Chapter 1

Introduction and scope of the thesis
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Melanoma is the most aggressive form of skin cancer and is responsible for over 70 percent of skin cancer deaths. [1] Melanomas develop from malignant melanocytes. The gross majority of melanomas occur in the skin, the so-called cutaneous melanomas (CM). Melanoma incidence is among the top ten of leading cancer sites in the United States (US) with a fifth place for men and a sixth place for women. [1] Moreover, based on the years lost to cancer, melanoma would merit a higher ranking because relatively young people are affected by this malignancy. [2-4] Among Caucasian populations in Northern and Western Europe, melanoma incidence rates are increasing steadily by at least three percent each year. [5]

Melanoma prognosis depends on the stage at diagnosis. Melanoma staging is performed according the validated and internationally standarized Melanoma Staging System of the American Joint Committee on Cancer (AJCC). [6] This AJCC melanoma staging system is based on the TNM criteria; that is, thickness of the tumor (T), extent to which it has spread to the lymph nodes (N), and extent to which it has metastasized to other parts of the body (M). Tumor thickness, also referred to as Breslow’s thickness, is one of the strongest prognostic factors [6] and is measured from the skin surface until the deepest point of invasion as described by Alexander Breslow in 1970 [7]. Other factors that predict poor prognosis include advanced age at diagnosis, male gender, ulceration, race, anatomic site (trunk, head-neck region, extremities), and certain histogenetic subtypes, such as acral melanoma. The histopathological subtypes are classified according to the World Health Organization Classification of Tumours. [8]

Often CM are diagnosed at an early stage while the disease is still confined to the local site. For these patients, prognosis is favorable with 5-year relative survival proportions of 98.7 percent in the United States. In contrast, if the disease has spread regionally or in case of distant metastasis, 5-year relative survival proportions drop to 65.2 and 15.3 percent, respectively. [1] For these advanced stages of melanoma, effective treatment options are lacking [9], except may be surgical excision for localized metastasis. In spite of this lack of effective treatment options for advanced melanoma, melanoma mortality rates seem to be stabilizing or (slightly) decreasing. [10] In summary, overall melanoma incidence rates are increasing while mortality rates are stable or decreasing.
In rare cases, melanomas can also arise at noncutaneous sites such as primary melanomas of mucous membranes, the uvea or choroid of the eye, the meninges, or in organ tissue. Due to their rarity, reliable estimates of the incidence and survival rates of such extracutaneous melanomas (ECM), e.g., from population-based registries, are sparse. Establishing the incidence rate of ECM, possible time trends in this incidence and the relative survival of ECM patients in The Netherlands, is a first objective of this thesis.

In chapter 2 we will determine (trends in) the incidence rates of ECM in the Netherlands Cancer Registry. Additionally, we will present 5-year relative survival proportions among ECM patients in this chapter.

As mentioned earlier, melanoma mortality rates are stable or decreasing, while melanoma incidence rates are increasing. Since, additionally, melanoma is usually diagnosed in patients of a relatively young age, overall, the total number of patients suffering from melanoma is accumulating. Consequently, the total burden of melanoma is assumed to be increasing among Caucasian populations. Indeed, evidence from the US and Belgium has also suggested an increase in the burden of cutaneous melanoma. Recent European data estimating (trends in) the different measures of the burden of CM, such as incidence rates, mortality rates, the prevalence, the number of years lost due to disability (YLD), and the number of years of life lost due to premature mortality (YLL), are sparse. The second objective of this thesis is to estimate of the burden of melanoma for the Dutch population. In chapter 3 we will present estimates of the burden of melanoma in The Netherlands.

As the overall burden of melanoma is increasing; prognosis strongly depends on the stage at diagnosis; and, most importantly, effective treatments for advanced stages are lacking, there is a high potential benefit for the prevention of melanoma. However, most of the established risk factors for melanoma, such as fair skin type, freckles, light eye color, older age, history of sun burns, clinical atypical nevi, prior melanoma, and family history of melanoma, are not amenable to intervention. Only sun burns and sun exposure are, at least in theory, amenable. Indeed, sun protection measures are part of melanoma prevention programs. In some high risk countries, such as Australia, comprehensive sun protection programs have been implemented over a decade ago and sun screen use is widely promoted to the general public. These public health campaigns have increased awareness on skin cancer and the adverse events of excessive sun exposure, but failed to change the sun exposure behaviour in the general population which is referred to as the so-called ‘knowledge-behaviour gap’.
Lack of behavioral changes and possibly also the increased awareness explain why the incidence of melanoma in Australia is still increasing. [13] Therefore, alternative approaches in melanoma prevention, such as chemoprevention, should be considered for high risk populations. Chemoprevention, as defined by Sporn and colleagues, is the use of natural or synthetic drugs to reverse, suppress, or prevent premalignant molecular or histological lesions from progressing to invasive cancer. [14]

Ideal candidate drugs for chemoprevention should have additional major health benefits, few (long-term) adverse events and would be inexpensive. Several drug classes, such as statins, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme inhibitors (ACE inhibitors), have been suggested to be of interest in melanoma chemoprevention. [15-17] However, it is unclear which of these and other candidate drugs for melanoma chemoprevention have the potential to be useful and safe. Therefore, the third and main objective of this thesis is to explore which candidate chemopreventive drugs could be beneficial in melanoma and which drugs may be unfavourably associated with the incidence or progression of melanoma.

In chapter 4 we will perform a qualitative review on a subset of the literature available on melanoma chemoprevention on these potential chemopreventive drugs. We will define this subset of the scientific literature with a systematic literature search in Medline, Embase, Web of Science, and The Cochrane Library.

To further explore if drugs have a chemopreventive effect on melanoma in humans, one could use several research designs, such as a prospective randomized controlled trial (RCT), prospective cohort study, retrospective cohort study or a case control study for instance by means of telephone surveys or by the use of pharmacy databases. However, in research practice, the choice of the study design is limited because one needs sufficiently long follow up and large numbers of participants to show chemopreventive effects on melanoma, a relatively rare malignancy that develops over long time periods. In addition, research funds are limited, and retrospective collection of drug exposure by telephone survey is time-consuming and may even be unreliable. For many chemopreventive candidate drugs, such as statins, NSAIDs and estrogens, it is reasonable to assume that exposure allocation is unrelated to the outcome of interest, melanoma. In explanation, at the time of prescribing these drugs, both doctors and patients are not aware of potential effects on melanoma incidence. For such research topics, where the prescriber is effectively blind for the potential effect of interest, observational research may be as credible as RCTs. [18] Therefore, we
will perform a number of case-control studies in a general population-based dataset linking drug-dispensing data from the pharmaco-morbidity linkage network (PHARMO) with pathological data (PALGA) from the nationwide network and registry of histo- and cytopathology in The Netherlands. By means of this pharmacoepidemiological approach, we will attempt to estimate the causal effects on the incidence and progression of melanoma of a few candidate chemopreventive drugs.

In **chapter 5**, we investigate the association between use of statins and the incidence of CM. In addition, potential effects of prior statins use on Breslow’s thickness at diagnosis of CM is studied as well as effects on time to metastasis. As will be described in chapter 4, non-steroidal anti-inflammatory drugs (NSAIDs), both acetylsaliylic acid (aspirin) and non-acetylsaliylic acid-NSAIDs have been suggested to have beneficial effects on melanoma incidence. Therefore, in **chapter 6**, we will study the association between use of NSAIDs including (low-dose) aspirin on melanoma development.

In **chapter 7** an etiological association study on the association between use of ACE inhibitors and angiotensin receptor antagonists on melanoma incidence and progression is executed.

Gender differences in melanoma have been established on both incidence and prognosis. Interestingly, although melanoma incidence is higher among women, survival is improved in female CM patients as compared to male CM patients. This female survival benefit is maintained after adjusting for well-established prognostic factors. [19] Until now, gender differences in melanoma are not well understood. One of the factors that could play a role in these gender differences are the effects of female hormones, such as estrogens. [20] Therefore, in **chapter 8 and 9**, we will study the association between use of estrogens and development and tumor thickness at diagnosis of melanoma, respectively.

Finally, in **chapter 10** the results of the studies presented in this thesis are interpreted and placed into perspective, the potential of drug chemoprevention for melanoma is discussed, and suggestions for future research are postulated. The theme of this thesis is summarized in **chapter 11**.
Reference List


(18) Vandenbroucke JP. When are observational studies as credible as randomised trials? The Lancet 2004, 363, 1728-1731.
