Drug effects on melanoma

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Chapter 11

Summary

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Summary

Melanoma is an accumulating health problem in Caucasian populations. Cutaneous melanoma is responsible for the majority of skin cancer deaths and is, therefore, considered the most aggressive form of skin cancer. Moreover, its incidence among Caucasian populations has increased over the past decades whereas mortality rates are stabilizing or in some areas even decreasing. Overall, the total burden of cutaneous melanoma is expected to be increasing in The Netherlands. In rare cases, melanomas arise on noncutaneous sites, so-called extracutaneous melanoma. Due to its rareness, the epidemiology of extracutaneous melanoma is poorly described in literature.

As the burden of cutaneous melanoma is expected to increase, effective treatment options for advanced melanoma are lacking, and beneficial prognosis of melanoma patients strongly depends on early diagnosis, melanoma prevention is likely to be a key issue in melanoma disease control. Although sun protection programs and educational attempts have led to increased awareness, they have not resulted in behavioral changes to sun exposure and protection nor to a decrease in cutaneous melanoma incidence. In addition, most melanoma risk factors are not amenable. Alternative approaches to melanoma prevention, such as cancer chemoprevention are, therefore, important research topics. Several agents, such as statins, non-steroidal anti-inflammatory drugs including aspirin, and angiotensin-converting enzyme inhibitors, have been claimed to have chemopreventive properties. However, it is unknown which of these potential chemopreventive agents have the best potential to be useful and safe.

This thesis presents:

- cancer registry-based studies from The Netherlands on the epidemiology of extracutaneous melanoma and on the burden of disease due to cutaneous melanoma (*epidemiology of melanoma*)
- a qualitative review, based on a systematically literature search, discussing candidate drugs for melanoma chemoprevention, their possible mechanisms of action and summarizing the existing evidence for their chemopreventive efficacy, safety and tolerability (*chemoprevention of melanoma*)
- pharmacoepidemiological studies testing hypotheses on chemopreventive activity on melanoma of statins, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers (*chemoprevention of melanoma*)
- pharmacoepidemiological studies on the hypothesized association between estrogen use and melanoma (*hormonal and gender differences in melanoma*)

Epidemiology of melanoma

In **chapter 2** we explored the (long-term trends in the) incidence and survival of extracutaneous melanoma in The Netherlands. Based on data from the Netherlands Cancer Registry combined with vital status, we determined the incidence and relative survival of extracutaneous melanoma between 1989 and 2006. We estimated extracutaneous melanoma incidence rates, long-term trends in extracutaneous melanoma incidence, and 5-year relative survival proportions and compared them with those of cutaneous melanoma.

Between 2003 and 2006, extracutaneous melanoma compromised 6.4% of all primary melanomas in The Netherlands. Of all extracutaneous melanoma subsites, ocular melanomas were the most common extracutaneous melanoma subsite with European Standardized incidence Rates of 10.7 and 8.2 per million person-years for males and females, respectively. In addition, ocular melanomas had the best survival. Five-year relative survival for extracutaneous melanoma was worse if compared to cutaneous melanoma for all subsites, but differed largely between anatomical subtypes ranging from 74% for ocular melanomas to 15% for certain subsites of mucosal melanomas. In contrast with cutaneous melanoma for which an annual increase in incidence of 4.4 percent for men and 3.6 percent for women was detected, no statistically significant trends in the incidence of (subsites of) extracutaneous melanoma were observed.

Chapter 3 describes the total burden of cutaneous melanoma within The Netherlands. As we hypothesized, the total burden of cutaneous melanoma increased between 1989 and 2006. The cumulative incidence of cutaneous melanoma almost doubled between 1989 and 2006. In addition, the number of melanoma deaths, the number of years of life lost (YLL), the number of years lost due to disability (YLD), and the number of years of life lived with disease (YLWD) all accumulated in time. On average, patients lived 21.5-28.4 years with a melanoma diagnosis and melanoma resulted in a loss of about 18-20 years per before the age of 95 for those that died of their melanoma. Including all patients diagnosed with an melanoma, not only those that die from it, the average life loss is about 3 years.

Overall, the burden of melanoma to society increased rapidly between 1989 and 2006.

Chemoprevention of melanoma

In **chapter 4** we discuss the available evidence for candidate drugs that have potential to be used in melanoma chemoprevention. Cancer chemoprevention, as defined by Sporn *et al.*, is the use of an agent to reverse, suppress, or prevent premalignant

molecular or histological lesions from progressing to invasive cancer. A systematic literature search was performed and a qualitative review of the selected scientific papers on drug chemoprevention of cutaneous melanoma is presented. This review show that considerable preclinical evidence of efficacy as a melanoma chemopreventive drug exists for aspirin, non-steroidal anti-inflammatory drugs, and statins. However, definite data on efficacy in humans and profound long-term safety data in the required doses are lacking. Therefore, only relatively safe drugs indicated for other health effects but with additional chemopreventive properties in cancer development, such as low-dosed aspirin and statins, can currently be encouraged in people at increased risk of cancer. Less evidence is available for other potential chemopreventive drugs, such as fibrates, retinoids, imiquimod, dehydroepiandrosterone, and acetaminophen.

In the next part of the thesis, we report on a number of pharmacoepidemiological studies using a general population-based dataset (PHARMO) with drug-dispensing data from the pharmaco-morbidity linkage network linked with the national pathological database (PALGA).

Chapter 5 presents a case-control study into the hypothesized association between the incidence and progression of CM and exposure to statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors). We study both the association between use of statins and the incidence of cutaneous melanoma as well as the potential effects of prior statins use on Breslow's thickness at diagnosis of cutaneous melanoma. Cutaneous melanoma risk was not associated with statin use for at least 0.5 year in the 3 years before diagnosis. Although none of the statin-related independent variables consistently supported a risk reduction of statin use on the incidence of cutaneous melanoma, statin use was associated with a reduced Breslow's thickness at diagnosis (–19%, 95% CI = –33, –2.3). This apparent disparity suggests that statins slow melanoma progression but do not protect against cutaneous melanoma development. However, the disparity could also result from the relatively short follow-up.

Surprisingly, after stratification for gender, the finding of a reduced Breslow's thickness among statin users was confirmed for men (–27.8%, 95% CI =–43.7, –7.4) but not for women (–4.8%, 95% CI=–29.6, 28.8). This suggest a clinically relevant reduction of 0.58 mm on average in Breslow's thickness among men. As Breslow's thickness at diagnosis is one of the strongest determinants for prognosis, this should be considered an important finding. However, (residual) bias cannot be excluded and our study is the first study to investigate statin use as a determinant of Breslow's depth. Therefore, validation of these findings is necessary.

In **chapter 6** we study the association between use of non-steroidal anti-inflammatory drugs (NSAIDs) on melanoma development. We included both acetylsaliylic acid (aspirin, ASA) as well as non-ASA NSAIDs.
Cutaneous melanoma incidence was not significantly associated with ever ASA use (adjusted OR = 0.92, 95% CI = 0.76-1.12) or ever non-ASA NSAID use (adjusted OR = 1.10, 95% CI = 0.97-1.24). However, continuous use of low-dose ASAs was associated with a significant reduction of CM risk in women (adjusted OR = 0.54, 95% CI = 0.30-0.99) but not in men (adjusted OR = 1.01, 95% CI = 0.69-1.47). A significant trend (p = 0.04) between categories of ASA use from no use, non-continuous use to continuous use was observed in women.
Continuous use of low-dose ASAs may be associated with a reduced incidence of cutaneous melanoma in women, but not in men.

Angiotensin-converting enzyme inhibitors (ACEi) and possibly angiotensin II receptor blockers (ARb) have also been claimed to have chemopreventive properties. In **chapter 7** we explored the possibility of an association between exposure to ACEi and ARb and the development of cutaneous melanoma.
This study showed no statistically significant associations between the incidence of melanoma and the use of ACEi (adjusted OR= 1.0, 95% CI = 0.8-1.3) or ARb (adjusted OR = 1.0, 95% CI = 0.7-1.5). In addition, the use of ACEi or ARb was not associated with decreased Breslow's thickness. Thus, the use of ACEi or ARb does not seem to protect against the development of cutaneous melanoma. However, due to limited numbers of ACEi and ARb users, we cannot exclude an association between ACEi and ARb exposure and either a (moderately) increased or decreased incidence of cutaneous melanoma. Moreover, residual confounding cannot be excluded. For example, sun exposure may be indirectly related to ACEi and ARb exposure because it may be associated with increased physical activity and a reduced chance of hypertension. Likewise, high social economic status is associated with increased sun exposure and may also be associated with a reduced chance of hypertension. Both these potential biases would in an underestimation of any effect of ACEi and ARb and would thus produce bias toward the null.

Hormonal and gender differences in melanoma

To our surprise, female melanoma cases in the previous studies (chapter 5, 6 and 7) were more likely to be estrogen users than controls. After reviewing literature, we were confronted with several clues indicating possible hormonal influences in melanoma. First, hyperpigmentation is a side-effect of oral contraceptive (OC) use

and may also occur during pregnancy (chloasma) or with the use of hormonal replacement therapy (HRT) both indicating an effect of estrogens on melanocyte proliferation. Second, the pattern of cutaneous melanoma incidence rates with advancing age in women mimic those of breast cancer and differs from the pattern of cutaneous melanoma rates among men. In addition, improved survival among female melanoma patients as compared to males has been demonstrated to remain after adjusting for demographic and tumor characteristics.

As female sex steroids could be involved, we decided to study exposure to estrogens, both oral contraceptives (OC) and hormonal replacement therapy (HRT), and a possible association with the incidence of CM in more detail. In **chapter 8** an association between estrogen use, both OC and HRT, was confirmed for exposure expressed as use for at least half a year, and for the highest categories of cumulative dose and prescription duration. The results suggest a cumulative dose-dependent increased risk of cutaneous melanoma with the use of estrogens, both OC and HRT. However, most previous studies on estrogen use and melanoma are not in agreement with our findings.

As some *in vitro* studies have suggested a direct inhibitory effect on melanoma tumor growth, the use of OC and HRT may be associated with a decreased Breslow's thickness. If so, the clinical impact of an increased cutaneous melanoma incidence with OC and HRT use would be limited. In **chapter 9** we investigated if estrogen use is associated with a decreased Breslow's thickness. However, we could not confirm an association between either OC use or HRT and Breslow's thickness.

In conclusion, the modest level of association between cutaneous melanoma incidence and OC use that resulted from our studies is not in agreement with previous studies, and as cutaneous melanoma risk is generally low, we can conclude there is no need to change OC prescription. Abandoning regular prescribing of HRT for uncomplicated menopausal complaints should be advocated, but for more urgent reasons than increased melanoma risk.

In **chapter 10** the results of this thesis are discussed, possible future directions are outlined and final conclusions are drawn. Since 1989-1998, cutaneous melanoma incidence has further increased between 1998 and 2006 in The Netherlands. Likewise, the total burden of cutaneous melanoma has accumulated over the last decades. These new estimates of the incidence and burden of cutaneous melanoma should be used in health-care planning for melanoma care and surveillance.

Although prognosis is favorable for the majority of melanoma patients, prognosis is poor for some subgroups of patients. Survival for all extracutaneous melanoma

subsites was poor compared to cutaneous melanoma patients but differed substantially for extracutaneous melanoma subsites being most favorable for ocular melanomas.

Several strategies for cancer chemoprevention exist, such as primary, secondary or tertiary cancer prevention and the population or the high risk strategy. As most chemopreventive agents have demonstrated toxicity at some level and long-term compliance is required, the high risk strategy would be the choice of interest for melanoma chemoprevention. Because the absolute risk of getting a melanoma is small, tertiary cancer chemoprevention, at least as a first goal, would seem to be the most realistic as these patients would be at sufficiently high risk of developing a second invasive melanoma. As an additional advantage, in tertiary prevention, one could select a chemopreventive agent for its (additional) potential to prevent metastasis.

Based on current evidence, it is not yet possible to determine which candidate chemopreventive drug(s) is likely to be the most efficacious in medical practice. However, considerable preclinical evidence of chemopreventive efficacy exists for aspirin, NSAIDs, and statins. Lack of definite data on efficacy in humans and profound long-term safety data in the required doses, however, preclude the use of chemopreventive drugs for melanoma in current practice. Future research should explore possible differential effects within a drug class, temporal dose-response relationships, and possible synergistic or antagonistic effects.

In addition, focus should be on how to define high risk subpopulations at whom chemoprevention to target on. Such strategies should be based upon validated prediction models. Candidate items to select for such prediction models could include individual melanoma risk factors including an individual's mutational status of genetic susceptibility genes, validated early biomarkers of invasive melanoma risk, validated molecular and histopathological aspects of any prior tumor, and individual risk factors predicting adverse events of the chemopreventive drug.

In addition, we conclude that gender may have a complex relationship with melanoma development and progression as indicated by several findings. Although these relationships have been studied over a long time, gender differences and possible hormonal influences in melanoma remain are still poorly understood.

To understand these gender differences in melanoma, future studies are warranted. However, as cutaneous melanoma risk is generally low, we can conclude there is no need to change OC prescription. In contrast, abandoning regular prescribing of HRT for uncomplicated menopausal complaints should be advocated, but for more urgent reasons than increased melanoma risk.