, sensitivity analyses were performed in subsets without beta-blocker users and current smokers. Proportionality assumptions were evaluated graphically using scaled Schoenfeld residuals and tested with an interaction of RHR with the logarithm of time. Some non-proportionality of RHR was observed for cancer mortality (p -value=0.02). Hence, the presented HRs for this outcome should be interpreted as the weighted average effect over follow-up²². Restricted cubic spline functions with four knots of RHR were used to assess the linearity assumptions. No significant non-linearity was observed (p -values>0.05). Potential effect modification by age, sex, and smoking status was tested for by adding multiplicative interaction terms to the models. Significant interaction between age and RHR was observed for total cancer mortality (p -value=0.02) and all-cause mortality (p -value<0.001), with a decreasing effect of RHR with increasing age (*Appendix 2*). Statistical analyses were performed in R, version 3.0.2 (www.r-project.org; packages: 'powerSurvEpi', 'Hmisc', 'riskRegression', 'cmprsk').

RESULTS

Baseline characteristics

A total of 6,007 patients with vascular disease were included (*Figure 1*), with a mean age of 59.6 +10.3 years, of whom 73% were male and ≥95% were Caucasian. Baseline characteristics of the study population according to quartiles of RHR (Quartile 1 [Q1] ≤55 bpm; Q2 56-62 bpm; Q3 63-71 bpm and Q4 ≥72 bpm) are shown in *Table 1*. The proportion of males decreased from 81% in Q1 to 69% in Q4, whereas the number of current smokers increased from 28% in Q1 to 41% in Q4. Patients with CAD were more prevalent in the lower quartiles of RHR, while patients with PAD, AAA, CVD, diabetes and metabolic syndrome were more prevalent in the higher quartiles of RHR. As expected, the proportion of patients using beta-blockers decreased from RHR Q1 to Q4.

Follow-up

Patients were followed-up for a median of 6.0 years (IQR: 3.1-9.3 years) and 231 patients (4%) were lost to follow-up. During follow-up 907 patients had died, 248 (27%) of whom died from cancer. Through 2010, 491 patients (8%) were diagnosed with cancer. Lung cancer was most common, with 111 cases (2% of total population and 23% of all incident cancers), followed by prostate cancer ($n=75$; 2% of all men and 20% of incident cancers in men), colorectal cancer ($n=67$; 1% of total population and 14% of all incident cancers) and breast cancer ($n=24$; 2% of women and 20% of incident cancers in women).

Relation between RHR and cancer incidence, cancer mortality and all-cause mortality

There was no relation between RHR and total cancer incidence (HR Q4 vs. Q1: 0.98, 95% CI: 0.76-1.27) (*Table 2*). Furthermore, there was no statistically significant relation between RHR and incident lung cancer (HR Q4 vs. Q1: 0.83, 95% CI: 0.49-1.41), colorectal cancer (HR Q4 vs. Q1: 1.61, 95% CI: 0.80-3.27), breast cancer in women (HR Q4 vs. Q1: 0.46, 95% CI: 0.11-1.83) or prostate cancer in men (HR Q4 vs. Q1: 0.92, 95% CI: 0.48-1.76). Although the risk of all-cause mortality increased over quartiles of RHR (HR Q4 vs. Q1: 1.86, 95% CI: 1.53-2.27), RHR was not a risk factor for cancer mortality (HR Q4 vs. Q1: 1.01, 95% CI: 0.70-1.46). Some attenuation of the effect of RHR on all-cause mortality was observed when adjusted for BMI, diabetes, physical activity and hsCRP in the explanatory models, but not for cancer incidence and cancer mortality.

Similar effects were observed for RHR as continuous variable per 10 bpm (*Table 3*), although there was a trend toward increase in colorectal cancer (HR: 1.15, 95% CI: 0.97-1.36). The latter effect was statistically significant when further adjusted for BMI, diabetes, physical activity and hsCRP (HR: 1.19, 95% CI: 1.00-1.42). The risk of all-cause mortality increased per 10 bpm RHR with 16% (95% CI: 11%-22%). No important differences in results were observed when excluding mortality in the first year of follow-up making reverse causality unlikely. Exclusion of beta-blocker users and current smokers did not markedly change the effect estimates (*Appendix 3*).

Table 1. Baseline characteristics of study population according to quartiles of resting heart rate

	Quartile 1 ≤ 55 bpm (n = 1,512)	Quartile 2 56 - 62 bpm (n = 1,518)	Quartile 3 63 - 71 bpm (n = 1,503)	Quartile 4 ≥72 bpm (n = 1,474)	P-value ^a
Age	59 (10)	59 (11)	59 (10)	60 (10)	0.13
Male gender %	81	75	70	69	<0.01
Smoking, current %	28	30	34	41	<0.01
Smoking, past %	49	48	47	42	<0.01
Pack-years of smoking ^b	22 [10 - 34]	22 [10 - 34]	23 [11 - 36]	26 [12 - 40]	<0.01
Current alcohol consumption %	83	83	81	80	0.07
Physical activity (hours*MET per week)	37 [17 - 67]	34 [15 - 65]	32 [14 - 56]	27 [8 - 53]	<0.01
Body Mass Index (kg/m ²)	26 (3)	27 (4)	27 (4)	27 (5)	<0.01
Waist circumference (cm)	95 (11)	95 (11)	96 (12)	96 (13)	<0.01
Systolic blood pressure (mmHg)	137 (20)	140 (21)	142 (21)	144 (21)	<0.01
Diastolic blood pressure (mmHg)	79 (11)	81 (11)	82 (11)	84 (12)	<0.01
Metabolic parameters					
eGFR (ml/min/1.73 m ²)	76 (16)	76 (17)	77 (18)	77 (20)	0.71
Total cholesterol (mmol/l)	4.8 (1.2)	4.8 (1.1)	5.0 (1.3)	5.1 (1.3)	<0.01
High density lipoprotein (mmol/l)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	0.93
Low density lipoprotein (mmol/l)	2.9 (1.0)	2.9 (1.0)	3.0 (1.1)	3.0 (1.1)	<0.01
Serum triglycerides (mmol/l)	1.3 [0.9 - 1.8]	1.3 [1.0 - 1.9]	1.5 [1.0 - 2.1]	1.5 [1.1 - 2.2]	<0.01
C-reactive protein (mg/l)	1.5 [0.8 - 3.2]	1.8 [0.8 - 3.9]	2.1 [1.0 - 4.5]	2.9 [1.3 - 6.3]	<0.01
Fasting serum glucose (mmol/l)	5.7 [5.3 - 6.2]	5.7 [5.3 - 6.3]	5.8 [5.4 - 6.6]	5.9 [5.4 - 7.0]	<0.01
Hemoglobin levels (mmol/l)	8.9 [8.4 - 9.4]	8.9 [8.4 - 9.4]	8.9 [8.4 - 9.4]	8.9 [8.3 - 9.4]	0.43
Medical history					
Years since first vascular event					
< 1 year before enrollment %	62	60	58	58	0.03
1-2 years before enrollment %	10	10	10	8	0.45
≥ 2 years before enrollment %	28	30	32	34	<0.01
Coronary artery disease %	72	61	58	48	<0.01
Cerebrovascular disease %	22	31	31	35	<0.01
Peripheral arterial disease %	13	17	20	28	<0.01
Abdominal aortic aneurysm %	6	8	9	10	0.01
Hypertension %					<0.01
Diabetes mellitus %	10	13	21	25	<0.01
Metabolic syndrome ^c %	45	50	57	59	<0.01
Medication					
Beta blocker %	67	58	50	34	<0.01
Diuretic %	15	18	22	25	<0.01
ACE-i / ARB %	33	34	39	41	<0.01
Calcium channel blocker %	21	19	20	19	0.36
Alpha blocker %	1	1	1	1	0.82
Glucose-lowering medication %	7	10	17	21	<0.01
Lipid-lowering medication %	70	68	66	60	<0.01
Platelet aggregation inhibitor %	83	79	75	68	<0.01
Oral anticoagulants %	8	9	10	12	<0.01

All data are expressed as mean (S.D.), percentage of group or median [interquartile range]. MET = Metabolic equivalent of task; eGFR = Glomerular filtration rate estimated by the Modification of Diet in Renal Diseases (MDRD)-formula; ACE-i = angiotensin converting enzyme-inhibitor; ARB = angiotensin receptor blocker. ^aAnalysis of variance was used for continuous normally distributed variables, the Kruskal-Wallis test for non-normally distributed variables and chi-square test for non-continuous variables; ^bFor ever smokers only; ^cAccording to the revised National Cholesterol Education Program definition.

Table 2. Hazard ratio's per quartile of resting heart rate for cancer incidence and mortality in patients with vascular disease

	Quartile 1 (n = 1,512)		Quartile 2 (n = 1,518)		Quartile 3 (n = 1,503)		Quartile 4 (n = 1,474)		
	Model	n events	HR (95% CI)	n events	HR (95% CI)	n events	HR (95% CI)	n events	HR (95% CI)
Lung cancer	I	27	1 (reference)	23	0.89 (0.51 - 1.55)	27	1.03 (0.60 - 1.76)	34	1.23 (0.74 - 2.05)
	II		1 (reference)		0.79 (0.45 - 1.39)		0.84 (0.49 - 1.45)		0.83 (0.49 - 1.41)
	III		1 (reference)		0.80 (0.46 - 1.40)		0.87 (0.51 - 1.50)		0.86 (0.50 - 1.48)
Colorectal cancer	I	17	1 (reference)	11	0.65 (0.31 - 1.40)	13	0.75 (0.36 - 1.55)	26	1.39 (0.75 - 2.58)
	II		1 (reference)		0.69 (0.32 - 1.50)		0.83 (0.39 - 1.78)		1.61 (0.80 - 3.27)
	III		1 (reference)		0.71 (0.32 - 1.53)		0.87 (0.41 - 1.87)		1.82 (0.86 - 3.84)
Breast cancer (in women only)	I	4	1 (reference)	8	1.72 (0.51 - 5.82)	7	1.19 (0.35 - 4.05)	5	0.75 (0.20 - 2.78)
	II		1 (reference)		1.38 (0.40 - 4.74)		0.83 (0.23 - 2.98)		0.46 (0.11 - 1.83)
	III		1 (reference)		1.40 (0.40 - 4.83)		0.92 (0.25 - 3.40)		0.54 (0.13 - 2.21)
Prostate cancer (in men only)	I	24	1 (reference)	19	0.86 (0.47 - 1.57)	10	0.47 (0.22 - 0.99)	22	0.97 (0.54 - 1.74)
	II		1 (reference)		0.86 (0.47 - 1.58)		0.44 (0.20 - 0.97)		0.92 (0.48 - 1.76)
	III		1 (reference)		0.85 (0.46 - 1.56)		0.45 (0.21 - 0.98)		0.87 (0.45 - 1.70)
Total cancer	I	126	1 (reference)	111	0.91 (0.71 - 1.17) ^b	117	0.94 (0.73 - 1.21) ^b	137	1.04 (0.81 - 1.33) ^b
	II		1 (reference)		0.89 (0.69 - 1.15) ^b		0.92 (0.71 - 1.19) ^b		0.98 (0.76 - 1.27) ^b
	III		1 (reference)		0.90 (0.70 - 1.16) ^b		0.94 (0.73 - 1.22) ^b		1.03 (0.79 - 1.34) ^b
Cancer mortality	I	56	1 (reference)	55	1.02 (0.71 - 1.48) ^{b,c}	67	1.24 (0.87 - 1.76) ^{b,c}	70	1.17 (0.82 - 1.67) ^{b,c}
	II		1 (reference)		0.98 (0.68 - 1.42) ^{b,c}		1.15 (0.80 - 1.64) ^{b,c}		1.01 (0.70 - 1.46) ^{b,c}
	III		1 (reference)		0.99 (0.68 - 1.43) ^{b,c}		1.18 (0.83 - 1.69) ^{b,c}		1.06 (0.73 - 1.54) ^{b,c}
All-cause mortality	I	161	1 (reference)	194	1.31 (1.06 - 1.61)	214	1.41 (1.15 - 1.73)	338	2.23 (1.84 - 2.69)
	II		1 (reference)		1.24 (1.01 - 1.54)		1.28 (1.04 - 1.57)		1.86 (1.53 - 2.27)
	III		1 (reference)		1.23 (1.00 - 1.52)		1.26 (1.02 - 1.55)		1.73 (1.41 - 2.12)

Model I: Adjusted for age and sex. Model II: model I with additional adjustment for current smoking, hemoglobin levels, beta-blockers, calcium channel-blockers, alpha-blockers and diuretics. Model III (explanatory model): model II with additional adjustment for body mass index, diabetes mellitus, physical activity and high sensitivity C-reactive protein. HR: hazard ratio ; CI: confidence interval. ^a Patients included after 2011 (n=408) were excluded from analyses for incident cancer, because of unavailability of data on cancer incidence. ^b Significant interaction with age (p-value < 0.05); interpret as the weighted average effect over the ages of 19-82 years (see Appendix 2). ^c Some non-proportionality of resting heart rate (p-value = 0.02); interpret as the weighted average effect over follow-up

Table 4 shows HRs of RHR per 10bpm increase for cancer incidence and mortality as well as for all-cause mortality in strata of vascular disease. There was no effect of RHR on incident cancer in CAD, CVD, PAD or AAA patients or patients with polyvascular disease. Similarly, no statistically significant effect of RHR on cancer mortality was observed in any of the strata of vascular disease; patients with CAD: HR: 1.08, 95% CI: 0.92-1.26; CVD: HR: 0.96, 95% CI: 0.77-1.18; PAD or AAA: HR: 0.96, 95% CI: 0.80-1.13; polyvascular disease: HR: 0.97, 95% CI: 0.82-1.14). The effect of RHR on all-cause mortality was not markedly different over the various strata of vascular disease.

Table 3. Hazard ratio's of resting heart rate per 10 beats per minute for cancer incidence and mortality

	Model	Entire follow-up		Exclusion of first year of follow-up	
		n events	HR (95%CI)	n events	HR (95%CI)
Lung cancer ^a	I	111	1.07 (0.95 - 1.20)	94	1.08 (0.95 - 1.23)
	II		0.96 (0.84 - 1.09)		0.97 (0.84 - 1.12)
	III		0.96 (0.84 - 1.10)		0.99 (0.86 - 1.15)
Colorectal cancer ^a	I	67	1.12 (0.96 - 1.31)	56	1.18 (1.00 - 1.39)
	II		1.15 (0.97 - 1.36)		1.21 (1.02 - 1.42)
	III		1.19 (1.00 - 1.42)		1.24 (1.04 - 1.47)
Breast cancer ^a (in women only)	I	24	0.85 (0.64 - 1.12)	22	0.87 (0.65 - 1.16)
	II		0.72 (0.51 - 1.02)		0.74 (0.51 - 1.06)
	III		0.76 (0.55 - 1.07)		0.79 (0.56 - 1.13)
Prostate cancer ^a (in men only)	I	75	1.04 (0.87 - 1.26)	70	1.03 (0.83 - 1.26)
	II		1.04 (0.85 - 1.28)		1.02 (0.81 - 1.28)
	III		1.03 (0.83 - 1.27)		1.02 (0.80 - 1.28)
Total cancer ^a	I	491	1.01 (0.95 - 1.08) ^b	412	1.02 (0.95 - 1.10) ^b
	II		1.00 (0.93 - 1.07) ^b		1.00 (0.93 - 1.08) ^b
	III		1.01 (0.94 - 1.08) ^b		1.02 (0.95 - 1.10) ^b
Cancer mortality	I	248	1.05 (0.97 - 1.14) ^{b,c}	237	1.04 (0.96 - 1.13) ^{b,c}
	II		1.00 (0.92 - 1.09) ^{b,c}		0.99 (0.91 - 1.09) ^{b,c}
	III		1.02 (0.93 - 1.11) ^{b,c}		1.01 (0.92 - 1.11) ^{b,c}
All-cause mortality	I	907	1.22 (1.17 - 1.27)	826	1.21 (1.15 - 1.26)
	II		1.16 (1.11 - 1.22)		1.16 (1.10 - 1.22)
	III		1.13 (1.08 - 1.19)		1.13 (1.08 - 1.19)

Model I: Adjusted for age and sex. Model II: model I with additional adjustment for current smoking, hemoglobin levels, beta-blockers, calcium channel-blockers, alpha-blockers and diuretics. Model III (explanatory model): model II with additional adjustment for body mass index, diabetes mellitus, physical activity and high sensitivity C-reactive protein. HR: hazard ratio ; CI: confidence interval. ^a Patients included after 2011 (n=408) were excluded from analyses for incident cancer, because of unavailability of data on cancer incidence. ^b Significant interaction with age (p-value < 0.05): interpret as the weighted average effect over the ages of 19-82 years (see *Appendix 2*). ^c Some non-proportionality of resting heart rate (p-value = 0.02): interpret as the weighted average effect over follow-up

Table 4. Hazard ratios of resting heart rate per 10 beats per minute for cancer incidence and mortality in strata of vascular disease

	CAD (n = 2,876)			CVD (n = 1,309)			PAD or AAA (n = 918)			Polyvascular disease (n = 904)		
	Model	n events	HR (95%CI)	n events	HR (95%CI)	n events	HR (95%CI)	n events	HR (95%CI)	n events	HR (95%CI)	
Total cancers	I	177	0.95 (0.84 - 1.08)	101	0.96 (0.82 - 1.11)	104	1.06 (0.94 - 1.19)	109	1.00 (0.89 - 1.13)			
	II		0.95 (0.83 - 1.09)		0.97 (0.83 - 1.13)		1.03 (0.91 - 1.17)		1.00 (0.88 - 1.14)			
	III		0.97 (0.84 - 1.11)		0.98 (0.83 - 1.15)		1.06 (0.93 - 1.20)		0.99 (0.87 - 1.13)			
Cancer mortality	I	82	1.12 (0.96 - 1.31)	56	0.99 (0.82 - 1.20)	57	1.01 (0.85 - 1.19)	53	0.94 (0.81 - 1.10)			
	II		1.08 (0.92 - 1.26)		0.96 (0.77 - 1.18)		0.95 (0.80 - 1.13)		0.97 (0.82 - 1.14)			
	III		1.13 (0.97 - 1.32)		0.95 (0.76 - 1.18)		1.00 (0.83 - 1.20)		0.98 (0.83 - 1.16)			
All-cause mortality	I	213	1.22 (1.11 - 1.34)	189	1.18 (1.07 - 1.31)	219	1.16 (1.07 - 1.26)	286	1.13 (1.04 - 1.22)			
	II		1.16 (1.05 - 1.29)		1.17 (1.05 - 1.30)		1.15 (1.06 - 1.25)		1.11 (1.02 - 1.21)			
	III		1.14 (1.02 - 1.28)		1.14 (1.02 - 1.27)		1.14 (1.04 - 1.24)		1.10 (1.01 - 1.20)			

Model I: Adjusted for age and sex. Model II: model I with additional adjustment for current smoking, hemoglobin levels, beta-blockers, calcium channel-blockers, alpha-blockers and diuretics. Model III (explanatory model): model II with additional adjustment for body mass index, diabetes mellitus, physical activity and high sensitivity C-reactive protein. HR: hazard ratio ; CI: confidence interval ; CAD: coronary artery disease ; CVD: cerebrovascular disease ; PAD: peripheral artery disease, AAA: abdominal aorta aneurysm. ^a Patients included after 2011 (n=408) were excluded from analyses for incident cancer, because of unavailability of data on cancer incidence.

DISCUSSION

In this prospective cohort study in patients with manifest vascular disease, RHR was not related to risk of overall cancer incidence. A marginally statistically significant effect of elevated RHR on incident colorectal cancer risk was observed. Although patients with elevated RHR had a higher risk of all-cause mortality, RHR was not related to the risk of cancer mortality.

In contrast to the results of the present study, several previous studies among employed men and women, observed a relation between RHR and cancer mortality, with HRs for the highest tertile or quartile of RHR compared to the lowest stratum ranging from 1.2 to 2.4^{4,7,13}. However, no effect of RHR on cancer mortality was found in two prospective studies in male industrial and non-industrial employees^{2,5}. The study populations were quite similar and all studies adjusted for age, smoking and BMI. Although additional adjustment for confounders differed among the studies, there was no distinct pattern that explains the difference between the studies that did find a relation^{4,7,13} and those that did not^{2,5}. In contrast to previous studies, a model including additional adjustment for medication was used in the present study, but this did not markedly affect the estimates. In several studies, the HRs were additionally adjusted for factors including physical activity and hemoglobin, but this did not lead to important changes in the estimates, similar to the present study. The studies that did find a relation between RHR and cancer mortality had a long follow-up (at least 17 years), however, in the study with the longest follow-up period (40 years) no effect of RHR on cancer mortality was observed. One of the few prospective studies investigating the relation between RHR and cancer incidence found a relative risk of 1.66 (95% CI 1.03-2.65) for the highest quintile of RHR compared to the lowest quintile²³, whereas another study in elderly men reported a relation between elevated RHR and risk of incident prostate cancer²⁴. In line with the observed relation between RHR and colorectal cancer in the present study, only the risk of colorectal cancer mortality was independently associated with RHR in a study evaluating the effect of RHR on specific cancers among men¹³.

The lack of a relation between RHR and overall cancer incidence and mortality in patients with vascular disease might be explained by their high risk of cardiovascular mortality, which is strongly related to RHR. Due to the high risk of cardiovascular death, patients with elevated RHR might not have a long enough lifespan to develop cancer. Furthermore, beta-blocker use and smoking can greatly affect RHR and both are highly prevalent among patients with vascular disease^{3,25,26}. However, it is unlikely that these factors are responsible for the lack of a relation between RHR and cancer, as both adjustment in the models and exclusion of beta-blocker users and current smokers from the analysis did not markedly change the results.

Increased sympathetic activation and a subsequent increase in RHR by the presence of undiagnosed cancer in patients at baseline could lead to overestimation of the effect of RHR on cancer risk. Some previous publications were indeed suggestive of such bias, often referred to as reverse causality, as an apparent relation between RHR and cancer

mortality disappeared after excluding the first period of follow-up¹³. Presence of reverse causality in the present study, however, is unlikely, as the results were virtually identical after excluding events in the first year of follow-up. In addition to insulin resistance, inflammation and physical fitness, direct adverse effects of elevated RHR on cardiac and vascular function have been proposed to underlie the relation between RHR and cardiovascular mortality. These effects include an increased susceptibility for cardiac arrhythmias and negative effect on the balance between myocardial oxygen demand and supply at higher heart rate^{3,27}. Furthermore, elevated RHR has been observed to induce endothelial dysfunction and to directly stimulate atherogenesis and atherosclerotic plaque rupture^{3,28}. First reports of trials investigating the effects of ivabradine, a selective heart rate-lowering agent, suggest that lowering of RHR reduces the risk of cardiovascular events in patients with heart failure or CAD^{29,30}. Although selective lowering of RHR is unlikely to affect cancer risk, the direct effects of increased sympathetic activation might play an essential role in the relation between RHR and cancer. Beta-adrenergic signaling has been found to regulate multiple cellular processes that contribute to the initiation and progression of cancer and might therefore provide a new therapeutic target for several solid tumors¹². Given the minor difference between the results with and without additional adjustment for BMI, diabetes, physical activity and hsCRP in the present study, the observed effect of RHR on colorectal cancer is more likely to reflect the direct effects of sympathetic activation rather than indirectly linked factors such as insulin resistance, inflammation and physical fitness. It is conceivable that the effects of physical fitness on the relation between RHR and cancer are mitigated in patients with vascular disease, because overall, these patients are likely to have low fitness levels³¹.

Notable strengths of this study include the prospective design and the completeness of data on mortality as well as cancer diagnoses obtained from the Netherlands Cancer Registry, which has a near complete coverage³². Furthermore, as the risk of cardiovascular, and thus competing mortality is high in this population of patients with manifest vascular disease, we used competing risk models to avoid bias and to allow direct interpretation of the effect estimates in terms of risk²¹.

Some study limitations should be considered. First, only a single measurement of RHR was available, whereas RHR might fluctuate during the day. However, the measurements of RHR in this study were well standardized, based on ECG in rest and reflect clinical practice. Second, the statistical power of the analysis for the specific cancer types was limited. However, it is unlikely that important effects were missed with regard to total cancer incidence and mortality, since the power was >80% to detect an HR of 1.16 or higher (*Appendix 1*). Third, as with any observational study, there is a risk of residual confounding (e.g. by work-related exposure to carcinogens, which was not recorded in the SMART-study). However, we adjusted for the most important potential confounders, including age, sex, smoking and several medications that could affect both RHR and cancer risk. Furthermore, using data on insulin resistance, systemic inflammation and physical activity we were able to determine whether these were important factors in the relation between RHR and cancer.

In conclusion, RHR is not related to risk of overall cancer incidence in patients with manifest vascular disease. A relation between elevated RHR and incident colorectal cancer risk could not be ruled out. Although vascular patients with elevated RHR have a higher risk of all-cause mortality, RHR does not affect the risk of cancer mortality.

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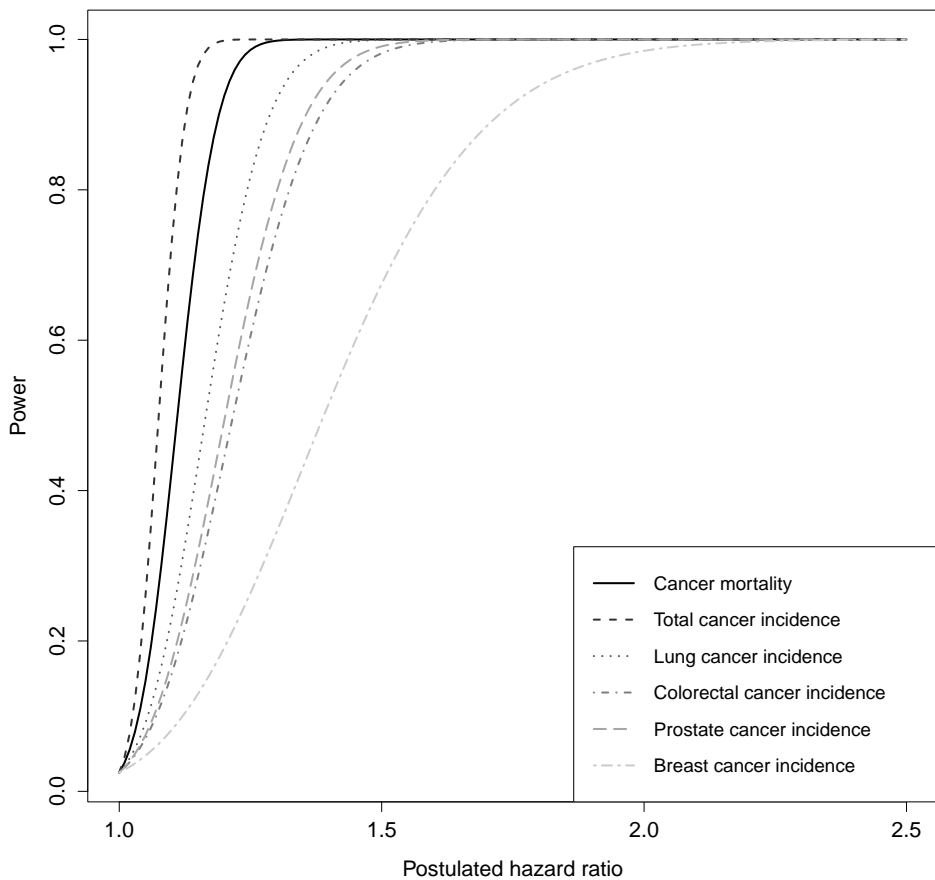
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APPENDIX 1

Power calculations for cancer outcomes. Postulated hazard ratios are for 10 beats per minute increase in resting heart rate. Analysis were performed using the formula for power calculation for survival analysis in epidemiological studies by Hsieh and Lavori¹, implemented in the R package 'powerSurvEpi' version 0.0.6.

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APPENDIX 2

Hazard ratios of resting heart rate per 10 beats per minute for cancer mortality and all-cause mortality in quartiles of age

Model	Quartile 1 (n = 1,681) (19-53 years)		Quartile 2 (n = 1,408) (53-60 years)		Quartile 3 (n = 1,446) (60-67 years)		Quartile 4 (n = 1,472) (67-82 years)		
	n events	HR (95%CI)	n events	HR (95%CI)	n events	HR (95%CI)	n events	HR (95%CI)	
Cancer mortality	I	22	1.26 (0.91 - 1.74)	45	1.12 (0.96 - 1.30)	70	1.09 (0.95 - 1.25)	111	0.97 (0.85 - 1.10)
	II		1.13 (0.77 - 1.67)		1.05 (0.88 - 1.27)		1.05 (0.91 - 1.22)		0.93 (0.81 - 1.06)
	III		1.10 (0.72 - 1.69)		1.12 (0.94 - 1.34)		1.05 (0.91 - 1.22)		0.94 (0.82 - 1.08)
All-cause mortality	I	91	1.47 (1.28 - 1.68)	141	1.29 (1.17 - 1.42)	236	1.19 (1.10 - 1.30)	439	1.16 (1.09 - 1.24)
	II		1.39 (1.21 - 1.61)		1.21 (1.09 - 1.35)		1.15 (1.05 - 1.25)		1.12 (1.05 - 1.21)
	III		1.34 (1.15 - 1.56)		1.21 (1.08 - 1.36)		1.12 (1.03 - 1.23)		1.09 (1.01 - 1.17)

Model I: Adjusted for age and sex. Model II: model I with additional adjustment for current smoking, hemoglobin levels, beta-blockers, calcium channel blockers, alpha-blockers and diuretics. Model III (explanatory model): model II with additional adjustment for body mass index, diabetes mellitus, physical activity and high sensitivity C-reactive protein. HR: hazard ratio ; CI: confidence interval. ^a Patients included after 2011 (n=408) were excluded from analyses for incident cancer, because of unavailability of data on cancer incidence.

APPENDIX 3

Sensitivity analysis: Hazard ratio's of resting heart rate per 10 beats per minute for cancer incidence and mortality, excluding users of betablockers and current smokers

	Full study population (n=6,007)			Exclusion of beta blocker users (n=2,862)			Exclusion of current smokers (n=4,023)		
	Model	n events	HR (95%CI)	n events	HR (95%CI)	n events	HR (95%CI)		
Lung cancer	I	111	1.07 (0.95 - 1.20)	76	1.03 (0.88 - 1.20)	56	1.08 (0.92 - 1.28)		
	II		0.96 (0.84 - 1.09)		1.00 (0.85 - 1.17)		0.99 (0.83 - 1.17)		
	III		0.96 (0.84 - 1.10)		0.99 (0.84 - 1.17)		0.98 (0.83 - 1.17)		
Colorectal cancer	I	67	1.12 (0.96 - 1.31)	31	0.96 (0.72 - 1.29)	46	1.11 (0.91 - 1.35)		
	II		1.15 (0.97 - 1.36)		0.99 (0.74 - 1.33)		1.08 (0.86 - 1.35)		
	III		1.19 (1.00 - 1.42)		1.07 (0.79 - 1.43)		1.09 (0.86 - 1.38)		
Breast cancer (in women only)	I	24	0.85 (0.64 - 1.12)	18	0.65 (0.45 - 0.95)	17	0.93 (0.68 - 1.29)		
	II		0.72 (0.51 - 1.02)		0.62 (0.43 - 0.89)		0.82 (0.55 - 1.21)		
	III		0.76 (0.55 - 1.07)		0.65 (0.46 - 0.91)		0.89 (0.61 - 1.30)		
Prostate cancer (in men only)	I	75	1.04 (0.87 - 1.26)	38	0.96 (0.71 - 1.31)	47	1.00 (0.79 - 1.26)		
	II		1.04 (0.85 - 1.28)		0.96 (0.70 - 1.31)		1.02 (0.80 - 1.30)		
	III		1.03 (0.83 - 1.27)		0.93 (0.68 - 1.28)		1.04 (0.81 - 1.34)		
Total cancer	I	491	1.01 (0.95 - 1.08) ^b	271	0.97 (0.89 - 1.07) ^b	323	0.99 (0.92 - 1.08) ^b		
	II		1.00 (0.93 - 1.07) ^b		0.98 (0.89 - 1.07) ^b		0.98 (0.90 - 1.06) ^b		
	III		1.01 (0.94 - 1.08) ^b		0.99 (0.90 - 1.09) ^b		0.99 (0.91 - 1.08) ^b		
Cancer mortality	I	248	1.05 (0.97 - 1.14) ^{b,c}	147	1.01 (0.90 - 1.13) ^{b,c}	162	1.04 (0.94 - 1.15) ^{b,c}		
	II		1.00 (0.92 - 1.09) ^{b,c}		1.00 (0.89 - 1.12) ^{b,c}		1.01 (0.91 - 1.12) ^{b,c}		
	III		1.02 (0.93 - 1.11) ^{b,c}		1.00 (0.89 - 1.12) ^{b,c}		1.02 (0.92 - 1.13) ^{b,c}		
All-cause mortality	I	907	1.22 (1.17 - 1.27)	548	1.18 (1.11 - 1.24)	545	1.20 (1.14 - 1.27)		
	II		1.16 (1.11 - 1.22)		1.15 (1.09 - 1.22)		1.17 (1.10 - 1.25)		
	III		1.13 (1.08 - 1.19)		1.11 (1.04 - 1.17)		1.15 (1.08 - 1.22)		

Model I: Adjusted for age and sex. Model II: model I with additional adjustment for current smoking, hemoglobin levels, beta-blockers, calcium channel-blockers, alpha-blockers and diuretics. Model III (explanatory model); model II with additional adjustment for body mass index, diabetes mellitus, physical activity and high sensitivity C-reactive protein. HR: hazard ratio ; CI: confidence interval. ^a Patients included after 2011 (n=408) were excluded from analyses for incident cancer, because of unavailability of data on cancer incidence. ^b Significant interaction with age (p-value < 0.05); interpret as the weighted average effect over the ages of 19-82 years (see Appendix 2). ^c Some non-proportionality of resting heart rate (p-value = 0.02); interpret as the weighted average effect over follow-up.

PART TWO

INDIVIDUALIZED TREATMENT EFFECT PREDICTION

Rob C.M. van Kruijsdijk
Frank L.J. Visseren
Paul M Ridker
Johannes A.N. Dorresteijn
Julie E. Buring
Yolanda van der Graaf
Nancy R. Cook

CHAPTER 7

INDIVIDUALISED PREDICTION OF ALTERNATE-DAY
ASPIRIN TREATMENT EFFECTS ON THE COMBINED RISK
OF CANCER, CARDIOVASCULAR DISEASE AND
GASTROINTESTINAL BLEEDING IN HEALTHY WOMEN

Heart (in press)

ABSTRACT

Background

The value of aspirin in primary prevention of cancer and cardiovascular disease (CVD) remains unclear. The aim of this study was to identify women who benefit from alternate-day aspirin with regard to all relevant outcomes, including cancer, CVD and major gastrointestinal bleeding.

Methods

Long term follow-up data of 27,939 healthy women with baseline plasma samples in the Women's Health Study, a randomised trial of 100mg alternate-day aspirin versus placebo, were used to develop competing risks models for individualised prediction of absolute risk reduction (ARR) of the combination of CVD, cancer and major gastrointestinal bleeding by aspirin.

Results

Although aspirin was associated with a modestly decreased 15-year risk of colorectal cancer, CVD, and in some women non-colorectal cancer, aspirin treatment resulted in a negative treatment effect in the majority of women if gastrointestinal bleeding was also taken into account. The excess risk of major gastrointestinal bleeding by aspirin increased with age, but the benefits for colorectal cancer and CVD risk were also greater at higher age. Decision curves indicated that selective treatment of women ≥ 65 years may improve net benefit compared to treating all, none and prediction-based treatment. The observed 15-year number needed to treat to prevent one event among women ≥ 65 years was 29 (95% confidence interval: 12-102).

Conclusion

Concurrent evaluation of the absolute effects on cancer, CVD and major gastrointestinal bleeding showed that alternate-day use of low-dose aspirin is ineffective or harmful in the majority of women in primary prevention. Selective treatment of women ≥ 65 years with aspirin may improve net benefit.

INTRODUCTION

Emerging data convincingly show that aspirin, in addition to its effects on cardiovascular risk, reduces cancer risk^{1,4}. Recent meta-analyses of individual patient data from randomised trials of daily aspirin showed a notable decrease in both cancer incidence and mortality, particularly for colorectal cancer^{2,3,5}. The protective effects were more pronounced in trials with longer duration of treatment and emerged only after a delay of 5 to 10 years, depending on the dose used^{1-3,5,6}. In contrast to daily aspirin, no effect of alternate-day aspirin on cancer risk was observed in previous analyses of the two largest randomised trials of aspirin, the Women's Health Study (WHS) and the Physicians' Health Study (PHS)^{7,8}. Recently, however, analysis of long-term observational follow-up data of the WHS revealed a reduction in colorectal cancer risk in the aspirin group, emerging after a median follow-up of 18 years (hazard ratio [HR]: 0.80, 95% confidence interval [CI]: 0.67 to 0.97)⁹.

Despite these findings, the role of aspirin in primary prevention remains unclear, as it is uncertain whether the combined benefits for cancer and cardiovascular disease (CVD) outweigh the increase in major bleeding events^{4,10}. The U.S. Food and Drug Administration recently published a consumer update in which the use of aspirin for primary prevention of CVD is discouraged¹¹, whereas current guidelines, focusing on CVD, recommend to consider use of aspirin prophylaxis for individuals at high cardiovascular risk¹² and in those of ≥ 65 years of age, if the benefit for CVD prevention is likely to outweigh the risk of bleeding events^{13,14}. However, for whom the latter is the case, especially if the potential benefits for cancer prevention are also considered, remains to be established.

As treatment effect may be determined by multiple patient characteristics, using models to predict treatment effect for individuals could help to select patients for aspirin treatment¹⁵⁻²⁰. This would enable clinicians to estimate the response of an individual to aspirin prophylaxis and only treat those who are expected to benefit.

Using data from the WHS, we developed models for predicting aspirin treatment effect (i.e. 15-year absolute risk reduction (ARR) of the combination of CVD, cancer and major bleeding events), aimed at identifying initially healthy women who could benefit from aspirin. Moreover, we evaluated which of the following aspirin treatment strategies would lead to the most favourable clinical outcome: treat none, treat everyone, treat only women ≥ 65 years and prediction-based treatment.

METHODS

The WHS was a randomised trial evaluating the effect of 100mg alternate-day aspirin compared with placebo for primary prevention of CVD and cancer in 39,876 women ≥ 45 years of age, without a history of CVD or cancer. Detailed methods and outcomes have been described previously^{7,9,21,22}. Written informed consent was obtained from all participants and the trial was approved by the Institutional Review Board of Brigham and Women's Hospital. After the end of randomised treatment on 31 March 2004, with an

average 10 years of follow-up, participants were invited for further observational follow-up⁹. A detailed description of the post-trial follow-up and endpoint ascertainment is provided in *Appendix 1*. The present analyses include end points accrued and confirmed through 14 March 2012, using data of women who provided an adequate baseline plasma sample (n=27,939).

Model derivation

To obtain individualised predictions of treatment effect of aspirin, proportional subdistribution hazards models²³ for four outcomes were developed: (I) CVD (i.e. non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), (II) invasive colorectal cancer (III) non-colorectal cancer (i.e. any invasive neoplasm, excluding colorectal and non-melanoma skin cancer) and (IV) major gastrointestinal bleeding. The latter was defined as gastrointestinal bleeding events requiring hospitalization. Reports of cancer were confirmed by pathology or cytology reports or, rarely, were based on strong clinical and radiologic or laboratory marker evidence^{7,9}. Given that the evidence of a preventive effect of aspirin is most abundant for colorectal cancer, this outcome was modeled apart from other cancers, so that any specific effects of aspirin on colorectal cancer risk could be evaluated separately. To avoid non-additivity of risks for individual endpoints, outcomes were modeled in a competing risks framework, mutually accounting for the events of interest, as well as for death by causes other than CVD, cancer or gastrointestinal bleeding (*Appendix 2.1*)^{23,24}. Models were developed for treatment effect prediction at 10 and 15 year. To reduce overfitting, predictors that were deemed to be easily available in clinical practice, including age, smoking status, body mass index, systolic blood pressure, use of blood pressure lowering medication, total cholesterol, high density lipoprotein cholesterol, high sensitivity C-reactive protein, family history of premature coronary heart disease, hemoglobin A1c if diabetic, height, diabetes mellitus, alcohol use, menopausal status, hormone replacement therapy use, family history of cancer and history of dyspepsia, were preselected based on existing literature (*Appendix 1*). The relative treatment effect of aspirin was assumed constant in the main analysis. Findings of effect modification by any risk factors are inconsistent in previous studies^{3,7,9,21,25}, although significant effect modification was found by age and smoking for CVD in the WHS²¹. To evaluate these potential relative subgroup effects, sensitivity analyses were performed in which treatment interactions were considered (*Appendix 1*).

To obtain individualised absolute risk reductions (ARRs), the models were used to predict the absolute risk of all individual outcomes with and without aspirin. Subsequently, the ARR was calculated as the difference between the predicted absolute risk with and without aspirin treatment and the ARR of the individual outcomes were summed to get a total ARR. As some women and/or physicians may consider CVD or cancer diagnosis to be more important than gastrointestinal bleeding, the total ARR was also calculated applying different weights (i.e. 0.5, 0.25 and 0.1) for gastrointestinal bleeding.

Model validation

To adjust for overfitting, bootstrap-based uniform shrinkage was applied for the models²⁶ (*Appendix 1*). Discriminatory ability of each model was evaluated using an optimism-corrected estimate of the c-index that is adapted for competing risks²⁷. Calibration was assessed graphically using calibration plots.

Decision curve analysis²⁰ was used to evaluate whether use of the models for selecting of women for aspirin prophylaxis would improve the clinical outcome compared to other treatment strategies, including treating no one, treating all and treating only women ≥ 65 years. This method focuses on the effects of (changes in) treatment decisions that result from a treatment strategy and is based on calculation of 'net benefit'. Calculation of net benefit starts with choosing a treatment threshold, that is the smallest treatment effect (expressed as ARR) at which one would opt for treatment. This treatment threshold can also be expressed as the number-willing-to-treat (NWT), which is the reciprocal of the treatment threshold and can be interpreted as the maximum acceptable number needed to treat (NNT)^{17,19}. Subsequently, this threshold is used for weighing the reduction in event rate by a certain treatment strategy against the harms of treatment. As the appropriate NWT is subjective and can vary among different patients and clinicians, net benefit was calculated for 15-year NWT values ranging from infinite to 20 (i.e. treatment threshold of 0% to 5%). The net benefit results were presented graphically as decision curves. Given that no effect of cancers other than colorectal cancer was observed in previous analysis of the WHS, sensitivity analysis were performed in which the treatment effect of aspirin on non-colorectal cancer was assumed null. Further details on the model development and validation are provided in *Appendix 1*.

RESULTS

Baseline characteristics of the present study population ($n=27,939$) are shown in *Table 1*. During the trial (median follow-up of 10.1 years, interquartile range (IQR): 9.5–10.8), 604 cases of CVD, 168 colorectal cancer diagnoses, 1832 non-colorectal cancer diagnosis and 302 gastrointestinal bleedings requiring hospitalization were recorded. An additional 107 colorectal and 1388 noncolorectal cancer cases were confirmed during the post-trial period (median follow-up: 7.2 years, IQR: 4.6–7.3).

Model derivation and validation

The computational formulas for 10- and 15-year treatment effect of aspirin are provided in *Appendix 2.2* and *Appendix 2.3*. Discrimination of the 10-year CVD-model was good (c-index: 0.785), whereas the discrimination of the model for colorectal cancer (c-index: 0.65), non-colorectal cancer (c-index: 0.59) and gastrointestinal bleeding (c-index: 0.641) was moderate. The models for 15-year predictions of colorectal and non-colorectal cancer showed similar discriminatory power (c-index: 0.655 and 0.582, respectively). Model calibration was generally well balanced (*Appendix 2.4*).

Table 1. Baseline characteristics of the total study population and according to predicted 15-year absolute risk reduction of major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding with aspirin treatment.

	Total study population (n = 27,939)	<0% predicted ARR (n = 18,524)	≥0% and <1% predicted ARR (n = 8,943)	≥1% predicted ARR (n = 472)
Age (years)	54.7 ± 7	52.3 ± 5	59.0 ± 7	64.9 ± 7
Age > 65 years	2968 (11)	582 (3)	2130 (24)	256 (54)
Caucasian ethnicity	26401 (95)	17664 (95)	8526 (95)	441 (93)
Current smoking	3252 (12)	818 (4)	2220 (25)	217 (46)
Past smoking	10239 (37)	7399 (40)	2750 (31)	98 (21)
Never smoking	14424 (52)	10307 (56)	3973 (44)	157 (33)
Alcohol use (≥ 1 drink/wk)	11327 (41)	8012 (43)	3184 (36)	133 (28)
Peri- or postmenopausal	20210 (72)	11609 (63)	8173 (91)	465 (99)
Hormone replacement therapy use	14353 (51)	9336 (50)	4819 (54)	219 (46)
Body mass index (kg/m ²)	25.9 ± 5.0	25.4 ± 4.7	26.9 ± 4.9	28.1 ± 5.2
High density lipoprotein (mg/dL)	53.7 ± 15.0	56.5 ± 14.4	48.3 ± 13.1	41.8 ± 11.4
Total cholesterol (mg/dL)	211.8 ± 41.8	204.5 ± 37.9	225.1 ± 40.8	234.3 ± 40.4
High sensitivity C-reactive protein (mg/L)	2.0 [0.8 - 4.4]	1.5 [0.6 - 3.5]	3.1 [1.5 - 5.8]	5.3 [2.7 - 8.6]
Systolic blood pressure (mmHg)	124 ± 14	118 ± 10	134 ± 13	148 ± 14
Blood pressure lowering medication use	3739 (13)	812 (4)	2640 (30)	292 (62)
Lipid lowering medication use	893 (3)	319 (2)	516 (6)	58 (12)
Diabetes mellitus	685 (2)	35 (0)	425 (5)	227 (48)
Family history of premature CHD	3959 (14)	2177 (12)	1753 (20)	93 (20)
Family history of cancer ^a	4966 (18)	3205 (17)	1701 (19)	101 (21)
History of dyspepsia	2575 (9)	1836 (10)	703 (8)	36 (8)
Randomized to aspirin use	13976 (50)	9239 (50)	4498 (50)	239 (51)
15-year predicted risk (%) of				
Major cardiovascular events	1.78 [0.96 - 3.70]	1.17 [0.77 - 1.77]	4.95 [3.45 - 7.58]	26.91 [22.11 - 33.59]
Colorectal cancer	0.81 [0.50 - 1.28]	0.64 [0.43 - 0.96]	1.27 [0.84 - 1.88]	1.85 [1.27 - 2.55]
Non-colorectal cancer	9.72 [8.29 - 11.84]	9.09 [7.94 - 10.63]	11.50 [9.51 - 14.05]	14.51 [12.09 - 16.87]
Major gastro-intestinal bleeding	1.01 [0.75 - 1.51]	0.85 [0.68 - 1.14]	1.53 [1.10 - 2.18]	2.91 [2.22 - 3.67]

ARR: Absolute risk reduction (in %); CI: Confidence interval; ^aNNT: Number needed to treat; ^bNNH: Number needed to harm. Risks were estimated based on the cumulative incidence function, accounting for competing risks.

Absolute risk reduction by aspirin

The WHS participants had a median predicted 15-year risk of 11.4% for all adverse outcomes combined (1.5% for CVD, 0.5% for colorectal cancer, 8.7% for non-colorectal cancer and 0.8% for major gastrointestinal bleeding). The distribution of individualised 15-year ARR of aspirin are shown in *Figures 1-2* and the ARRs with NNTs with 95% CI's observed in the WHS population and age subgroups are shown in *Table 2*. Overall, there was a small benefit from aspirin treatment with regard to CVD (15-year ARR: 0.27%, 95% CI: 0.06-0.86%, NNT: 371) and colorectal cancer (15-year ARR: 0.14%, 95% CI: 0.02% - 0.59%, NNT: 709). No effect on non-colorectal cancer was observed (15-year absolute-risk-increase [ARI]: 0.08%, 95% CI: -0.64% to 0.80%, number needed to harm (NNH): 709) and aspirin increased the risk of gastrointestinal bleeding in all women (15-year ARI: 0.75%, 95% CI: 0.50% to 1.00%, NNH: 133). Consequently, aspirin non-significantly increased the median 15-year risk for all outcomes combined by 0.42% (95% CI: -0.45% to 1.29%). However, a more beneficial distribution of ARRs was observed if a weight was applied for gastrointestinal bleeding. The 10-year estimates were largely similar, although effects of aspirin were closer to the null (*Appendix 2.5*). A stronger protective effect of aspirin on CVD was observed in women ≥ 65 years (15-year ARR: 3.11%, 95% CI: 1.67% to 5.27%, NNT: 29). The risk of gastrointestinal bleeding was also increased in this group, but this increase was relatively smaller than the decrease in CVD, especially if bleeding is given less weight than CVD and cancer (*Appendix 2.6*).

The predicted ARR of CVD and, in lesser degree, of colorectal cancer increased with higher baseline CVD and colorectal cancer risk (*Appendix 2.7*). In contrast, the absolute risk of gastrointestinal bleeding increased notably in women with high baseline risk when on aspirin. Only women with a total baseline risk of $>40\%$ for all outcomes would derive benefit from aspirin, although at which baseline risk aspirin yields benefit is dependent on the weight that is applied for bleeding. A similar effect of age on the predicted 15-year ARR was observed, with increasing benefit for CVD and colorectal cancer with higher age. However, the increase in absolute risk of bleeding by aspirin was also stronger in older individuals.

Table 1 displays the characteristics of the study participants by predicted 15-year ARR for the combination of all adverse outcome ($<0\%$, between 0 and 1%, and $\geq 1\%$), calculated with a weight of 0.25 for bleedings. Notably, 66% of women had a negative overall treatment effect. Older age was an important determinant for treatment effect, as of the women with a predicted overall treatment effect of $\geq 1\%$ ARR (NNT:100), 54% were ≥ 65 years.

Net benefit assessment

Decision curves for evaluating the net benefit of different aspirin treatment strategies with regard to the total outcome, with different weights for gastrointestinal bleeding, are shown in *Figure 3*. Treating all women of ≥ 65 years was the most favourable treatment strategy if the 15-year NWT is >32 (i.e. one is willing to treat 32 women to prevent one event), but the limit is lower if gastrointestinal bleeding is given less weight. If treatment indeed would

be reserved for women ≥ 65 years, the NNT to prevent one adverse event would be 29 (95% CI: 12 to 102). Because the models predicted only a small benefit or even harm for the vast majority, and thus almost no women would be selected for treatment, prediction-based treatment yielded similar benefit as treating none over the whole range of treatment thresholds. Decision curves for the individual outcomes (*Appendix 2.8*), show that treating all women ≥ 65 years results in the highest net benefit for CVD and non-colorectal cancer, although treating none would be the optimal strategy if the NWT is lower than 30 and 50, respectively.

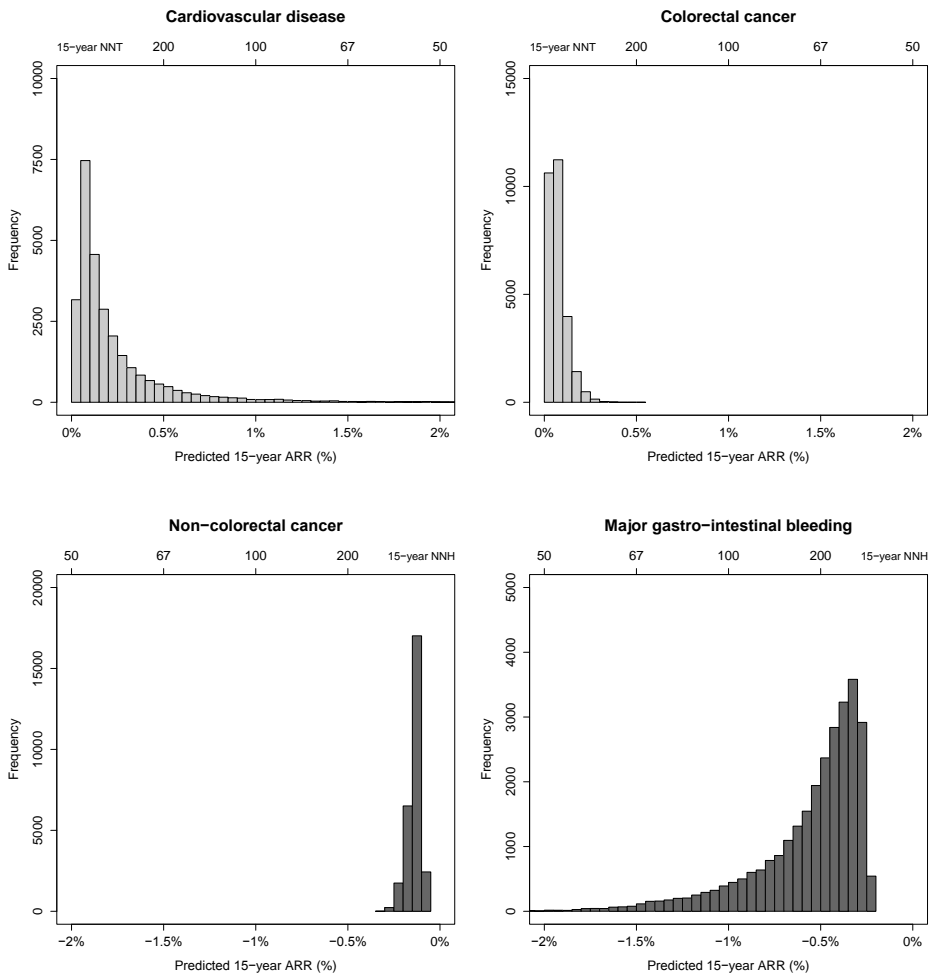


Figure 1. Distribution of predicted 15-year absolute risk reduction for major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastrointestinal bleeding with aspirin treatment in the study population. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.

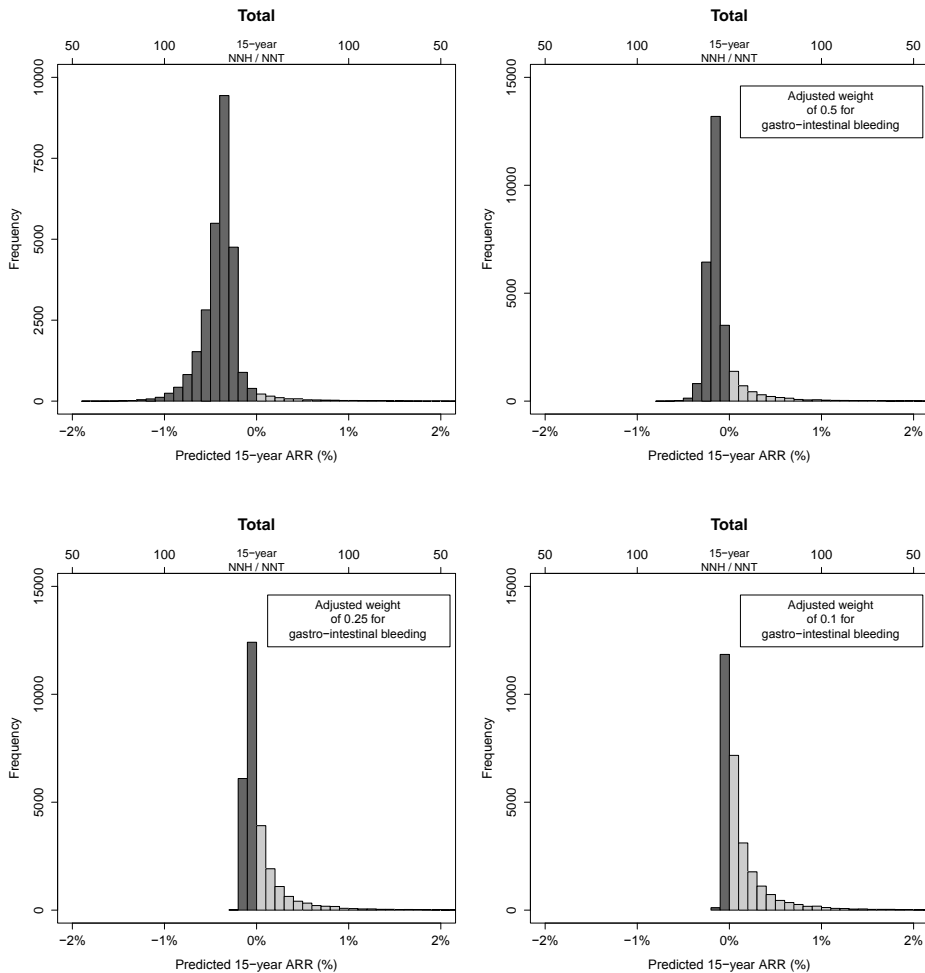


Figure 2. Distribution of predicted 15-year absolute risk reduction for the total of all outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastrointestinal bleeding) applying different weights for gastrointestinal bleeding, in participants in the Women’s Health Study. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.

Sensitivity analyses

Results of sensitivity analyses are provided in *Appendix 3*. In short, the predicted ARR from the models with treatment interactions were more widely distributed, particularly for non-colorectal cancer, with benefit in 48% of the study population and caused harm in the other 52%. When the effect of aspirin on non-colorectal cancer was assumed null, the total ARR tended to be slightly higher. Overall, however, the results from the sensitivity analysis were similar to the main results and in both scenarios, decision curve analysis indicated that prediction-based treatment was inferior to treating none or treating only women ≥ 65 years.

Table 2. Observed 15-year absolute risk reductions and numbers needed to treat/harm for aspirin

	Total study population		Women < 65 years		Women ≥ 65 years	
	ARR (95% CI)	^a NNT or ^b NNH (95%CI)	ARR (95% CI)	^a NNT or ^b NNH (95%CI)	ARR (95% CI)	^a NNT or ^b NNH (95%CI)
Major cardiovascular event	0.27 (0.06 to 0.86)	371 (116 to >1000) ^a	-0.06 (-0.39 to 0.26)	>1000b (259 ^b to 382 ^a)	3.11 (1.67 to 5.27)	32 (19 to 60) ^b
Colorectal cancer	0.14 (0.02 to 0.59)	709 (170 to >1000) ^a	0.17 (0.04 to 0.55)	581 (181 to >1000) ^a	-0.11 (-1.15 to 0.93)	924 ^b (87 ^b to 107 ^a)
Non-colorectal cancer	-0.08 (-0.80 to 0.64)	>1000 ^b (124b to 156 ^a)	-0.32 (-1.06 to 0.42)	312 ^b (94b to 237 ^a)	2.05 (0.43 to 6.28)	49 (16 to 235) ^a
Major gastro-intestinal bleeding	-0.75 (-0.50 to -1.00)	133 (100 to 198) ^b	-0.64 (-0.40 to -0.87)	157 (114 to 251) ^b	-1.66 (-0.50 to -2.82)	60 (35 to 199) ^b
Total	-0.42 (-1.29 to 0.45)	238 ^b (78b to 223 ^a)	-0.85 (-1.72 to 0.03)	118 ^b (58 ^b to >1000 ^a)	3.39 (0.98 to 8.42)	29 (12 to 102) ^a
Total, adjusted weight of 0.5 for gastro-intestinal bleeding	-0.05 (-0.92 to 0.82)	>1000 ^b (109b to 121 ^a)	-0.53 (-1.40 to 0.34)	189 ^b (71 ^b to 291 ^a)	4.22 (1.59 to 8.90)	24 (11 to 63) ^a
Total, adjusted weight of 0.25 for gastro-intestinal bleeding	0.14 (0.00 to 7.59)	703 (13 to >1000) ^a	-0.37 (-1.24 to 0.50)	271 ^b (81 ^b to 199 ^a)	4.64 (1.92 to 9.19)	22 (11 to 52) ^a
Total, adjusted weight of 0.1 for gastro-intestinal bleeding	0.25 (0.00 to 3.43)	393 (29 to >1000) ^a	-0.27 (-1.15 to 0.60)	365 ^b (87 ^b to 167 ^a)	4.89 (2.13 to 9.38)	20 (11 to 47) ^a

ARR: Absolute risk reduction (in %); CI: Confidence interval; ^aNNT: Number needed to treat; ^bNNH: Number needed to harm. Risks were estimated based on the cumulative incidence function, accounting for competing risks.

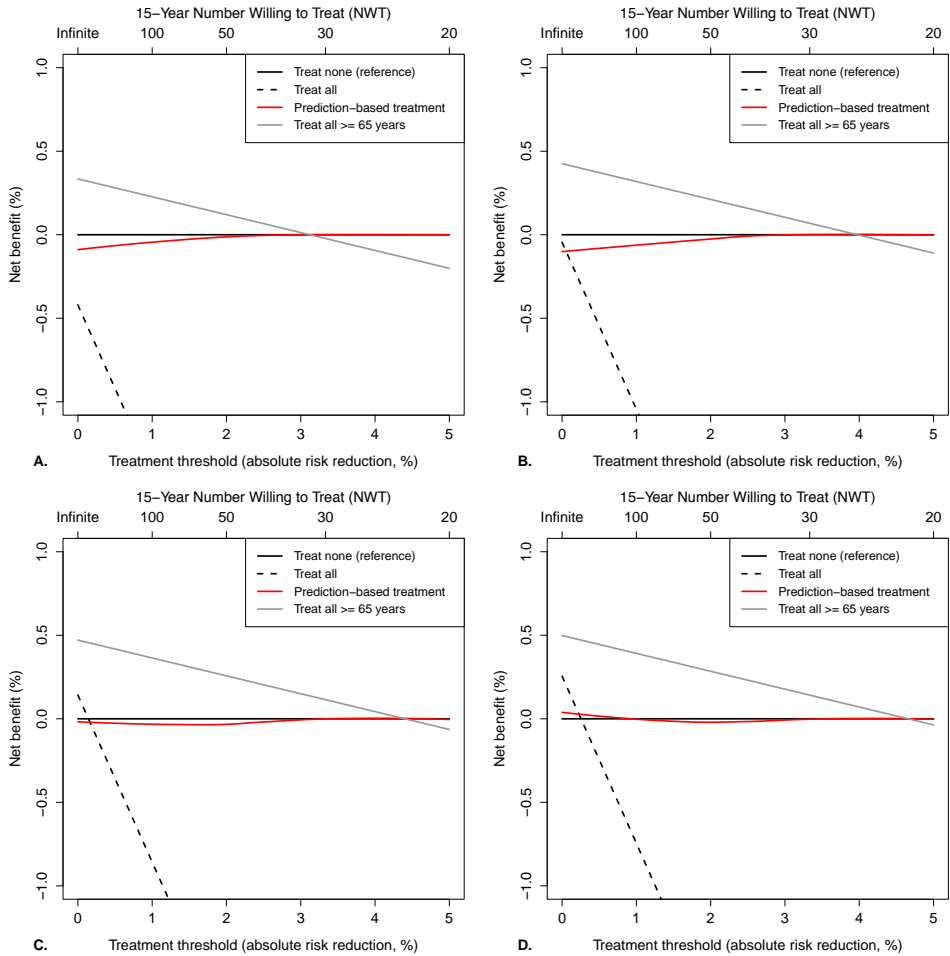


Figure 3. Decision curves for different aspirin treatment strategies, with different weights applied to major gastrointestinal bleeding: A. No weight (one bleeding is equal to one cardiovascular event or cancer diagnosis); B. Weight of 0.5 (two bleedings are equal to one cardiovascular event or cancer diagnosis); C. Weight of 0.25 (four bleedings are equal to one cardiovascular event or cancer diagnosis); D. Weight of 0.1 (ten bleedings are equal to one cardiovascular event or cancer diagnosis). Reading the net benefit plot starts with choosing a treatment threshold, that is the absolute risk reduction (ARR) at which one would opt for treatment, or number-willing-to-treat (NWT). A NWT of 30 implies that one is willing to treat 30 women to prevent at least 1 event. Since major gastrointestinal bleeding is already incorporated in the total outcome, the treatment threshold is mainly chosen depending on how important one would deem less serious complications, inconvenience of taking pills and costs. Positive net benefit means that the treatment strategy led to a more favourable trade-off between benefits (observed decrease in event rate) and harms (the proportion of patients receiving treatment weighted by the reciprocal of the treatment threshold). For example, when using a weight of 0.25 for bleeding (panel C) and a NWT of 30 (treatment of all women with predicted risk reduction of 3.3% or more, i.e. a threshold of 3.3%), treating only women ≥ 65 years yields a positive net benefit of observed reduction in event rate – (proportion receiving treatment * treatment threshold) = $0.03748 - (0.11 * 0.033) = 0.12\%$ and would be the optimal treatment strategy, whereas prediction-based treatment gives a net benefit of zero (predicted ARR are below the treatment threshold for all women, so equal to treating none) and treating all worsens clinical outcome (negative net benefit).

DISCUSSION

In the present study, data of the WHS were used to develop models for treatment effect prediction of alternate-day aspirin on the combination of CVD, cancer and major gastrointestinal bleeding in initially healthy women. Although aspirin was associated with a modestly decreased 15-year risk of CVD and colorectal cancer, aspirin treatment resulted in small benefit or even harm in the majority of women if gastrointestinal bleeding were also taken into account. Age was the most important determinant for benefit of aspirin treatment; this was also reflected by the observation that treating only women of ≥ 65 years of age resulted in a higher net benefit with regard to the combined outcomes compared to other treatment strategies, including prediction-based treatment.

Recent findings that both daily and alternate-day aspirin can reduce cancer risk, particularly for colorectal cancer, have reignited the debate on aspirin in primary prevention. Given that aspirin only modestly lowers cardiovascular risk, while increasing the risk of major gastrointestinal bleeding^{10,25}, the benefits for cancer could tip the balance in favor of aspirin in primary prevention. Moreover, it is important to correctly identify those for whom these benefits of aspirin prophylaxis outweigh the harms and vice versa. Our results indicate that selectively treating women of ≥ 65 years of age may yield the most favourable clinical outcome, given that the harms (i.e. minor adverse effects, inconvenience and costs) of treating 32 (or fewer, if one would consider CVD or cancer to be more important than major gastrointestinal bleeding) women with aspirin during 15 years are considered to be acceptable to prevent one case of CVD or cancer. This finding is notable, especially since older age was associated with higher bleeding risk on aspirin treatment. However, in many women of ≥ 65 years of age the benefits of aspirin with regard to cancer and particularly CVD risk outweigh the increased bleeding risk, especially if one bleeding events are considered to be less important. The finding that the protective effect of aspirin with regard to CVD risk increases with age is in line with results in men from the PHS²⁸.

A previous cost-effectiveness study evaluating the benefits of daily aspirin with regard to CVD, showed that aspirin could yield net benefit in individuals with a high CVD risk²⁹. Although we did observe that the benefits of aspirin were dependent on CVD risk, selective treatment of women with $>10\%$ 10-year CVD risk did not improve overall net benefit and was inferior to selective treatment of women of ≥ 65 years when the effects on cancer and bleeding were also taken into account.

As the predicted net benefit of aspirin treatment for most women is small, less serious side effects (i.e. minor bleeding and peptic ulcers) become important in aspirin treatment decisions. Extrapolating the combined incidence rates of minor gastrointestinal bleeding and peptic ulcers during the trial period results in a 15-year ARR of -3.4% . This means that for every 29 women using alternate day aspirin during 15 years, one experiences a minor gastrointestinal bleeding or peptic ulcer.

Treatment based on predictions from multivariable models resulted in lower net benefit than treating women of ≥ 65 years of age. This is possibly due to the usage of multiple models, which might increase the probability of misclassification. In particular the prediction

model for non-colorectal cancer showed a slightly unsatisfactory performance. This outcome comprises a heterogeneous group of cancers, which might have led to the introduction of noise by some of the predictors other than age. This unexpected finding emphasises the importance of evaluating different treatment strategies based on their clinical benefit with regard to all relevant outcomes (e.g. by means of decision curve analysis). In the sensitivity analysis, no important changes in treatment effect predictions were observed, indicating that the results are robust.

Some study limitations need to be considered. First, the participants of the WHS are generally at low risk due to selection criteria (e.g. all female health professionals). This might limit extrapolation of the results to the general population. Secondly, the present analyses only included first events, meaning that for example when a participant experienced both CVD and major gastrointestinal bleeding during the study, only the first event was used. In our view, however, this is similar to clinical practice, where, after non-fatal CVD, bleeding or cancer diagnosis the changes in one's medical condition usually call for a new aspirin treatment decision moment. Thirdly, we presented results with differing weights for major gastrointestinal bleeding, because some might consider bleeding events to be less important than CVD or cancer, but, of course, any weight would be arbitrary. However, if the 15-year NWT would be 32 or higher, the weight for bleeding is irrelevant, as for any lower NWT selective treatment of women ≥ 65 years of age would be the optimal treatment strategy. Lastly, our results may not apply for daily aspirin as the effects on cancer risk occur earlier than those on alternate-day low-dose aspirin use^{1,3,6}.

Whether aspirin prophylaxis could indeed be beneficial in the elderly is currently being evaluated in a randomised trial (NCT01038583). Meanwhile, simultaneous evaluation of absolute treatment effects on all relevant outcomes on an individual patient level such as presented in this study, rather than evaluating each outcome at a time on a group level, could provide a sensible approach to determine the value of aspirin in primary prevention.

CONCLUSIONS

Alternate day use of low-dose aspirin for primary prevention is ineffective or harmful in the majority of women with regard to the combined risk of CVD, cancer and major gastrointestinal bleeding. Age is the most important determinant of aspirin treatment effect and the protective effects of aspirin with regard to CVD increased with age. Although the excess risk of major gastrointestinal bleeding by aspirin is higher in women of ≥ 65 years of age, selective treatment of this group is may improve net benefit.

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APPENDIX 1

DETAILED DESCRIPTION OF METHODS

Design overview

The WHS was a randomized trial evaluating the effect of 100mg of aspirin on alternate days compared with placebo for primary prevention of CVD and cancer in 39,876 women of 45 years of age or older, without a history of cardiovascular disease or cancer. Detailed methods and outcomes have been described previously¹⁻⁴. Written informed consent was obtained from all participants and the trial was approved by the Institutional Review Board of Brigham and Women's Hospital and was monitored by an external data and safety monitoring board. Endpoints were ascertained using yearly questionnaires and were confirmed using medical records. All relevant information was reviewed by an endpoints committee comprising physicians blinded to treatment allocation^{1,2}. After the end of randomized treatment on 31 March 2004, with an average 10 years of follow-up, participants were invited for further observational follow-up⁴. Of the survivors 33,682 (88.6%) women agreed to continue participation. During the posttrial follow-up, use of aspirin was allowed for women from both study arms. The posttrial use of aspirin for at least three days per month was higher in the randomized aspirin group (46%) compared to the placebo group (43%). Women who used nonstudy aspirin during the posttrial follow-up used aspirin for a median of three years (IQR: 2-5 years)⁴. Information on outcomes was collected and confirmed in a similar manner as during the trial period. End point review is complete for 95% of reported cancer cases, 95% of myocardial infarctions, and 94% of strokes. The confirmation rate among participants with records is 82% for cancer, 61% for myocardial infarction, and 68% for stroke. For the present study, only events confirmed by medical records and deaths with confirmed cause were used. Reports of gastrointestinal bleeding were collected intermittently during posttrial follow-up and were not confirmed⁴. The present analyses include end points accrued and confirmed through 14 March 2012, using data of participants who provided an adequate baseline plasma sample (n=27,939).

Model development

Data of women who provided a baseline plasma sample (n=27,939) were used for model development. For the 10-year predictions, endpoints that occurred during the trial period were used. In order to capture any delayed effects of aspirin on cancer risk^{4,5}, the cancer outcomes were also modeled using cases ascertained during the entire follow-up, for prediction of 15-year treatment effect. Since the effects of aspirin on CVD and bleeding seem to be more immediate^{4,6} and the randomized aspirin intervention stopped after 31 March 2004, modeling these outcomes using posttrial data would likely lead to underestimation of the treatment effect. Hence, 15-year predictions for CVD and bleeding were obtained by extrapolating the 10-year risk estimates under the assumption of

exponential risk over time, to mimic the effects of taking aspirin for a duration of 15-years. As the CVD endpoint included all strokes, hemorrhagic strokes were not evaluated separately.

To minimize over-fitting, predictors for each outcome were selected based on existing risk scores and/or literature⁷⁻¹¹. Only predictors that were deemed to be easily available in clinical practice were selected. As a result, the following predictors, besides aspirin treatment, were used for major cardiovascular events (CVD): age, current smoking, body mass index (BMI), systolic blood pressure (SBP), use of blood pressure lowering medication, total cholesterol, high density lipoprotein cholesterol (HDLc), high sensitivity C-reactive protein (hs-CRP), family history of premature coronary heart disease (CHD) and hemoglobin A1c (HbA1c) if diabetic; for colorectal cancer: age, ever smoking, BMI, height, diabetes mellitus, alcohol use (no. of drinks per day), menopausal status, hormone replacement therapy use, family history of colorectal cancer; for non-colorectal cancer: age, ever smoking, BMI, height, diabetes mellitus, alcohol use, menopausal status, hormone replacement therapy use, family history of breast, colorectal, or ovarian cancer; for major bleeding events: age, current smoking, BMI, alcohol use, diabetes mellitus, history of dyspepsia.

The relative treatment effect of aspirin was assumed constant in the main analysis. Findings of effect modification by any risk factors are inconsistent in previous studies^{1, 2, 12-14}, although significant effect modification was found by age and smoking for CVD in the WHS². To evaluate these potential relative subgroup effects, sensitivity analyses were performed in which treatment interactions with age, smoking status and BMI were considered. These interactions terms were chosen based on previous findings of interaction^{1, 2, 15} and/or strong pathophysiological evidence^{16, 17}. To avoid including non-relevant treatment interactions, estimation of model coefficients with implicit variable selection was done using component-wise likelihood-based boosting¹⁸. Aspirin use was included as an mandatory (unpenalized) covariable, whereas the other candidate predictors and treatment interactions were subjected to penalization in penalized partial likelihood estimation. The optimal number of boosting steps was determined by 10-fold cross-validation¹⁹.

Similar to previous analysis of the WHS^{1, 4}, no effect of aspirin on non-colorectal cancer was observed in the present competing risks analysis (HR 1.02, 95% CI 0.95-1.09). Since the incidence of non-colorectal cancer is high compared to the other competing outcomes, even a small non-significant coefficient could potentially have considerable effects on the overall treatment effect predictions. To evaluate these effects and to test the robustness of the results, sensitivity analysis were performed in which the treatment effect of aspirin on non-colorectal cancer was assumed null. Accordingly, the competing risks endpoint was adjusted in these analyses.

One or more covariable data were missing in 865 (3.1%) participants and these were singly imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package)²⁰: family history of premature CHD (n=464), SBP (n=292), HbA1c (n=140), hormone replacement therapy use (n=55), menopausal status (n=51), smoking status (n=36), BMI (n=23), blood pressure lowering medication use (n=18), diabetes mellitus (n=15), total cholesterol (n=1), HDLc (n=1), alcohol use (n=6), family history of cancer

(n=865) and height (n=18). To limit the effect of outliers, continuous predictors were truncated at the 1st and 99th percentile. Continuous predictors that were not linearly associated to the outcome were transformed to optimize model fit²¹. Accordingly, HDLc, total cholesterol, systolic blood pressure and hsCRP were log-transformed.

Model validation

An estimate of the optimism in the calibration slope was obtained for all models by repeating the complete modeling process in 500 bootstrap samples. The optimism was 0.9% for the CVD model, 9.7% for the 10-year colorectal cancer model, 7.7% for the 15-year colorectal cancer model, 4.1% for the 10-year non-colorectal cancer model, 3.2% for the 15-year non-colorectal cancer model and 4.9% for the bleeding model. Subsequently, the obtained uniform shrinkage factors were applied to the models to adjust for overfitting²¹. The proportional subdistribution hazards assumptions were assessed graphically by plotting the scaled Schoenfeld residuals against failure time and formally by a Wald test of the interaction term of a specific covariable with the logarithm of time. Some non-proportionality was observed for age and family history of cancer in the 15-year model for non-colorectal cancer (p-values: <0.001 and 0.039, respectively). In addition, the proportionality assumption appeared to be violated for history of dyspepsia in the gastro-intestinal bleeding model (p-value: 0.044). Hence, the reported coefficients for these predictors should be interpreted as the weighted average effect over follow-up²².

Discriminatory ability of each model was evaluated using an inverse probability of censoring weighted estimate of the c-index that is adapted for competing risks²³. C-indices were truncated at 10 or 15-year and corrected for optimism by repeating the complete modeling process in 500 bootstrap samples. Calibration was assessed graphically using calibration plots.

Net benefit assessment

To evaluate the clinical value of prediction-based treatment with aspirin in a primary prevention setting, a decision analytic approach as proposed by Vickers et al.²⁴ was used. This method focuses on the effects of (changes in) treatment decisions that result from a treatment strategy (e.g. prediction-based treatment) and is based on calculation of 'net benefit'. Net benefit is defined as the treatment benefit (reduction in event rate) minus the treatment harm (adverse effects, costs, etc.), where the relative weighting of treatment harm is given by a treatment threshold (i.e. ARR at which one would opt for treatment). This treatment threshold is the reciprocal of the maximum acceptable number-needed-to-treat (NNT) to prevent one event or 'number-willing-to-treat' (NWT)^{7, 25}. Consequently, the net benefit of a certain treatment strategy is calculated as the observed decrease in event rate minus the treatment rate multiplied by the treatment threshold. Using the aggregated ARRs of all outcomes for each individual, the clinical value of the combination of the benefit and harm models can be assessed. Net benefit was calculated for the following treatment strategies: (I) treat no one (reference, i.e. net benefit equals zero), (II) treat everyone, (III) treat according to guidelines²⁶, i.e. women ≥ 65 years and (IV) prediction-based treatment.

Since major gastro-intestinal bleeding is already incorporated in the total ARR, the treatment threshold for aspirin is mainly determined by less serious complications, inconvenience of taking pills and costs. As the appropriate treatment threshold (or NWT) is subjective and can vary among different patients and clinicians, the net benefit was calculated for threshold values ranging from 0 to 5% (10-/15-year NWT between infinite and 20). Net benefit for the different treatment strategies was also calculated applying a weight of 0.5, 0.25 and 0.1 for gastro-intestinal bleeding. The net benefit results were presented graphically as decision curves after local polynomial regression fitting.

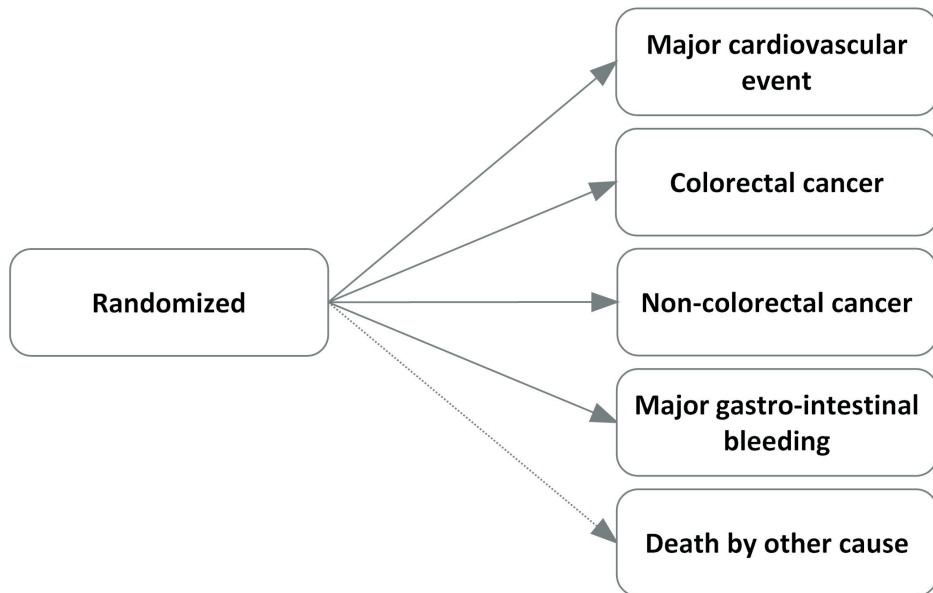
All analyses were performed in R, version 3.0.2 (R Core Team, Vienna, Austria; packages: 'Hmisc', 'pec', 'riskRegression').

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APPENDIX 2



Appendix 2.1. Competing risks framework with number of events during trial period (i.e. from baseline through 31 March 2004, average follow-up of 10.1 years) in women included in the Women's Health Study who provided an adequate baseline plasma sample. Models for the prediction of absolute effects of aspirin on major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding were developed. No separate model was developed for prediction of the effects on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account. Death by other causes was taken into account as competing risks outcome when modelling the other outcomes, because not taking competing risks into account may lead to bias in predictions of absolute risks.

Appendix 2.2. Models for prediction of 10-year absolute risk reduction with aspirin treatment

Predicted 10-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.

Total risk on aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.

Model for prediction of 10-year major cardiovascular event risk

$(1 - \exp(- (0.01068 * \exp(A - 20.51836)))) * 100\%$, where

$A = 0.07750 * \text{age (years)} + 0.91719 [\text{if current smoker}] - 0.02174 * \text{body mass index (kg/m}^2) + 3.27143 * \text{natural logarithm(systolic blood pressure, mmHg)} + 0.25540 [\text{if using blood pressure lowering medication}] + 0.28204 [\text{if family history of premature myocardial infarction}] + 0.83017 * \text{natural logarithm(total cholesterol, mg/dL)} - 0.90235 * \text{natural logarithm(high-density lipoprotein cholesterol, mg/dL)} + 0.11419 * \text{natural logarithm(high-sensitivity C-reactive protein, mg/L)} + 0.17444 * \text{hemoglobin A1c (\%)} [\text{if diabetic}] - 0.09592 [\text{if using aspirin}]$

Model for prediction of 10-year colorectal cancer risk

$(1 - \exp(- (0.00287 * \exp(B - 4.854)))) * 100\%$, where

$B = 0.06907 * \text{age (years)} + 0.15647 [\text{if ever smoker}] + 0.03173 * \text{body mass index (kg/m}^2) + 0.00180 * \text{height (inches)} - 0.01487 [\text{if diabetic}] + 0.03258 * \text{no. of alcoholic drinks per day} + 0.28102 [\text{if peri- / postmenopausal}] - 0.26464 [\text{if ever used hormone replacement therapy}] + 0.12076 [\text{if family history of colorectal cancer}] - 0.05372 [\text{if using aspirin}]$

Model for prediction of 10-year non-colorectal cancer risk

$(1 - \exp(- (0.05554 * \exp(C - 3.40691)))) * 100\%$, where

$C = 0.04287 * \text{age (years)} + 0.14222 [\text{if ever smoker}] + 0.00125 * \text{body mass index (kg/m}^2) + 0.01469 * \text{height (inches)} - 0.14474 [\text{if diabetic}] + 0.07571 * \text{no. of alcoholic drinks per day} - 0.14239 [\text{if peri- / postmenopausal}] + 0.04985 [\text{if ever used hormone replacement therapy}] + 0.00181 [\text{if family history of cancer}] + 0.046578 [\text{if using aspirin}]$

Model for prediction of 10-year major gastro-intestinal bleeding risk

$(1 - \exp(- (0.00742 * \exp(D - 4.53537)))) * 100\%$, where

$D = 0.06209 * \text{age (years)} + 0.22339 [\text{if current smoker}] + 0.03316 * \text{body mass index (kg/m}^2) + 0.26552 [\text{if diabetic}] + 0.00652 * \text{no. of alcoholic drinks per day} + 0.21780 [\text{if history of dyspepsia}] + 0.45399 [\text{if using aspirin}]$

Outcomes were modelled in a competing risks framework, mutually accounting for all outcomes as well as death by other causes (*Appendix 2.1*), because not taking competing risks into account may lead to bias in predictions of absolute risks and non-additivity of risks for the individual outcomes^{23,24}. No separate model was developed for prediction of the effects of aspirin on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account.

Appendix 2.3 Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.

Total risk on aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.

Model for prediction of 15-year major cardiovascular event risk

$(1 - \exp(-(0.01602 * \exp(A - 20.51836)))) * 100\%$, where

$A = 0.07750 * \text{age (years)} + 0.91719 [\text{if current smoker}] - 0.02174 * \text{body mass index (kg/m}^2) + 3.27143 * \text{natural logarithm(systolic blood pressure, mmHg)} + 0.25540 [\text{if using blood pressure lowering medication}] + 0.28204 [\text{if family history of premature myocardial infarction}] + 0.83017 * \text{natural logarithm(total cholesterol, mg/dL)} - 0.90235 * \text{natural logarithm(high-density lipoprotein cholesterol, mg/dL)} + 0.11419 * \text{natural logarithm(high-sensitivity C-reactive protein, mg/L)} + 0.17444 * \text{hemoglobin A1c (\%)} [\text{if diabetic}] - 0.09592 [\text{if using aspirin}]$

Model for prediction of 15-year colorectal cancer risk

$(1 - \exp(-(0.00428 * \exp(B - 6.89174)))) * 100\%$, where

$B = 0.05465 * \text{age (years)} + 0.18407 [\text{if ever smoker}] + 0.03713 * \text{body mass index (kg/m}^2) + 0.03973 * \text{height (inches)} - 0.27643 [\text{if diabetic}] + 0.15733 * \text{no. of alcoholic drinks per day} + 0.62717 [\text{if peri-/postmenopausal}] - 0.29949 [\text{if ever used hormone replacement therapy}] + 0.14094 [\text{if family history of colorectal cancer}] - 0.14483 [\text{if using aspirin}]$

Model for prediction of 15-year non-colorectal cancer risk

$(1 - \exp(-(0.09493 * \exp(C - 3.61989)))) * 100\%$, where

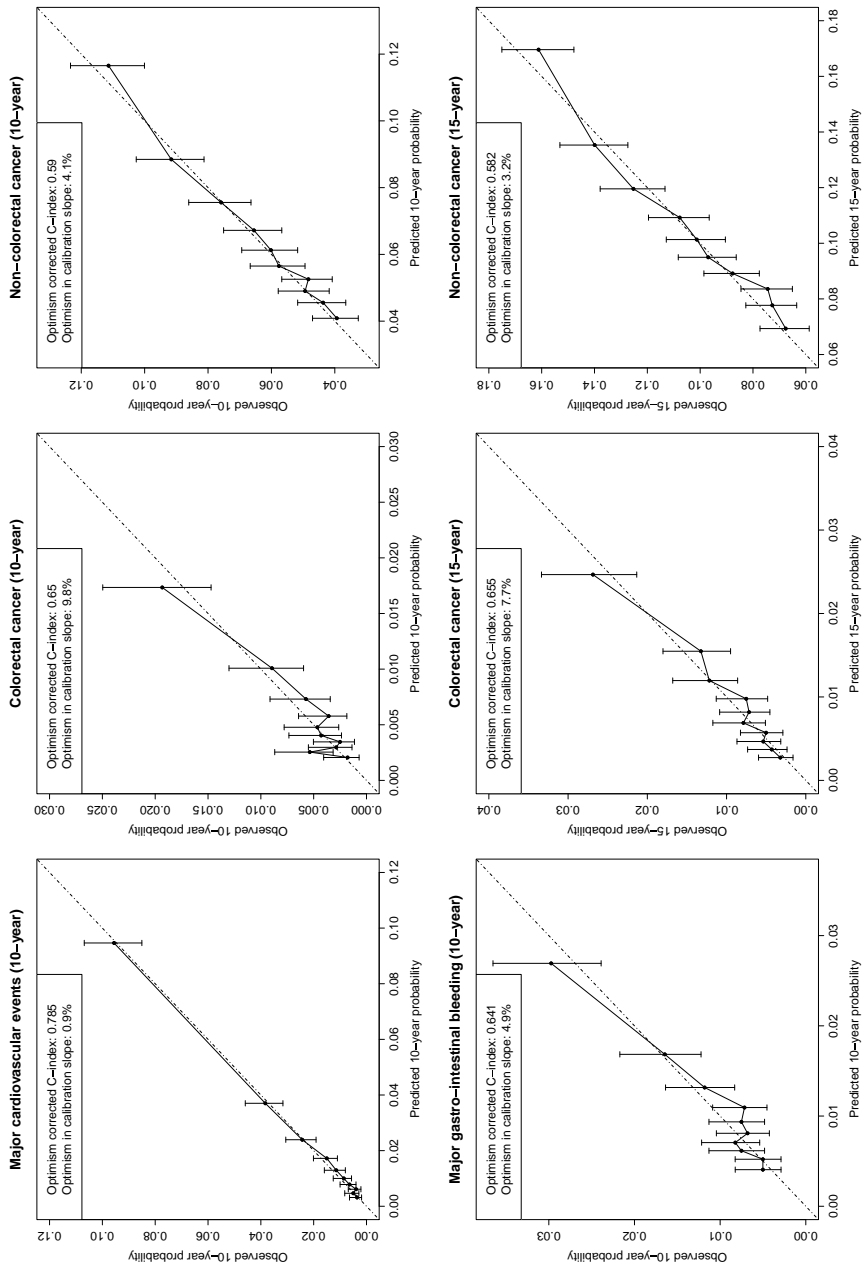
$C = 0.03598 * \text{age (years)} + 0.17283 [\text{if ever smoker}] + 0.00735 * \text{body mass index (kg/m}^2) + 0.02162 * \text{height (inches)} - 0.03080 [\text{if diabetic}] + 0.09586 * \text{no. of alcoholic drinks per day} - 0.13779 [\text{if peri-/postmenopausal}] + 0.06473 [\text{if ever used hormone replacement therapy}] + 0.06062 [\text{if family history of cancer}] + 0.01568 [\text{if using aspirin}]$

Model for prediction of 15-year major gastro-intestinal bleeding risk

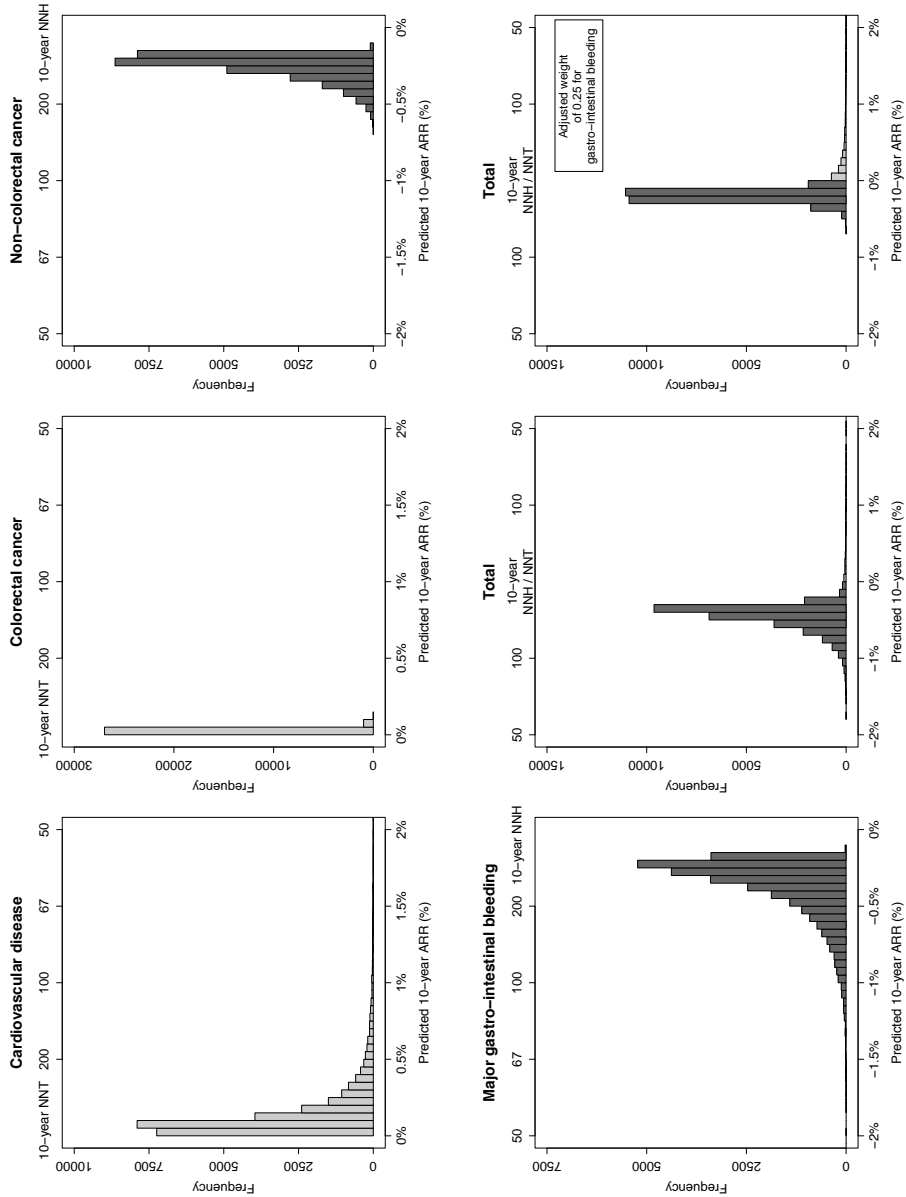
$(1 - \exp(-(0.01113 * \exp(D - 4.53537)))) * 100\%$, where

$D = 0.06209 * \text{age (years)} + 0.22339 [\text{if current smoker}] + 0.03316 * \text{body mass index (kg/m}^2) + 0.26552 [\text{if diabetic}] + 0.00652 * \text{no. of alcoholic drinks per day} + 0.21780 [\text{if history of dyspepsia}] + 0.45399 [\text{if using aspirin}]$

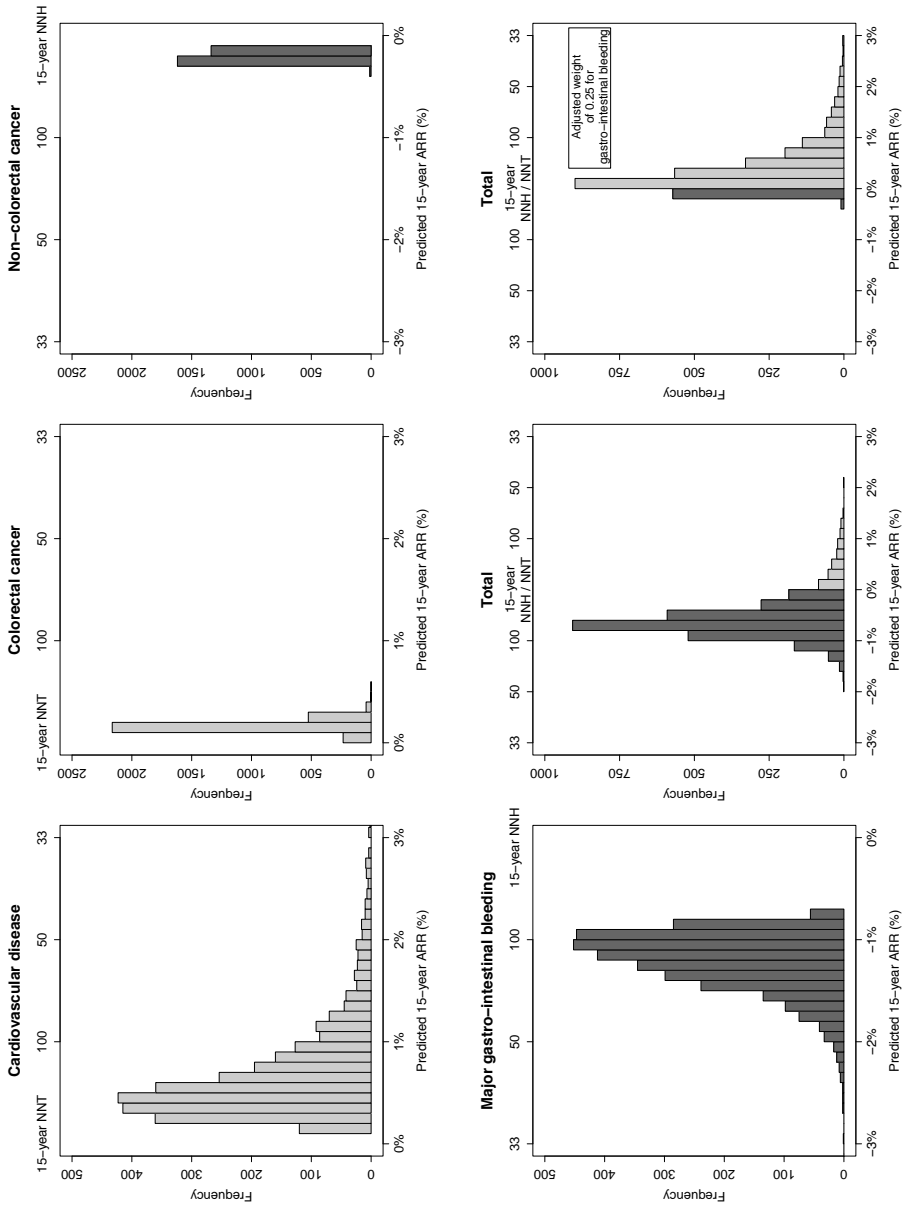
Outcomes were modelled in a competing risks framework, mutually accounting for all outcomes as well as death by other causes (*Appendix 2.1*), because not taking competing risks into account may lead to bias in predictions of absolute risks and non-additivity of risks for the individual outcomes^{23 24}. No separate model was developed for prediction of the effects of aspirin on death by other causes, since no effects of aspirin on this outcome was expected, given that all relevant outcomes (major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding) are already taken into account.



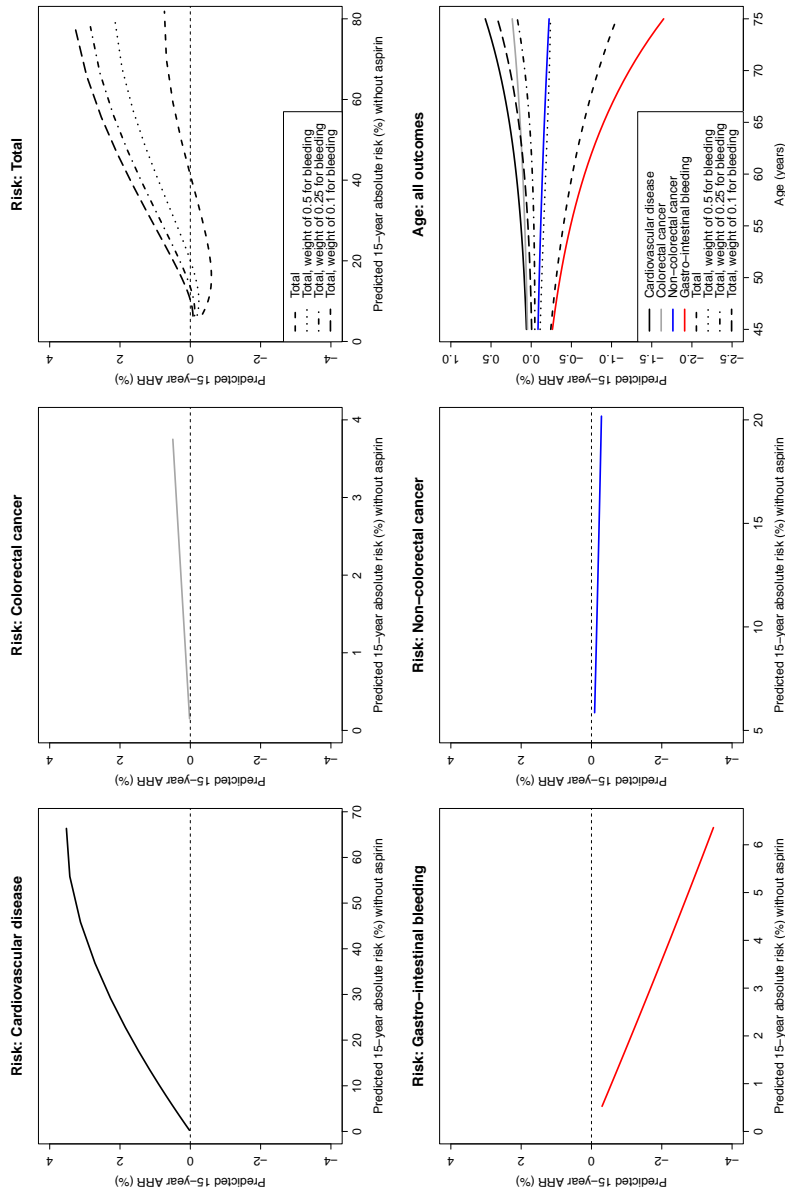
Appendix 2.4. Calibration plots. Axis scales differ between plots. Plots were created with R-code adjusted from: N.P. Bleda. Interval-censored semi-competing risks data : a novel approach for modelling bladder cancer. Thesis, Universitat Politècnica de Catalunya, Barcelona, June 2010.



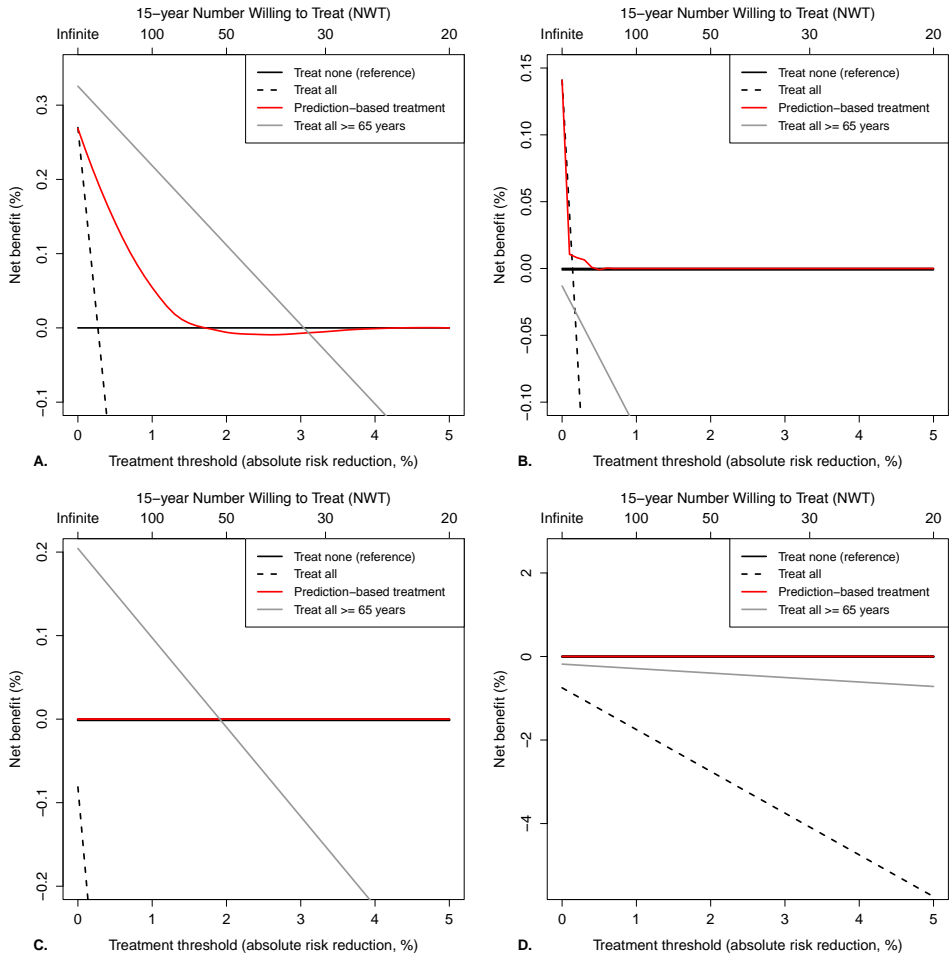
Appendix 2.5. Distribution of predicted 10-year absolute risk reduction for major cardiovascular events, colorectal cancer and major gastro-intestinal bleeding with aspirin treatment in participants of the Women’s Health Study. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.



Appendix 2.6. Distribution of predicted 15-year absolute risk reduction for major cardiovascular events, colorectal cancer, non-colorectal cancer and major gastro-intestinal bleeding with aspirin treatment in participants of the Women’s Health Study of 65 years and older. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.



Appendix 2.7. Effect of baseline risk and age on predicted 15-year absolute risk reduction. ARR: absolute risk reduction. ARR in plot for age apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m² and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2.0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy) with alternating age.



Appendix 2.8. Decision curves for different aspirin treatment strategies for the individual outcomes: A. Major cardiovascular events ; B. Colorectal cancer ; C. Non-colorectal cancer ; D. Major gastro-intestinal bleeding. Reading the net benefit plot starts with choosing a treatment threshold, that is the absolute risk reduction (ARR) at which one would opt for treatment, or number-willing-to-treat (NWT). A NWT of 30 implies that one is willing to treat 30 women to prevent at least 1 event. Positive net benefit means that the treatment strategy led to a more favourable trade-off between benefits (observed decrease in event rate) and harms (the proportion of patients receiving treatment weighted by the reciprocal of the treatment threshold). Since for non-colorectal cancer and major gastro-intestinal bleeding all patients had a negative predicted absolute risk prediction (meaning that their risk of those outcomes increases with aspirin), none will selected for treatment over the full range of threshold values when applying prediction-based treatment and the net benefit for this treatment strategy is equal to zero.

APPENDIX 3

SUMMARY OF RESULTS

Using the models with treatment interactions, the protective effect of aspirin for CVD increased with age, whereas current smoking attenuated the benefits of aspirin (*Appendix 3A*). BMI and ever smoking were inversely related to treatment effect on colorectal cancer. The HR of aspirin for non-colorectal cancer risk slightly decreased with higher age and was lower for ever smokers. Current smoking increased the risk of major bleeding when using aspirin. Compared to the main results, the predicted ARR from the models with treatment interactions were more widely distributed, particularly for non-colorectal cancer, as aspirin was associated with benefit in 48% of the study population and caused harm in the other 52%. If a weight was applied for gastro-intestinal bleeding, the models with treatment interactions yielded a higher net benefit compared to the models without interaction, but treating only women ≥ 65 years was still the most favourable treatment strategy.

When the effect of aspirin on non-colorectal cancer was assumed null in sensitivity analysis, the total ARR tended to be slightly higher (*Appendix 3B*). When a weight of 0.25 was applied for bleeding, 3.1% of the women had a predicted 15-year ARR of $>1\%$ (iNNT:100) versus 1.7% in the main analysis. Although some improvement in the net benefit of prediction-based treatment was observed, treating only women ≥ 65 years was still superior if the 15-year NWT was >60 , whereas treating none was the most favorable treatment strategy for lower ranges of NWT.

APPENDIX 3A

Appendix 3A (1). Models for prediction of 15-year absolute risk reduction with aspirin treatment

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.

Total risk on aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.

Model for prediction of 15-year major cardiovascular event risk

$(1 - \exp(- (0.01597 * \exp(A - 20.78737)))) * 100\%$, where

$A = 0.08225 * \text{age (years)} - 0.00883 * \text{age (years) [if using aspirin]} + 0.75154 \text{ [if current smoker]} + 0.37331 \text{ [if current smoker and using aspirin]} - 0.02022 * \text{body mass index (kg/m}^2\text{)} + 0.00063 * \text{body mass index (kg/m}^2\text{) [if using aspirin]} + 3.28886 * \text{natural logarithm(systolic blood pressure, mmHg)} + 0.25407 \text{ [if using blood pressure lowering medication]} + 0.82587 * \text{natural logarithm(total cholesterol, mg/dL)} - 0.87803 * \text{natural logarithm(high-density lipoprotein cholesterol, mg/dL)} + 0.10963 * \text{natural logarithm(high-sensitivity C-reactive protein, mg/L)} + 0.17672 * \text{hemoglobin A1c (\%)} \text{ [if diabetic]} + 0.27403 \text{ [if family history of premature myocardial infarction]} + 0.33118 \text{ [if using aspirin]}$

Model for prediction of 15-year colorectal cancer risk

$(1 - \exp(- (0.00674 * \exp(B - 6.96952)))) * 100\%$, where

$B = 0.05783 * \text{age (years)} + 0.10755 \text{ [if ever smoker]} + 0.15955 \text{ [if ever smoker and using aspirin]} + 0.03632 * \text{height (inches)} + 0.03483 * \text{body mass index (kg/m}^2\text{)} + 0.00930 * \text{body mass index (kg/m}^2\text{) [if using aspirin]} - 0.20511 \text{ [if diabetic]} + 0.15214 * \text{no. of alcoholic drinks per day} + 0.59635 \text{ [if peri- / postmenopausal]} - 0.27149 \text{ [if ever used hormone replacement therapy]} + 0.11092 \text{ [if family history of colorectal cancer]} - 0.47292 \text{ [if using aspirin]}$

Model for prediction of 15-year non-colorectal cancer risk

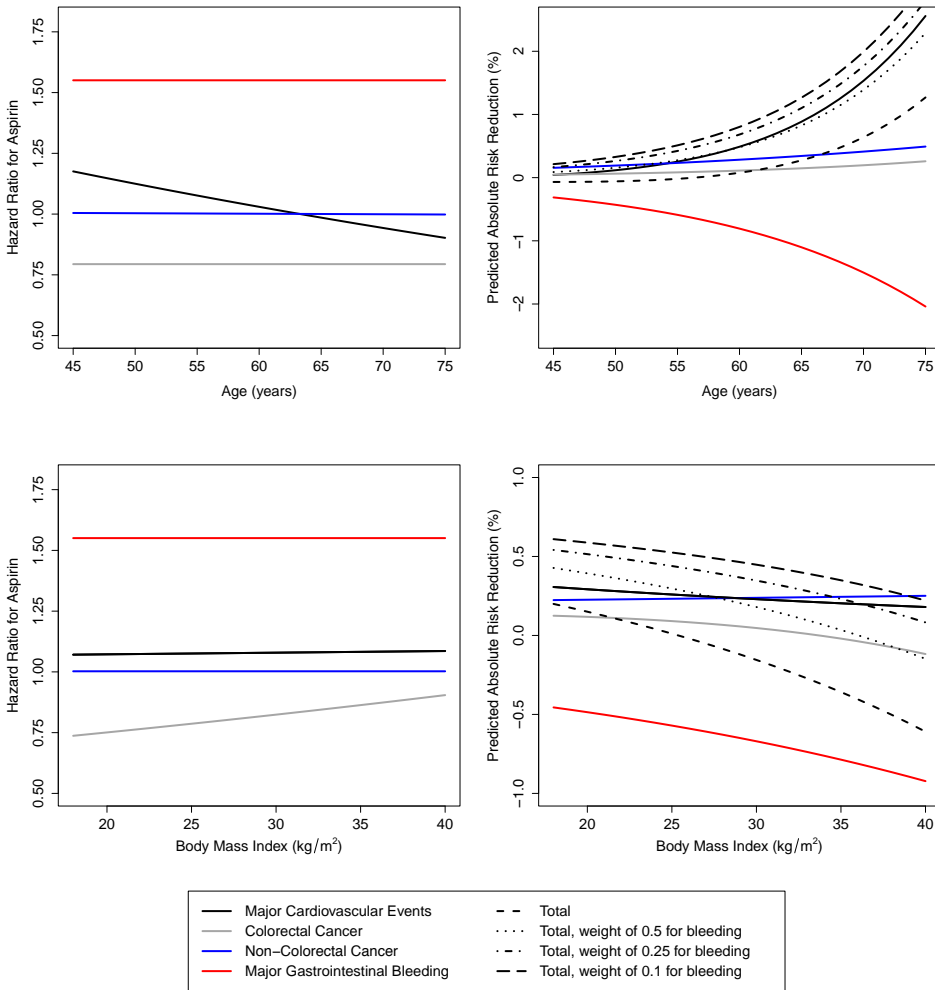
$(1 - \exp(- (0.0677 * \exp(C - 3.46478)))) * 100\%$, where

$C = 0.03481 * \text{age (years)} - 0.00021 * \text{age (years) [if using aspirin]} + 0.21150 \text{ [if ever smoker]} - 0.08502 \text{ [if ever smoker and using aspirin]} + 0.02085 * \text{height (inches)} + 0.00585 * \text{body mass index (kg/m}^2\text{)} - 0.02323 \text{ [if diabetic]} + 0.09414 * \text{no. of alcoholic drinks per day} - 0.10978 \text{ [if peri- / postmenopausal]} + 0.0535 \text{ [if ever used hormone replacement therapy]} + 0.05403 \text{ [if family history of cancer]} + 0.07276 \text{ [if using aspirin]}$

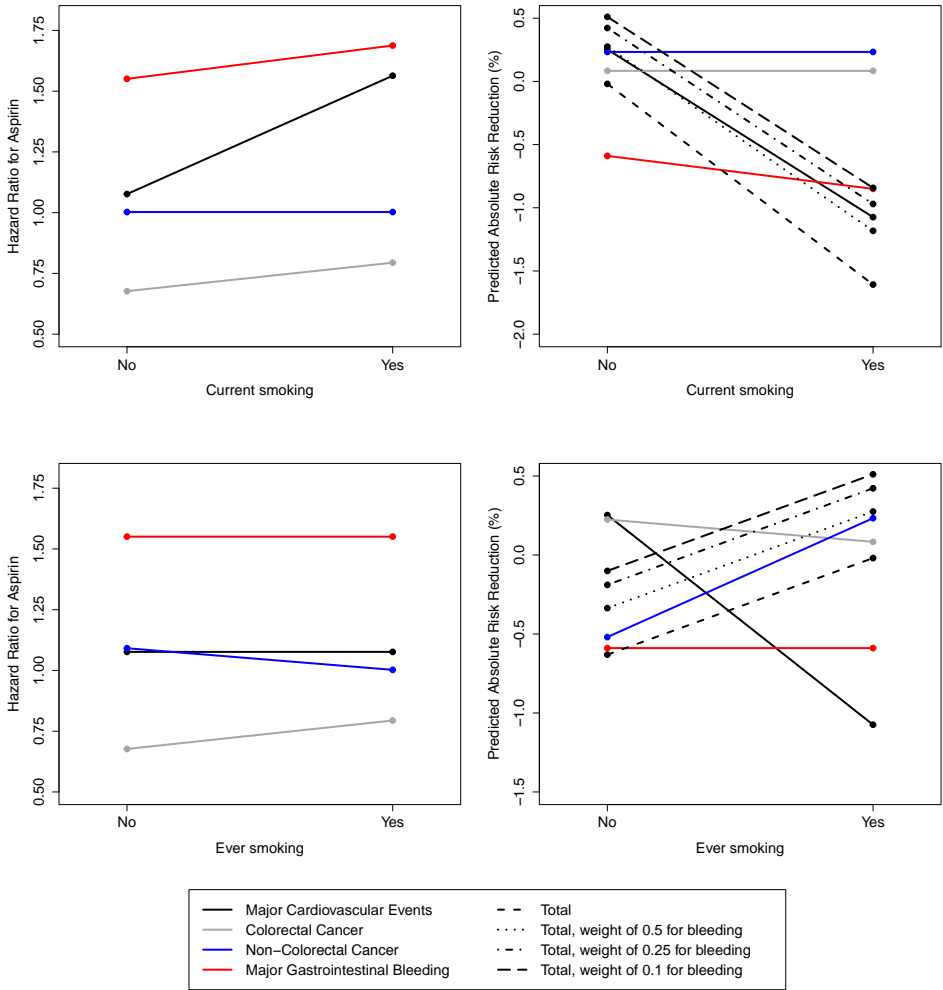
Model for prediction of 15-year major gastro-intestinal bleeding risk

$(1 - \exp(- (0.01094 * \exp(D - 4.38127)))) * 100\%$, where

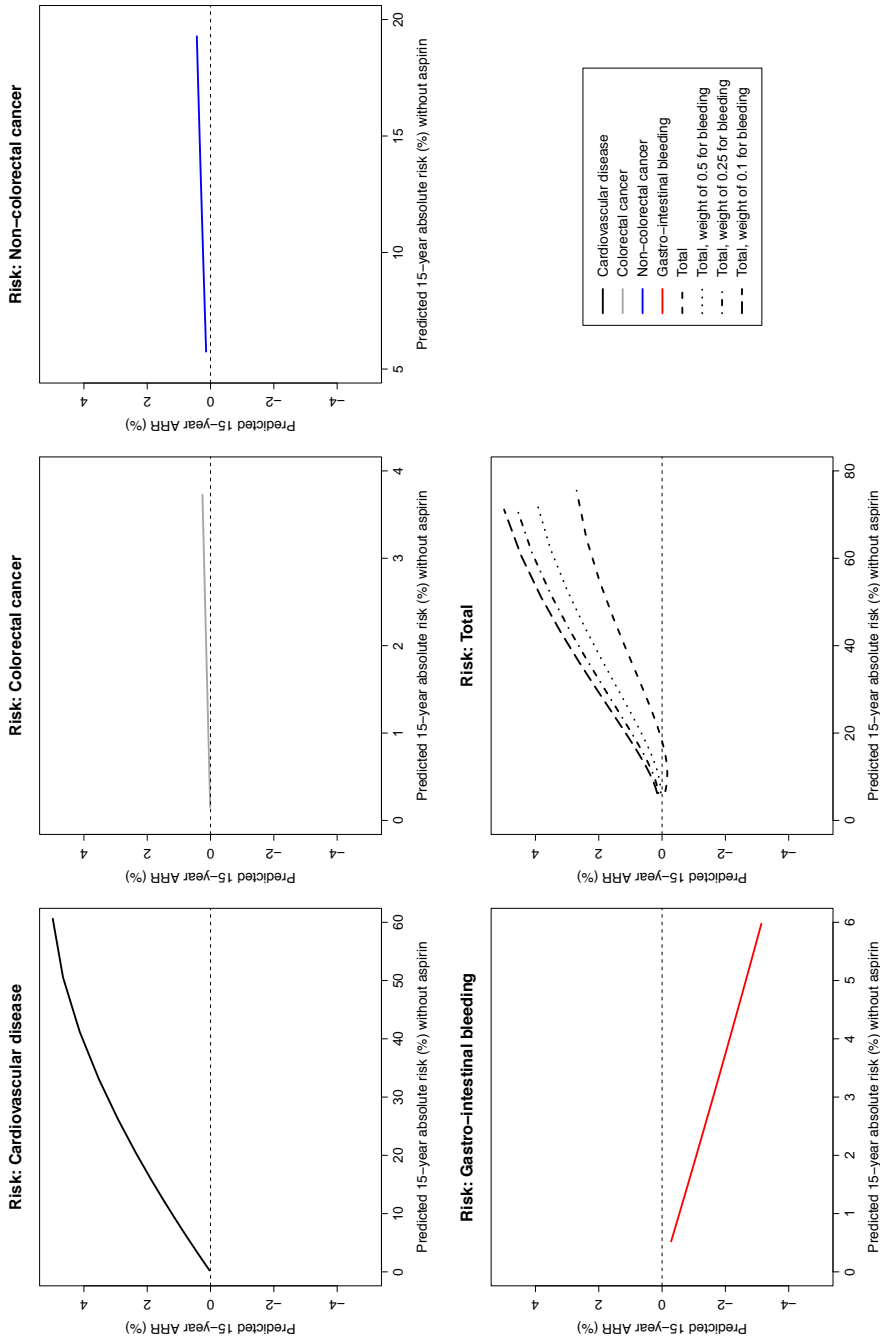
$D = 0.06386 * \text{age (years)} + 0.14899 \text{ [if current smoker]} + 0.08470 \text{ [if current smoker and using aspirin]} + 0.03257 * \text{body mass index (kg/m}^2\text{)} + 0.24747 \text{ [if diabetic]} + 0.19232 \text{ [if history of dyspepsia]} + 0.44374 \text{ [if using aspirin]}$



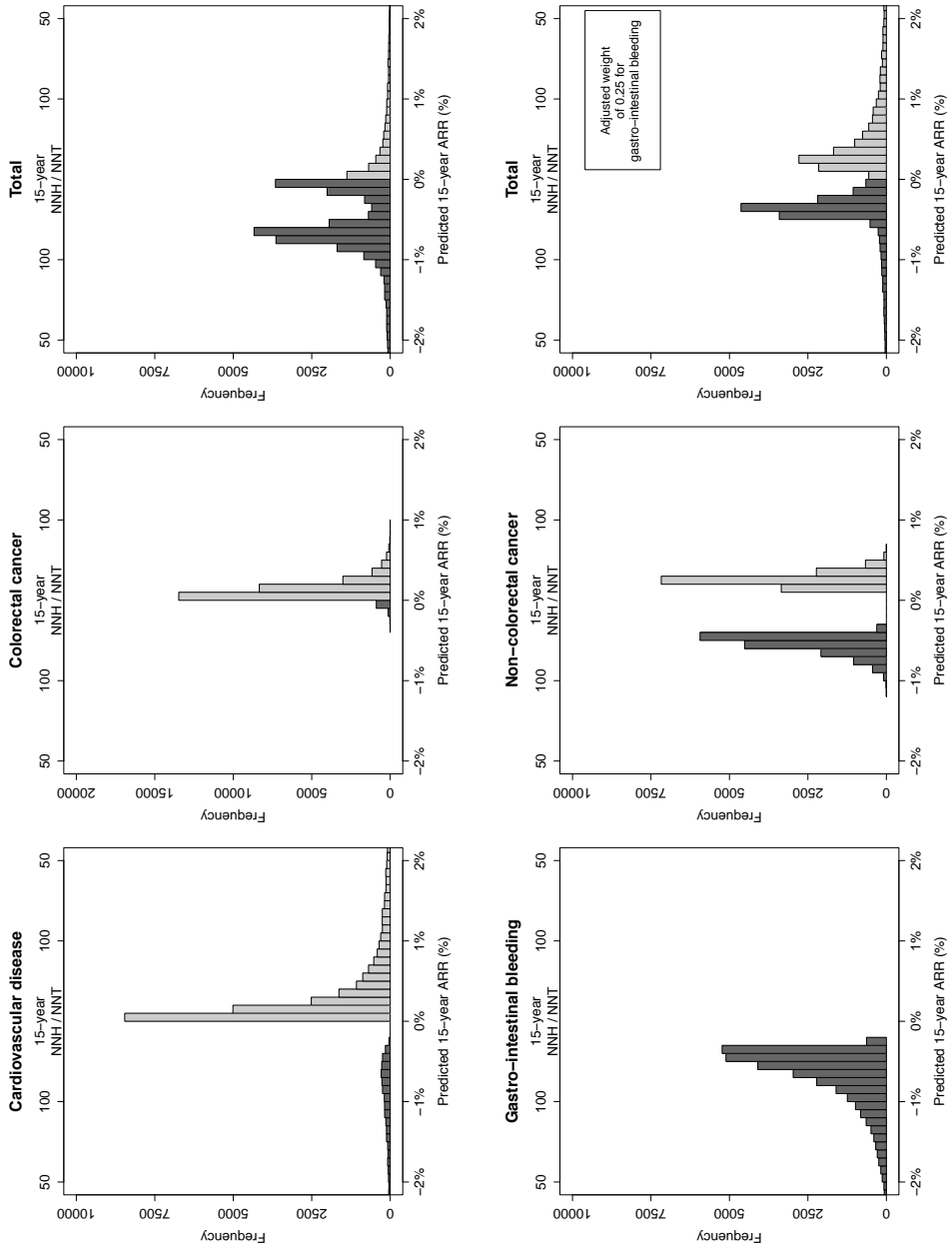
Appendix 3A (2.1). Sensitivity analysis - Effect of treatment interactions with age and body mass index on hazard ratio's and predicted 15-year absolute risk reductions for aspirin. Presented hazard ratio's and absolute risk reductions apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m² and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2.0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy). For the specific plots, all the above characteristics were kept constant with the exception of the characteristic displayed on the x-axis (e.g. for the age-plot, a women with the aforementioned average characteristics with age alternating from 45 to 75 years).



Appendix 3A (2.2). Sensitivity analysis - Effect of treatment interactions with smoking status on hazard ratio's and predicted 15-year absolute risk reductions for aspirin. Presented hazard ratio's and absolute risk reductions apply to an average participant of the Women's Health Study (i.e. a 55-year old postmenopausal woman who never smoked, does not have diabetes, history of dyspepsia or a family no family history of premature myocardial infarction or cancer, has a height of 65 inches, a BMI of 26 kg/m² and a systolic blood pressure of 124 mmHg and does not receive treatment for hypertension, with a serum level of high sensitivity C-reactive protein of 2.0 mg/L, total cholesterol of 212 mg/dL and a HDL-cholesterol of 54 mg/dL, drinks 2 alcoholic beverages per week and has never received hormone replacement therapy). For the specific plots, all the above characteristics were kept constant with the exception of the characteristic displayed on the x-axis (e.g. for the current smoking-plot, a women with the aforementioned average characteristics with current smoking set to no/yes).



Appendix 3A (3). Sensitivity analysis - Effect of baseline risk on predicted 15-year absolute risk reduction for aspirin using models with treatment interactions. ARR: Absolute risk reduction.



Appendix 3A (4). Sensitivity analysis - Distribution of predicted 15-year absolute risk reduction with aspirin treatment in participants of the Women’s Health Study based on models with treatment interactions. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.

APPENDIX 3B**Appendix 3B (1). Models for prediction of 15-year absolute risk reduction with aspirin treatment**

Predicted 15-year absolute risk reduction = Total risk without aspirin treatment – Total risk with aspirin treatment, where

Total risk without aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'FALSE'.

Total risk on aspirin treatment: Total of model risk estimates for all outcomes, when aspirin treatment is set to 'TRUE'.

Model for prediction of 15-year major cardiovascular event risk

$(1 - \exp(- (0.01539 * \exp(A - 19.9348)))) * 100\%$, where

$A = 0.08057 * \text{age (years)} + 0.95481 [\text{if current smoker}] - 0.02471 * \text{body mass index (kg/m}^2) + 3.16178 * \text{natural logarithm(systolic blood pressure, mmHg)} + 0.28377 [\text{if using blood pressure lowering medication}] + 0.30422 [\text{if family history of premature myocardial infarction}] + 0.79060 * \text{natural logarithm(total cholesterol, mg/dL)} - 0.88894 * \text{natural logarithm(high-density lipoprotein cholesterol, mg/dL)} + 0.12118 * \text{natural logarithm(high-sensitivity C-reactive protein, mg/L)} + 0.17274 * \text{hemoglobin A1c (\%)} [\text{if diabetic}] - 0.10389 [\text{if using aspirin}]$

Model for prediction of 15-year colorectal cancer risk

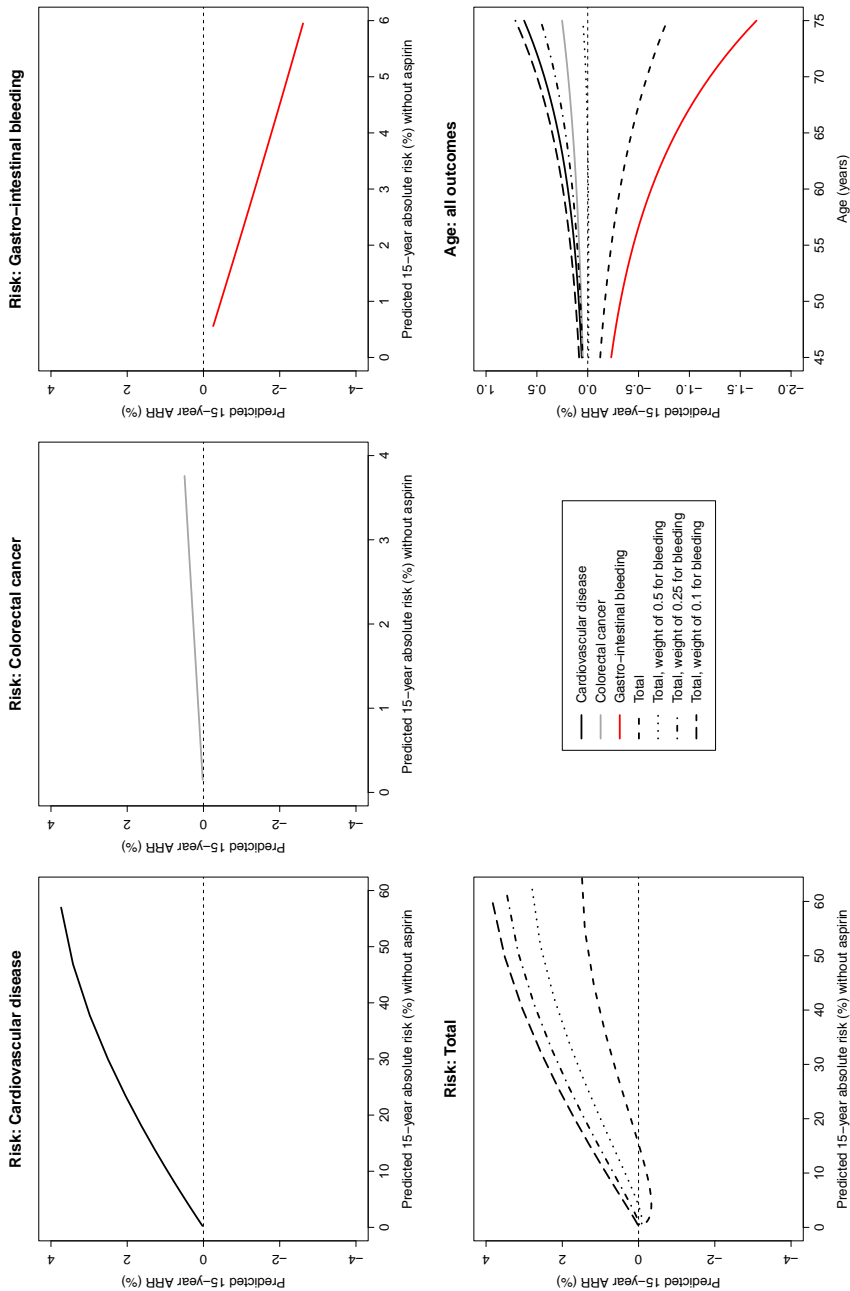
$(1 - \exp(- (0.00454 * \exp(B - 6.95442)))) * 100\%$, where

$B = 0.05519 * \text{age (years)} + 0.18649 [\text{if ever smoker}] + 0.03746 * \text{body mass index (kg/m}^2) + 0.04004 * \text{height (inches)} - 0.27782 [\text{if diabetic}] + 0.15837 * \text{no. of alcoholic drinks per day} + 0.63234 [\text{if peri- / postmenopausal}] - 0.30225 [\text{if ever used hormone replacement therapy}] + 0.14242 [\text{if family history of colorectal cancer}] - 0.14411 [\text{if using aspirin}]$

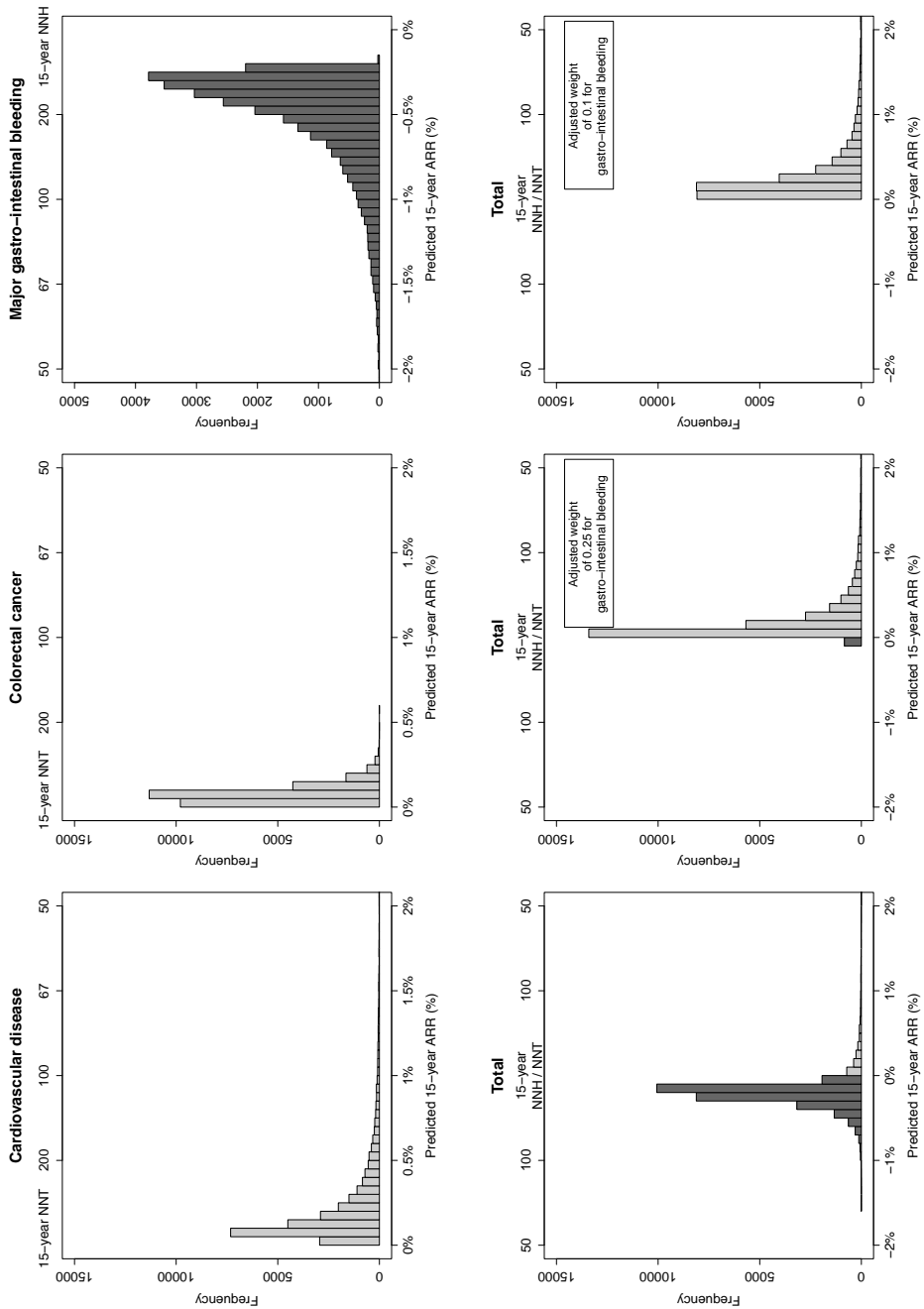
Model for prediction of 15-year major gastro-intestinal bleeding risk

$(1 - \exp(- (0.01238 * \exp(D - 4.70541)))) * 100\%$, where

$D = 0.06713 * \text{age (years)} + 0.31456 [\text{if current smoker}] + 0.03054 * \text{body mass index (kg/m}^2) + 0.32720 [\text{if diabetic}] + 0.01474 * \text{no. of alcoholic drinks per day} + 0.16382 [\text{if history of dyspepsia}] + 0.37788 [\text{if using aspirin}]$



Appendix 3B (2). Sensitivity analysis – Effect of baseline risk and age on predicted 15-year absolute risk reduction using models for prediction of treatment effect of aspirin on major cardiovascular events, colorectal cancer and major gastro-intestinal bleeding, while assuming no effect of aspirin on non-colorectal cancer. ARR: absolute risk reduction. Absolute risk reductions in plot for age apply to an average participant of the Women’s Health Study.



Appendix 3B (3). Sensitivity analysis - Distribution of predicted 15-year absolute risk reduction with aspirin treatment in participants of the Women’s Health Study assuming no effect of aspirin on non-colorectal cancer. ARR: absolute risk reduction ; NNT/NNH: Number needed to treat/harm.

Rob C.M. van Kruijsdijk
Frank L.J. Visseren
Luca Boni
Harry J.M. Groen
Anne-Marie C. Dingemans
Joachim G.J.V. Aerts
Yolanda van der Graaf
Andrea Ardizzoni
Egbert F. Smit

CHAPTER 8

PEMETREXED PLUS CARBOPLATIN VERSUS PEMETREXED
IN PRETREATED PATIENTS WITH ADVANCED
NON-SQUAMOUS NON-SMALL CELL LUNG CANCER:
TREATING THE RIGHT PATIENTS BASED ON
INDIVIDUALIZED TREATMENT EFFECT PREDICTION

Manuscript draft

ABSTRACT

Purpose

To develop and validate a prediction model for estimating absolute treatment effect of pemetrexed plus carboplatin (Pem-Carbo) versus single-agent pemetrexed (Pem) in the second-line treatment of patients with advanced non-squamous non-small cell lung cancer (NSCLC).

Methods

Using data of relapsed patients with advanced non-squamous NSCLC from the NVALT-7 trial, a Weibull model for prediction of gain in median progression-free survival (PFS) by Pem-Carbo was derived based on patient and tumor characteristics that are routinely available in clinical practice. The model was externally validated in the GOIRC 02-2006 trial. The clinical value of using the model for guiding decision-making was evaluated using decision-curve analysis.

Results

A wide distribution of predicted gain in median PFS by Pem-Carbo over Pem was found, with a median of 0.7 months (interquartile range:-0.1 to 1.5 months). Patients who benefited most included women, those with stage IV, high body mass index and/or adenocarcinoma. External validation showed satisfactory calibration and moderate discrimination (C-index: 0.61, 95% confidence interval: 0.56-0.67). Overall, the model adequately identified patients who benefit from Pem-Carbo. This was confirmed by decision curve analysis, as prediction-based treatment led to improvement in net benefit with regard to PFS and overall survival, compared to treating all patients with Pem-Carbo or treating all with Pem.

Conclusions

There is important heterogeneity in the effects on PFS of Pem-Carbo versus Pem in pretreated patients with advanced non-squamous NSCLC. The effects of Pem-Carbo can be estimated based on routinely available clinicopathologic characteristics. The method of individualized treatment effect predictions could be used to guide clinical decision-making to improve clinical outcome and to select patients for randomized trials.

INTRODUCTION

Despite improvement in quality of life and survival by first-line platinum-based chemotherapy, all patients with advanced non-small-cell lung cancer (NSCLC) will eventually experience disease progression. Several regimens have been registered for second-line treatment of advanced NSCLC, including single-agent pemetrexed, docetaxel or erlotinib¹⁻³. The effects on survival of these second-line treatments, however, remain unsatisfactory, as median survival is still only 6 to 8 months. Hence, several strategies have been suggested to improve therapeutic results, including pemetrexed-based combination chemotherapy. Two recent randomized phase II studies, the NVALT-7⁴ and the GOIRC 02-2006⁵, compared single agent pemetrexed (Pem) with pemetrexed plus carboplatin (Pem-Carbo) in patients with relapsed NSCLC. In a pooled analysis of these studies, no significant effect on progression free survival (PFS) or overall survival (OS) was observed (hazard ratio [HR] 0.85, 95%CI, 0.70-1.02 and HR 0.90, 95%CI, 0.74-1.10, respectively)⁵.

Translating group level estimates of these trials to individual patients is challenging, as average measures implicitly consider that all patients have an average risk and the same average response to treatment⁶⁻⁸. Absolute treatment effects, however, can vary substantially among individuals, for example depending on performance score or sex. As such, it is conceivable that some patients benefit from Pem-Carbo compared to Pem, whilst others have no benefit or even experience harm. Individualized prediction of treatment effects provides a comprehensive approach to identify those patients who benefit most from Pem-Carbo, enabling clinicians to make patient-tailored treatment decisions and better weigh treatment benefits against harms⁶⁻¹⁰. Furthermore, such treatment effect predictions could be used to select eligible patients for clinical trials to avoid inclusion of patients who have no benefit or may even experience harm from treatment¹¹.

In the present study, we aimed to develop and validate a model with patient and tumor characteristics, for individualized prediction of the effects of Pem-Carbo versus Pem on PFS in pretreated patients with non-squamous NSCLC, experiencing relapse after first-line platinum-based chemotherapy. For this purpose, data from the NVALT-7 and the GOIRC 02-2006 study^{4,5} were used. To evaluate the potential impact of using treatment effect predictions to guide decisions in clinical practice, we compared the net benefit of this approach to treating all patients with Pem and treating all with Pem-Carbo.

METHODS

Detailed methods and outcomes of the NVALT-7 and GOIRC 02-2006 trials have been published previously^{4,5}. In short, both trials assessed the efficacy and safety of Pem versus Pem-Carbo in pretreated patients with advanced NSCLC. Primary endpoints were PFS and OS. The NVALT-7 study enrolled 240 patients and, after a median follow-up of 14.7 months, time to progression was significantly prolonged by Pem-Carbo (4.2 months) compared to Pem (2.8 months; HR:0.67, 95%CI:0.51-0.89). In the GOIRC 02-2006 study, which enrolled

239 patients and with a median follow-up of 22.2 months, no differences in PFS or OS were observed (3.5 vs. 3.6 months; HR:1.05, 95%CI:0.81-1.36 and 9.2 vs. 8.8 months; HR:0.97, 95%CI:0.73-1.30, respectively).

For the present study, updated data from the NVALT-7 study (median follow-up: 18.6 months, interquartile range [IQR]: 13.5-35.1 months) and GOIRC 02-2006 (median follow-up: 21.5 months, IQR: 19.0-25.4 months) were used. Given that the *European Medicines Agency* no longer recommends Pem for patients with squamous cell NSCLC¹², these patients were excluded from the analyses (n=60 in NVALT-7 and n=29 in GOIRC 02-2006). The primary endpoint was PFS (*i.e.* composite of disease progression and death) and PFS time was defined as the interval between randomization and progression, death or end of follow-up, whichever occurred first.

Model derivation

Using data from the NVALT-7 trial, a parametric Weibull model was derived for prediction of gain in median PFS for individual patients (*i.e.* point in time from which onwards it is more likely that the patient has experienced progression or died than that he/she is alive without progression). PFS was chosen as outcome because this was likely to yield better treatment effect predictions compared to OS, due to greater statistical power. Moreover, the predictors for PFS and OS are likely very similar since disease progression accounted for 92% of the deaths and the interval between progression and death was generally short (median 3.3 months). OS was taken into account when evaluating the clinical benefit of prediction-based treatment. In addition, the limited number of grade 3/4 toxicity cases did not allow reliable individualized estimation of the effects of Pem-Carbo vs. Pem on toxicity risk. As an alternative, group-level estimates of the effects on toxicity were used, so that the benefits of Pem-Carbo could be weighed against the adverse effects in determining the optimal treatment strategy.

To minimize the chance of overfitting, predictors were prespecified based on existing literature^{5,13-18}. Only patient and tumor characteristics that are routinely available in clinical practice were selected as predictor, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index (BMI), tumor stage, response to previous platinum-based chemotherapy, treatment-free interval, leucocyte count and large-cell histology. To evaluate the presence of heterogeneity in treatment effect on a relative scale, multiplicative interaction terms between treatment and predictors were added to the core model. Subsequently, to prevent the inclusion of spurious treatment interaction terms, the treatment interactions were subjected to backward selection based on Akaike's Information Criterion^{19,20}. One or more predictors were missing in 3.3% of NVALT-7 participants and these were imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package), assuming that these values were missing at random, because excluding patients with missing values often leads to bias and loss of statistical power^{20,21}. Continuous predictors were truncated at the 1th and 99th percentile prior to modeling to limit the effect of outliers²⁰. Continuous predictors that were not linearly associated to PFS were transformed to optimize model fit²⁰. The Weibull assumption was

verified by empirical estimation of the survival function²². The optimism in the calibration slope and corresponding shrinkage factor were determined by repeating the full modeling process in 1,000 bootstrap repetitions²⁰.

External validation

The model was externally validated in the GOIRC 02-2006 study. Using the same methods as described above, missing predictors were imputed (in 5.0% of patients) and continuous predictors were truncated. Model coefficients were penalized using a uniform shrinkage factor of 0.77 prior to obtaining predictions²⁰. The model performance in terms of discrimination (i.e. the ability to distinct between patients with and without the outcome) was evaluated using an inverse probability of censoring weighted estimate of the C-index, truncated at the median PFS (3.7 months)²³. Calibration curves, for evaluating how close the predictions were to the observed median PFS, were estimated non-parametrically using the loess-algorithm²⁰.

Treatment effect predictions and net benefit

The model was used to predict the median PFS in months with Pem and with Pem-Carbo for all individual patients in the NVALT-7 and GOIRC 02-2006 studies. The predicted gain in median PFS of Pem-Carbo vs. Pem was subsequently calculated as the difference between these survival estimates. Corresponding 95% CI's and p-values were calculated using the model's variance-covariance matrix.

Besides evaluating the statistical model performance, we assessed the clinical value of treatment decision-making based on predicted treatment effect using decision curve analysis²⁴. This method focuses on the effects of (changes in) treatment decisions that result from a treatment strategy and is based on calculation of net benefit. Calculating net benefit starts with choosing a treatment threshold, which is the smallest gain in median PFS at which a patient and doctor would opt for Pem-Carbo. For example, a threshold of one month gain in PFS implies that at that point the benefits (gain in PFS) and harms (e.g. toxicity) of Pem-Carbo are considered equal. In that case, all patients who have a predicted effect of >1 month gain in PFS would be treated with Pem-Carbo. This threshold is then used in the calculation of net benefit for weighing the observed benefits against the harms of treatment. As such, net benefit is calculated as the observed gain in median PFS minus the treatment rate multiplied by the treatment threshold. For example, with a threshold of 1 month, 40% of the patients with a predicted effect of >1 month and a gain of 2.1 months in median PFS observed in those patients by Pem-Carbo, the net benefit would be $2.1 - 0.4 \times 1 = 1.7$. Positive net benefit indicates that the treatment strategy is superior to treating all with Pem, which serves as reference (net benefit equals zero), whereas negative net benefit indicates a worse clinical outcome. Using the pooled data of NVALT-7 and GOIRC 02-2006, the net benefit with regard to PFS and OS of the following treatment strategies was compared: (I) treat all with Pem, (II) treat all with Pem-Carbo, (III) prediction-based treatment and (IV) prediction-based treatment treating only those with significant ($p < 0.05$) predicted treatment effect. As the appropriate treatment threshold is subjective,

we calculated the net benefit for thresholds ranging from 0 to 5 months gain in median PFS and presented the results graphically as decision curves using the loess-algorithm^{20,24}. The number of extra cases of grade 3/4 toxicity for different treatment thresholds was estimated using the observed increase in toxicity risk in the pooled data.

All analyses were performed in R, version 3.0.2 (R Core Team, Vienna, Austria; packages: 'rms', 'Hmisc', 'pec', 'cmprsk').

RESULTS

The baseline characteristics of the patients included in the analyses are shown in *Table 1*. Patients had a mean age of 61 years, 66% were men, 83% had stage IV (AJCC 6th edition) and 72% had an adenocarcinoma. Overall, the NVALT-7 population included more women, was younger, had a worse performance status, had more large-cell histology, had higher response rates to first-line chemotherapy and had longer treatment-free intervals compared

Table 1. Baseline characteristics of NVALT-7 and GOIRC 02-2006 patients with advanced non-squamous non-small cell lung cancer

	NVALT-7 (Derivation set) (n = 180)	GOIRC 02-2006 (Validation set) (n = 210)	Total (n = 390)
Age (years)	59 (10)	62 (9)	61 (9)
Male sex, %	57	74	66
WHO performance status, %			
0	31	64	49
1	62	33	46
2	7	3	5
Stage, %			
IIIb	19	15	17
IV	81	85	83
Histology, %			
Adenocarcinoma	60	81	72
Large cell	30	6	17
Not otherwise specified	10	13	12
Response to first-line platinum chemotherapy, %			
CR + PR	36	62	50
SD + PD	64	38	50
Treatment-free interval (months)	8 [5 - 12]	4 [1 - 8]	6 [3 - 9]
Body mass index (kg/m ²)	25.2 (4.3)	25.5 (4.5)	25.4 (4.4)
Leucocyte count (*10 ⁹)	8 [7 - 11]	8 [6 - 10]	8 [6 - 11]

Data are presented as mean (SD), median [interquartile range] or percentage. CR: Complete response ; PR: Partial response ; SD: Stable disease ; PD: Progressive disease. Data are based on unimputed values.

Table 2. Model coefficients

Predictor	AFT coefficient (95% CI) ^a	P value	Hazard ratio (95% CI) ^a
Age in years	0.00 (-0.01 to 0.01)	0.43	1.01 (0.99 to 1.02)
Male sex ^b	0.25 (-0.02 to 0.52)	0.02	0.59 (0.37 to 0.92)
ECOG performance status	-0.22 (-0.40 to -0.05)	<0.01	1.61 (1.20 to 2.17)
BMI (kg/m ²) ^b	-0.03 (-0.06 to 0.00)	<0.01	1.07 (1.02 to 1.13)
Large cell histology	-0.19 (-0.40 to 0.02)	0.02	1.50 (1.07 to 2.12)
Tumor stage IV ^b	-0.50 (-0.83 to -0.17)	<0.01	2.91 (1.65 to 5.13)
Complete or partial response to previous platinum-based therapy	-0.18 (-0.37 to 0.01)	0.02	1.47 (1.06 to 2.03)
Natural logarithm of treatment free interval in months	0.29 (0.13 to 0.44)	<0.01	0.54 (0.41 to 0.70)
Natural logarithm of leucocyte count (*10 ⁹ /L)	-0.16 (-0.39 to 0.08)	0.10	1.39 (0.94 to 2.08)
Pemetrexed plus carboplatin vs. pemetrexed alone ^b	-1.41 (-2.71 to -0.11)	<0.01	20.66 (2.34 to 182.80)
Pemetrexed plus carboplatin vs. pemetrexed alone * Male sex	-0.38 (-0.75 to 0.00)	0.01	2.24 (1.20 to 4.18)
Pemetrexed plus carboplatin vs. pemetrexed alone * BMI	0.04 (0.00 to 0.09)	0.01	0.91 (0.84 to 0.98)
Pemetrexed plus carboplatin vs. pemetrexed alone * Tumor stage IV	0.80 (0.34 to 1.27)	<0.01	0.18 (0.08 to 0.40)

AFT: Accelerated failure time ; CI: confidence interval ; ECOG: Eastern Cooperative Oncology Group ; BMI: Body mass index. ^aUniform shrinkage was applied to the AFT coefficients, but not the hazard ratios, because penalization increases external validity of the model overall, yet leads to underestimation of the importance of the predictors. ^bTo interpret the coefficients and hazard ratios of the main effects of sex, BMI, stage and pemetrexed plus carboplatin, the interaction effects need to be taken into account. For example, the AFT coefficient of pemetrexed plus carboplatin vs. pemetrexed alone for a man with a BMI of 26 kg/m² and stage IV is: $1 * -1.41 + 1 * -0.38 + 26 * 0.04 + 1 * 0.80 = 0.05$; and the hazard ratio is: $\exp(1 * \ln(20.66) + 1 * \ln(2.24) + 26 * \ln(0.91) + 1 * \ln(0.18)) = 0.72$

to the GOIRC 02-2006 population. In the NVALT-7 data, the median PFS was 4.3 months in the Pem-Carbo arm vs. 2.9 months in the Pem arm. Median OS was 7.8 months vs. 8.0 months. Of the patients receiving Pem-Carbo, 53% experienced grade 3/4 toxicity (National Cancer Institute Common Toxicity Criteria version 3.0), versus 48% in the control group. The median PFS in the data from the GOIRC 02-2006 study was 3.6 months in the Pem-Carbo arm vs. 3.8 months in the Pem arm, the median OS was 9.3 months vs. 8.4 months, whereas 26% vs. 23% experienced grade 3/4 toxicity.

Model derivation

The model coefficients, p-values and (unpenalized) hazard ratio's with corresponding 95%CI's are presented in *Table 2*. Time since previous platinum-based chemotherapy and leucocyte count were log-transformed to improve model fit. Treatment interactions with sex ($p_{\text{interaction}}=0.01$), BMI ($p_{\text{interaction}}=0.01$) and tumor stage ($p_{\text{interaction}}<0.01$) were retained in the model during selection. The effect on PFS of carboplatin was larger in women, in patients with stage IV and in those with higher BMI (*Appendix 1*).

Model validation

Calibration plots of predicted versus observed median PFS in the derivation and validation data show that the overall model calibration was good, although there was some overestimation in a few patients with the highest predicted probabilities (*Appendix 2*). The C-index in the derivation set was 0.69 (95%CI: 0.64-0.75) and 0.61 (95%CI: 0.56-0.67) in the external validation set.

Treatment effect prediction

The computational formula for predicted gain in median PFS by Pem-Carbo versus Pem is provided in *Appendix 3*, and an example of treatment effect prediction for an individual patient using a calculation sheet is shown in *Figure 1*. A wide distribution of predicted gain

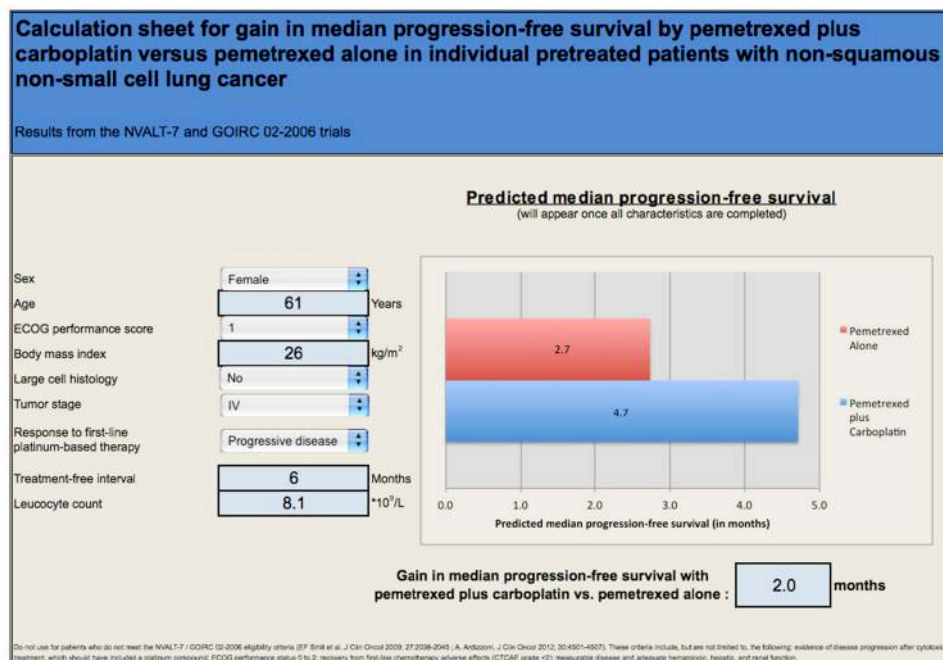


Figure 1. Example of pemetrexed plus carboplatin treatment effect prediction for an individual patient

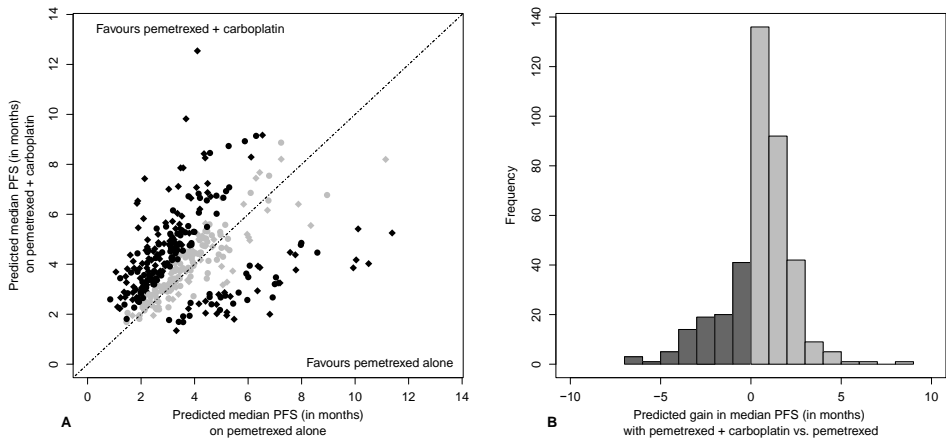


Figure 2. Distribution of predicted effects of pemetrexed plus carboplatin vs. single-agent pemetrexed in NVALT-7 and GOIRC 02-2006 trials.

A. Scatter plot with predicted median PFS on pemetrexed plus carboplatin vs. predicted median PFS on pemetrexed alone. Statistically significant ($p < 0.05$) predictions are colored black and non-significant predictions ($p \geq 0.05$) are colored gray. Squared dots represent patients from the NVALT-7 trial (derivation data) and round dots represent patients from the GOIRC 02-2006 (validation data). B. Histogram of predicted gain in median PFS in months with pemetrexed plus carboplatin vs. single-agent pemetrexed in pooled data from NVALT-7 and GOIRC 02-2006 trials. PFS: Progression-free survival.

in PFS by Pem-Carbo was observed in the NVALT-7 and GOIRC 02-2006 populations, with a median of 0.7 months (IQR: -0.1 to 1.5 months; *Figure 2*). Of the patients, 15.1% had a predicted gain in median PFS by Pem-Carbo of >2 months, 58.5% had a predicted gain between 0 and 2 months and 26.4% had a predicted treatment effect in favor of Pem. Forty-five percent had a statistically significant PFS prediction in favor of Pem-Carbo ($p < 0.05$) versus 13% who had a significant PFS prediction in favor of Pem. Of the patients with a predicted benefit of >2 months, 75% was female, all had tumor stage IV and 78% had adenocarcinoma (*Appendix 4*). Furthermore, these patients were more likely to be overweight (mean BMI of 29.0kg/m² vs. 24.8kg/m² in other patients).

Net benefit

Decision curve analysis indicated that prediction-based treatment resulted in the most favorable outcome compared to treating all with Pem or treating all with Pem-Carbo, not only with regard to PFS, but also for to OS (*Figure 3*). If, for example, the treatment threshold would be a gain of 2 months, 15.1% of the patients in NVALT-7 and GOIRC 02-2006 would be treated with Pem-Carbo (those with predicted gain in median PFS of ≥ 2 months) and the average gain in median PFS and OS in these patients would be 3.0 and 2.2 months, respectively (*Table 3*). This benefit would come at the cost of 2.3 extra cases of grade 3/4 toxicity per 100 months gained in OS compared to Pem. Treating all patients with Pem-Carbo regardless of the predictions would result in some benefit in PFS if the threshold is <1 month, although, this would not lead to benefit in OS and gives a worse

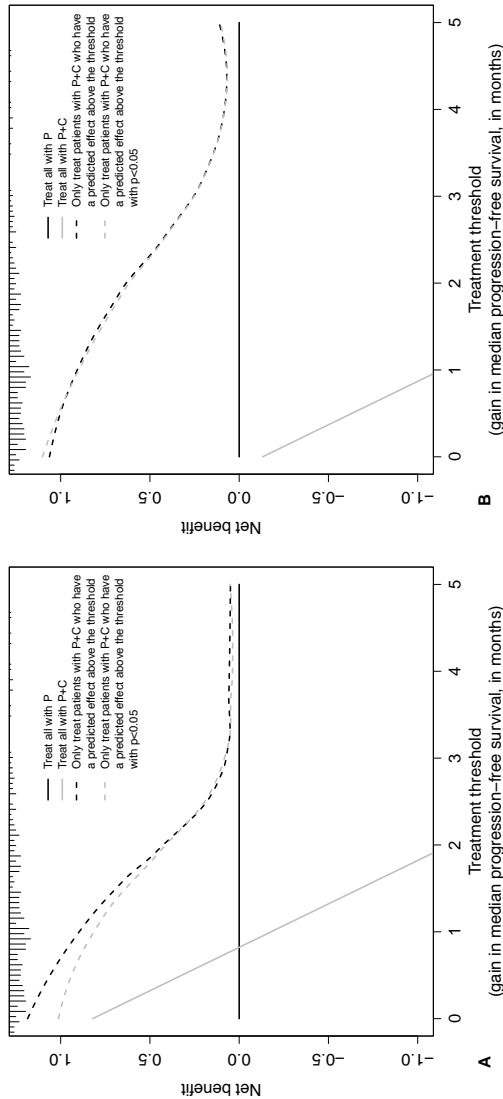


Figure 3. Decision curves for net benefit assessment of various treatment strategies for pemtredex plus carboplatin vs. single-agent pemtredex.

A. Net benefit with regard to progression-free survival. B. Net benefit with regard to overall survival. P: Pemetrexed ; C: Carboplatin. Reading the net benefit plot starts with choosing a treatment threshold, that is the gain in median progression-free survival at which one would opt for treatment with pemtredex plus carboplatin instead of single-agent pemtredex (i.e. from that point onwards, the benefits are considered to outweigh the harms, e.g. toxicity).

Positive net benefit means that the treatment strategy led to a more favorable trade-off between benefits (observed gain in median progression-free or overall survival) and harms (the proportion of patients that would be treated with pemtredex plus carboplatin instead of single-agent pemtredex, weighted by the reciprocal of the treatment threshold). The tick marks at the top axis represent the distribution of the treatment effect predictions as present in the pooled data of the NVALT-7 and GOIRC 02-2006 trials.

clinical outcome than prediction-based treatment. Treating only patients with a statistical significant treatment effect yielded slightly less net benefit with regard to PFS than treating patients with a predicted effect above the threshold regardless of statistical significance at thresholds <2 months although overall it resulted in similar net benefit.

Table 3. Inferences and consequences for clinical practice

Tx threshold (gain in median PFS in months)	Tx strategy associated with optimal net benefit	Tx rate ^a	Average gain in median PFS (in months) ^b	Average gain in median OS (in months) ^b	Extra cases of grade 3/4 toxicity per 100 months gained in median OS ^c
0	Prediction-based treatment	73.6%	1.3	0.8	6.7
1	Prediction-based treatment	38.7%	2.0	1.5	3.6
2	Prediction-based treatment	15.1%	3.0	2.2	2.3
3	Prediction-based treatment	4.4%	4.4	3.1	1.7
4	Prediction-based treatment	2.1%	5.2	3.8	1.4
5	Prediction-based treatment	0.8%	6.6	5.2	1.0
>5	Treat all with pemetrexed alone	0%	NA	NA	NA

Tx: Treatment ; PFS: Progression-free survival ; OS: Overall survival. ^aPercentage of patients who would be treated with pemetrexed plus carboplatin instead of pemetrexed alone according to the optimal treatment strategy. ^bEffect achieved by pemetrexed plus carboplatin vs. pemetrexed alone in patients who would be treated according to the optimal treatment strategy. ^cEstimated using the observed 5.2% absolute risk increase of grade 3/4 toxicity for pemetrexed plus carboplatin vs. pemetrexed alone in pooled data estimated based on cumulative incidence function (accounting for competing risk by mortality).

DISCUSSION

The results of the present study indicate that there is considerable heterogeneity in the effects of Pem-Carbo versus Pem on PFS in patients with advanced non-squamous NSCLC. These effects can be estimated with our prediction model based on patient and tumor characteristics that are routinely available in clinical practice, including age, sex, ECOG performance status, BMI, large-cell histology, stage, response to previous platinum-based therapy, treatment-free interval and leucocyte count. Importantly, we demonstrated that the model's predictive performance remain adequate in an external population. Moreover, decision curve analysis indicated that using the model to select patients for treatment with Pem-Carbo could improve net benefit compared to treating all patients with Pem-Carbo or treating all with Pem.

Previous group-level analysis of the NVALT-7 and GOIRC 02-2006 phase II-trials showed no benefit from Pem-Carbo vs. Pem in patients with advanced non-squamous NSCLC^{4,5}. The important heterogeneity in treatment effect presented in this study underline the limitations of applying average summary results to individual patients.

Conventional subgroup analyses may give some idea about variation in treatment effect, but evaluate only one variable at a time without adjustment for other relevant characteristics or interactions. Furthermore, subgroup analyses have low power and are generally presented as relative average effects, rather than absolute effects for individuals^{7,8}. Prediction-based treatment provides an evidence-based tool to guide decisions in various clinical settings including second-line chemotherapy in patients with advanced non-squamous NSCLC by identifying those who benefit most. This way, treatment can be reserved for these patients, while preventing unnecessary treatment and reducing treatment-related toxicity. Furthermore, the presented prediction model could be used to select patients for a randomized phase-III trial. Including only those patients with a predicted treatment effect above a certain threshold could improve the statistical power and avoids inclusion of patients who have no benefit or may even experience harm from treatment¹¹. Treating only patients with a statistically significant treatment effect resulted in a slightly inferior clinical outcome compared to prediction-based treatment regardless of significance at thresholds <2 months. This finding questions the value of measures of uncertainty for individualized treatment effect estimates. Moreover, the value of communicating uncertainty (e.g. in terms of 95% CI's) to individual patients in clinical practice is questionable²⁵, especially considering that in case of a choice between two strategies, it is favorable to choose the one most likely to result in the best outcome, regardless of statistical significance^{26,27}. Importantly, using the predicted gain in median PFS by Pem-Carbo of individual patients to guide treatment decisions did not only improve net benefit with regard to PFS, but also to OS. This finding suggests that the predictors for PFS and OS are largely similar, which is not surprising, given that the majority of deaths in patients with advanced NSCLC are due to progression of disease and time from progression to death is generally short. In addition to improvement of net benefit, individualized treatment effect prediction could have other advantages. For instance, the predicted treatment effects can be used by clinicians for communicating prognosis and treatment possibilities to their patients. This could improve the patients' understanding of the benefits and harms of the different chemotherapy regimens and would facilitate shared decision-making. Important heterogeneity in relative treatment effect of Pem-Carbo vs. Pem was found, mainly driven by differences in sex, BMI and tumor stage. Despite uniform staging and treatment, women with NSCLC generally have better survival rates than men and have been found to respond better to chemotherapy²⁸, similar to the present findings. In addition, an improved PFS by Pem-Carbo was observed in patients with higher BMI. This finding is in line with previous studies that show that weight loss is related to a worse outcome when undergoing chemotherapy, whereas obesity is related to improved survival²⁹⁻³¹. Possibly, this is due to greater physiologic reserves, which may prolong life by slowing the progress of cancer cachexia³¹. Furthermore, almost all patients who were predicted to benefit from Pem-Carbo had stage IV, indicating that tumor stage is an important determinant for treatment response. Still, the present results emphasize that treatment response is determined by a combination of multiple characteristics, rather than by effects of a single factor.

There were some important differences between the NVALT-7 and GOIRC 02-2006 populations with regard to the number women, performance status, histology, previous chemotherapy response rates and treatment-free intervals, but conceivably also other unmeasured characteristics. Possibly these differences explain that the model's C-index was considerably lower in the GOIRC 02-2006 data. Yet, it is important to note that the C-index relates to predicted absolute risk, rather than predicted treatment effect. The wide distribution of the predicted effects of Pem-Carbo in both datasets, as well as the improvement in net benefit, indicate that the model is able to discriminate patients in terms of treatment effect. This underscores the importance of not only assessing a model's statistical properties, but to also evaluate the consequences of using a model to guide decisions in clinical practice^{20,24}.

Some study limitations need to be considered. In this analysis, we only considered clinicopathologic predictors that are routinely available in clinical practice. Advances in molecular biology, however, may reveal new biomarkers, such as thymidylate synthase expression³², which could further improve predictions of response to Pem-Carbo if added to the model. Furthermore, although using randomized trial data has the advantage of having an unbiased treatment effect estimate, the populations of the NVALT-7 and GOIRC 02-2006 trials were subject to eligibility criteria, which include, but are not limited to, evidence of disease progression after platinum-based chemotherapy; ECOG performance status 0 to 2; recovery from first-line chemotherapy adverse effects (CTCAE grade <2); measurable disease and adequate hematologic, hepatic, and renal function. Hence, the use of the model should be restricted to those patients who meet these criteria. Also, the low incidence of grade III/IV toxicity did not allow reliable estimation of such adverse treatment effects for individual patients. Hence, group-level effects of Pem-Carbo on toxicity risk were used to estimate the number of extra toxicity cases for different treatment thresholds. Overall, the excess toxicity risk of Pem-Carbo compared to Pem was very limited^{44,5}. Nonetheless, as there might also be heterogeneity in the adverse effects of Pem-Carbo among patients, individualized estimates of these effects could be valuable in deciding whether the gain in survival by Pem-Carbo outweighs the potential harm.

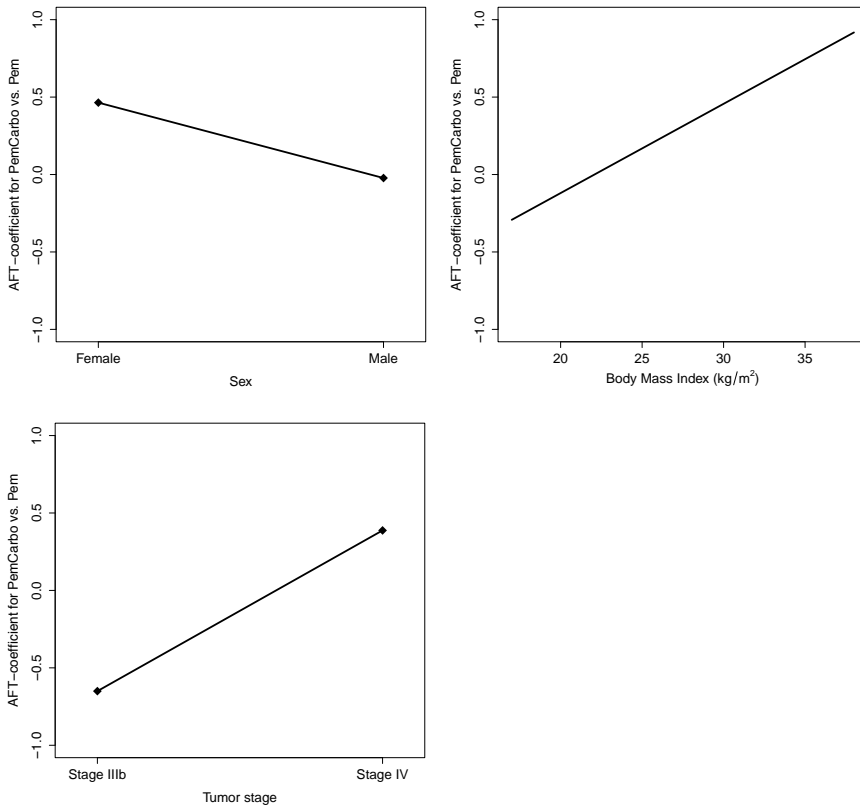
In conclusion, there is important heterogeneity in the effects on PFS of Pem-Carbo versus Pem in pretreated patients with advanced non-squamous NSCLC. The effects of Pem-Carbo can be estimated by a model that includes routinely available clinicopathologic characteristics. Treatment effect predictions could be used to select or stratify patients for inclusion in randomized trials and can guide clinical decision-making to improve net benefit with regard to PFS and OS.

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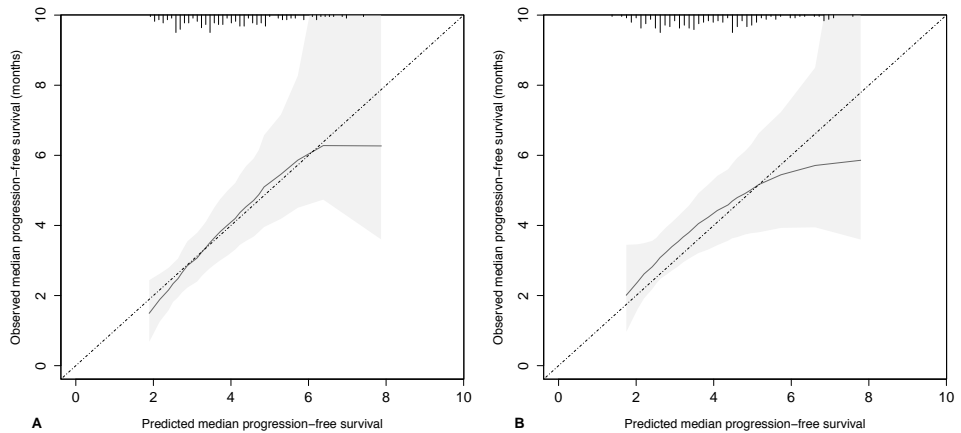
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APPENDIX 1

**Treatment interaction effects**

AFT: Accelerated failure time ; PemCarbo: Pemetrexed plus carboplatin ; Pem: Pemetrexed alone. Each predictor is expressed on the x-axis categorically (sex and tumor stage) or continuously (body mass index), for a patient of mean baseline characteristics. The AFT-coefficient can be interpreted as the ratio of survival time per unit change in the variable. As such, a coefficient of >0 indicates improvement in progression-free survival time by PemCarbo, whereas a coefficient of <0 indicates a reduction in progression-free survival time.

APPENDIX 2



Calibration plots

Nonparametrically estimated calibration curves of predicted versus observed median progression-free survival. A. In the derivation sample: NVALT-7 trial. B. In the validation sample: GOIRC 02-2006 trial. The tick marks at the top axis represent the distribution of the predicted median progression-free survival as present in the respective dataset.

APPENDIX 3

Computational formula for absolute treatment effect of pemetrexed plus carboplatin versus pemetrexed alone in patients with advanced non-squamous non-small-cell lung cancer

$$\begin{aligned} & \text{Predicted gain in median PFS} \\ & = \\ & \text{Predicted median PFS with pemetrexed plus carboplatin} \\ & - \\ & \text{Predicted median PFS with pemetrexed alone} \end{aligned}$$

Median PFS (in months) = $(-\log(0.5))^{0.61557} \cdot \exp(LP)$, where
 $LP = 2.80785 - 0.00331 \cdot \text{age (years)} + 0.25017 [\text{if male}] - 0.22288 \cdot \text{ECOG performance status} - 0.03254 \cdot \text{body mass index (kg/m}^2) - 0.19049 [\text{if large cell histology}] - 0.49781 [\text{if tumor stage IV}] - 0.17952 [\text{if complete or partial response to first-line platinum-based chemotherapy}] + 0.28796 \cdot \text{natural logarithm of treatment-free interval (in months)} - 0.15526 \cdot \text{natural logarithm of leucocyte count } (*10^9/\text{L}) - 1.41312 [\text{if pemetrexed plus carboplatin}] - 0.37608 [\text{if pemetrexed plus carboplatin and male}] + 0.04451 \cdot \text{body mass index (kg/m}^2) [\text{if pemetrexed plus carboplatin}] + 0.80159 [\text{if pemetrexed plus carboplatin and tumor stage IV}]$

PFS: Progression-free survival ; ECOG: Eastern Cooperative Oncology Group

APPENDIX 4

Baseline characteristics of NVALT-7 and GOIRC 02-2006 patients with relapsed non-squamous non-small cell lung cancer according to predicted progression free survival by pemetrexed plus carboplatin vs. pemetrexed alone.

	Predicted gain in median PFS			
	≤ -2 months (n = 42)	> -2 and ≤ 0 months (n = 61)	> 0 and ≤ 2 months (n = 228)	> 2 months (n = 59)
Age (years)	60 (11)	60 (8)	62 (9)	59 (10)
Male sex, %	67	80	73	25
WHO performance status, %				
0	57	51	45	54
1	40	41	50	44
2	2	8	5	2
Stage, %				
IIIb	100	38	1	0
IV	0	62	99	100
Histology, %				
Adenocarcinoma	57	74	72	78
Large cell	24	15	17	14
Not otherwise specified	14	5	8	0
Response to first-line platinum chemotherapy, %				
CR + PR	50	52	49	51
SD + PD	50	48	51	49
Treatment-free interval (months)	9 [5 - 12]	4 [1 - 6]	5 [3 - 8]	9 [8 - 13]
Body mass index (kg/m ²)	23.9 (3.3)	22.6 (4.2)	25.5 (3.6)	29.0 (4.6)
Leucocyte count (*10 ⁹)	9 [7 - 10]	8 [7 - 11]	8 [7 - 11]	8 [6 - 9]

Data are presented as mean ± SD, median [interquartile range] or percentage. CR: Complete response ; PR: Partial response ; SD: Stable disease ; PD: Progressive disease.

CHAPTER 9

GENERAL DISCUSSION

PART I

CANCER RISK IN PATIENTS WITH MANIFEST VASCULAR DISEASE

Shared risk factors

The abundance of high-calorie convenience food and increasing lack of physical activity have led to a major increase in overweight and obesity in the past decades¹. This health problem has taken on epidemic proportions and is not only restricted to the western world, but affects people worldwide^{1,2}. Combined with an increasing life-expectancy due to improvements in medical care, it is likely that the number of patients with obesity-related chronic diseases including diabetes, metabolic syndrome, cardiovascular disease, but also cancer, will continue to rise in the coming years. Patients with manifest vascular disease encompass a population with a high prevalence of excess bodyweight and related metabolic disorders, but also of other important independent risk factors, such as smoking and physical inactivity^{3,4}. These risk factors and important pathophysiology, including insulin resistance and chronic low-grade inflammation, are related to the development and progression of both cardiovascular disease and cancer^{5,6} (**chapter 2** of this thesis). Indeed, patients with manifest vascular disease are not only at increased risk of new vascular events, but also of cancer, as was shown in **chapter 3** and **4** of this thesis. Compared to the general population, these patients have a 19% higher risk of incident cancer. In women, the risk was even increased by 48%. The increase in risk was not limited to cancer incidence, since patients with vascular disease also lost potential life-years to cancer more than expected based on general population data, particularly middle-aged persons and those with peripheral artery disease. Overall, patients with vascular disease die 5.5 years younger compared to the general population. Smoking was the most important determinant for risk of incident cancer, as well as for vascular and non-vascular mortality in patients with vascular disease, but also male gender, physical inactivity, abdominal obesity, impaired renal function, peripheral artery disease and polyvascular disease were important risk factors.

These results warrant a better understanding of the mechanisms that interconnect the development of cardiovascular disease and cancer. The pathophysiological pathways underlying the relation between the shared risk factors and these diseases are intertwined and arise from complex metabolic deregulation. The shared molecular pathways currently considered as key culprits include adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs) and fatty acid synthase (FASN)⁷. The common thread between these factors is the regulation of key metabolic processes necessary for proper homeostasis⁷. A better understanding of this molecular nexus of cardiovascular disease and cancer could lead to new treatment targets that may simultaneously reduce the burden of these diseases. Meanwhile, improving lifestyle and reducing risk factors to prevent cardiovascular disease and cancer remains number one priority.

Shared treatment strategies

Traditionally, prevention and management of cardiovascular disease and cancer have mostly been organized separately. This separation is apparent in the focus of guidelines, advocacy groups and clinical care. However, besides the shared risk factors and etiology described above, the patient populations in oncology and cardiovascular care also partly comprise the same high-risk patients, including smokers, diabetics and those with obesity. Furthermore, given the increasing life expectancy and higher risk of incident cancer in patients with cardiovascular disease (as shown in **chapter 3**), the number of vascular patients that develop cancer is likely to grow. Likewise, the survival of cancer patients is ever improving^{8,9}, while cancer survivors are at increased risk of cardiovascular disease due to the long-term effects of chemotherapy and radiotherapy as well as to the presence of shared risk factors for cancer and cardiovascular disease¹⁰⁻¹². Hence, it seems reasonable to pursue intensified partnerships between advocacy groups and guideline makers for cardiovascular disease and cancer, as well as clinicians in oncology and cardiovascular care. In 2005, Renehan and Howell noted the overlap in major risk factors for cardiovascular disease, cancer and diabetes in a comment in *The Lancet* and already called for more collaboration across the traditional disease barriers to simultaneously reduce the burden of these diseases⁶. Studies since have suggested that indeed management of risk factors, including weight, serum glucose, physical activity, smoking and diet not only reduces the risk of cardiovascular disease, but also the risk of cancer¹³⁻¹⁵. The results showed that ideal levels of these health metrics are related to a notable decrease in cancer risk, ranging from 36 to 51% compared to meeting none of the goals.

In this light, we hypothesized that meeting treatment goals for secondary cardiovascular prevention could be related to a lower cancer risk in patients with vascular disease. Knowledge on such preventative measures would be valuable, especially given the increased cancer incidence and mortality in this population. As described in **chapter 5**, we found that optimal cardiovascular health metrics were related to lower cancer incidence. In fact, patients with vascular disease who attained all 5 goals, including smoking cessation, weight management, adequate levels of physical activity, diabetes management and use of antiplatelets/anticoagulants, had a 30% lower risk of incident cancer compared to patients who attained 0-2 goals.

Although physicians and health care professionals generally educate patients with vascular disease about the cardiovascular benefits of healthy life style, its cancer prevention effects are probably underemphasized. Given the large proportion of cancers that is attributable to lifestyle and environmental factors, more emphasis on the cancer prevention effects, however, would not go amiss. Recent estimates from the United Kingdom (UK) indicate that 42.7% of cancers in 2010 was attributable to lifestyle and environmental factors¹⁶, which, even compared to the population attributable fraction of 70.2% for cardiovascular disease¹⁷, is substantial. The results presented in this thesis confirm the necessity of lifestyle improvement in patients with manifest vascular disease. Thus far, however, the results of lifestyle intervention programs are disappointing, particularly those with regard to weight management. Although in most programs the majority of patients successfully

lose weight in the first year, only modest long-term effects on weight are observed and these effects are not consistently associated with improvements in related cardiovascular risk factors¹⁸⁻²⁰. The ever-growing number of patients with obesity highlights this lack of effective interventions in the past decades¹. Pharmaceutical interventions in combination with dietary/lifestyle therapies do slightly improve the outcomes¹⁹, but provide no panacea. While novel treatments to achieve weight loss and reduce obesity-related metabolic disturbances and carcinogenesis, such as mammalian target of rapamycin (mTOR) inhibitors^{21,22}, are being developed, lifestyle improvement remains the cornerstone for achieving and maintaining healthy weight.

In contrast to obesity, the prevalence of smoking has been in decline for the past few decades^{23,24}. Nevertheless, the burden of cigarette smoking continues to be high, particularly among persons living below poverty levels and with low educational attainment²⁴. Government campaigns to increase awareness of the adverse health effects of smoking and foremost, regulations, including increased taxes on tobacco and smoking bans in public places, have led to the decrease in smoking prevalence and have been linked to lower hospitalization rates for myocardial infarction and lung disease²³⁻²⁵. Although not widely instigated yet, governments can also play an important role in reducing the obesity epidemic, e.g. by taxing unhealthy food and drinks or reducing portion sizes^{21,22}, but one can foresee a variety of political and commercial obstacles to overcome.

In individual healthcare for patients with vascular disease, implementation of the results presented in this thesis could consist of communicating to patients that many of the healthy behaviors can reduce risk of multiple diseases, as some patients may be more motivated by cancer prevention and others by cardiovascular disease prevention²⁶. On a public health level, the collaboration between chronic disease advocacy groups should be intensified to create a broad and powerful coalition to promote primary prevention of chronic disease^{6,14}. To be maximally effective, this collaboration should include not only efforts to advocate healthy lifestyle to the public, but also promotion for more research into primary prevention and effective ways to implement behavior change²⁶. All considered, moving beyond the traditional disease barriers both in clinical practice and research could yield substantial extras in improving health.

In conclusion, patients with manifest vascular disease due to presence of and improved survival. In part I of this thesis, we show that cancer incidence and mortality is increased in patients with vascular disease compared to the general population. Optimal adherence to goals for secondary cardiovascular prevention is related to a decreased cancer risk. These results call for awareness of the increased cancer risk in patients with vascular disease and underline the necessity of lifestyle improvement, not only for reducing cardiovascular risk.

PART II

INDIVIDUALIZED TREATMENT EFFECT PREDICTION

The art of over-simplification

Sir Karl Popper (1902-1994) has once described science as “the art of over-simplification - the art of discerning what we may with advantage omit”. Various examples of useful simplification can be found in clinical research, including the use of population averages. As such, many treatment recommendations in guidelines are based on average effects observed in large study populations. Still, clinicians know from experience that treatment effects can differ importantly among patients. Hence, it can be questioned whether applying group-level effects for individual patients is not too over-simplified. Does this approach overlook important heterogeneity in treatment effect – what we may not with advantage omit?

In the current trend towards personalized medicine, a growing number of papers consider evidence-based approaches to individualize treatment²⁷⁻³³. However, the call for a more individualized treatment approach is not new, as already two decades ago several researchers pointed out the limitations of applying group-level trial results to individual patients^{34,35}. It was argued that it is both erroneous and limiting to focus on the eligibility criteria and setting of clinical trial when determining whether a trial result applies to a particular patient³⁴. This is on the grounds that treatment effect varies among different patients and trial results can sometimes be valid for a broader group of patients than those included in the trial. For example, the results of a trial that was performed in a tertiary referral center need not be confined to only patients in that specific setting. The proportion of patients with many risk factors is generally higher in tertiary referral centers than in a primary or secondary care setting. As treatment effects are often proportional to baseline risk for disease, the patients at higher risk will generally benefit more from treatment. On average, patients in tertiary care are thus likely to have greater treatment effect than those in the primary or secondary care setting. However, this does not imply that none of the latter patients will also have important benefit from treatment. Rather than the setting, the patient's specific characteristics are important in deciding whether the results of a trial apply^{34,35}.

Treatment effect prediction for individual patients

Using multivariable models to predict the absolute effects of specific treatments for individual patients may provide a comprehensive approach towards individualized treatment. Although not widely appreciated, data from randomized clinical trials can be used to derive such prediction models^{28,30,33,36}. Importantly, because the effect of treatment is estimated based on a randomized trial, this method is not vulnerable to confounding bias or reverse causality. In **part II** of this thesis we presented two different examples of individualized treatment prediction based on clinical trial data; for aspirin prophylaxis in primary prevention

and for pemetrexed plus carboplatin as second-line chemotherapy for patients with non-small cell lung cancer. The approach of individualized treatment effect prediction based on clinical trial data has only been used since a few years^{27,28,30,36} and several methodological aspects are still evolving.

One of the advantages of individualized treatment effect prediction is that it provides an approach in which heterogeneity in treatment effect can be assessed on both an absolute and a relative scale. The latter is done by including treatment interaction terms in the model³⁷. Choosing the appropriate interaction terms (if any) is important because they can substantially affect the treatment effect predictions. Similar to the main effect terms in the model, the selection of treatment interaction effects is preferably done based on previous evidence of strong treatment effect modification or strong biological mechanisms. However, such prior knowledge is not always available, especially given the limitations of traditional subgroup analysis to detect differences in response to treatment^{28,29}. As an alternative, it has been proposed to focus on the overall baseline risk when evaluating heterogeneity in relative treatment effect³⁸. Particularly for medication to reduce cardiovascular risk this approach could be sensible as baseline risk may adequately represent the stage of the atherosclerosis process³⁹. Relative treatment effects may differ across the early and late stages of atherosclerosis and it is plausible that these differences are better captured by the summed effect of risk factors rather than by the effects of specific risk factors separately. Still, there are various examples of important treatment interaction with specific patient characteristics, particularly for cancer therapies^{31,40-43}. Such heterogeneity in relative treatment effect should be considered in individualized treatment effect prediction to be able to accurately distinct patients who benefit from those who will not. This can for example be done by including only those treatment interactions in the model that are importantly related to the outcome in the derivation data^{28,31,43}. In **chapter 8** of this thesis, we considered heterogeneity in relative treatment effect of pemetrexed plus carboplatin with regard to progression-free survival by selecting interaction terms based on the Akaike Information Criterion and penalizing the coefficients for overoptimism⁴⁴. This approach was chosen because the prior knowledge on potential treatment interactions for pemetrexed plus carboplatin was too limited to either rule out or confirm important treatment effect interaction on beforehand. Indeed, significant interaction by sex, body mass index and tumor stage was found. Moreover, using the therapeutic prediction model, which included these interaction effects, to guide treatment decisions led to a favorable clinical outcome compared to treating all patients with pemetrexed plus carboplatin or treating all with pemetrexed.

Another principal aspect of individualized treatment effect prediction is the specification of the outcome measure. Especially in cardiovascular research, absolute risk reduction (ARR) is often used as a measure to express treatment effect. Although ARR is generally considered an improvement compared to relative risk when it comes to interpretation, this measure can still be quite abstract to some patients. A useful alternative is the number-needed-to-treat (NNT), which is the reciprocal of the ARR. This metric can also be used to express individualized estimates of treatment effect. The 'individualized NNT' represents

the estimated number of individuals with the same characteristics (same age, sex, laboratory measures, etc.) that need to be treated with the new treatment rather than the standard treatment for one additional patient to benefit^{30,45}. This measure can be useful in clinical practice as a way to communicate the potential benefits of treatment to patients. Still, some argue that the NNT has as much potential to confuse as to enlighten⁴⁶. Both the ARR and NNT are based on the probability of an event at a specific time point. Instead of these measures, the focus in oncology is generally on (event-free) survival time. This is not surprising given that after a diagnosis of a potentially fatal condition such as cancer, patients are most interested in an individual estimate of their remaining lifetime⁴⁶. Accordingly, the results of clinical trials investigating the effects of cancer therapy are generally expressed as difference in median progression-free or overall survival. Metrics such as differences in (disease-free) survival time may also be useful to express risk or treatment effect for individual patients. In fact, in **chapter 8** of this thesis, the effects of pemetrexed plus carboplatin versus pemetrexed alone were expressed as gain in median progression-free survival. Median progression-free survival here represents the point in time from which onwards it is more likely that the patient has experienced progression or died than that he/she is alive without progression. Such outcome measures might be more intuitive for patients and, with regard to cardiovascular disease risk, may also better motivate lifestyle changes⁴⁷. An increasing number of prognostic studies is already adopting this methodology, for example in the most recent Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3), in which a risk calculator for the average expected age of survival without a heart attack or stroke is presented⁴⁸.

Determining the optimal treatment strategy

Although intuitively appealing, it is feasible that in some cases risk-based treatment strategies do not improve the clinical outcome compared to other 'traditional' approaches, such as treating all, none or a specific subgroup of patients. This can be the case when there is a very strong treatment interaction effect, for example in the case of cancer therapy that is targeted at a specific mutation. Ideally, such therapy will work in all patients with the mutation and in none without the mutation. A perfect treatment effect model would then predict a beneficial treatment effect in only those patients with the mutation. However, since no model perfectly predicts the outcome, it is more likely that a prediction-based treatment strategy in that case would lead to inaccurate patient selection and an inferior clinical outcome compared to the simpler strategy of treating patients based on the presence of the specific mutation. Although this is an extreme example, it is conceivable that a lesser extent of such effects can be seen in the presence of a strong treatment interaction effect. Furthermore, the lack of strong predictors might in some cases make it difficult to adequately predict a specific outcome. The results presented in **chapter 7** most likely exemplify a combination of these two situations. In a decisive attempt to determine the value of aspirin in healthy women with regard to all relevant outcomes (cardiovascular disease, cancer and gastro-intestinal bleeding), we found that aspirin was ineffective of

even harmful in the majority of women. Although the apparent statistical performance of the therapeutic predictions models was generally adequate, decision curve analysis indicated that model-based treatment yielded similar net benefit to treating none. Depending on the treatment threshold and how important one deems gastro-intestinal bleeding, selective treatment of women of 65 years and older was associated with optimal net benefit. Here, the inability of the models to adequately predict the effects of aspirin compared to treating only women of 65 years and older, is likely caused by the strong interaction between age and aspirin that was observed in the Women's Health Study^{49,50} as well as the slightly unsatisfactory performance of the model for prediction of cancer risk. Possibly, using this outcome, which comprised a heterogeneous group of various cancer types, might have led to the introduction of noise by some of the predictors other than age. This finding emphasizes the importance of evaluating different treatment strategies based on their clinical benefit (e.g. by means of decision curve analysis) beyond traditional statistical performance. Importantly, traditional performance measures, such as the C-index, tell us something about the validity of predictions of absolute risk, while for the purpose of individualized treatment effect prediction, we are more interested in the validity of the predictions of treatment effect (e.g. absolute risk reduction). Moreover, rather than the statistical properties of a model, the effects of (changes in) treatment decisions that result from using a model in clinical practice may be more relevant. This area of ongoing research into model validation is certainly not confined to the field of treatment effect prediction, but is an important topic in prediction research in general⁵¹⁻⁵³. In any case, it is imperative that the performance of prognostic models, including models for the prediction of treatment effects, should be assessed in preferably an external validation data set and that the focus of this assessment should be on the impact of using the model on clinical outcome.

Applications of individualized treatment effect prediction

In clinical practice, prediction models are generally used to stratify patients in terms of risk to more accurately determine whether and/or which therapy is needed. However, the step of determining the appropriate treatment strategy is usually not explicitly done based on risk-stratified, let alone individualized, estimates of treatment effect. Furthermore, although the predicted absolute risk is often communicated to patients, the expected effects of specific therapies are rarely made explicit for individual patients beyond group-level averages from a trial or meta-analysis, while this is possible by e.g. multiplying the predicted absolute risk with the average relative treatment effect. Although exceptional, there are some examples in clinical practice where this latter approach is applied, including the widely used 'Adjuvant! Online' tool which is aimed to guide treatment decisions for specific cancer types⁵⁴. Still, this approach does not explicitly consider heterogeneity in relative treatment effect and typically only the validity absolute risk predictions is evaluated rather than the predicted treatment effects. The methods for individualized treatment prediction based on clinical trials as described in **chapter 7** and **8** of this thesis can overcome these issues and help clinicians to better identify patients that could benefit from treatment.

These individualized estimates can be used by clinicians to communicate prognosis as well as treatment possibilities to their patients. This could improve the patients' understanding of the benefits and harms of specific treatments and would better enable shared decision-making. To facilitate an easier implementation of individualized treatment effect prediction in clinical practice it is preferable to only include routinely available predictors in the model, or those that are easy to measure. Still, successful incorporation of the use of therapeutic prediction models by physicians in patient counseling can be challenging, since there is only limited time for each patient and applying model formulas or nomograms can be time consuming. However, this argument is partly mitigated with the growing use of electronic patient record systems and possibilities to implement therapeutic prediction models in these systems and/or in applications for mobile devices.

Furthermore, in earlier phases of drug research, treatment effect prediction could be used to select patients for inclusion in clinical trials. For example, a therapeutic prediction model can be derived based on data of a phase II trial, which can then be used to select patients for a phase III trial. This could improve the statistical power of the trial and avoids inclusion of patients who have no benefit or may even experience harm from treatment.

Future perspectives

The methods described in **chapter 7** and **8** of this thesis could be applied for various therapies, both in cardiovascular medicine and oncology. Particularly for those treatment that can have important adverse effects, such as cytotoxic cancer agents and novel anticoagulants for cardiovascular disease prevention, individualized treatment effect prediction could be valuable by discerning between patients who benefit and those who do not or may even be harmed by treatment. Besides finding novel molecular markers for prediction of risk, future studies should aim to find markers that determine the response to therapy to further improve individualized predictions of treatment effect.

To further advance the methodology of individualized treatment effect prediction, future research should focus on several key topics. First, the abovementioned different strategies for determining the appropriate treatment effect interaction should be evaluated to determine the most adequate methods for assessing the presence of heterogeneity in relative treatment effect. Second, the use of intuitive measures for treatment effect, such as gain in (disease-free) survival, should be promoted. Implementation of these measures can be more challenging when the follow-up in studies is short compared to the life expectancy of the specific patient group, as is often the case in cardiovascular research. Yet, various methodologies to estimate life-time risk and years of life lost, which account for important related issues such as competing risk, to overcome these difficulties have been proposed⁵⁵⁻⁵⁷. Given the increasing performance capability of modern computers and upcoming machine learning techniques, the possibilities for (treatment effect) prediction will continue to grow. As mentioned above, however, it remains priority that the clinical value of such novel approaches for prediction is thoroughly evaluated before implementation in medical care. Furthermore, the value of confidence intervals for treatment estimates for individual patients should be further explored. Lastly, to increase efficiency, the prior

probability that prediction-based treatment can improve net benefit compared to other treatment strategies for specific treatment situations should be carefully assessed before attempts to apply individualized treatment effect prediction.

In conclusion, in **part II** of this thesis, we showed that, based on randomized trial data, the effects of specific treatments can be predicted for individual patients using routinely available patient characteristics. Individualized treatment effect predictions can be used to guide treatment decisions in clinical practice and could improve net benefit compared to treating patients based on group-level effects.

Concluding remarks

In this thesis, it was shown that:

- Adipose tissue dysfunction plays an important role in the relation between obesity and cancer through mechanisms of insulin resistance, low-grade inflammation and altered secretion of adipokines and sex steroids.
- Patients with vascular disease have a 19% higher risk of incident cancer compared to the general population.
- On average, patients with vascular disease die 5.5 years younger compared to the general population not only from cardiovascular disease, but also from cancer, particularly middle-aged patients and those with peripheral artery disease.
- Meeting treatment goals for shared risk factors of cardiovascular disease and cancer, as defined in secondary cardiovascular prevention guidelines, is related to lower risk of incident cancer in patients with vascular disease.
- Elevated resting heart rate is related to a higher risk of premature all-cause mortality, but not to cancer incidence or mortality, in patients with vascular disease.
- Alternate-day use of low-dose aspirin is ineffective or harmful in the majority of women in primary prevention when the absolute effects on cancer, cardiovascular disease and major gastrointestinal bleeding are taken into account, although selective treatment of women ≥ 65 years may improve net benefit.
- The effects on progression-free survival by pemetrexed plus carboplatin in pretreated patients with advanced non-squamous non-small cell lung cancer can be predicted for individual patients based on routinely available clinicopathologic characteristics.

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APPENDIX

SUMMARY

SAMENVATTING

CONTRIBUTING AUTHORS

DANKWOORD

LIST OF PUBLICATIONS

CURRICULUM VITAE

SUMMARY

Part I

Cancer risk in patients with manifest vascular disease

Advances in the treatment of cardiovascular disease have led to a significant decrease in cardiovascular-related mortality in the past decades. However, the number of patients in a chronic phase of cardiovascular disease is still growing. Cardiovascular disease shares several important modifiable risk factors with cancer, including tobacco smoking, excess bodyweight, insulin resistance and systemic low-grade inflammation. Given these shared risk factors, patients with manifest vascular disease might not only be at increased risk of recurrent vascular events, but also of cancer. Knowledge about the risk of cancer in these patients, as well as a better understanding of important risk factors may yield treatment strategies that could simultaneously reduce the burden of these diseases. In this thesis we therefore evaluated shared risk factors for cardiovascular disease and cancer, evaluated the risk of incident cancer and cause-specific mortality, and explored potential shared treatment strategies in patients with manifest vascular disease.

Obesity is an important risk factor, not only for cardiovascular disease and type 2 diabetes mellitus, but also for various types of cancer. Excess bodyweight is strongly associated with changes in the physiological function of adipose tissue, leading to insulin resistance, chronic inflammation, and altered secretion of adipokines. Several of these factors, such as insulin resistance, increased levels of leptin, plasminogen activator inhibitor-1, and endogenous sex steroids, decreased levels of adiponectin, and chronic inflammation, are involved in carcinogenesis and cancer progression. In **chapter 2** of this thesis we review these mechanisms and propose that adipose tissue dysfunction is an important unifying factor in the relation between obesity and cancer.

Using data from the Second Manifestations of ARterial disease (SMART)-study, it was shown in **chapter 3** that the risk of incident cancer in patients with manifest vascular disease is 19% (95% confidence interval[CI]: 10% - 29%) higher compared to the general population. Particularly the risk of lung cancer, bladder cancer, cancer of the lip, oral cavity or pharynx, colorectal cancer and kidney cancer was increased. Women had a higher relative risk of incident cancer than men (1.48, 95% CI: 1.25 - 1.75 vs. 1.13, 95% CI: 1.03 - 1.24). Smoking was the most important determinant for overall cancer risk and abdominal obesity increased the risk of breast cancer in female patients with vascular disease. As described in **chapter 4** of this thesis, we also evaluated whether cancer mortality and years of potential life lost by cancer were increased in patients with manifest vascular disease included in the SMART-study, by comparing specific causes of death in these patients to those in the general population. A 26% (95% CI: 18% - 34%) higher all-cause mortality was observed in vascular patients. Patients with peripheral artery disease and polyvascular disease were at highest risk, especially for death by ischemic heart disease. Notably, patients with peripheral artery disease had a 67% (95% CI: 25% - 117%) higher risk of dying from cancer compared to the general population. On average, patients with vascular

disease died 5.5 years younger than the general population, with 80% of the excess years of life lost attributable to cardiovascular disease. Middle-aged patients lost an excess ten years of potential life, of which 24% were lost due to cancer. Important determinants for mortality were male sex, smoking, physical inactivity, body mass index $< 20\text{kg/m}^2$, impaired renal function and polyvascular disease.

Given the shared risk factors and pathophysiology for cardiovascular disease and cancer, we hypothesized that secondary cardiovascular prevention could be related to a lower cancer risk in patients with vascular disease. As described in **chapter 5**, we evaluated this hypothesis by relating the number of treatment goals for secondary cardiovascular prevention, as defined in evidence-based clinical guidelines, that patients met at baseline to the risk of incident cancer. Meeting all treatment goals for smoking, weight management, physical activity, diabetes management and antithrombotics was related to a 30% (95% CI: 4% - 49%) lower cancer risk compared to meeting 0-2 of the treatment goals. Each extra attained treatment goal was related to a 10% (95% CI: 2% - 18%) lower cancer risk.

Previous evidence suggests that increased sympathetic activation may also be a shared risk factor for cardiovascular disease and cancer. In addition to the well-established relation between resting heart rate (RHR) – a marker of sympathetic activity – and cardiovascular disease, several studies found an increased risk of cancer mortality in patients with elevated RHR. However, knowledge about the effects of RHR on cancer incidence, as well as the effects of RHR in patients with vascular disease, is limited. In **chapter 6**, we therefore evaluated the relation between RHR and cancer incidence, cancer mortality and all-cause mortality in patients with manifest vascular disease included in the SMART-study. Elevated RHR was related to a higher risk of premature all-cause mortality (hazard ratio highest quartile of RHR compared to the lowest quartile: 1.86, 95%CI 1.53 - 2.27), 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.

Part II

Individualized treatment effect prediction

Evaluating the efficacy of clinical interventions in randomized trials is a cornerstone of present-day evidence-based medicine. Translating the group-level treatment effects derived from clinical trials to individual patients in clinical practice, however, can be challenging since average measures implicitly consider that all patients have an average risk and the same average response to treatment. Absolute treatment effects, however, can vary substantially among individuals, for example depending on age or sex. To provide patient-tailored medicine, it is important to focus on the patient's specific characteristics in deciding whether the results of a trial apply. As the response to treatment is determined by multiple patient characteristics, treatment effects could be estimated for individual patients using prediction models. Such individualized prediction of treatment effects provides a

comprehensive approach to identify those patients who benefit most from treatment, enabling clinicians to make patient-tailored treatment decisions and better weigh treatment benefits against harms.

Chapter 7 of this thesis describes a study in which we evaluated different treatment strategies, including prediction-based treatment, for alternate-day aspirin in women in a primary prevention setting. Rather than focusing one of the relevant outcomes, we evaluated the combined effect of aspirin on the risk of cancer, cardiovascular disease and gastro-intestinal bleeding. Using data from the Women's Health Study, competing risks models were developed for prediction of absolute risk reduction of these outcomes for individual women. Although aspirin was associated with a modestly decreased 15-year risk of colorectal cancer, CVD, and in some women non-colorectal cancer, aspirin treatment resulted in a negative treatment effect in the majority of women if gastrointestinal bleeding was also taken into account. The excess risk of major gastrointestinal bleeding by aspirin increased with age, but the benefits for colorectal cancer and CVD risk were also greater at higher age. Decision curve analysis indicated that selective treatment of women ≥ 65 years may improve net benefit compared to treating all, none and treating patients according to the predictions of treatment effect. The observed 15-year number needed to treat to prevent one of the relevant outcomes among women ≥ 65 years was 29 (95% confidence interval: 12-102).

In **chapter 8** we present a model for prediction of gain in median progression-free survival by pemetrexed plus carboplatin (Pem-Carbo) versus single-agent pemetrexed (Pem) as second-line chemotherapy in patients with advanced non-squamous non-small cell lung cancer. The model was developed using data from the NVALT-7 clinical trial and included patient and tumor characteristics that are routinely available in clinical practice. There was important heterogeneity in the predicted treatment effect, with a gain in median progression-free survival ranging from -6 to 8 months. Patients who benefited most included women, those with stage IV, high body mass index and/or adenocarcinoma. External validation of the model in the GOIRC 02-2006 trial showed satisfactory calibration and moderate discrimination (C-index: 0.61, 95% CI: 0.56-0.67). Overall, the model adequately identified patients who benefit from Pem-Carbo. This was confirmed by decision curve analysis, as prediction-based treatment led to improvement in net benefit with regard to progression-free and overall survival, compared to treating all patients with Pem-Carbo or treating all with Pem. These results confirm that the effects of chemotherapy in cancer patients can be estimated based on routinely available clinicopathologic characteristics. The method of individualized treatment effect predictions could be used to guide clinical decision-making to improve clinical outcome and to select patients for randomized trials.

SAMENVATTING

(voor niet ingewijden)

Deel I

Het risico op kanker bij patiënten met hart- en vaatziekte

Door verbeteringen in de medische zorg is het percentage mensen dat aan hart- en vaatziekte overlijdt aanzienlijk afgenomen in de afgelopen decennia. Echter, het aantal patiënten met chronische hart- en vaatziekte wordt alsmear groter. Hart- en vaatziekte deelt een aantal belangrijke risicofactoren met kanker, zoals roken, weinig lichaamsbeweging en overgewicht. Het is dan ook aannemelijk dat vaatpatiënten niet alleen een grotere kans hebben om opnieuw acute hart- en vaatproblemen te krijgen, maar ook om kanker te ontwikkelen. Kennis over het risico op kanker bij deze patiënten en ook een beter begrip van de belangrijke risicofactoren zouden behandelstrategieën kunnen opleveren waarmee beide aandoeningen gelijktijdig beter voorkomen kunnen worden. In deel I van dit proefschrift hebben we daarom de gedeelde risicofactoren van hart- en vaatziekte en kanker onderzocht. Tevens hebben we geëvalueerd hoe groot het risico op kanker is en wat de belangrijkste doodsoorzaken zijn bij patiënten met hart- en vaatziekte. Ook beschrijven we een onderzoek waarbij we gekeken hebben of behandeldoelen voor het verlagen van het risico op nieuwe hart- en vaatziekte, mede gerelateerd zijn aan een verlaagd risico op kanker. Overgewicht is een belangrijke risicofactor, niet alleen voor het ontwikkelen van hart- en vaatziekte en diabetes mellitus type 2, maar gebleken is ook evident voor verschillende soorten kanker. Naast het opslaan van vet heeft vetweefsel ook andere belangrijke functies in het lichaam voor de stofwisseling, zoals het produceren van hormonen die de eetlust reguleren. Bij mensen met overgewicht wordt vaak gezien dat deze functies verstoord zijn, waardoor er bijvoorbeeld ongevoeligheid voor insuline ontstaat. Ook kunnen chronische ontsteking en verandering in de uitscheiding van verscheidene hormonen ontstaan. Een belangrijk deel van deze ontregelingen speelt een rol in het ontstaan van kanker. In **hoofdstuk 2** van dit proefschrift beschrijven we de onderliggende mechanismen in de relatie tussen overgewicht en kanker en stellen dat de ontregelingen in het vetweefsel bij overgewicht hierin een cruciale rol spelen.

In **hoofdstuk 3** laten we zien dat de kans om kanker te ontwikkelen bij patiënten met hart- en vaatziekte met 19% verhoogd is ten opzichte van de algemene Nederlandse bevolking. Vooral het risico op long-, blaas-, hoofd en hals-, darm- en nierkanker is verhoogd. Bij vrouwen met hart- en vaatziekte is het risico op kanker hoger dan bij mannen met hart- en vaatziekte (48% tegenover 13% verhoogd risico). Roken is de belangrijkste bepalende factor voor het risico op kanker en een teveel aan buikvet is gerelateerd aan een verhoogde kans op borstkanker. Zoals beschreven in **hoofdstuk 4** hebben patiënten met hart- en vaatziekte een 26% verhoogde kans om vroegtijdig te overlijden vergeleken met de totale bevolking. Patiënten met vaatziekte in de benen of vaatziekte op meerdere plekken hebben het hoogste risico, vooral om te overlijden ten gevolge van hartziekte. Opmerkelijk is dat patiënten met vaatziekte in de benen ook een 67% hogere kans hebben om te overlijden

aan kanker. Gemiddeld genomen, sterven patiënten met hart- en vaatziekte op 5.5 jaar jongere leeftijd dan de algemene populatie, waarbij 80% van deze voortijdige sterfte aan acute hart- en vaatproblemen is te wijten. Patiënten van middelbare leeftijd gaan ongeveer 10 jaar eerder dood dan verwacht; in 24% van de gevallen komt dit door kanker. Het risico op vroegtijdig overlijden wordt voor het grootste deel bepaald door roken, mannelijk geslacht, weinig lichaamsbeweging, slechte nierfunctie en de aanwezigheid van vaatziekte op meerdere plekken.

In **hoofdstuk 5** beschrijven we een studie waarin we hebben onderzocht of het voldoen aan behandeldoelen voor het verlagen van het risico op nieuwe hart- en vaatziekte zoals gesteld in de huidige richtlijnen, gerelateerd was aan een verlaagd risico op kanker bij patiënten met hart- en vaatziekte. Hierbij is gebleken dat het voldoen aan alle doelen voor niet-roken, gewicht, lichaamsbeweging, regulering van diabetes en gebruik van bloedverdunners, geassocieerd is met een 30% lager risico om kanker te ontwikkelen vergeleken met het voldoen aan slechts 0-2 van deze doelen. Per extra behaald doel wordt het risico op kanker met 10% verlaagd.

Eerdere onderzoeken hebben laten zien dat een verhoogde hartslag in rust niet alleen gerelateerd is aan een verhoogde kans op hart- en vaatziekte, maar ook op overlijden door kanker. Een verhoogde hartslag in rust wordt vaak veroorzaakt door een te actief autonoom zenuwstelsel, wat een rol zou kunnen spelen in de ontwikkeling van kanker. Omdat de effecten van een verhoogd hartritme op het ontwikkelen van kanker nog niet goed bekend zijn, hebben we in **hoofdstuk 6** de relatie tussen een de hartslag in rust en het risico op het ontwikkelen van en overlijden aan kanker en de totale kans op overlijden, onderzocht bij patiënten met hart- en vaatziekte. Hierbij is gezien dat patiënten met een verhoogde hartslag meer kans hebben om vroegtijdig te overlijden, maar ook dat deze verhoogde kans niet toe te schrijven is aan een verhoogde kans op kanker. Een relatie tussen verhoogde hartslag in rust en de kans om darmkanker te ontwikkelen kon in deze studie echter niet uitgesloten worden.

Deel II

Voorspellen van behandel-effect voor individuele patiënten

De effectiviteit van medische behandelingen wordt doorgaans onderzocht middels zogenaamde gerandomiseerde klinische studies. Hierin willekeurig toegewezen of een patiënt de behandeling of een controle behandeling (zoals een placebo) krijgt. Vaak worden de resultaten van dergelijke studies alleen als gemiddelde behandel-effecten gerapporteerd. In de klinische praktijk is het echter een grote uitdaging voor artsen om deze gemiddelde effecten te vertalen naar individuele patiënten. Een impliciete aanname bij het gebruik van deze gemiddelde behandel-effecten is namelijk, dat alle patiënten hetzelfde risico hebben en ook hetzelfde reageren op therapie. Het is echter zeer de vraag of deze aannames voor alle patiënten en verschillende behandelingen opgaan. De individuele respons op behandeling hangt vaak af van een combinatie van verschillende factoren, zoals bijvoorbeeld

leeftijd en geslacht van de patiënt en het stadium van de betreffende ziekte. Met behulp van statistische modellen kan op basis van deze factoren, het effect van een behandeling voorspeld worden. Met deze methode kan bepaald worden wie daadwerkelijk baat heeft bij behandeling en wie niet. Dit stelt artsen in staat om de verwachte voordelen van behandeling beter te kunnen afwegen tegen de nadelen ervan en daarmee de behandeling beter toe te kunnen spitsen op de individuele patiënt.

In **hoofdstuk 7** hebben we het behandelen op basis van behandel-effectvoorspellingen vergeleken met andere behandelingsstrategieën met aspirine voor het voorkomen van hart- en vaatziekte en kanker bij vrouwen. In plaats van te focussen op één van deze aandoeningen, hebben we het effect van aspirine op de combinatie van deze aandoeningen onderzocht en daarbij ook het negatieve effect van aspirine op maag- en darmbloedingen in ogenschouw genomen. Hiervoor is gebruik gemaakt van de gegevens van ongeveer dertigduizend vrouwen uit de Amerikaanse Women's Health Studie. Hoewel aspirine het risico op hart- en vaatziekte en darmkanker iets verlaagt, wegen de baten bij de meeste vrouwen niet op tegen de bijwerkingen. Aspirine is echter effectiever in het voorkomen van hart- en vaatziekte en kanker in vrouwen van 65 jaar en ouder en beslistkundige analyses laten ook zien dat het selectief behandelen van deze groep de beste behandelstrategie is. In **hoofdstuk 8** beschrijven we een studie waarin de methode van het voorspellen van behandel-effect voor individuele patiënten is toegepast binnen de oncologie en presenteren we een statistisch model voor het voorspellen van het effecten van verschillende typen chemotherapie voor patiënten met uitgezaaide longkanker. Het model is ontwikkeld met de gegevens van de Nederlandse NVALT-7 studie, waarin de combinatie van de middelen pemetrexed en carboplatin vergeleken is met alleen pemetrexed als tweedelijns chemotherapie. Op basis van een aantal karakteristieken van de patiënt, waaronder leeftijd, geslacht en type/stadium van de tumor, kan worden voorspeld hoeveel maanden winst in overleving de combinatietherapie oplevert vergeleken met alleen pemetrexed. De voorspelde behandel-effecten voor individuele patiënten laten zeer uiteenlopende effecten zien. Sommige patiënten hebben enkele maanden winst in voorspelde levensverwachting, terwijl het bij andere geen of zelfs schadelijke effecten heeft. Vervolgens is met behulp van de data van een extern onderzoek, de Italiaanse GOIRC 02-2006 studie, bepaald of het model de behandel-effecten accuraat voorspelt. Hierbij is gezien dat de voorspelde behandel-effecten aardig overeenkomen met de daadwerkelijke effecten. Bovendien blijkt uit beslistkundige analyse dat gebruik van het model voor het sturen van behandelbeslissingen tot een betere gemiddelde overleving leidt in vergelijking met het behandelen van alle patiënten met combinatietherapie of alle patiënten met alleen pemetrexed. Deze resultaten bevestigen dat de effecten van chemotherapie in patiënten met kanker kunnen worden voorspeld op basis van eenvoudige gegevens die artsen voorhanden hebben in de klinische praktijk. Het voorspellen van het behandel-effect kan worden gebruikt voor het sturen van beslissingen omtrent behandeling en om patiënten te selecteren voor gerandomiseerde onderzoeken.

CONTRIBUTING AUTHORS

Dr. Joachim G.J.V. Aerts

Department of Pulmonary Diseases
Amphia Hospital
Breda, The Netherlands

Prof. dr. Ale Algra

Department of Neurology and Julius Centre for Health Sciences and Primary Care
University Medical Centre Utrecht
Utrecht, The Netherlands

Prof. Andrea Ardizzoni

Medical Oncology Unit
University Hospital
Parma, Italy

Dr. Remy H.H. Bemelmans

Department of Internal Medicine
Gelderse Vallei Hospital
Ede, The Netherlands

Dr. Gert Jan de Borst

Department of Vascular Surgery
University Medical Centre Utrecht
Utrecht, The Netherlands

Dr. Luca Boni

Clinical Trials Coordinating Center
Istituto Toscano Tumori, University Hospital Careggi
Florence, Italy

Prof. Julie E. Buring

Division of Preventive Medicine
Brigham and Women's Hospital, Harvard Medical School
Boston, Massachusetts, USA

Prof. Nancy R. Cook

Division of Preventive Medicine
Brigham and Women's Hospital, Harvard Medical School
Boston, Massachusetts, USA

Dr. Maarten J.M. Cramer

Department of Cardiology
University Medical Centre Utrecht
Utrecht, The Netherlands

Dr. Anne-Marie C. Dingemans

Department of Pulmonary Diseases
Maastricht University Medical Center
Maastricht, The Netherlands

Dr. Johannes A.N. Dorresteijn

Department of Vascular Medicine
University Medical Centre Utrecht
Utrecht, The Netherlands

Prof. dr. Yolanda van der Graaf

Julius Centre for Health Sciences and Primary Care
University Medical Centre Utrecht
Utrecht, The Netherlands

Prof. dr. Harry J.M. Groen

Department of Pulmonary Diseases
University Medical Center Groningen
Groningen, The Netherlands

Prof. dr. L. Jaap Kappelle

Department of Neurology
University Medical Centre Utrecht
Utrecht, The Netherlands

Dr. Hendrik Koffijberg

Julius Centre for Health Sciences and Primary Care
University Medical Centre Utrecht
Utrecht, The Netherlands

Dr. Hendrik M. Nathoe

Department of Cardiology
University Medical Centre Utrecht
Utrecht, The Netherlands

Prof. dr. Petra H.M. Peeters

Julius Centre for Health Sciences and Primary Care
University Medical Centre Utrecht
Utrecht, The Netherlands

Prof. Paul M Ridker

Division of Preventive Medicine
Brigham and Women's Hospital, Harvard Medical School
Boston, Massachusetts, USA

Prof. dr. Peter D. Siersema

Department of Gastroenterology and Hepatology
University Medical Centre Utrecht
Utrecht, The Netherlands

Prof. dr. Egbert F. Smit

Department of Pulmonary Diseases
Vrije Universiteit VU Medical Center
Amsterdam, The Netherlands

Prof. dr. Frank L.J. Visseren

Department of Vascular Medicine
University Medical Centre Utrecht
Utrecht, The Netherlands

Prof. dr. Elsken van der Wall

Department of Medical Oncology
University Medical Centre Utrecht
Utrecht, The Netherlands

SMART Study Group of the University Medical Center Utrecht

Prof. dr. A. Algra, Department of Neurology and Julius Centre for Health Sciences and Primary Care
Prof. dr. P.A. Doevendans, Department of Cardiology
Prof. dr. Y. van der Graaf, Julius Centre for Health Sciences and Primary Care
Prof. dr. D.E. Grobbee, Julius Centre for Health Sciences and Primary Care
Prof. dr. L.J. Kappelle, Department of Neurology
Prof. dr. T. Leiner, Department of Radiology
Prof. dr. F.L. Moll, Department of Vascular Surgery
Prof. dr. G.E.H.M. Rutten, Julius Centre for Health Sciences and Primary Care
Prof. dr. F.L.J. Visseren, Department of Vascular Medicine

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CURRICULUM VITAE

Rob was born on the 25th of June 1986 in Eindhoven, The Netherlands. After graduating from the Van Maerlant lyceum in Eindhoven in 2004, he studied Medicine at Utrecht University. During his studies he was involved in various research projects regarding the relation between adipose tissue dysfunction and cancer at the department of Vascular Medicine in the University Medical Centre Utrecht under the supervision of prof. dr. F.L.J. Visseren and prof. dr. Y. van der Graaf. These projects formed the basis of the present PhD thesis, which focused on the risk of cancer in patients with cardiovascular disease. Furthermore, part of his research included the development of models for individualized prediction of the effects of specific treatments. He combined his PhD research with a Masters in Clinical Epidemiology at Utrecht University from which he graduated in 2013. In October 2014 he started his residency in Internal Medicine at Meander Medical Centre under the supervision of dr. R. Bosma and dr. R. Fijnheer.

