Chapter 10

General discussion, future perspectives and conclusions
Epidemiology of melanoma

Cutaneous melanoma (CM) in general is a growing health problem in Caucasian populations. Fortunately, the majority of cases are usually diagnosed at an early stage of the disease, that is, while the disease is still confined to the local site. Prognosis in these melanoma patients is favorable with 5-year relative survival proportions reported to be as high as 90% for women and 81% for men in The Netherlands [1]. Nevertheless, CM incidence is among the top ten of leading cancer sites among both sexes in both the United States (US) [2] and in North-western European countries [3,4]. After surgical removal of the tumor, the majority of patients will survive CM, but will remain at risk of developing regional or distant metastases for many years. [5] This risk is low but extends over prolonged periods of time. In addition, these patients are at increased risk of new primary melanomas (~5% in 20 years). [6] As a consequence, melanoma can be considered a chronic, life-threatening disease which has a significant impact on the quality of life of these patients. [5] Moreover, the incidence of CM has increased rapidly over the last decades in these Caucasian populations. [2, 7] For example, in Sweden, over a 20-year period between 1987 and 2006, CM incidence has increased with an average annual increase of 2.3% among men and 2.1% among women. [3] For The Netherlands, de Vries and colleagues have reported an annual increase in CM incidence of 2.2% in women and 3.3% in men over a 10-year period between 1989 and 1998. [7] Although a 3% annual increase may not seem large, it increases exponentially to already 34% in just one decade (1.03^10). In contrast with US data reported by the American Cancer Society indicating that CM incidence has been stable in the US since 2000 [2], we show in this thesis (chapter 2) that CM incidence is still significantly increasing among both sexes in The Netherlands (men: EAPC = 4.4%, 95% CI = 3.9% to 4.9%; women: EAPC = 3.6%, 95% CI = 2.9% to 4.2%). Between 1989 and 2006, the increase in CM incidence did not change (join point analysis) in The Netherlands.

Risk factors for CM include a history of sunburns, especially in childhood, high chronic sun exposure, advanced age, prior melanoma, a family history of melanoma, presence of clinical atypical nevi, and phenotypic traits, such as fair skin type, freckles, light eye color and photosensitivity. Family history of melanoma and prior melanoma are likely to be surrogate markers for genetic risk factors. In the last two decades, melanoma research has focused on finding such genetic factors. Part of the familial clustering can be explained by rare mutations in CDKN2A (encoding p16INK4a and p14ARF) and
CDK4 which are high-penetrance genes. [8,9] In addition, some low-penetrance factors contributing to melanoma susceptibility, such as single-nucleotide polymorphisms in or near MC1R, ASIP, TYR and TYRP1, have been identified. These genes determine well-established melanoma risk factors as hair and skin pigmentation, but their exact role in melanoma development remains unclear. [10] As the majority of familial cases remain unaccounted for, one may expect future additional advances in revealing genetic susceptibility genes. An individual’s mutational status of such genes can in the future be used to develop personalized surveillance and prevention measures.

While the incidence of CM has increased over the last decades, mortality rates of CM seem to have stabilized or even slightly decreased. [11] In addition, CM patients are relatively young at diagnosis. [12-14] Consequently, the total burden of CM is expected to have increased in these populations. However, recent estimates of the burden of CM, other than just incidence and mortality rates, are sparse. Moreover, in most studies only a small number of the possible different measures of the burden of melanoma have been compared. [12,13,15,16] Estimates of the burden of melanoma within the Dutch population were not available. Data from the Belgium National Cancer Registry (1987-1992), however, have been published. These data showed that the years of life lost per death (average years of life lost, AYLL) was 8.1 years for men and 6.3 years for women prior to the age of 65 years. [13] Since then, the incidence of CM has increased and, moreover, life expectancy will also be affected beyond the age of 65 years. Therefore, these data are likely to underestimate the current burden of CM in the Dutch population. Indeed, in chapter 3, we demonstrated that the total burden of CM has accumulated in The Netherlands and that the AYLL in 2002-2006 was 17.7 and 20.4 years for men and women, respectively.

By estimating a series of different measures of burden, we determined the burden of CM to the Dutch population in 5-year periods between 1989 and 2006. These measures of burden were: cumulative incidence rates, cumulative mortality rates, number of years of life lost (YLL), average number of years of life lost (AYLL; the number of years of life lost per death; YLL/deaths), number years of life lost to disability (YLD), the number of years of life lived with disease (YLWD), the average number of years lived with disability (AYLD), and the average number of years lived with disease (AYLWD) by Dutch CM patients.

1 incidence & mortality rate, prevalence, number of years of life lost (YLL), average number of years of life lost (AYLL; the number of years of life lost per death; YLL/deaths), number years of life lost to disability (YLD), the number of years of life lived with disease (YLWD), the average number of years lived with disability (AYLD), and the average number of years lived with disease (AYLWD).
The incidence of melanoma almost doubled between 1989 and 2006 (cumulative incidence rate increased from 1.0-1.3% to 2.0-2.1%). Likewise, the cumulative mortality rates also doubled up to 0.61 for males and up to 0.40% for females. Surprisingly, age at diagnosis of melanoma increased over 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 before the age of 95 for those that died of their melanoma. Including all patients diagnosed with a 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.

As a consequence of the high burden of melanoma, some argue that melanoma is among the ‘Cinderella cancer types’. For example, Burnet and colleagues compared the average years of life lost due to 17 different cancer types with the research funds spent on these cancer types by the National Cancer Research Institute of the UK. This led to the conclusion that, based on this ratio, melanoma as well as tumors of the CNS, kidney and cervix would merit higher research funds. [16] Likewise, if one would define ranking not solely on the incident numbers or the estimated number of deaths due to a certain cancer type, but on a more detailed measure of the burden to the population, melanoma would most likely merit a higher ranking. [13] This disparity is, in part, due to the fact that relatively young people are affected by melanoma as compared to other malignancies, but, ironically, also due to the relatively favorable survival of most melanoma patients. Nevertheless, metastasis risk for CM patients is prolonged, effective treatment options are limited once (multiple) positive lymph nodes, skin metastasis or organ metastases have developed. In addition, CM incidence increases and patients with prior melanoma are at higher risk of a second primary melanoma. Therefore, in countries with high and increasing CM incidence, future health-care planning for melanoma care and surveillance is of great importance.

Although prognosis is favorable for the majority of CM patients, for some subgroups of melanoma patients, prognosis is poor. For example, patients with advanced stages of CM at diagnosis, such as regionally spread disease, have a dismal prognosis. In US data from 2008, CM patients with regional spread had a 5-year relative survival of 65.2% (versus 98.5% for CM local disease). [2] With further spread of the disease, that is, if distant metastasis has occurred, no effective treatment options are available [17] and the 5-year survival proportion even drops to 15.3%. [2]

Likewise, prognosis for patients with more rare subtypes of melanoma, such as acral lentiginous melanoma (ALM) or extracutaneous melanoma (ECM), is generally worse as compared to CM patients. [18,19] With data from the Surveillance Epidemiology
and End Results (SEER) dataset in the US, Bradford et al. recently estimated 5-year survival for ALM patients and CM patients to be 80.3% compared to 91.3% for CM patients. [18] However, for ECM subsites, reliable and recent incidence and survival estimates, for example, based on well-described national population-based databases or geographic regions, are largely lacking. Available European data are either outdated or concerned hospital-based series. [20,21] For the US, recent incidence data on ECM are available. Unfortunately, however, survival estimates and trends in the incidence of ECM were not reported. [22]

In chapter 2, we demonstrate that, in The Netherlands, 6.4% of all primary melanomas between 2003 and 2006 were ECM. In addition, we showed that, within the Dutch population between 1989 and 2006, five-year relative survival proportions of ECM patients were indeed worse in comparison with CM patients. Ocular melanoma was shown to be the most frequent subsite of ECM, and had the best survival. Five-year relative survival for ocular melanoma was 74% which was significantly less than the estimated 5-year relative survival for CM patients (86%; chapter 2). Mucosal melanomas were diagnosed less frequently, but survival of patients with this type of melanomas was dismal. Five-year relative survival for mucosal melanomas ranged from 15% for anorectal and esophageal melanomas combined to 40% for vulvar melanomas.

Incidence rates of ECM subsites with sufficient numbers, such as all mucosal melanomas, those of the ear-nose-throat region, and vulvar melanomas, did not show statistically significant trends in time (join point analyses and EAPC estimates). In contrast, CM incidence has significantly increased in the same time period among both sexes (men: EAPC = 4.4%, 95% CI = 3.9% to 4.9%; women: EAPC = 3.6%, 95% CI = 2.9% to 4.2%; chapter 2).

The increase in CM incidence is often assumed to be related to increased sun exposure (during childhood) and increased awareness. As the majority of ECM are not exposed to direct ultraviolet light and often not visible for the patient, one may postulate a lack of similar time trends in ECM incidence. Indeed, we did not demonstrate such trends. However, due to low incident numbers, the confidence intervals of the EAPC were wide for some subsites. Therefore, we cannot prove that time trends in the incidence of ECM subsites were significantly different from the time trends in CM incidence. Moreover, it is statistically impossible to prove a lack of association or, as Carl Sagan formulated, ‘Absence of evidence is not evidence of absence’.

Nevertheless, differences in the demographics of affected patients, and in clinico-pathologic and molecular aspects, such as presence of c-KIT mutations, do suggest different pathways in the development of ECM as compared to CM. For example, a large proportion of CM lesions contain a BRAF- or NRAS-mutation [23], whereas 39%
of mucosal, 36% of acral, and 28% of melanomas on chronically sun-damaged skin harbor mutations and/or copy number variants of receptor tyrosine kinase KIT. [24] These differences, next to late diagnosis, may explain clinical heterogeneity, poor survival, diversity in melanoma biology, and response to therapy, and are likely to reflect differences in the causal pathways involved in the development of these melanoma subtypes.

Due to the rarity of ECM, incident numbers in some ECM subsites were low and, therefore, stratifying for the clinical stage of ECM at diagnosis in the survival analysis was impossible. Likewise, very refined clustering, such as separate clustering of anorectal and esophageal melanomas, was also impossible. Larger datasets, such as through Eurocare, could help in varying out such analyses and would, if present, improve chances of determining time trends in incidence and join points. However, data quality for these rare tumors may not be sufficient in some national cancer registries.

In conclusion, in this part of the thesis we have shown the incidence of CM has further increased in The Netherlands, and the total burden of CM has accumulated over the last decades. More than 5% of all invasive melanomas in The Netherlands have an extracutaneous origin, but survival of these patients is poor with 5-year relative survival proportions ranging from 74% to 15%, and the worst survival concerned mucosal melanomas.

**Prevention of melanoma**

A number of observations suggest a high potential benefit for the prevention of melanoma. First, CM incidence is increasing and the total burden of CM is accumulating. Second, effective treatment options for stage IV melanoma are lacking. Third, metastasis risk is prolonged over long time periods. And, most importantly, prognosis strongly depends on the stage at diagnosis.

Indeed, prevention has gained much interest in melanoma research. As mentioned before in this thesis, most of the established risk factors for melanoma are not amenable to intervention. Sun burns and sun exposure, as exceptions, are in theory amenable. Thus far, however, educational attempts and sun protection measures have not led to behavioral changes with regard to sun exposure and protection nor has the incidence of melanoma decreased or stabilized. [25-27] In a telephone survey among parents in the US, although the parents were aware of the need for sun protection for themselves and their children, many still considered a tanned skin to be
a healthy sign. Moreover, 13% of children sunburned during the past week or weekend, and 9% of their parents experienced a sunburn during the past weekend. [25] In addition, in a series of studies in the US, 87% of young adults going to the beach in 2007 were aware of a link between skin cancer/melanoma and tanning. However, knowledge about limiting tanning was seemingly concurrent with an increase in the attitude that having a tan looks better. [26] Australia, where a predominantly susceptible fair-skinned population is combined with high ambient UV radiation levels, has one of the highest skin cancer incidence and mortality rates of the world. Since the 1980s, large sun protection and awareness campaigns have been implemented in this country. [28] In spite of these enormous efforts, incidence rates, especially among individuals aged 40 years and above, have not decreased. [27]

From these studies, one can conclude that although knowledge and awareness about melanoma can be improved, we do not seem to be able to sufficiently influence (long-term) UV risk behavior. This so-called ‘knowledge-behavior gap’ suggest that we need to explore alternative preventive measures that will either create opportunities to succeed in changing UV risk behaviors or will avoid the need for changing these behaviors in individuals at risk. Either way, such preventive measures will need to be more acceptable to the public it aims at, and should, obviously, be effective, safe, cost-efficient, and preferably easy to implement. As other known melanoma risk factors, such as prior melanoma, family history of melanoma, large numbers of nevi, clinical atypical nevi, skin phototype, freckles, light eye color, and advanced age, are not amenable, the number of alternative options is limited.

Population-based skin cancer screening is one of the suggested possibilities. Prerequisites for screening to be appropriate have been defined by Wilson and Jungner in 1968. [29] Whether skin cancer screening meets these requirements, however, is uncertain. Arguments against screening in the general population could include that CM incidence may not be high enough, melanoma mortality is relatively low, any screening interval would probably be too long for the most aggressive melanomas, the fact that most melanomas already are diagnosed at an early stage, and diagnosis of suspected lesions may not be specific enough leading to a high number of false positives and unnecessary biopsies. Nevertheless, skin cancer screening remains much debated in literature [30], and a number of studies have focused on such an approach.

Free skin checks, often referred to as ‘melanoma Monday’, have been organized in both the USA [31] and countries in Europe [32]. These skin checks are successful in creating good publicity, an opportunity for education on melanoma, and sometimes a large number of the public attending. The number needed to prevent (NNP) one
melanoma, in explanation, the number of pathologically proven melanomas calculated per participant, varied from one melanoma per 110 (Belgium) [32], 277 (UK) [33] or 667 (Australia) [31] attendees. The lower NNPs resulted from studies in which high risk subpopulations were selectively invited to attend the free skin checks. In a US study that was neither randomized nor controlled, a reduced melanoma mortality was reported. [34] However, these study designs are insufficient to assess the merits of (skin) cancer screening for which a RCT design is indispensable.

In Australia, such a RCT was planned. Population screening was carried out in small Queensland towns, where some residents were selected for the screening, and compared with control towns, where mass screening was not offered. [35] This trial showed that such a population skin cancer screening program was feasible, increased melanoma awareness, and resulted in a higher number of CM diagnosed among men older than 50 years. [36] Specificity of screening for melanoma was 86%, and the positive predictive value was 2.5%. Follow-up of participants with a negative screening examination was, however, not conducted. Therefore, the number of true negative results and the true specificity is unknown. [37] Lack of true RCTs precludes true assessment of cancer screening programs as only these study designs can exclude lead time, length time and volunteer bias. Unfortunately, lack of funding, even in Australia with the highest world-wide incidence of CM, hampered the original plan to extend the work to a larger national trial which is needed to establish the overall merits of skin cancer screening.

Overall, these data suggest that skin cancer screening may not be efficient enough for a screening program aimed at the general public, but could be beneficial for selected high risk populations, such as men aged 50 years and older.

Another preventive measure, as an alternative or additional to classic sun prevention measures, would be the use of motivational interviewing by dermatologists to enhance patient motivation to reduce UV risk behaviors. Such motivational interviewing has been successfully implemented in health care settings by physicians to modify a variety of behaviors such as smoking. [38] In addition, cancer chemoprevention, more specifically melanoma chemoprevention, is another alternative option with potential to be an effective preventive measure among individuals at high risk of CM (Table 1).

**Chemoprevention of melanoma**

The concept of cancer chemoprevention was first described and defined by Sporn et al. in 1976. They defined ‘cancer chemoprevention’ as ‘the use of natural or synthetic drugs to reverse, suppress, or prevent premalignant molecular or histological lesions from progressing to invasive cancer’. [39]
Agents proposed in literature for cancer chemoprevention differ both in origin and type of application. For example, macronutrients, micronutrients, such as vitamins & antioxidants, non-nutritive phytochemicals and several drugs have been suggested. In addition, for some agents, such as retinoids, both oral and topical application has been suggested. Some authors suggest that ‘diet modification should be considered as a preferred preventive intervention given the low toxicity, low cost, and relative ease of implementation’. [40] However, any a priori statement on an agent’s safety based on its origin is premature. For any agent, irrespective of their origin, the first requirement should be efficacy. In addition, the safety of a substance as a cancer chemopreventive agent can only be assessed after the target population and effective dosages have been established. History has taught us that even agents that were

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**Table 1** Potential target populations for melanoma chemoprevention in a high risk strategy

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk estimate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous invasive CM</td>
<td>SIR = ~ 4 - 25</td>
<td>[42,43]</td>
</tr>
<tr>
<td>Atypical mole syndrome</td>
<td>SMR = ~ 18</td>
<td>[44]</td>
</tr>
<tr>
<td>Invasive CM in first-degree relatives(^1)</td>
<td>RR = ~ 2 - 10</td>
<td>[45,46]</td>
</tr>
<tr>
<td>Clinical atypical (dysplastic) nevi</td>
<td>RR (single) = ~ 2</td>
<td>[47]</td>
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<tr>
<td></td>
<td>RR (2-4 nevi) = ~ 7</td>
<td></td>
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<tr>
<td></td>
<td>RR (5-9 nevi) = ~ 5</td>
<td></td>
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<tr>
<td></td>
<td>RR (&gt;10 nevi) = ~ 12</td>
<td></td>
</tr>
<tr>
<td>Several large nevi (3-5 moles ≥ 3 mm in diameter on arms or lower legs)</td>
<td>RR = ~ 2.1 - 3.4</td>
<td>[46]</td>
</tr>
<tr>
<td>MC1R variants</td>
<td>RR = ~ 1.5 - 2.5</td>
<td>[48]</td>
</tr>
<tr>
<td>Red hair color</td>
<td>RR = ~ 2</td>
<td>[46]</td>
</tr>
<tr>
<td>High solar exposure in early childhood (&lt;10 yrs)</td>
<td>RR / OR = ~ 2 - 4</td>
<td>[49]</td>
</tr>
<tr>
<td>History of severe sunburn</td>
<td>RR / OR = ~ 1.5 - 2.5</td>
<td>[46,49]</td>
</tr>
<tr>
<td>Past sunbed use at ages &lt;35 yrs</td>
<td>RR = ~ 1.2</td>
<td>[50]</td>
</tr>
<tr>
<td>Occupation (airline crew)</td>
<td>SIR = ~ 2.5</td>
<td>[51]</td>
</tr>
<tr>
<td>Occupational chemical / toxic exposure(^2)</td>
<td>Risk estimate = ~ 1.5 - 3.0</td>
<td>[52]</td>
</tr>
</tbody>
</table>

\(^1\) One or more first-degree relatives (parent, sibling or child) with invasive cutaneous melanoma.

\(^2\) These include: pesticides, polycyclic aromatic hydrocarbon (PAHs), benzene, and polychlorinated biphenyls (PCBs), trichloroethylene solvents, dioxin, and polyvinyl chloride (PVC), ionizing and non-ionizing radiation.

SIR = Standardized Incidence Ratio, SMR = Standard Morbidity Ratio, RR = Relative Risk, OR = Odds Ratio.
considered to be safe can, in fact, have serious safety issues. For example, beta carotene in a (long-term) chemoprevention trial of lung cancer has been associated with an increase rather than a reduction of the incidence of lung cancers. This unexpected toxicity, that had not been observed previously, most likely was explained by differences in drug dosing scheme, more specifically the cumulative dose, and the target population. [41]

For melanoma chemoprevention, several potential high risk populations can be considered. These are presented in Table 1. The level of CM risk in a target population should be high enough in order to lead to a sufficiently high NNP and to outweigh the disadvantages of long-term chemopreventive therapy. Nevertheless, simply selecting the subpopulations with the highest risk estimates may not always lead to the best results from a public health perspective.

Several strategies are available for cancer prevention. First, one can aim primary prevention of the initial cancer in individuals at risk, secondary prevention of invasive cancer in patients with premalignant conditions, or one can aim at tertiary prevention among cancer patients in order to prevent second primary cancers. [53] 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. Moreover, in tertiary prevention, one could select a chemopreventive agent for its (additional) potential to prevent metastasis and, thus, combine adjuvant and chemopreventive effects increasing the potential overall benefit.

Second, cancer prevention can be performed according to a high risk strategy or the population strategy. In the high risk strategy, one detects certain individuals in the population that are most susceptible to the disease, and aims preventive interventions at these high risk individuals. In contrast with the population strategy, where one attempts to control the determinants of incidence in order to lower the overall risk of the total population. [54] In explanation, sun protection campaigns to change awareness and UV risk behavior of the general public are examples of the population strategy and examples of primary cancer prevention.

Advantages of population strategies include that the preventive intervention usually is radical (one attempts to eliminate the ‘true cause’), all individuals at risks are aimed at and, thus, there is a large potential benefit for the population, and the intervention often is behaviorally appropriate. Disadvantages, however, include that the benefit on an individual level can be small (the so-called prevention paradox, a small risk for a large number of individuals at risk may give rise to more cases than a small number of
subjects at high risk of disease) which may lead to poor motivation of physicians and subjects. Moreover, as the potential benefit at an individual level can be small, the risk-benefit ratio, for a number of the subjects aimed at, can be worrisome. The high risk strategy, on the other hand, has the advantage that the intervention is appropriate to the individual which supports both the motivation of the physician as well as the patient, it leads to a cost-effective use of resources (intervention on a subset of the population), and the benefit-risk ratio is more favorable. [54] Nevertheless, the advantages of the population strategy, obviously, also reveal the disadvantages of the high risk strategy.

As mentioned, the limited effects of sun protection programs have stressed the importance of enhancing patient motivation in melanoma prevention which seems to be one of the key issues. Therefore, the high risk strategy (see Table 1) which supports the patient’s and physician’s motivation may be of interest. As most chemopreventive agents have demonstrated toxicity at some level (chapter 4), the high risk strategy certainly would be the choice of interest for melanoma chemoprevention.

For melanoma chemoprevention, several candidate drugs have been suggested. However, it is unclear which of these have the potential to be useful and safe. Therefore, in chapter 4, we carried out a systematic literature search in Medline, Embase, Web of Science and The Cochrane Library. We selected scientific papers on drug chemoprevention of cutaneous melanoma, restricted our review to drugs for which human data were available from clinical trials or observational research, and also included papers identified through cross referencing if they met these definitions. The efficiency of our literature search was relatively low (~75% of the finally included references did not emerge from the systematic literature search, and ~95% of the output of the literature search was excluded). This was probably caused by the fact that no MESH term is defined for ‘chemoprevention’. Research would certainly benefit from such a MESH term.

Our systematic literature search identified 13 potential chemopreventive drug classes for CM. For 7 of these, human efficacy data were available. Consequently, we focused our review on the drug classes of NSAIDs, statins, fibrates, retinoids, imiquimod, dehydroepiandrosterone, and acetaminophen. On this subset from literature, we subsequently conducted a qualitative review.

In summary, the general conclusions from this review are that considerable preclinical evidence of efficacy as a melanoma chemopreventive drug exists for aspirin, NSAIDs, and statins, but clinical efficacy and long-term safety data with doses required for melanoma chemoprevention are still sparse. Moreover, validated preclinical models
are urgently needed to move melanoma chemoprevention forward. In future research, special attention should be paid to explore possible differential effects within a drug class, temporal dose–response relationships, and to possible synergistic or antagonistic effects. In addition, research should also focus on how to define the target populations and large randomized trials in high risk populations are required. Thus far, lack of definite data on efficacy in humans and profound long-term safety data in the required doses, preclude the use of chemopreventive drugs for melanoma in current practice. However, the use of relatively safe drugs indicated for other health effects but with additional chemoprophylactic properties in cancer development, such as low-dosed aspirin and statins, may be encouraged in people at increased risk of cancer. Success factors for melanoma chemoprevention to be useful in patient practice will likely be: 1) little-or-no toxicity, to ensure safety, tolerability, and adherence (note: even mild but inconvenient side effects may have significant influence on adherence), 2) a sufficiently motivated target population, 3) a clear-cut definition of the high risk subpopulations at whom chemoprevention should target based upon validated prediction models, mutational status and, if possible, validated early biomarkers of invasive melanoma risk, and 4) a clear-cut definition of contraindications and predictors for individuals prone for the adverse events the chemopreventive drug may cause in order to withhold the drug from these individuals or to present additional preventive measure to them.

In chapter 5, we investigated the association between use of statins and the incidence of CM. In addition, the potential effects of prior statins use on Breslow’s thickness at diagnosis of CM as well as effects on time to metastasis were studied. None of the statin-related independent variables in our study consistently supports a risk reduction of statin use on the incidence of CM. Possibly, the average daily doses in our population (median: 1.3 to 2.0 DDD) are not high enough to show a chemopreventive effect. Follow-up may have been too short and adherence may have been too poor. However, in spite of several studies and (systematic) reviews published on the subject, evidence for a reduced melanoma incidence with statin use is lacking so far. [55,56] Interestingly, our data did suggest that statin use is associated with a significantly reduced Breslow’s thickness at diagnosis (−19.2%, 95% CI = −33.2, −2.3, p = 0.03). As non-statin-users in our database had a mean Breslow’s thickness of 1.8 mm, this would indicate an average reduction in the depth of the lesion of 0.35 mm with statin use. Among men this effect was even more pronounced with a reduction in Breslow’s
thickness of –27.8% (95% CI = –43.7%, –7.4%, \( p = 0.01 \)). Male non-statin users had a mean Breslow’s thickness of 2.1 mm. Therefore, statin use for 0.5 year or more would result in a mean reduction of 0.58 mm. One could also argue that statin use among men is simply associated with earlier diagnosis of a CM lesion and not with slower progression of the CM lesion as especially male cases had a significant higher number of unique ICD diagnoses compared to male controls (0.84 versus 0.66, \( p = 0.02 \)). However, if it is causal, this is an important finding since Breslow’s thickness at diagnosis is one of the strongest prognostic determinants. [57, 58]

In chapter 6 we studied potential effects on melanoma incidence associated with the exposure to non-steroidal anti-inflammatory drugs (NSAIDs), both acetylsalicylic acid (aspirin) and non-acetylsalicylic acid-NSAIDs. CM incidence was not significantly associated with ever non-ASA NSAID use (OR = 1.10, 95% CI = 0.97–1.24) or ever ASA use (OR = 0.92, 95% CI = 0.76–1.12) during the 3 years before index date. The use of larger quantities of non-ASA NSAIDs (>600 pills in 3 years) seemed to be protective for CM but did not reach significance (OR = 0.67, 95% CI = 0.36–1.23). The explanation, in part, could be the relatively short time of observation (3 years), limited sample size in this subgroup (<225 patients), and/or that non-ASA NSAIDs were administered as analgetics (‘on demand’ use). However, continuous low-dose use of ASAs was associated with a reduced likelihood of developing CM in women (OR = 0.54, 95% CI = 0.30–0.99) but not in men (OR = 1.01, 95% CI = 0.69–1.47). A significant trend (\( p=0.04 \)) from no use, non-continuous use to continuous use of ASAs was observed in women.

In conclusion, in accordance with three large observational studies [59-61], we did not find a reduced CM incidence among overall non-ASA NSAID or ASA users. However, our results do suggest that, among women, continuous low-dosed ASA may be associated with a reduced incidence of CM in women. Gender-related differences in the pharmacokinetics and -dynamics of ASA [62,63] as well as gender-related differences in the biology of melanoma could be involved [64,65].

ACE inhibitors and angiotensin II antagonists have also been suggested as chemopreventive agents. In chapter 7 we described an exploratory study investigating a possible etiological association between use of these agents on melanoma incidence and progression.

The use of ACEi or ARb did not seem to protect against the development of cutaneous melanoma nor was it associated with decreased Breslow’s depth. However, the limited numbers of ACEi and ARb users, especially for the stratified analyses, has led to limited
statistical precision. Thus, these study results 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.

The design of the studies described in chapters 5, 6, and 7 may have several limitations because, at the time of designing these studies and often still, effective chemopreventive dosages, latency times, possible differential effects within subclasses, possible synergistic and antagonistic effects, and required temporal relationships were unknown. In retrospect, the duration of follow up prior to developing a melanoma should have been longer. In explanation, the latency time between exposure and effects on CM incidence could be substantially longer than three years. To compare, melanoma carcinogenesis may involve over 10 years. [66] Such latency times after exposure are, however, unknown, and will depend on the precise chemopreventive mechanism of action which determines the stage of development from benign nevus, dysplastic nevus, in situ melanoma until invasive cutaneous melanoma in which the agent is effective. In research practice, available data will limit study design possibilities.

Our relatively short follow-up (3 years) resulted from the decision to use only cases and controls with complete follow-up to guarantee that cases and controls were active members of the PHARMO network and, thus, all prescription drugs dispensed would be registered in PHARMO. Due to sample size limitations, we did not study the effects of drug use longer than 3 years before cutaneous melanoma. In retrospect, one may prefer to select cohorts of drug users (in explanation, statin-users, NSAID users, ASA-users, ACE and ARB users) and compare the melanoma incidence among these cohorts with a cohort of non-drug-users. Alternatively, one could compare with a cohort of users of a drug unlikely to have any chemopreventive or causative effect on melanoma. In such a design, one could perform Cox regression in order to efficiently use all available follow-up and, in addition, one could compare with melanoma incidence among both non-drug-users as well as drug users.

Currently, we cannot point out which agents are likely to be the most efficacious.
However, agents with additional major health benefits and few (long-term) adverse events, such as low-dosed aspirin, would in theory, have the best chance to result in a positive risk-benefit ratio. Nevertheless, efficacy essentially is the first important feature in this decision making process.

Ideally, effectiveness at the individual level would dictate the drug of choice in order to reach the best prediction of the benefit for the patient and, additionally, to create the best motivation among patients and physicians. As any chemopreventive effect would always demand long-term drug treatment in the order of at least 5-10 years, patient motivation is required for compliance to be achieved.

Important in this respect to point out is the fact that molecular diagnostics and new melanoma biomarkers have generated great interest in research. For example, some initiatives focus on such melanoma markers to predict prognosis or even therapeutic efficacy. Goal is to develop a more accurate, therapeutically predictive classification of human melanomas, and, in addition to select patient populations that would profit from specific therapeutic interventions. [67] Useful markers may include both classic prognostic factors such as Breslow’s thickness and ulceration, as well as molecular markers indicating (new) pathophysiological melanoma subtypes. Hopefully, in a few years, we will have melanoma marker tests comparable with the tests available in some adjuvant or therapeutic settings, such as for estrogen and progesterone receptors in breast and prostate cancer or with the FDA approved assays for HER2, epidermal growth factor receptor and KIT [68]. For example, many targeted agents such as imatinib and cetuximab are effective only if their respective molecular markers are available for pharmaceutical intervention. Candidate markers for melanoma would include both validated susceptibility genes, such as mutational status of the high-penetrance genes CDKN2A, CDK4, and possibly of low-penetrance genes MC1R, ASIP, TYR and TYRP1, as they may prove to be markers for distinct melanoma subtypes, as well as molecular markers related to the mechanism of action of the (targeted) drug or chemopreventive agent to be used.

For cancer chemoprevention such biomarker strategies could be of great interest. For example, for chemoprevention among patients with a previous tumor, so-called tertiary cancer prevention, it may be interesting to be able to select the type of chemopreventive agent based on both molecular and histopathological aspects of the previous tumor, and the patient’s risk factors.

If chemopreventive drug candidates could be tested for efficacy in validated melanoma models predictive for certain tumor types, for example, in a validated KIT mutated melanoma model, a BRAF melanoma model or a RAS mutated model, information would become available as to which agent is likely to be most efficacious.
for which tumor type (targeted therapy). New and promising drugs in melanoma treatment, such as the BRAF inhibitor PLX4032 and the anti-CTLA4 antibody ipilimumab, as well as potential synergistic combinations (PLX 4032 combined with statins) should be tested in such models. Final goal would then be to test all melanoma patients for several biomarkers and use these biomarker results to classify their tumor (in combination with classical prognostic factors), predict prognosis, select which therapeutic interventions are indicated (excision range, sentinel node procedure, additional therapies, such as interferon, chemotherapy et cetera), to decide whether the patient would likely benefit from chemoprevention in order to prevent second primaries or to delay melanoma progression and, if so, to select the chemopreventive agent of choice. Ideally, one would select both the therapeutic interventions, adjuvant therapies as well as possible (chemo)preventive options on an individual level in such a strategy.

Before such a strategy could be developed, however, research progress is needed to (better) define available and new predictive biomarkers, to validate experimental melanoma models predicting the behavior of certain melanoma tumor types, such as a BRAF, N-RAS or c-KIT mutated melanomas, to test potential candidate chemopreventive drugs in these experimental models, to create melanoma risk prediction models, and to create prediction rules to select the chemopreventive drug which is most likely to be efficacious.

The chemopreventive drugs tested in validated experimental models should focus on those agents of a drug class that are pharmacologically and chemically most distinct and keeping in mind which agents of the drug class are most likely to result in an acceptable risk-benefit ratio. For example, as representatives of NSAIDs one should consider the distinct properties of several NSAIDs taking into account which NSAIDs score best with respect to cardiovascular risks, bleeding risks, which NSAIDs have differential pharmacologic effects, such as low-dosed aspirin, and which agents represent distinct chemical subclasses. Present experimental research has often focused on a very limited subset of NSAIDs and has included NSAIDs which have been established to have a more worrisome safety profile.

In addition, validated experimental melanoma models could be helpful in defining dose-effect relationships and temporal cause-effect relationships in melanoma chemoprevention, and in possible heterogeneity of effects between different melanoma cancer subtypes and different agents of a drug class.

Predictive models should include prognostic information that can be available at diagnosis (or shortly after) and should consider both risk factors predictive for a second melanoma, factors prognostic for metastasis risk (such as Breslow’s thickness
and ulceration), molecular markers (S100, MC1R, c-KIT, BRAF, N-RAS), as well as mutational status (such as CDKN2A/p16\(^{INK4a}\) mutations, CDK4 mutations, MC1R variants). Prediction rules to select the chemopreventive drug of choice, however, may additionally include information on available patient risk factors that predict potential adverse effects of potential chemopreventive drugs (for example, risk factors for or evidence of previous ulcers or bleeding with respect to NSAID therapy).

**Hormonal and gender differences in melanoma**

In many of the studies presented in this thesis we were confronted with numerous gender differences in (the chemoprevention of) melanoma. For example, in chapter 2 and 3, gender differences in epidemiological measures of CM and ECM, such as the incidence, mortality, age at diagnosis, and several measures of the burden of melanoma were present. In chapter 5, statin use was associated with a reduced Breslow's depth only among men. In addition, in chapter 6, we demonstrated that continuous low-dosed aspirin use may be associated with a reduced incidence of CM in women, but not in men. Moreover, in the PHARMO-PALGA dataset we studied, estrogen use, both oral contraceptives (OC) and hormonal replacement therapy (HRT), was associated with an increased incidence of CM (chapter 8). Based upon these observational studies we can only speculate about the causality. However, the significant dose-effect relationships between estrogen use and CM incidence we detected did support our hypothesis. Nevertheless, most previous studies on estrogen use and melanoma are not in agreement with our findings. [69-71] In chapter 9 we could not confirm an association between either OC use or HRT and Breslow’s thickness.

Several issues related to the studies presented in chapters 8 and 9 should be mentioned here. First, we studied estrogen use, either OC or HRT, regardless of whether they were used as unopposed estrogens or as combined estrogen-progestin. In breast cancer, combined preparations have demonstrated a clear risk increase, whereas only a slight increase was observed for unopposed estrogens. [72,73] Future studies of hormonal influences on CM, should therefore also study progestagenic effects, both progestin single therapy as well as in combined preparations. Second, we need to learn from the debate on the effects of HRT on coronary heart disease and breast cancer. [74] In this debate, conflicting results from observational research and randomized controlled trials were finally brought together by analyzing the data according to time since start of HRT. Similar data analysis seems indicated to study estrogen use and melanoma incidence. Such analysis methods, however, would require very large datasets with long follow up periods.
Third, procarcinogenic effects of estrogens through the ER-β receptor, the hypothesized mechanism for a potential increase in CM incidence, do seem to be realistic, at least for lung cancer, as was demonstrated in a post-hoc analysis of the Women’s Health Initiative Trial. [75]

Gender differences in melanoma have also been described in other countries and datasets. For example, female gender has been demonstrated to be an independent predictor of survival in several populations of different geographical origin, such as in a German dataset [65], in The Netherlands Cancer Registry [76], in both the UK and Australia [77], and in the Sunbelt Melanoma Trial (North America) [78]. A female survival benefit was maintained after adjusting for well-established prognostic factors and, thus, is independent of Breslow’s thickness, histological subtype, and tumor site. [76] Even more striking, this female survival benefit seems to disappear on ageing and is no longer present for women aged 65 years and older. [65]

Although chemopreventive studies in melanoma usually do not stratify across gender or predefine a statistical method to check for effect modification by gender, our results at least indicate that such gender differences should not be excluded in advance.

In conclusion, several findings all indicate that there must be some complex relationship between gender, possibly through hormones, and melanoma development and progression. These relationships have been studied over a long time, but these gender differences in melanoma are still not well understood. Influence of hormonal factors playing a role in these gender differences can still not be excluded. Nevertheless, the modest level of association between CM incidence and OC use that resulted from our studies is not in agreement with previous studies [69-71], and as CM 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.

**The power of a pharmaco-epidemiologic approach to the investigation of drug effects on a malignancy**

We showed that it is feasible to study etiological research questions on unintended drug effects on a rare malignancy, such as cutaneous melanoma, with a pharmacoepidemiological approach through the linking of large national pathology and pharmacy databases. As such drugs, such as statins, are used by a relatively small proportion of the general population, gathering the required sample sizes would otherwise not have been feasible. This approach, therefore, creates research opportunities for many
other research questions on drugs and malignancies. For nearly all malignancies, data are well registered in The Netherlands and drug dispensing records are available for about 25% of the country within PHARMO. However, we should focus only on research topics in which it is realistic to assume that exposure allocation is unrelated to the outcome of interest. Within this type of study, one may use proxy's of health care consumption, such as the number of different drugs an individuals uses or the number of different diagnoses registered in the LMR, to gain information on possible ascertainment bias. More importantly, the type of probabilistic linkage we used between the PHARMO database and other registries has meanwhile been validated. [79]

Although, a pharmacoepidemiological approach creates many opportunities in studying (unintended) drug effects on a malignancy, the design, collection and analysis of such studies coincides with many hurdles and pitfalls. For instance, defining the indexdates, required follow up ("follow back") periods in PHARMO in the right time relation with this indexdate, defining the exposure time window, and a minimal exposure threshold (either in minimal exposure time, minimal daydose or a minimal cumulative dose) is a complex issue. Assumptions with regard to temporal relationships between exposure and occuring events including latency times, effective chemopreventive dosages, and possible differential effects within subclasses need to be made and restrictions, sensitivity analyses or adjustments during analysis should be implemented to prevent biases. This type of research may be subject to some specific biases, such as guarantee-time bias or immortal time bias (as a consequence of exposure definition, exposed versus non-exposed seem to have a survival benefit), protopathic bias (exposure results from symptoms of the subclinical malignancy), and ascertainment bias (sampling chances differ between subgroups; for instance individuals may not always be unsubscribed from the pharmacy database if they moved out of the area). Some of the difficulties we encountered were the lack of some therapeutic / prognostic information (metastases that were not pathologically confirmed), information available in plain text field only requiring reading and scoring of all pathological records manually (e.g., pathological details of the melanoma, such as Breslow's thickness, subtype, and anatomical location), and some technical difficulties such as the fact that PALGA is not a patient centric database necessitating linkage of each pathological record to the PHARMO records.

In conclusion, linking large national databases such as PHARMO and PALGA creates many research opportunities and may enable researches to study rare (adverse) events caused by drugs used in the (general) population. Improvements to large national
databases (in-hospital drug use, standardization of diagnostic information in electronic records) such as PHARMO and PALGA will further expand such research possibilities.

Conclusions

CM is a growing health problem in Caucasian populations. We showed that CM incidence is still significantly increasing among both sexes in The Netherlands. Fortunately, prognosis is often favorable. Nevertheless, for ECM cases and advanced stages of CM, prognosis is less favorable. ECM compromised 6.4% of all primary melanomas. Five-year relative survival proportions for patients with ECM ranged from 74% for ocular melanomas until 15-40% for mucosal melanomas. Although, CM incidence continued to accumulate, we did not demonstrate such time trends for ECM incidence. Overall, the total burden of melanoma is increasing in The Netherlands.

Melanoma prevention has focused on education and sun protection measures. Thusfar, this has not led to behavioral changes or to a decreased or stabilized melanoma incidence. Cancer chemoprevention could be an alternative approach in which an agent is used to reverse, suppress, or prevent premalignant molecular or histological lesions from progressing to invasive cancer. Considerable preclinical evidence of efficacy is available in literature for aspirin, NSAIDs, and statins as melanoma chemopreventive drugs. However, lack of definite data on efficacy in humans and profound long-term safety data in the required doses, preclude the use of chemopreventive drugs for melanoma in current practice. Investigating unintended drug effects in a (rare)malignancy by a pharmacoepidemiological approach is feasible, can be validated, and may enable studies that would otherwise not have been feasible.

None of the statin-related independent variables in our study consistently supports a risk reduction of statin use on the incidence of CM. However, our data did suggest that statin use is associated with a significantly reduced Breslow’s thickness at diagnosis. This effect was even more pronounced among men and, if causally related, is an important finding as Breslow’s thickness at diagnosis is one of the strongest prognostic determinants.

Among users of non-steroidal anti-inflammatory drugs (NSAIDs), both acetylsalicylic acid (aspirin, ASA) and non-acetylsalicylic acid-NSAIDs, we did not find a reduced CM incidence. However, our results do suggest that, among women, continuous low-dosed ASA may be associated with a reduced incidence of CM in women.
The use of ACE inhibitors (ACEi) or angiotensin II antagonists (ARB) did not seem to protect against the development of cutaneous melanoma nor was it associated with decreased Breslow’s depth. Due to limited statistical precision, however, we cannot exclude an association between ACEi and ARB exposure and either a (moderately) increased or decreased incidence of cutaneous melanoma.

Gender may have a complex relationship with melanoma development and progression as indicated by several findings. Hormonal factors playing a role in these gender differences can still not be excluded. Although not in agreement with previous studies, we showed a modest level of association between (higher) exposure to estrogens, both oral contraceptives (OC) and hormonal replacement therapy (HRT), and increased CM incidence. As CM 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.

Overall, based on the current evidence, one cannot point out which agents are likely to be the most efficacious, but (tertiary) cancer chemoprevention, especially with agents that exhibit additional major health benefits and few (long-term) adverse events, remains an interesting option for patients at high risk of (second) melanomas.
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