Burden and Chemoprevention of Skin Cancer

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Lay out and printed by: Optima Grafische Communicatie, Rotterdam, The Netherlands

BURDEN AND CHEMOPREVENTION OF SKIN CANCER

Ziektelast en chemopreventie van huidkanker

Proefschrift

ter verkrijging van de graad van doctor

aan de Erasmus Universiteit Rotterdam

op gezag van de rector magnificus

Prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 11 december 2013 om 9.30 uur

door

Louisette Maria Hollestein

geboren te Rotterdam

PROMOTIECOMMISSIE

Promotor:	Prof.dr. T.E.C. Nijsten
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GENERAL INTRODUCTION

Epidemiology of Skin Cancer

The incidence of skin cancer is increasing in the Netherlands since 1989, the first year of the Netherlands Cancer Registry (NCR). In 2010 more than 43,000 patients were newly diagnosed with skin cancer in the Netherlands [1]. During a life time at least 1 in 5 persons living in the Netherlands will develop skin cancer [2].

The most common skin cancer is basal cell carcinoma (BCC), followed by squamous cell carcinoma (SCC) and melanoma. BCC and SCC combined are often referred to as nonmelanoma skin cancer (NMSC). However, technically the group of NMSC also includes other types of skin cancer, such as T cell lymphoma, Merkel cell carcinoma and Kaposi sarcoma. In this thesis we therefore refer to BCC and SCC combined as keratinocytic cancers, because BCC and SCC both arise from the cells located in the epidermis, which is the upper layer of the skin.

Melanoma

Melanoma is the most lethal type of skin cancer. In the Netherlands more than 4,500 people were diagnosed with melanoma in 2010 and almost 800 died due to melanoma [1,3]. In the Netherlands and in many other European countries the incidence of melanoma has increased substantially since the 1950s [4].

Incidence rates in Australia and New Zealand are among the highest in the world [4], but have remained rather stable in recent years, as has been the case in some other high-incidence countries such as the United States, Canada, Israel and Norway. This may be due to effective health care campaigns or may reflect that all genetically predisposed persons have developed skin cancer in those countries with extremely high sun exposure and incidence rates [5]. Mortality rates of melanoma remained stable or decreased in many countries [6-9]. Most of the increase in incidence is due to the increase in thin melanomas with a relatively good prognosis [10]. It is debated whether the increase in incidence represents a real melanoma epidemic or that this might have been caused by increased awareness or potential overdiagnosis [11-13].

Keratinocytic Cancer

In the Netherlands in 2010 approximately 33,000 patients were newly diagnosed with BCC and more than 6,000 with SCC [1,2,14]. The routinely reported incidence numbers and rates include only the first BCC or SCC, but at least 37% of all patients with keratinocytic cancer will develop at least one subsequent keratinocytic cancer [15]. It has been estimated that 60,000 keratinocytic cancers are diagnosed annually in the Netherlands. Mortality from keratinocytic cancer is rare. The exact number of deaths due to keratinocytic cancer in the Netherlands is unknown, but in 2010 94 persons died of NMSC [3]. Most countries do not have a reliable population-based cancer registry for keratinocytic cancer [16]. In the Netherlands, SCC

is registered nationwide, but of the Dutch comprehensive cancer centers only the Eindhoven Cancer Registry (ECR) routinely registers BCCs.

CARCINOGENESIS

Melanoma

Melanomas arise from the melanocytes. Melanocytes in the epidermis produce melanine, which has the important function to protect the skin against the damaging effect of ultraviolet (UV) radiation. Distinct molecular pathways to melanoma have been proposed, depending on the patient's susceptibility and the amount of sun exposure [17,18]. Early onset melanoma may reflect a gene-UV exposure interaction early in life. These occur in patients that are prone to melanocytic proliferation and have therefore more melanocytic nevi. These melanomas occur more often on the less sun exposed body parts, like the trunk and the legs. Late onset melanomas may be a result of cumulative sun exposure. These older patients may be less susceptible and have fewer nevi, but more sun-damaged skin around the lesion. The late onset melanomas occur more often on the head and neck, which are body sites that are more chronically exposed to sunlight. This divergent pathway hypothesis is supported by genetic evidence. Late onset melanomas arising in chronically sun-damaged skin are more often lentigo maligna melanomas and are associated with somatic KIT mutations and p53 overexpression [19 20 21]. In contrast, early onset melanomas, which occur without a sun-damaged skin are correlated with somatic BRAF or N-RAS mutations and germline MC1R mutations [22-25]. The observation from genetic epidemiological studies, that B-RAF mutations are common in melanoma has lead to the development of a new targeted therapy. B-RAF inhibitors are currently available as treatment for metastatic melanoma and showed a response rate of 48% in patients with B-RAF mutations [26]. This clearly illustrates that the combination of epidemiological and clinical observations has resulted in true therapeutic advances in melanoma [27].

SCC

SCC arise from the keratinocytes. The classical model of multistep carcinogenesis is useful for understanding the development from a premalignant lesion (SCC in situ) to SCC. According to this model, the accumulation of subsequent mutations causes progression from normal skin to a precancerous lesion (actinic keratosis [AK]) and ultimately to invasive cancer (SCC) [28-30]. Chronic sun exposure leads to DNA damage and an accumulation of gene mutations; the most important being the p53 tumor suppressor gene. In a normal cell p53 causes cell cycle arrest after DNA damage, giving the cell the opportunity to remove DNA damage before DNA synthesis and mitosis [31]. The p53 gene is mutated in many human cancers, leading to further accumulation of DNA damage [31]. Sun exposed skin contains many p53 mutations (74% compared to 5% in normal skin) [29]. The loss of function of p53 in combination with more UV-B

exposure may lead to further accumulation of mutations and ultimately the development of premalignant AK [32]. AK are dysplastic lesions, characterized by atypical enlarged nuclei, disorganized growth and a thickened stratum corneum with retained nuclei [29]. AK can be classified into three levels of keratinocytic intraepidermal neoplasia (KIN). KIN I are cellular atypia of basal keratinocytes confined to the lower third of the epidermis. KIN II shows atypical keratinocytes occupying the lower two-third of the epidermis and KIN III shows atypical keratinocytes throughout the epidermis, which is equivalent to carcinoma in situ [29]. AK occurs on chronically sun exposed body sites. AK progress to SCC at an estimated rate of 0% to 0.5% per lesion per year [33]. Most patients (56%) have 1 to 3 AK, but 21% of all patients have more than 10 AK [34]; therefore a patient with multiple AK may have an annual risk of developing invasive SCC up to 5%. However, AK may also regress with an estimated rate ranging between 15% and 63% per lesion per year, which makes the exact SCC risk difficult to predict [33].

BCC

BCC was thought to arise from bulge stem cells in the hair follicles, but using a genetic approach it was shown that the BCC progenitor cell is most likely a long-lived resident progenitor cell, which is localized in the interfollicular epidermis and the upper infundibulum [35,36]. UV light has limited penetration in tissue and is much more likely to induce DNA damage in the interfollicular epidermal cells than in hair follicle bulge stem cell, which are located deeper in the skin [36].

Most BCC (>99% of all BCCs) are sporadic BCCs. The nevoid BCC syndrome (NBCCS) is a hereditary disease, affected patients have a mutation in Patched gene, leading to the formation of multiple BCCs at a young age [37]. The patched gene is part of the hedgehog pathway [38]. The name of this pathway originates from its discovery in *Drosophila* flies, where a mutation in only one gene encoding such a protein produces a larva with spiky process (denticles) resembling a hedgehog [31]. Two transmembrane proteins, Patched and Smoothened, mediate the responses to all Hedgehog proteins. In a normal cell Patched inhibits Smoothened, resulting in a downstream inhibition of transcription of the target genes. In BCC, a loss of heterozygosity of Patched or an activating mutation of Smoothened leads to continued activation of the hedgehog pathway and therefore transcription of the target genes. Of the sporadic BCC 20% show Smoothened mutations and 30-40% Patched mutations [37]. The hedgehog signaling can be blocked by a selective hedgehog pathway inhibitor (vismodegib), which binds to Smoothened [39]. The safety and efficacy of vismodegib is currently evaluated in phase II trials among patients with multiple, locally advanced or metastatic BCC (e.g. NCT00833417, NCT01631331, NCT01367665) [40].

RISK FACTORS

The most well-known environmental risk factor for skin cancer is UV light from sun exposure (Table 1[41]). UV light on earth can be subdivided into UV-A (long wavelength, 320-400 nm) and UV-B (short wavelength, 280-320 nm). UV-B is absorbed in the epidermis and causes 'UV signature' DNA damage, such as the formation of TT dimers, TC/CT dimers and CC dimers and subsequent DNA mutations (i.e. C-T or CC-TT transitions) [42]. UV-A can penetrate deeper into the skin and causes indirect DNA damage by producing reactive oxygen species (ROS), which can cause single stranded and double stranded breaks. In melanoma, the role of UV-B is well established, but the exact role of UV-A remains to be unraveled. For example, a single high dose of UV-B was sufficient to induce melanoma in animal models, but a single high dose of UV-A did not lead to the formation of melanoma. Nevertheless there is *in vitro* and epidemiological evidence that UV-A plays an important role in melanoma development and progression [42,43] .

The pattern of sun exposure which leads to elevated risks differs between the different types of skin cancer. Acute sun exposure (i.e. sunburns with blisters and pain for more than two days) during childhood is a risk factor for developing melanoma [44]. This type of sun

Table 1[41]: Risk factors for the most common skin cancers

	BCC	SCC	Melanoma
Exogenous Risk Factors			
Acute UV exposure	++	+	++
Intermittent UV exposure	++	+	+++
Cumulative UV exposure	+	+++	+
Sun-damaged skin (e.g. AK)	++	+++	+
Smoking	n.a.	++	n.a.
Ionizing radiation	+	++	n.a.
HPV	+	+++	n.a.
Immunosuppression	+	+++	n.a.
Endogenous Risk Factors			
Sex	++	+++	n.a.
Age	++	+++	+
Pigmentation status (e.g. skin type)	+++	+++	+++
Number of nevi	+	n.a.	+++
Atypical nevi	+	n.a.	+++
History of skin cancer	+++	++	+
Chronic inflammation	+	+++	n.a.
Scarring	+	+++	n.a.
Genetics	+	+	++

n.a. not applicable

exposure pattern is associated with patients with many nevi who develop melanoma at a relatively young age [17]. But cumulative sun exposure may also add to the melanoma risk, especially to the risk of lentigo maligna melanoma. Lentigo maligna melanoma occurs on chronically sun exposed body sites, such as the face [44]. The amount of cumulative sun exposure is associated with the development of SCC, while a more intermittent pattern is probably more important for the development of BCC [45]. The role of artificial UV exposure (sunbed use) has been controversial for many years, because UV tanning devices emitted predominantly UV-A and this was believed to be 'safe' tanning [46]. Recent meta-analyses showed that the risk for melanoma, BCC and SCC increased with sunbed use [47,48] (relative risk [RR] estimates of 1.2 for melanoma, 1.7 for SCC and 1.3 for BCC). The risk is higher when sunbeds are used at a younger age. It was estimated that in the (United States [US]) alone 170,000 cases of keratinocytic cancer were attributable to indoor tanning [47]. For melanoma it was estimated that in Europe almost 3500 melanoma cases were related to sunbed use and that 800 persons die annually from melanoma as a result of sunbed use [48]. For the aforementioned reasons the World Health Organization (WHO) stated that sunbed use is carcinogenic and developed guidelines for government health authorities to protect the general public from artificial UV tanning devices [49].

In addition to UV exposure, many patient characteristics are also associated with a higher skin cancer risk. Factors that are associated with an increased skin cancer risk include a pale skin that burns easily and tans poorly, blue or green eyes and blond or red hair [50,51]. The risk of keratinocytic cancer is higher among males [52] and the risk of melanoma is generally equal between males and females, although in some countries the risk differs between females and males, probably depending on gender-specific exposure patterns [53].

Like many other malignancies, the risk of skin cancer increases with age. The median age of first SCC occurrence is 75 and of first BCC is 65 [2,54]. Melanoma occurs at younger ages compared to most malignancies: the median age of melanoma onset is 53 years [54].

Iatrogenic risk factors, such as use of immunosuppressive drugs, also contribute to the risk of skin cancer [55]. Organ transplant recipients receive the highest dose and are at an extremely high risk. These patients have a 65-fold to 250-fold increased risk of SCC, a 10-fold risk of BCC and a 3-fold increased risk of melanoma [56]. The number of patients that uses immunosuppressive drugs for other chronic diseases, like rheumatoid arthritis and inflammatory bowel diseases is much larger. Also relatively new systemic therapies, such TNF-α inhibitors are associated with an increased risk of cancer in general and keratinocytic cancer [57].

Patients may have a genetic predisposition for the development of skin cancer. Patients with Familial Atypical Multiple Mole Melanoma (FAMMM) syndrome have a life time risk of 70% to develop melanoma [58]. In 25-40% the cyclin-dependent kinase inhibitor 2A (CDKN2A) is mutated. This enzyme is important for cell cycle arrest in case of inappropriate mitotic divisions [59]. Patients with xeroderma pigmentosum (XP) have a defect in their nucleotide exision repair (NER) and DNA polymerase, which leads to an increased risk of DNA mutations

and subsequently the development of skin cancer [60]. Of all Patched mutations in XP patients, 80% show an UV signature, while this is 50% in sporadic BCC [37]. Besides the development of multiple BCC at a young age, these patients also show neurological degeneration [60], possibly due to DNA damage caused by oxidative stress in nondividing cells of the nervous system. Patients with NBCCS have a mutation in the Patched gene, leading to the formation of multiple BCCs at a young age [37]. Common variants in DNA identified by genome wide association studies (GWAS) have been associated with an increased susceptibility to skin cancer (i.e. BCC and melanoma) [61-64].

BURDEN OF SKIN CANCER

The diagnosis of skin cancer may have an impact on the quality of life of the patients. This is not captured by incidence and mortality rates. The duration of the disease, the impact of the disease and related complaints should be taken into account. Melanoma diagnosis can have a severe impact on patient's life, depending on staging [65]. Most patients are diagnosed with a stage I melanoma, which mainly has a psychological impact on patients lives. In addition to a severe psychological impact, metastatic melanoma also have a severe functional impairment. Melanoma leads on average to a loss of 20 life years if a patient dies due to melanoma. Around time of diagnosis and treatment one third of patients report high levels of distress [65]. Although most melanoma patients have a relatively good prognosis and live many years after their diagnosis, patients may experience different types of problems many years after diagnosis, such as the occurrence of second primary skin cancers, recurrence of melanoma, anxiety of the deleterious effects of UV-light, problems with work, insurance or mortgage [66,67]. Although keratinocytic cancer is generally not associated with high mortality it can be a burden to individual patients; a patient may suffer from facial scars of excised tumors, they may fear recurrence, multiple keratinocytic cancers or they may be bothered by multiple actinic keratosis [68,69].

The burden of a disease can be measured at a population level or at an individual level. The WHO has developed a concept to compare the impact of a disease across different diseases [70]. This burden of disease measure is the Disability Adjusted Life Year (DALY) and consist of the Years of Life Lost (YLL) and the Years of Life lived with Disability (YLD). In this measure the lost life years due to premature death, the duration of disease and the disability due to the disease and related conditions are taken into account altogether to make comparisons between different diseases possible. This measure can be used for prioritization of research, public health campaigns and allocation of limited health care resources [71].

CHEMOPREVENTION

Chemoprevention was defined by Sporn in 1976 as: 'The use of natural or synthethic drugs to reverse, suppress, or prevent premalignant molecular or histological lesions from progression to invasive cancer' [72]. Successful chemoprevention holds a tremendous potential to reduce the burden of cancer. Sporn described the potential use of vitamin A analogs (retinoids) to prevent epithelial tumors. Subsequently, several observational and experimental studies have been conducted and showed efficacy in the prevention of skin cancer, which was most notably in organ transplant recipients, patients with genodermatoses with increased cancer risk and Psoralen-UVA (PUVA) treated patients [73-75]. Another well-known example of chemoprevention is the use of tamoxifen for the treatment of estrogen-receptor positive breast cancer, which can reduce the incidence of breast cancer with 49% among women at high risk [76]. However both therapies are associated with severe side effects. For example, the use of retinoids is associated with a wide range of side effects, such as headaches, rash, hyperlipidaemia, alopecia, dry skin and mucosa, musculoskeletal symptoms and congenital abnormalities [74]. Therefore, these therapies cannot be used in large groups of people who are at average risk of developing a cancer in their lifetime. Long-term safety is pivotal, as chemopreventive drugs require lifelong therapy. Whether a drug is a good candidate for chemoprevention is determined by the balance between its positive effects and its long term risks (Figure 1[77]). Good candidates are drugs which are on the market for a long period of time with a good safety profile, such as low dose aspirin.

NSAIDs - mechanism of action

Non-steroidal anti-inflammatory drugs (NSAIDs) are effective against pain associated with inflammation, because they decrease the production of prostaglandins that sensitize pain receptors to inflammatory mediators by inhibiting the cyclooxygenase (COX) enzymes [78]. Two isoforms exist in humans: COX-1 and COX-2. COX-1 is continuously expressed in many cells at low levels to control normal physiological function like maintenance of the gastric mucosa, platelet function and vascular homeostasis [79]. The COX-2 isoform is expressed in cells upon many stimuli, such as inflammation, tissue repair and environmental stress. NSAIDs compete with arachidonic acid for the binding site at the COX enzymes [80]. Many studies show that COX-2 is upregulated in precancerous lesions and in tumor tissue, including skin cancer [79,81]. UV-B radiation induces an acute inflammation response in the skin, which may be mediated by COX-2. COX-2 upregulation is probably an early premalignant event, as constitutive COX-2 expression can already be observed in AK, the premalignant lesion of SCC [81]. In the early phase of tumor development, COX-2 derived prostaglandines may stimulate proangiogenic factors, such as VEGF, which promotes tumor associated angiogenesis [82]. The relative importance of COX-1 and COX-2 seem to be different between the different types of skin cancer. Melanoma cells express COX-1 in a similar degree as normal keratinocytes. The

results on COX-2 expression in the melanoma cells are contradictory [79]. The cells adjacent to the melanoma, like keratinocytes, fibroblasts and inflammatory cells do show increased COX-2 expression and therefore COX-2 signaling seems to regulate melanoma invasion, but not proliferation [83]. In SCC COX-2 upregulation seems to be an early event in carcinogenesis as AK also show increased COX-2 expression. COX-1 might not be causally related to SCC carcinogenesis, because some COX-1 deficient mice are not protected against tumor formation [79]. Contrary, the loss of both COX-1 and COX-2 in Patched$^{+/-}$ mice lead to a reduction in tumor size, demonstrating the importance of both enzymes in BCC progression [84].

NSAIDs - clinical observations

Evidence from non-experimental studies supports an association between long term use of NSAIDs and a reduced risk on colorectal cancer [85-87]. Several, but not all, randomized trials of NSAID treatment showed regression of adenomatous polyps in patients with familial adenomatous polyposis and other high risk populations [88-90]. Results on many other cancer types, such as breast cancer, prostate cancer, and lung cancer, are suggestive but not conclusive [91-94]. Results on melanoma and keratinocytic cancer are also contradicting. More than 5 years use of non-aspirin NSAIDs was observed to be protective against melanoma in a large population-based case-control study in the US [95]. A population-based case control study in the Netherlands did not show a result of non-aspirin NSAIDs [96], but this may have been due to a short follow-up time (3 years). Results from a meta-analysis did not indicate a protective effect of non-aspirin NSAID on melanoma risk [97]. A limitation of this meta-analysis, is that adjustment for confounding factors, dose and duration of NSAID use varied among

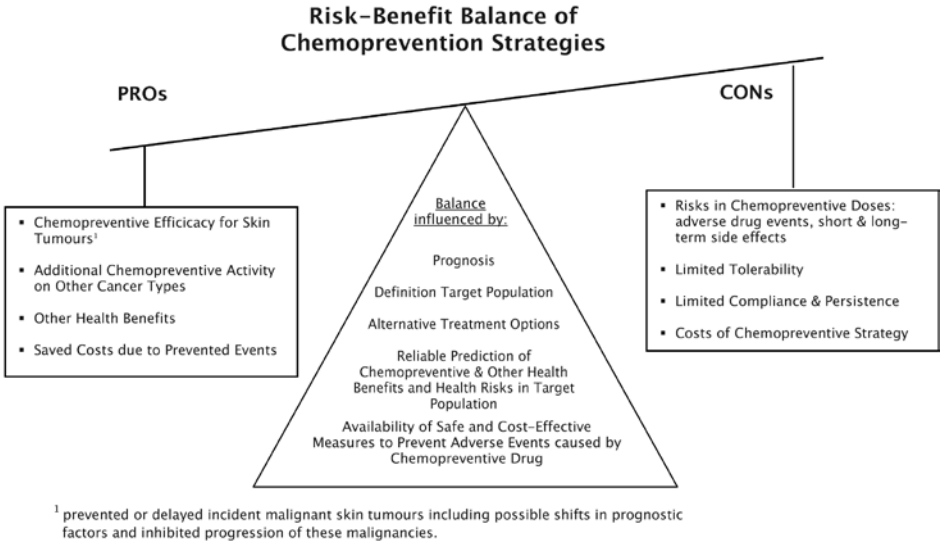

Figure 1[77]: Risk:benefit balance of chemoprevention.

the original studies. Contradicting results were also obtained from observational studies on keratinocytic cancer [98-101]. Selective COX-2 inhibitors showed to be protective for keratinocytic cancer among patients at high risk in clinical trials. In patients with NBCCS, the use of celecoxib (a COX-2 inhibitor) significantly reduced number and burden of BCC [84]. In another randomized controlled trial (RCT) on the prevention of AK by celecoxib, it was found that the number of SCC and BCC was reduced in the treatment arm [102].

Low dose aspirin - mechanism of action

Low dose aspirin is used for secondary prevention of cardiovascular disease. Aspirin irreversibly inactivates both COX-1 and COX-2 [80]. Recovery of COX activity after treatment with aspirin, requires *de novo* synthesis. Mature platelets, which contain only COX-1, lack a nucleus and are therefore particularly susceptible to the long lasting effect of low dose aspirin. Also, platelets receive a higher dose of aspirin during their passage through the portal circulation as the systemic concentration of aspirin is 50% lower [80]. The systemic concentration of aspirin for cardioprotection (≤ 100 mg) is too low for direct inhibition of COX-2. It seems a bit odd that low dose aspirin seems to prevent cancer, but is not able to block COX-2 directly, while early steps in multistep carcinogenesis seem to be COX-2 dependent [79,80]. Various COX-2 independent mechanisms have been proposed to explain why aspirin may prevent cancer [103-106]. In early stage carcinogenesis, platelets may facilitate proangiogenic and proinflammatory processes, which leads to an upregulation of COX-2 in precancerous lesion. The inhibition of COX-1 in platelets may suppress the induction of COX-2 in early stage carcinogenesis.

Low dose aspirin - clinical observations

Low dose aspirin has been associated with a reduced risk on colorectal cancer, and other digestive cancers [107]. Modest inverse associations were observed for breast cancer, prostate cancer and lung cancer [107]. Convincing evidence comes from meta-analysis of individual patient data of long term follow up of 51 cardiovascular trials including more than 70,000 individuals [108]. The randomization to low dose aspirin was associated with a decreased cancer risk after 3 years and a decreased cancer mortality after 5 years. Trial participants are a highly selected group and the results cannot be extrapolated to the general population. Despite the large sample size long term follow up of these trials lacked statistical power to determine an effect on site-specific cancer. Unfortunately, the risk on skin cancer was not assessed in these studies.

The reduced risk on melanoma in the US case-control study was mainly driven by long term use of aspirin [95]. An effect of aspirin on melanoma was only observed among women in the Dutch case-control study [96]. Other observational studies failed to show an effect of regular aspirin use on melanoma[99] or keratinocytic cancer [99,109].

β-Blockers - mechanism of action

β-blockers are mostly prescribed for their blood pressure lowering effects. Other indications include angina pectoris, arrhythmia, migraine prevention, chronic heart failure and secondary prevention after myocardial infarction [110]. β-blockers inhibit the β-adrenergic receptors of the sympathetic nervous system, which mediates the stress response [78]. β-blockers can be non-selective (i.e. blocking both the β_1- and β_2-adrenergic receptor) or selective (more potent β_1-adrenergic receptor blocker). Prescription of β_1-selective β-blockers is preferred for its main indication, because the β_1-adrenergic receptors are mainly expressed in the heart cells.

Stress can be a co-factor for the initiation and progression of cancer [111]. This is facilitated by the catecholamine stress hormone norepinephrine (NE). Many cancer cells express the β_2-adrenergic receptor, including melanoma [112-115]. Systemically released NE can bind to this receptor. After binding of the stress hormones the cancer cells attract macrophages [116]. These tumor educated macrophages are thought to promote tumor progression by releasing angiogenic factors, production of proteasen and release of growth factors [117]. This results in increased vascularization, growth of the tumor and breakdown of extracellular matrix, which facilitates invasion to the blood vessels and thus cancer metastasis [117]. β-blockers may prevent cancer metastasis by preventing stress hormones from binding to its receptor.

β-Blockers - clinical observations

Results from preclinical studies showed that the sympathetic nervous system induces a metastatic switch in breast cancer and that propranolol (non-selective β-blocker) is effective in reducing number and size of cancer metastasis [118,119]. NE signaling was also shown to be of importance for progression of melanoma *in vitro* [112]. Two observational studies on β-blockers and melanoma progression have been conducted. A small study showed a large impact of β-blocker use among patients with a thick melanoma (>1 mm), but this study suffered from immortal time bias [120], resulting in a survival benefit among the exposed because of the exposure definition. A large population-based cohort study showed an effect of β-blocker use before diagnosis on all-cause and melanoma-specific mortality [121]. The required dose and duration were not considered in this study. No RCTs have been performed evaluating β-blocker exposure on melanoma development or progression.

AIMS OF THIS THESIS

We know that skin cancer places a substantial burden on Dutch healthcare in terms of numbers of patients and finances involved. Upon initiating the work on this project, up-to-date estimates on incidence, survival and mortality of two main types of skin cancer, melanoma and SCC, were not available. Neither did we know the magnitude of the burden of skin cancer to the Dutch society in other terms than incidence and mortality. Therefore, the main research questions of this thesis were:

- What is the incidence, mortality and survival of melanoma and SCC in the Netherlands?
- What is the burden of disease attributable to skin cancer in the Netherlands?
- Can chemoprevention be used to reduce the incidence of skin cancer or prolong melanoma survival?

To answer these question we obtained data from the Netherlands Cancer Registry (NCR), Statistics Netherlands (CBS) and the linkage between the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (RLS).

DATASOURCES

Netherlands Cancer Registry

Information on newly diagnosed patients with an invasive cutaneous melanoma or SCC was obtained from the nationwide NCR, which covers the whole country by combining data from all comprehensive cancer centers in the Netherlands since 1989. [122] The NCR is based on all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnosis, haematology departments and radiotherapy institutions [122]. The completeness on cutaneous malignancies (excl. BCC) in 1994 was estimated to be at least 92.9% [123]. Information on patients who were newly diagnosed with BCC was obtained from the Eindhoven Cancer Registry (ECR), which is the only comprehensive cancer center in the Netherlands that registers BCCs routinely and systematically. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all Dutch citizens, including their dates of death.

Statistics Netherlands

Information on the Dutch population size in the past and population size predictions were obtained from CBS. CBS also collects information on cause of death. Mortality due to melanoma (C43 of the International Classification of Disease [ICD]-10) was obtained from CBS. Mortality due to cutaneous SCC is not registered separately on death certificates in the

Netherlands, but deaths due to NMSC (C44 of the ICD-10) are registered as a group. SCC mortality rates were estimated by imputing information on NMSC deaths.

Eindhoven Cancer Registry – PHARMO Record Linkage System cohort

The PHARMO RLS is a population-based patient centric database of approximately 3 million inhabitants [124,125]. The central patient database is linked to more than ten databases, including dispensed drugs via the community pharmacy database, hospital discharge diagnosis of the Dutch National Medical Register (LMR), clinical laboratory data and a general practitioner database. The community pharmacy database contains all prescribed drugs by general practitioners or specialists. Of each drug, the Anatomical Therapeutic Chemical (ATC) code, dispensing data, prescriber, prescribed dosage regimen, dispensed quantity are available. Patients can be followed over a long period of time.

In 2008 the PHARMO RLS has been linked to the ECR [125,126]. The ECR is a population-based cancer registry which covers 2.4 million inhabitants in the south of the Netherlands. Besides detailed information on tumor characteristics and initial treatment the ECR also collects information on comorbidities of the patients. The linkage of the ECR and the PHARMO RLS resulted in the possibility to follow patients over a prolonged period of time with detailed information on cancer, drug utilizations, and health resources utilization of approximately one million inhabitants.

OUTLINE OF THIS THESIS

In chapter 2 data of the NCR was used to describe the trends in melanoma (chapter 2.1) and SCC (chapter 2.2) incidence, mortality and survival during the past 20 years. In addition, predictions of SCC incidence rates were calculated up to 2020, as the rapidly increasing incidence rates may ask for new policies of allocation of health care resources. The incidence of BCC has been described by Flohil et al. [14]. In chapter 2.3 we describe the differences in epidemiology of SCC on sun exposed and covered body sites. The magnitude of a disease burden in a population can also be described using burden of disease measures. With these measures the fatal and non-fatal disease burden and the duration of disease can be taken into account. This was described for melanoma in chapter 3.1 and for BCC and SCC combined in chapter 3.2. Because skin cancer is becoming a great burden to society with more than 43,000 newly diagnosed patients each year, the possibility of chemoprevention to reduce the burden of skin cancer was investigated in chapter 4. Clinical (chapter 4.1) and methodological (chapter 4.2) aspects are described which are important in chemoprevention research. The first candidate drug that we considered was low dose aspirin (chapter 4.3), because of its good safety profile and possible additional health effects. In chapter 4.4 we investigate the role of NSAIDs in chemoprevention of keratinocytic cancer. In chapter 4.5 we investigate if survival from melanoma could be prolonged by using β-blockers.

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Chapter 2

Epidemiology of skin cancer

Chapter 2.1

Trends of cutaneous melanoma in the Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989

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Annals of Oncology. Feb 2012; 23 (2): 524-30

ABSTRACT

Background: It has been debated that the epidemic of melanoma is largely due to overdiagnosis, since increases in incidence were mainly among thin melanomas and mortality rates remained stable. Our objective was to examine this controversy in the Netherlands.

Patients and Methods: Information on newly diagnosed melanoma patients was obtained from the Netherlands Cancer Registry (NCR). European Standardised Rates (ESR) and Estimated Annual Percentage Change (EAPC) were calculated for the period 1989-2008. Cohort-based, period-based and multivariate survival analyses were performed.

Results: The incidence rate of melanoma increased with 4.1% (95% CI: 3.6-4.5) annually. Incidence rates of both thin melanomas (≤ 1mm) and thick melanomas (> 4 mm) increased since 1989. Mortality rates increased mainly in older patients (>65 years). Ten-year relative survival of males improved significantly from 70% in 1989-1993 to 77% in 2004-2008 ($p < 0.001$) and for females the 10-year relative survival increased from 85% to 88% ($p < 0.01$). Recently diagnosed patients had a better prognosis even after adjusting for all known prognostic factors.

Conclusion: Since incidence of melanomas among all Breslow thickness categories increased as well as the mortality rates, the melanoma epidemic in the Netherlands seems to be real and not only due to overdiagnosis.

INTRODUCTION

Worldwide, almost 200,000 patients are diagnosed with cutaneous melanoma (melanoma) each year [1]. Incidence rates are increasing in all countries, except in Australia and Canada [2]. Although, incidence rates in Australia remain very high. In the Netherlands the incidence of melanoma increased since 1989, the first year of the National Cancer Registry. Incidence, mortality and survival of cutaneous melanoma in the Netherlands were described by de Vries et al. up to 1998 [3]. Ten years of additional data have become available since these analyses. Incidence of all cutaneous malignancies in the Netherlands have recently been described by Holterhues et al., indicating that melanoma incidence has almost doubled in 2005 compared to 1989 [4]. As melanoma incidence rates are rising in many countries, it is debated if this increase represents a real melanoma epidemic or that this might have been caused by increased awareness leading to potential overdiagnosis. Overdiagnosis in melanoma could be the results of diagnostic drift, which reclassified what were previously found to be benign melanocytic nevi as truly malignant melanomas [5-7]. We hypothesized that there is a real increase in melanoma incidence and that, therefore, there is a real increase in thin and thick melanomas as well as melanoma related mortality. To examine this controversy in the Netherlands, incidence rates together with mortality rates and survival of melanoma patients were examined to better understand the recent trends of melanoma in the general Dutch population.

METHODS

Data collection

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres, were used [8]. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge, which accounts up to 8% of new cases, haematology departments and radiotherapy institutions. Information on patient characteristics like sex, date of birth, and tumour characteristics such as date of diagnosis, subsite (International Classification of Diseases for Oncology (ICD-O-3) [9] histology, stage (Tumour Lymph Node Metastasis (TNM) classification) [10] are obtained routinely from the medical records. The quality of the data is high, due to thorough training of the administrators and computerised consistency checks at regional and national levels. Completeness is estimated to be at least 95%. Follow-up of vital status of all patients was calculated as the time from diagnosis to death or to the 1st of February 2010. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all deceased Dutch citizens.

For the present study, all patients with invasive primary cutaneous melanoma (C43) diagnosed in the period 1989-2008 in the Netherlands were included (n=45,919). Age was divided in three groups (0-44, 45-64, ≥65years). The study period was divided in four categories: 1989-1993, 1994-1998, 1999-2003, and 2004-2008 to study trends. TNM was determined postoperative. Clinical stage was used in cases where postoperative stage was unknown. Tumour localisation was categorised into anatomical subsites: head and neck (C43.0, C43.1, C43.2, C43.3, C43.4), trunk (C43.5), arms (C43.6), legs (C43.7), and other (C43.8, C43.9). For the period 1989-1994 only survival data of five regional cancer registries was available, which are representative for the whole of the Netherlands. Patients younger than 15 years and older than 95 years were excluded from the survival analysis, as well as cases diagnosed by autopsy. Mortality data for the period 1989-2009 was obtained from Statistics Netherlands.

Statistical analyses

Annual incidence and mortality rates for the period 1989-2008 were calculated per 100,000 person-years, using the annual mid-year population size as obtained from Statistics Netherlands. Rates were age-standardised to the European standard population (European Standardised Rates (ESR)). Changes were evaluated by calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (CI). To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y=ax + b$ where $y = \ln(\text{rate})$ and x = calendar year, then EAPC = $100 * (e^{a} - 1)$). Incidence rates were also calculated per sex, age group, histological subtype, bodysite and stage.

Due to changes in staging of melanoma over time, time trends were tested by comparing nodular status (N) and metastatic status (M) of the TNM of which the definition remained unchanged over time. Breslow thickness was used to test for trends in melanoma thickness over time, because classification of tumour thickness (T of TNM) changed over time. Time trends in melanoma thickness were calculated for the period 1994-2008, because Breslow thickness was routinely registered since 1994.

Traditional cohort-based 10-year relative survival analysis was used for the period 1989-1998 which represents the survival of patients diagnosed during 1989-1998. Since follow-up was available until January 2010 period-based 10-year relative survival analysis was used for the most recent period 1999-2008, which gives the most up-to-date estimates for this period [11]. Multivariate relative survival analyses, using Poisson regression modeling, were carried out to estimate relative excess risk (RER) of dying adjusted for follow-up interval [12]. Two multivariate models were fit; a model without Breslow thickness, covering the whole period (1989-2008) and a model with Breslow thickness, excluding the first time period (1989-1993). SAS software (SAS system 9.2, SAS Institute, Cary, NC) was used to perform the statistical analyses. P-values were two-sided and considered significant if $p< 0.05$.

RESULTS

The average population size of the Netherlands between 1989 and 2008 was 15.7 million. During this 20-year period 19,393 males and 26,526 females were diagnosed with melanoma. Between 1989 and 2009 5,840 males and 4,769 females died due to melanoma.

Trends in incidence

The age-standardised incidence (ESR per 100,000 person-years) increased from 11.3 in 1989 to 21.7 in 2008 (EAPC 4.1, 95% CI: 3.6-4.5) (Figure 1). In table 1 ESR are provided per 100,000 person-years for four 5-years periods by sex, age, histopathologic subtype, bodysite, nodular status, metastatic status and Breslow thickness. For both sexes the highest incidence rates were observed in patients older than 65 years. Superficial Spreading Melanoma (SSM) was the most commonly diagnosed subtype in males and females and the incidence of this subtype increased more rapidly than the incidence of other subtypes (EAPC 7.6, 95% CI: 7.1-8.2 and 6.5, 95% CI: 6.0-7.0 for males and females, respectively). The trunk was the most commonly affected body site in males and the legs were the most commonly affected body site in females.

The incidence of melanoma in each of the 4 Breslow thickness categories increased significantly in the study period. Thin melanomas (≤ 1mm) increased each year with 7.0% and 6.1% for males and females, respectively. Thick melanomas (>4 mm) increased as well, with an annual increase of 5.3% for males and 6.5% for females. Thick melanomas increased with approximately the same rate as thin melanomas in females. In contrast to Breslow thickness and nodal involvement, the presence of systemic metastasis did not increase significantly between 1989 and 2008.

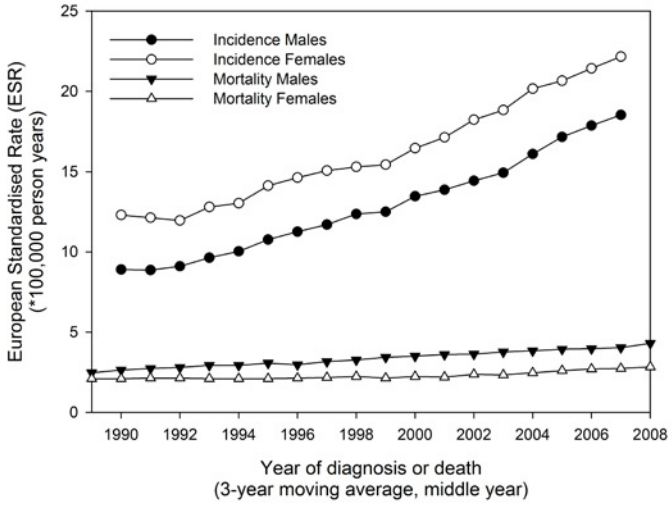

Figure 1: Three-year moving averages of age standardised incidence rates and mortality rates (ESR) of melanoma in the Netherlands, 1989-2008.

Table 1: Age standardised incidence rates (ESR) of melanoma in the Netherlands, 1989-2008

	Males							Females						
	N[a]	1989-1993	1994-1998	1999-2003	2004-2008	EAPC (95% CI)		N[a]	1989-1993	1994-1998	1999-2003	2004-2008	EAPC (95% CI)	
Incidence														
Overall	**21306**	**9.0**	**11.3**	**13.8**	**17.9**	**4.54**	**(4.01-4.97)**	**28889**	**12.2**	**14.6**	**17.2**	**21.5**	**3.72**	**(3.22-4.22)**
Age														
0-44	5758	2.6	3.0	3.4	4.1	2.80	(2.33-3.28)	10057	4.6	5.3	6.3	7.6	3.36	(2.78-3.94)
45-64	9152	4.0	5.0	6.3	8.1	4.62	(4.02-5.22)	10846	5.2	6.3	7.4	9.2	3.73	(3.14-4.32)
≥65	6396	2.3	3.2	4.2	5.7	5.98	(5.53-6.44)	7986	2.4	3.0	3.5	4.7	4.33	(3.64-5.02)
Subtype														
SSM	10924	3.4	5.3	7.0	10.6	7.64	(7.05-8.22)	16388	5.4	7.9	10.3	14.3	6.50	(6.01-6.98)
NM	3434	1.5	2.0	2.4	2.5	3.65	(2.84-4.47)	3626	1.6	1.9	2.1	2.2	2.08	(1.27-2.89)
ALM	153	0.1	0.1	0.1	0.1	6.95	(2.77-11.13)	256	0.1	0.1	0.1	0.2	6.42	(3.67-9.16)
LMM	652	0.3	0.4	0.4	0.5	4.43	(2.54-6.32)	944	0.3	0.4	0.5	0.6	5.74	(4.37-7.11)
Other	6143	3.8	3.5	3.8	4.2	0.52	(-0.24-1.29)	7675	4.8	4.2	4.2	4.2	-0.95	(-1.67- -0.23)
Bodysite														
Trunk	9815	4.1	5.0	6.3	8.5	4.95	(4.47-5.43)	7326	2.8	3.7	4.6	6.0	5.23	(4.80-5.65)
Head/Neck	3465	1.5	1.9	2.4	2.7	3.77	(2.89-4.66)	3219	1.3	1.5	1.7	2.0	2.95	(2.43-3.47)
Legs	3406	1.5	1.9	2.2	2.8	3.98	(3.20-4.77)	11306	5.2	5.8	6.9	8.1	2.98	(2.31-3.66)
Arms	3455	1.3	1.8	2.2	3.0	5.40	(4.57-6.22)	6112	2.5	3.0	3.5	4.7	4.09	(3.27-4.90)
Other	1165	0.6	0.6	0.8	0.9	2.69	(1.67-3.71)	926	0.5	0.5	0.5	0.6	1.59	(0.35-2.83)
Breslow thickness[b]														
<= 1 mm	7162		3.9	5.2	7.8	7.01	(6.10-7.92)	11960		6.5	9.0	11.9	6.14	(5.35-6.92)
1.01-2 mm	3686		1.9	3.0	3.8	6.81	(5.56-8.06)	4873		2.5	3.7	4.7	6.16	(5.41-6.91)
2.01-4 mm	2805		1.5	2.3	2.8	6.19	(4.82-7.56)	2769		1.4	2.0	2.4	5.37	(3.92-6.83)
>4 mm	1909		1.1	1.6	1.9	5.26	(4.05-6.47)	1547		0.7	1.0	1.2	6.51	(5.12-7.89)

Table : (Continued)

	Males							Females						
	N[a]	1989-1993	1994-1998	1999-2003	2004-2008	EAPC (95% CI)		N[a]	1989-1993	1994-1998	1999-2003	2004-2008	EAPC (95% CI)	
Unknown	2490		2.9	1.7	1.6	-5.13	(-7.55- -2.72)	2857		3.5	1.5	1.3	-8.23	(-11.5- -4.96)
Nodular status														
TNM-N0/X	19710	8.6	10.6	12.6	16.3	4.22	(3.77-4.67)	27672	12.0	14.1	16.3	20.4	3.46	(2.95-3.97)
TNM-N1+	1596	0.4	0.7	1.2	1.5	9.12	(7.60-10.64)	1217	0.2	0.4	0.9	1.1	11.53	(9.78-13.28)
Metastatic status														
TNM-M0/X	21036	8.8	11.1	13.6	17.7	4.59	(4.16-5.03)	28695	12.1	14.4	17.2	21.4	3.74	(3.23-4.26)
TNM-M1+	270	0.1	0.2	0.2	0.1	0.10	(-2.09-2.29)	194	0.1	0.1	0.1	0.1	0.88	(-1.78-3.54)

[a] values may not add up to 100% of all melanomas due to missing values.

[b] Breslow thickness was routinely registered since 1994.

Trends in survival

Over time, a small increase in relative survival was observed for both sexes (Table 2, Figure 2). The 10-year relative survival for males increased significantly from 70% in the period 1989-1993 to 77% in the period 2004-2008 ($p < 0.001$). In the same period, the 10-year relative survival for females increased significantly from 85% to 88% ($p < 0.01$). The relative excess risk (RER) of dying decreased significantly over time for males and females (Table 2). Relative survival improved significantly in more recent periods of diagnosis, also after adjusting for age, histological subtype, bodysite, nodular status, metastatic status and Breslow thickness. Relative excess risks showed the expected patterns for all mentioned covariates (Table 2).

Since Breslow thickness has not been routinely registered during the period 89-93, this first period was not included in multivariate analyses. A multivariate model without Breslow thickness was fit over all four time periods, using the period 89-93 as a reference, showing decreasing RER of dying for the more recent periods [data not shown].

Trends in mortality

The absolute number of annual deaths due to melanoma increased from 337 in 1989 to 794 in 2009. The age-standardised mortality rate due to melanoma increased from 2.2 per 100,000 person years in 1989 to 3.9 per 100,000 person years in 2009 (EAPC 2.3, 95% CI: 2.0-2.6) (Figure 1). Mortality rates in younger patients (0-44 year) remained stable over the years (Figure 3). A significant increase in mortality was observed in patients aged 45 to 64 years. The steepest increase in mortality was observed in males and females older than 65 years (EAPC 4.1, 95% CI: 3.1-5.0 and 2.2, 95% CI: 1.4-3.0, respectively).

DISCUSSION

The aim of our study was to assess concordance in time in trends of incidence, mortality and survival of cutaneous melanoma in the Dutch general population. The findings of this study suggest that the melanoma incidence is truly rising and is not solely depending on increased diagnosis, because melanoma incidence among all Breslow categories increased as well as melanoma mortality.

Trends in incidence

An overall increase in incidence rate was observed, which is in line with results from many countries [2,13-15]. However, in Australia and Canada incidence rates have been observed to be stabilizing or even decreasing in younger individuals [16,17], possibly as result of successful health care campaigns in avoiding sun exposure [17]. In most countries the increase in incidence rate is primarily due to an increase of thin melanomas while the incidence rate of thick melanomas is no longer increasing [18,19]. It has been debated that this epidemiologic pattern

Table 2: Multivariate relative survival analysis of melanoma in the Netherlands, 1989-2008

	Males				Females			
	Univariate[a]		Multivariate[a,b]		Univariate[a]		Multivariate[a,b]	
	RER	95% CI	RER	95% CI	RER	95% CI	RER	95% CI
Period of diagnosis								
1989-1993	1				1			
1994-1998	0.88	(0.79- 0.98)	1		0.84	(0.74- 0.96)	1	
1999-2003	0.81	(0.72- 0.90)	0.90	(0.82- 0.99)	0.75	(0.65- 0.85)	0.92	(0.82- 1.03)
2004-2008	0.69	(0.62- 0.78)	0.83	(0.75- 0.92)	0.69	(0.59- 0.80)	0.88	(0.77- 1.00)
Age								
00-44	1		1		1		1	
44-64	1.27	(1.16- 1.38)	1.25	(1.14- 1.38)	1.41	(1.27- 1.56)	1.29	(1.15- 1.45)
65+	1.83	(1.66- 2.02)	1.61	(1.45- 1.79)	2.55	(2.27- 2.86)	1.78	(1.57- 2.03)
Subtype								
SSM	1		1		1		1	
NM	4.45	(4.01- 4.93)	1.30	(1.17- 1.46)	6.01	(5.24- 6.89)	1.42	(1.23- 1.64)
ALM	3.50	(2.38- 5.15)	1.37	(0.90- 2.09)	5.64	(3.91- 8.13)	2.61	(1.81- 3.76)
LMM	0.35	(0.15- 0.85)	0.27	(0.11- 0.70)	0.77	(0.38- 1.55)	0.16	(0.03- 0.77)
Other	4.10	(3.73- 4.51)	1.40	(1.26- 1.56)	5.13	(4.54- 5.81)	1.51	(1.33- 1.73)
Bodysite								
Trunc	1		1		1		1	.
Head/Neck	1.22	(1.09- 1.36)	0.98	(0.87- 1.11)	0.980	(0.83- 1.16)	0.84	(0.71- 1.00)
Legs	0.99	(0.89- 1.11)	0.82	(0.73- 0.93)	0.53	(0.47- 0.61)	0.54	(0.48- 0.61)
Arms	0.70	(0.61- 0.80)	0.70	(0.61- 0.80)	0.52	(0.44- 0.61)	0.47	(0.40- 0.56)
Other	7.46	(6.78- 8.20)	4.07	(3.54- 4.68)	9.26	(8.20- 10.46)	4.32	(3.59- 5.20)
Breslow thickness								
<= 1 mm	1		1		1		1	
1.01-2 mm	7.19	(5.35- 9.67)	5.26	(4.08- 6.78)	7.44	(5.45- 10.15)	5.54	(4.21- 7.28)
2.01-4 mm	20.43	(15.39- 27.12)	11.39	(8.88- 14.61)	21.06	(15.57- 28.48)	10.87	(8.25- 14.32)
>4 mm	36.40	(27.43- 48.29)	17.15	(13.32- 22.09)	54.73	(40.60- 73.79)	21.53	(16.25- 28.53)
Unknown	29.93	(22.58- 39.66)	10.20	(7.92- 13.14)	25.20	(18.69- 33.98)	8.68	(6.56- 11.49)
Nodular status								
TNM-N0/X	1		1		1		1	
TNM-N1+	4.70	(4.32- 5.11)	2.32	(2.10- 2.56)	7.77	(6.97- 8.67)	2.87	(2.53- 3.26)
Metastatic status								
TNM-M0/X	1		1		1		1	
TNM-M1	17.25	(15.01- 19.81)	7.00	(5.95- 8.23)	31.26	(26.31- 37.13)	7.31	(5.97- 8.96)

[a]The analysis is adjusted for follow-up time

[b]The first period could not be included in the multivariate model, because Breslow thickness was not routinely registered before 1994

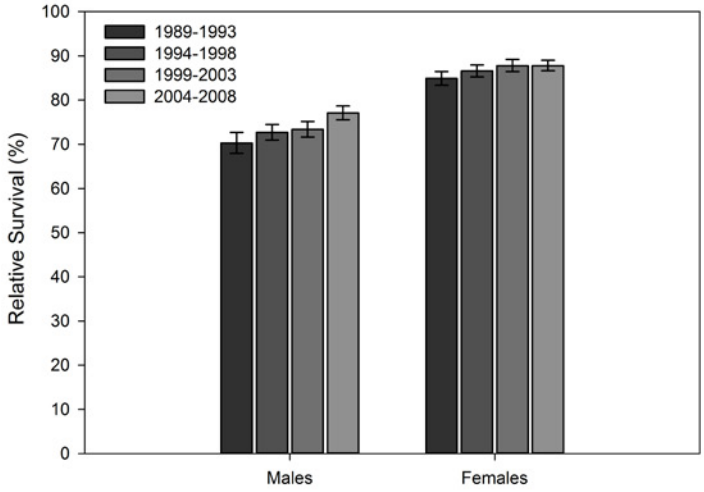

Figure 2: Ten-year relative survival of melanoma in the Netherlands by period of diagnosis and sex, 1989-2008

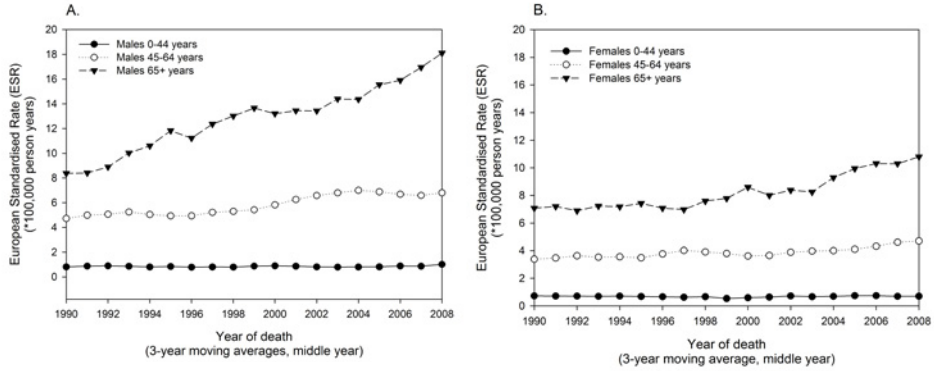

Figure 3: Three-year moving averages of age-standardised mortality rates (ESR) of melanoma by age of males (A) and females (B) in the Netherlands, 1989-2008.

indicates early diagnosis due to improved awareness and possibly overdiagnosis by pathologists rather than a real increase in the disease.

We observed an increase in thin as well as thick (>4 mm) melanomas. In females, the thick melanomas increased annually with the same percentage as thin melanomas. Similar results are reported in England and the USA among older patients (>65 years)[13,15]. The observed increase over the whole spectrum of all stages of melanoma is an argument in favor of a real increase in incidence of disease [7]. Alternative explanations would include a more conservative approach of the pathologists or improvements in the cancer registry practices. The more conservative pathologist explanation would mainly result in increases in the thin melanomas. It is possible that the cancer registry has improved over time, resulting in a larger proportion of melanomas of all thicknesses appearing in the cancer registry. Indeed, in a study verifying

data from 3 regional Dutch cancer registries from 1990 it was found that the completeness of skin malignancies (excluding basal cell carcinomas) was 92.9% [20]. However, the proportion of cases not being included in the database would largely depend on histopathology diagnosis, and presumably most of the 7.1% of 'missed' cases would be squamous cell carcinomas. Moreover, an increase in completeness of the registry above the 92.9% is unlikely to result in EAPCs as strong as observed among all thickness categories in our study.

Although awareness of potential harmful effects of sun exposure has increased in the Netherlands in recent years [21], incidence rates of melanoma have not stabilized and are expected to rise even further [22]. Incidence rates were increasing most steeply in older patients (>65 years). Due to unawareness of potential harmful effects of sunlight in their younger years, these older patients could have accumulated high amounts of sun exposure and high number of sunburns during their (adolescent) lifetime. Prevention campaigns started at the end of the eighties, when the Dutch cancer society (KWF) started campaigns at the Dutch and Spanish beaches to increase awareness of risk factors for skin cancer among these high risk populations [personal communication][21].

The largest incidence rates and mortality rates were observed in older patients. Therefore, future secondary prevention campaigns should aim to increase awareness in this high risk group. Although it might be difficult to reach specific subgroup of patients, targeted secondary prevention campaigns may be possible [23].

Trends in survival

The survival of Dutch melanoma patients has been described for three geographic regions in the Netherlands [24,25], showing that survival rates of females were significantly better and independent of patient's demographics and classical melanoma characteristics. We observed an increase in 10-year relative survival for both sexes over time. In most European countries, the 5-year relative survival improved as well, with a relative increase varying from 1 to 30% [26]. In the observed time period no major improvements in the treatment of melanoma have been introduced. The improvements in relative survival may partly have been caused by increased awareness and earlier detection, which artificially prolongs survival time leading to a lead time bias in the analysis [27]. Our multivariate survival analyses were adjusted for follow-up time of each patient to correct for lead time bias as much as possible. Observed changes in distribution of melanoma thickness, histological subtype and other prognostic factors could have caused the change in survival. Multivariate analysis on survival showed that period of diagnosis decreased relative survival, independent of changes in distribution of all known prognostic factors over time. This result might be caused by the introduction of the sentinel lymph node procedure for melanoma patients in 1992, although the effect on survival is still unclear and under evaluation [28]. Another possibility is that dermatologist and pathologists in more recent periods became more cautious and classified slightly atypical

pigmented lesions more often as malignant melanomas [7]. This diagnostic drift leads to a bias of prolonged survival times in the more recent periods.

It is expected that survival may improve even further in the future, particularly for advanced disease, because new promising therapies are currently tested in clinical trials [29]. These therapies include B-RAF inhibitors and cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) inhibitors. B-RAF is part of the mitogen-activated protein kinase (MAPK) pathway and is mutated in approximately 60% of all melanomas [30]. Increased expression of CTLA-4 downregulates the immune response [31]. By inhibiting CTLA-4 the naturally occurring immune responses to tumor cells can be enhanced. Recently a phase III trial on ipilimumab was published, showing improved overall survival in patients with metastatic melanoma [32].

Trends in mortality

We observed increased mortality rates, which is in contrast with findings in most other countries, where mortality rates remain stable over the years [14,15,33]. As melanoma thickness is a strong predictor for disease progression, the observed increase in thick melanomas could have been the cause of the increased mortality rates [34-36]. In other European countries, like England, France, Italy, Sweden and Poland, mortality rates increased as well [26,37]. In our data mortality rates did not increase as rapidly as incidence rates, which could have been caused by the improved survival of melanoma patients. Incidence rates of patients diagnosed with metastatic melanomas did not increase over time, but mortality rates did increase during the study period and do not seem to stabilize [Figure 3]. This indicates that a subgroup of melanomas without distant metastasis at diagnosis metastasize over time leading to death.

Increased incidence rates accompanied by increased mortality rates suggest a true increase in the amount of melanomas, rather then a potential overdiagnosis [6,7,38]. We therefore state that the observed increase in incidence reflects a real increase of melanoma patients in the Netherlands, rather than an artifact which have been caused by diagnostic drift.

Conclusion

We observed increased incidence rates of melanoma in the Netherlands since 1989. This was due to the increase of thin as well as thick melanomas, which is a worrying trend as melanoma thickness is a strong predictor for prognosis [34-36]. The increase in incidence was accompanied by an increase in mortality. Survival improved over time independent of the distribution of all known prognostic factors. This pattern points at a real melanoma epidemic in the Netherlands. To improve survival and decrease incidence and mortality rates in the future, efforts should be made to increase primary and secondary prevention of melanoma. Primary prevention campaigns should aim at parents to protect their children from sunburns in childhood and adolescence. Secondary prevention campaigns should include older and male patients to increase awareness of melanoma.

Acknowledgements

The work on this research was performed within the framework of the project 'Progress against cancer in the Netherlands since the 1970s?' (Dutch Cancer Society grant 715401). The authors thank the working group Output (K. Aben, R. Damhuis, J. Flobbe, M. van der Heiden, P. Krijnen, L. van de Poll, S. Siesling, J. Verloop) of the NCR for providing data from the cancer registry and the registration clerks for the dedicated data collection.

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Chapter 2.2

Trends of cutaneous squamous cell carcinoma in the Netherlands: increased incidence rates, but stable relative survival and mortality 1989-2008

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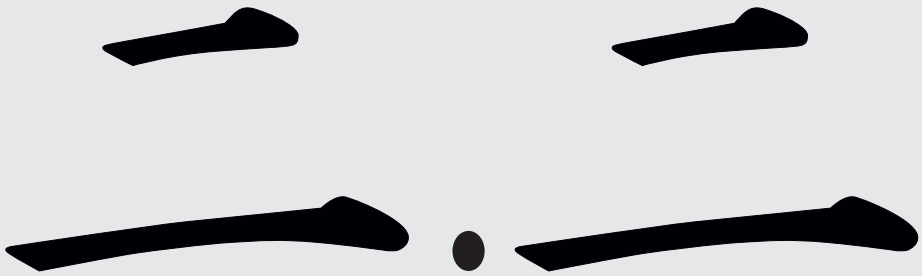
European Journal of Cancer. Sep 2012; 48 (13): 2046-53



ABSTRACT

Background: Incidence rates of cutaneous squamous cell carcinoma (SCC) are increasing in many countries, though detailed information is scarce.

Objectives: To describe detailed trends in incidence rates, relative survival and estimate mortality rates of SCC in the Netherlands.

Methods: Information on newly diagnosed SCC patients between 1989-2008 was obtained from the Netherlands Cancer Registry (NCR). Information of nonmelanoma skin cancer (NMSC) mortality was obtained from Statistics Netherlands. European Standardised Rates (ESR) and Estimated Annual Percentage Change (EAPC) were calculated. Incidence rates were fitted to 2 different models and predicted by the best fitted model. Cohort-based and multivariate survival analyses were performed to assess changes over time.

Results: The ESR increased from 22.2 to 35.4 per 100,000 inhabitants for males and from 7.8 to 20.5 for females. The EAPC was 6.9% (95% CI: 5.8-8.7) for males and 9.2% (95% CI: 7.5-11.0) for females. Incidence rates increased for all body sites, except for the lips, where a decreasing trend for males was observed. The predicted ESR in 2020 is 46.9 per 100,000 inhabitants for males and 28.7 for females. The 5-year relative survival rate was 92.0% (95% CI: 91.3-92.8) for males and 94.9% (95% CI: 94.0-95.7) for females and remained stable over time. Overall relative survival was better for females, but females with advanced disease had a 30.4 relative excess risk of dying compared to those in stage I. This difference was 9.9 for men. The estimated mortality rate decreased with -1.9% (95% CI: -3.1- -0.7%) annually.

Conclusions: Incidence rates of SCC increased rapidly. Relative survival was high, as most SCC were diagnosed in stage I. Nevertheless, the number of newly diagnosed patients may exceed 11,000 by 2020, emphasizing the need to improve methods to prevent skin cancer.

INTRODUCTION

Incidence rates of cutaneous squamous cell carcinoma (SCC) are rising in many countries [1-5]. Despite the high incidence rates, population based data on SCC incidence, survival and mortality in many countries are rather sparse. Recently, population based studies on incidence were performed in Ireland, Sweden and Denmark and demonstrated that age-standardised incidence rates are rapidly increasing with absolute increases of approximately two thousand new SCC cases annually in populations of 4.5 to 9 million inhabitants [1-3].

SCC and other nonmelanoma skin cancers (NMSC) are not reported to cancer registries in many countries including Australia and the United States (US) and therefore incidence rates can only be estimated using other data sources. Results from a national survey in Australia in 2002 showed that 118,000 new SCC cases were diagnosed among the 21 million inhabitants [4]. According to estimates from medical claims data in the US, 2.2 million persons of the 298 million inhabitants in 2006 were treated for NMSC of which roughly 20-30% were SCC [5].

Observational cancer registry studies are important because they provide input for a (European) keratinocytic cancer health care policy. Since the Dutch population is ageing and SCC is strongly age-dependent, this skin cancer will become more frequent. The cosmetic and functional morbidity associated with SCC is high because it often occurs on the face and is treated with surgical excision. About 5% of SCCs progresses to systemic disease for which there is no adequate therapy. Despite the straightforward treatment for early disease, but due to the very high incidence, SCC is a major public health problem and is one of the most costly cancers [6].

The objective of this study was to describe the recent trends of SCC incidence rates and relative survival and to estimate SCC mortality rates in the general Dutch population.

PATIENTS AND METHODS

Information on newly diagnosed patients with an invasive cutaneous SCC was obtained from the nationwide Netherlands Cancer Registry (NCR), which covered the whole country by combining data from all Comprehensive Cancer Centres in the Netherlands since 1989. [7] The NCR is based on all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnosis, haematology departments and radiotherapy institutions [7]. The following morphology codes combined with topography 'skin' were considered invasive cutaneous SCC: 8010, 8050-8084 (excluding 8077: intraepithelial neoplasia, 8080: Erythroplasia of Queyrat, 8081: Bowen disease, 8082: lympho-epithelial carcinoma).

Patient's demographic characteristics such as gender and date of birth, and tumour characteristics such as date of diagnosis, subsite (as specified in the International Classification

of Diseases for Oncology (ICD-O-3) [8], histology and stage (Tumour Lymph Node Metastasis [TNM] classification) [9] are obtained routinely from the medical records. The quality of the data is high, due to thorough training of the administrators and computerised consistency checks at regional and national levels. Completeness on cutaneous malignancies (excluding basal cell carcinomas) is estimated to be at least 92.9% [10]. Follow-up of vital status of all patients was calculated as the time from diagnosis to death or until end of follow up on the 1st of February 2010. The information on vital status was initially obtained from municipal registries and from 1995 onwards from the nationwide population registries network. These registries provide virtually complete coverage of all Dutch citizens, including their dates of death. Information on the Dutch population size in the past and population size predictions were obtained from Statistics Netherlands (Centraal Bureau voor Statistiek [CBS]).

All patients with a first primary invasive cutaneous SCC who were diagnosed between 1 January 1989 and 31 December 2008 in the Netherlands were included (n=69,408) (i.e. patients with multiple primary SCC were only counted once). Age was divided in three groups of equal size (<70, 70-79 and ≥80 years). The study period was divided in four categories: 1989-1993, 1994-1998, 1999-2003, and 2004-2008 to study trends. TNM was determined postoperatively, in cases where postoperative stage was unknown clinical TNM stage was used. Stage I SCC were less than 2 cm in diameter. Stage II SCC were larger than 2 cm, stage III SCC invaded deep extradermal structures or with regional lymph node metastasis and stage IV SCC had distant metastasis[9]. Tumour localisation was categorised in the following anatomical subsites: lips (C44.0), eyelid (C44.1), ear (C44.2), face (C44.3), scalp/neck (C44.4), trunk (C44.5), arms (C44.6), legs (C44.7), and unknown (C44.8, C44.9). For the period 1989-1994 only survival data of five regional cancer registries was available, which have been shown for other cancer types to be representative for the whole of the Netherlands [11]. In total, 2,262 SCC patients (3.4% of all patients) with missing vital status were excluded from our survival analyses.

Mortality due to cutaneous SCC is not registered separately on death certificates in the Netherlands, but deaths due to NMSC (C44 of the ICD-10) are registered on death certificates. A recent study using the same data demonstrated that 91% of all NMSC associated mortality in The Netherlands is due to SCC[12]. SCC mortality rates were estimated by imputing information on NMSC deaths from Statistics Netherlands.

Statistical analyses

Annual age-standardised incidence and mortality rates (European standardised rates [ESR]) were calculated by using mid-year population obtained from Statistics Netherlands. The European standard population does not reflect the elderly very well and therefore crude incidence rates were calculated as well. Trends were analysed by calculating the Estimated Annual Percentage Change (EAPC) and by performing joinpoint regression analyses to identify the year in which a significant change in incidence rates occurred. Incidence rates were

also calculated per sex, age group, body site and stage. One patient with unknown sex was excluded from all analyses which were stratified by sex.

To predict SCC incidence rates up to 2020 two models were fitted for predictions with a positive slope [13,14]. The fitted models were:

$Ec_{it} = n_{it}(\alpha_i + \beta_i t)$ (1)

$Ec_{it} = n_{it}\alpha_i (1+\beta t)$ (2)

Where Ec_{it} is the expected number of cases in age group i in the year t, n_{it} is the number of person-years in the same stratum and α_i and β are the model parameters. The first model assumes linear changes over time. The second model assumes proportional effects for different age groups and therefore within the period of prediction this model retains the age-dependent pattern of incidence rates existing in the data. Age-specific predictions can therefore be made with greater accuracy. The second model was the best fitting model and was used for our predictions.

Five-year relative survival was calculated by traditional cohort-based analysis. Due to very small numbers of patients diagnosed with stage IV SCC (maximal 7 patients per year), stage III and IV patients were combined into one subgroup for survival analyses.

To study possible changes in survival over time, multivariate relative survival analyses, using Poisson regression modeling, were carried out to estimate relative excess risk (RER) of dying adjusted for follow-up interval [15]. The model was fitted on the first 5 years of follow up after diagnosis. The proportional hazards assumption was tested with log minus log plots. Hazards for body site were not proportional, and numbers were too small for stratification, therefore body site was not included in the model. Exclusion of body site from the multivariate model had only a small effect on the RER estimates and did not change the results substantially. We ran separate models for males and females, because sex was an independent prognostic factor ($p<0.01$) in a multivariate analysis and we felt it important to present sex-specific estimates.

The number of avoidable deaths represented the difference between the observed number of excess deaths and the expected number of excess deaths and was calculated by using the following formula: $(1\text{-relative survival}_{\text{stageIII/IV}})*N_{\text{stageIII/IV}} - (1\text{-relative survival}_{\text{stageI}})*N_{\text{stageIII/IV}}$ where N represents the number of diagnosed patients.

Statistical analyses were performed with SPSS 17.0 statistical software (SPSS inc., Chicago, IL, USA), SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA) and Joinpoint version 3.4.3 (National Cancer Institute, http://surveillance.cancer.gov/joinpoint). All statistical test were two-sided and considered significant at the $P < 0.05$ level.

RESULTS

Incidence

In total, 69,408 patients were diagnosed with primary invasive SCC during the 20-year study period. The Dutch population size increased from 14.8 million in 1989 to 16.4 million inhabitants in

2008. The absolute annual number of SCC patients increased from 2,247 in 1989 to 6,158 in 2008. In males, the crude incidence rate doubled between 1989 and 2008 from 20.0 to 42.5 per 100,000 inhabitants. The age-standardised incidence rate (ESR) increased from 22.2 per 100,000 inhabitants in 1989 to 35.4 per 100,000 inhabitants in 2008. Crude incidence rates for females increased from 10.4 in 1989 to 32.5 per 100,000 inhabitants in 2008. The age-standardised incidence rates increased from 7.8 to 20.5 per 100,000 inhabitants. In table 1, age-standardised incidence rates of SCC are provided by sex, period of diagnosis, age group, body site and TNM stage. Incidence rates were increasing for almost all subgroups. The face was the most affected body site for both sexes and SCC on the ear, neck or scalp were much more frequent in males than females (Figure 1). Of all SCC, 73% was diagnosed in stage I. The incidence rates of SCC of the skin increased exponentially with age starting at age 50 (Table 1, Figure 2). The age-specific incidence rates increased with each study period with the largest increment during the most recent period (Figure 2). Incidence rates that were previously observed among the 85+ population were already observed in an almost 10 year younger population between 2004 and 2008. Joinpoint analyses showed an accelerated increase in incidence rates since 2002 with an EAPC of 9.2% (95% CI: 7.5-11.0) for females and an EAPC of 6.9% (95% CI: 5.8-8.7) for males since 2003 (Figure 3). Predictions showed expected increases of up to 11,826 newly diagnosed SCC patients per year in 2020 compared to 6,158 in 2008 (Table 2), corresponding with predicted age-standardised incidence rates (ESR) of 46.9 per 100,000 inhabitants for males and 28.7 per 100,000 inhabitants for females.

Survival

The 5-year relative survival over the entire study period was 92.0% (95% CI: 91.3-92.8) for males and 94.9% (95% CI: 94.0-95.7) for females (Table 1). The 5-year relative survival by sex, age group, body site and stage are shown in Table 1. No changes over time were observed (data not shown). Females diagnosed with a stage III or IV SCC had a significantly worse prognosis compared to males (relative survival of 46% vs 62%, $p<0.001$). This combined stage III/IV group consisted of 7.2% and 11.1% stage IV SCC in males and females, respectively.

The relative survival of males with a SCC on the scalp or neck (88.9%, 95%CI: 86.7-91.0) was significantly lower than that of a SCC on lip and ear (95.2%, 95% CI: 92.1-98.2 and 92.9%, 95% CI: 91.1-94.7, respectively).

To study possible changes in relative survival over time, multivariate regression analyses on relative survival were carried out (Table 3). Strikingly, the adjusted RER of dying among female SCC patients diagnosed with a stage III or IV SCC was 30.4 times increased compared to those in stage I. For males with stage III/IV SCC, this risk was 9.9 fold higher.

To translate this result to absolute differences, the number of 'avoidable deaths' over a period of 5 years after diagnosis was calculated. If these patients would have been diagnosed earlier with a stage I SCC, 143 deaths could have been avoided (84 avoidable deaths per 100 SCC deaths) of the 315 female patients who were diagnosed with a stage III/IV SCC during the

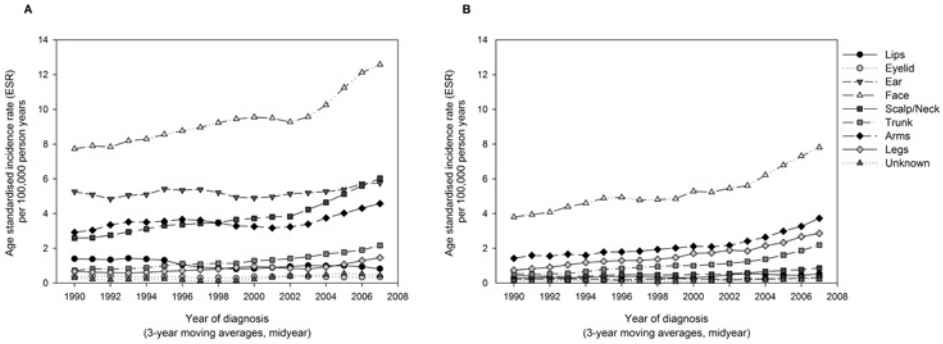


Figure 1: Three-year moving averages of age standardised incidence rates of cutaneous SCC in the Netherlands by body site for males (A) and females (B).

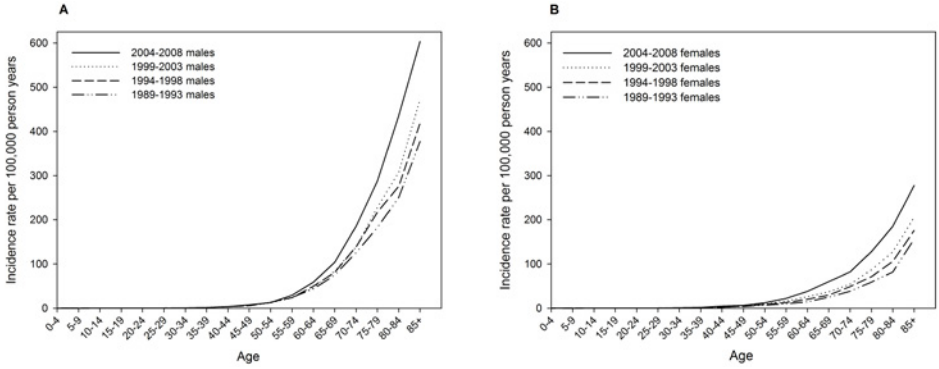


Figure 2: Age-specific incidence rates of cutaneous SCC in the Netherlands by period of diagnosis for males (A) and females (B)

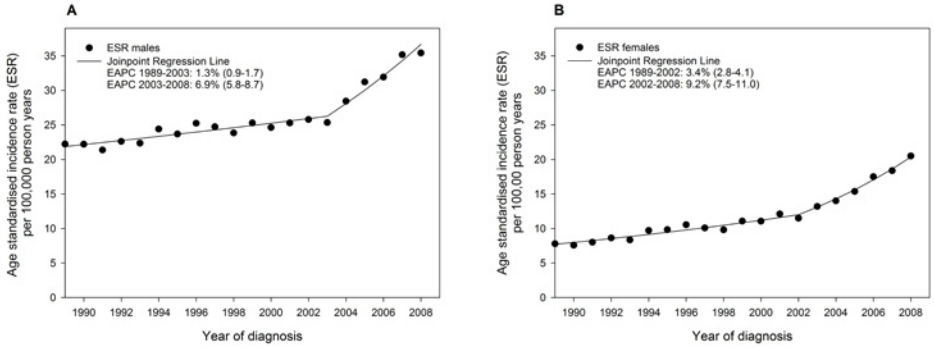


Figure 3: Joinpoint analyses of age standardised incidence rates (ESR) of cutaneous SCC in the Netherlands, 1989-2008 of males (A) and females (B) with estimated annual percentage change (EAPC).

Table 1: Numbers, age-standardised incidence rates (ESR) and 5-year relative survival of cutaneous SCC in the Netherlands

	Males							Females						
		ESR[a]				5-year Relative survival[b]			ESR[a]				5-year Relative survival[b]	
	N	1989-1993	1994-1998	1999-2003	2004-2008	Relativesurvival	95% CI	N	1989-1993	1994-1998	1999-2003	2004-2008	Relative survival	95% CI
Overall	41556	22.2	24.4	25.3	32.4	92	(91-93)	27851	8.1	10.0	11.8	17.2	95	(94-96)
Age (years)														
< 70	14160	9.1	9.6	9.4	11.5	92	(92-93)	8206	3.6	4.6	5.5	8.1	95	(95-96)
70-79	15220	149	171	175	226	90	(88-91)	7987	47	58	67	100	94	(93-95)
>=80	12176	314	347	390	520	95	(93-98)	11658	119	141	167	231	95	(93-98)
Body site														
Lips	1641	1.4	1.1	0.9	0.9	95	(92-98)	817	0.3	0.4	0.4	0.5	99	(94-103)
Eyelid	552	0.4	0.3	0.4	0.3	94	(88-100)	461	0.2	0.2	0.2	0.3	102	(96-107)
Ear	8257	5.1	5.3	5.0	5.6	93	(91-95)	553	0.2	0.2	0.2	0.3	93	(86-99)
Face	15125	7.8	8.8	9.4	11.9	93	(92-94)	13463	4.0	4.8	5.3	7.3	95	(94-97)
Scalp/Neck	6271	2.7	3.4	3.8	5.6	89	(87-91)	1317	0.4	0.5	0.5	0.8	90	(85-94)
Trunk	2107	0.7	1.0	1.3	2.0	90	(87-92)	2184	0.5	0.8	1.1	1.9	90	(88-93)
Arms	5692	3.2	3.6	3.2	4.3	91	(89-93)	5107	1.5	1.8	2.2	3.4	95	(94-97)
Legs	1423	0.6	0.7	0.9	1.3	95	(92-99)	3628	0.8	1.3	1.8	2.6	95	(93-97)
Unknown	488	0.2	0.2	0.3	0.5	92	(86-99)	321	0.1	0.1	0.1	0.2	95	(88-103)
Stage														
I	30161	14.8	16.4	17.9	25.7	95	(94-95)	20682	5.3	6.8	8.7	14.2	98	(97-99)
II	3447	1.9	2.0	2.2	2.7	76	(73-79)	2014	0.6	0.6	0.8	1.0	76	(72-80)
III	595	0.4	0.4	0.4	0.4	62	(56-68)[c]	296	0.1	0.1	0.1	0.1	46	(38-53)[c]
IV	47	0.0	0.0	0.0	0.0	62	(56-68)[c]	35	0.0	0.0	0.0	0.0	46	(38-53)[c]
Unknown	7306	5.0	5.5	4.7	3.7	91	(89-93)	4824	2.0	2.3	2.1	1.9	93	(91-95)

Abbreviations: ESR, European Standardised Rate; N, number of cases

[a]ESR per 100,000 person years, [b]Relative survival in %, [c]Stage III and IV were combined in the survival analyses due to small subgroups

study period. In the same situation, 203 deaths of the 621 males that were diagnosed with a stage III/IV SCC could have been avoided resulting in 86 avoidable deaths per 100 SCC deaths.

Mortality

During the 20-year study period, 1,513 patients died due to NMSC. The crude mortality rate of NMSC remained 0.5 per 100,000 person-years between 1989 and 2008, whereas age-standardised mortality rates decreased slightly from 0.5 per 100,000 person-years in 1989 to 0.4 per 100,000 person-years in 2008, with an EAPC of -1.9% (95% CI:-3.1- -0.7).

Table 2: Predictions of age-standardised incidence rates and number of newly diagnosed SCC patients up to 2020

	2008	2010		2015		2020	
	Observed	Predicted	95% PI	Predicted	95% PI	Predicted	95% PI
Males							
N	3453	3776	(3610- 3942)	5177	(4916- 5438)	6925	(6530- 7320)
ESR	35.4	36.8	(35.2- 38.4)	43.3	(41.1- 45.5)	49.7	(46.9- 52.2)
Females							
N	2705	2797	(2680- 2913)	3761	(3620- 3901)	4902	(4735- 5069)
ESR	20.5	20.5	(19.6- 21.4)	25.1	(24.1- 26.1)	29.8	(28.7- 30.9)

Abbreviations: ESR, European Standardised Rate; N, number of cases; PI, Prediction Interval

Table 3: Multivariate analyses on relative survival of cutaneous SCC

	Males					Females				
		Univariate[a]		Multivariate[a]			Univariate[a]		Multivariate[a]	
	N	RER	95% CI	RER	95% CI	N	RER	95% CI	RER	95% CI
Period										
1989-1993	6353	1.00		1.00		3521	1.00		1.00	
1994-1998	8689	1.35	(0.96-1.91)	1.30	(1.04-1.63)*	5439	1.11	(0.69-1.78)	0.99	(0.73-1.32)
1999-2003	10199	1.45	(1.05-2.02)*	1.34	(1.07-1.67)*	7049	0.91	(0.56-1.48)	0.95	(0.72-1.26)
2004-2008	14897	1.08	(0.76-1.53)	1.14	(0.91-1.43)	10998	0.71	(0.41-1.18)	0.83	(0.62-1.11)
Age (years)										
<70	13642	1.00		1.00		7980	1.00		1.00	
70-79	14685	1.30	(1.12-1.50)*	1.22	(1.06-1.41)*	7735	1.26	(0.99-1.61)	1.44	(1.16-1.78)*
≥80	11811	0.41	(0.20-0.82)*	0.91	(0.71-1.17)	11292	1.06	(0.70-1.59)	1.32	(1.02-1.69)*
Stage										
I	29303	1.00		1.00		20204	1.00		1.00	
II	3341	6.5	(5.1-8.3)*	4.3	(3.6-5.1)*	1946	15.3	(8.9-26.2)*	7.7	(5.9-10.0)*
III + IV	621	14.1	(10.7-18.5)*	9.9	(8.1-12.1)*	315	55.1	(32.1-94.7)*	30.4	(23.2-39.7)*
Unknown	6873	2.3	(1.7-3.0)*	1.5	(1.2-1.9)*	4542	3.9	(2.2-7.1)*	1.9	(1.4-2.6)*

Abbreviations: CI, confidence interval; N, number of cases; RER, Relative Excess Risk

[a]All models are fitted on the first 5 years after diagnosis and adjusted for follow-up time of the patients

*Significant

DISCUSSION

To our knowledge, this is the first study which describes detailed trends of incidence rates, relative survival and mortality rates for cutaneous SCC in the Netherlands. As more population based information on keratinocytic malignancies in Europe is needed [16,17], this study adds important information for the development of public health policies.

Incidence

Similar to observations from other countries [2-5], age-standardised incidence rates increased rapidly: 1.5 fold for men and threefold for women between 1989 and 2008. Trends in crude rates were even stronger, but should be interpreted with caution as they are heavily influenced by ageing of the population. Relative increases in incidence were higher among females, because incidence rates at the beginning of the study were lower compared to males. The increase in absolute number of newly diagnosed patients was approximately equal for both sexes. This may be associated with an equal increase in the distribution of risk factors for both sexes.

As age-specific incidence rates also increased, ageing of the population only partly explains the observed increases. Most likely, an increased number of people are reaching high levels of cumulative UV exposure, resulting in higher SCC risks. This is in line with the observation that incidence rates of other UV-related skin tumors increased more steeply than those of other skin malignancies in the Netherlands [12,18]. Holidays to sunny countries have become more affordable and popular and an increasing proportion of the retired Dutch population emigrates (temporarily during the winter) to sunny climates such as Spain, Portugal and South of France, increasing their cumulative UV exposure considerably. Also, people may spend more time outdoors during leisure activities (e.g., sports, gardening, walking and biking) compared to prior generations.

Public health campaigns (against melanoma) have primarily advocated avoidance of sunburns (especially in children) and to a lesser extent reducing cumulative UV exposure to the general population. Informing middle-aged and elderly people about the risk of (cumulative) UV exposure may be beneficial in reducing the burden of SCC. However, only informing people about the risk is not enough to change behavior and more effective methods should be explored by health promotion researchers.

Steep increments in incidence rates were observed since 2002 for females and 2003 for males, for which there is no simple explanation. The public campaigns warning for excessive sun exposure may in part be responsible for this increase, but a recent study showed that increased skin cancer surveillance resulted in a higher likelihood of being diagnosed with truncal BCC and not SCC suggesting that this bias has relatively little impact on our findings [19]. Another possibility is an improvement in completeness of the national cancer registration since 2002. However, in 1990 the completeness of skin malignancies (excluding basal cell

carcinomas) was already 92.9% [10] and a small increase in completeness could not explain the observed increases in SCC. The increased number of solid organ transplantations and the associated immunosuppressive drug use may have contributed to the increased incidence rates as well [20]. The number of solid organ transplantations increased from 511 in 1989 to 1048 in 2008 and the total number of immunosuppressive drugs users increased fourfold from 25,400 in 1994 to 101,600 users in 2008 (personal communication) [21,22]. Unfortunately, in our database we are not able to identify SCC patients who had a solid organ transplantation or who were longterm immunosuppresive drug users for other reasons. The increased use of biologics in immune mediated inflammatory diseases may also contribute to the increased SCC incidence in the last decade [23,24]. However, these iatrogenic risk factors would result in a more gradual increase in incidence rates and not the abrupt accelerations in incidence rates since 2002.

Incidence rates increased among almost all body sites, except for males with a SCC on the lips. This pattern followed the decreasing trend of smoking among males and the increasing trend of smoking among females in the Netherlands, which is an important risk factor for developing lip cancer [25,26]. An Israeli study found a comparable pattern and observed a 40-fold higher incidence of cancer of the external lip compared to cancer of the internal lip, suggesting that the role of sun exposure is more important than smoking in causing SCC [27].

We may have underestimated the SCC incidence rates, because we may have missed some cases due the following reasons [16]: the number of nonhospital practices that treat SCC has increased in the last decade and not all of these private practices are affiliated to the national cancer registry. Furthermore, not all SCC are diagnosed, especially in elderly people with multiple comorbidities where skin cancers are often not treated. Also a small proportion of SCC may be treated without histological confirmation and will therefore not be registered in the cancer statistics [28].

Survival and mortality

Only a small proportion of all SCC patients were at high risk of dying at time of diagnosis (1.4% diagnosed in stage III/IV), but some lesions may progress after diagnosis also leading to death. It is estimated that in Europe, annually 2,016 deaths are due to SCC [29]. In the Netherlands we observed a small decreasing trend in NMSC mortality, mainly caused by SCC, which is in line with studies from Finland and the United States [30,31].

The observed 5-year relative survival rates were comparable with those observed in Denmark [32] and no significant changes over time were observed. Relative survival was better for females than for males, in contrast to relative survival of advanced disease: a third of all male patients and almost half of all female patients with advanced disease died. SCCs in the head and neck region were associated with a significantly lower relative survival. Truncal SCCs in men and women also had a negative impact on survival which may be explained by a diagnostic delay (i.e., truncal SCCs may have been missed more easily by patients and physicians).

Due to a higher prevalence of mortality risk factors (e.g. solid organ transplantation, use of immunosuppressive drugs) among SCC patients compared to the general population, we might have overestimated SCC-specific mortality, resulting in lower relative survival estimates.

Increased tumor thickness, increased horizontal size, immunosuppression and localization on the ear and possibly the lips are known to be prognostic factors for the development of metastasis, but were not all available in the cancer registry [33]. The Dutch SCC guideline, approved in 2010, recommends recording the tumor thickness in the pathology report, which is of interest for future evaluations [34].

Conclusion

Incidence rates of SCC increased rapidly. Overall relative survival was stable and the mortality rate due to NMSC decreased slightly during the study period. We recommend that primary prevention programmes aim to reduce the cumulative amount of UV exposure among the young and the older population. Secondary prevention programs should encourage the elderly to recognise skin changes and to seek early diagnosis to prevent progression of the lesion.

Acknowledgements

We gratefully acknowledge Rob Verhoeven and his colleagues of the Netherlands Cancer Registry for providing data and the registration clerks for the dedicated data collection. We would like to thank Dr. Senada Koljenovic for reviewing the selection of morphology codes. We also would like to thank Sten Willemsen and Gerard Borsboom for their support with the programming of SAS. We thank Emmilia Dowlatshahi for critically reviewing the manuscript.

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Chapter 2.3

Different epidemiology of squamous cell carcinoma on sun exposed and covered body sites emphasizes the need for full body examination

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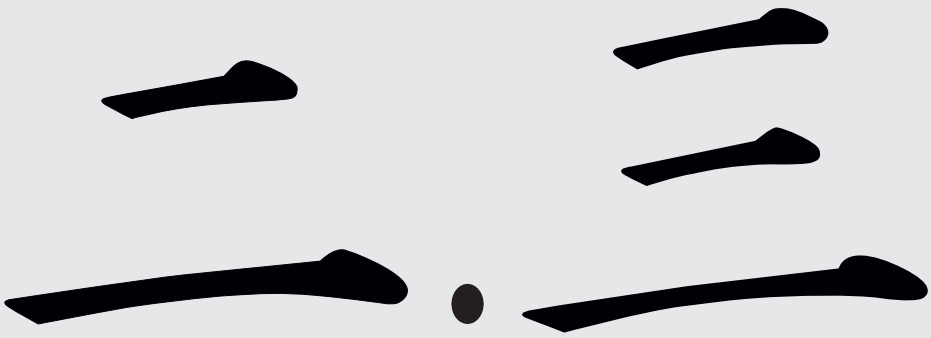

ABSTRACT

Background: Recently, it was shown that incidence rates of cutaneous squamous cell carcinoma (SCC) on sun exposed body sites, in contrast to covered body sites, correlated strongly with age.

Objective: To validate the different age-dependent patterns of SCC incidence on sun exposed and covered body sites and to estimate the annual increases in the Dutch general population.

Methods: Information on newly diagnosed cutaneous SCC patients between 1989 and 2008 was obtained from the Netherlands Cancer Registry (NCR). Age-specific and age-standardised incidence rates (European Standardised Rates [ESR]) were calculated. Mean annual increase in numbers of SCC patients and Estimated Annual Percentage Change (EAPC) in incidence rates were calculated by sex, age group and period of diagnosis.

Results: Incidence rates were strongly dependent on age for SCC at sun exposed body sites, but not at covered body sites. On sun exposed body sites, the ESR in 2008 was 30.6 per 100,000 inhabitants for males and 17.7 for females. For covered body sites the ESR was 4.2 per 100,000 inhabitants for males and 2.5 females. The EAPCs were substantially higher on covered body sites than at sun exposed body sites (EAPC for the most recent period; males: 12.6%, 95% confidence interval [CI]: 11.1-14.2; females: 14.1%, 95% CI: 11.5-16.8) (males: 6.4%, 95% CI: 4.5-8.3; females: 9.3%, 95% CI: 8.5-10.2).

Conclusion: We confirmed the different age-dependent patterns of SCC. Absolute numbers of patients with an SCC on covered body sites are lower, but incidence rates accelerate with calendar year. Therefore we recommend full body examination.

INTRODUCTION

Incidence rates of cutaneous squamous cell carcinoma (SCC) are increasing across the world [1-5] and assumed to be primarily related to increased cumulative exposure to ultraviolet (UV) radiation [6,7]. The higher incidence rates of cutaneous SCC in older age groups can be explained by the higher likelihood of elderly people to surpass the critical threshold of carcinogenic levels of cumulative UV exposure combined with the longer time for a carcinoma to progress into a clinical symptomatic lesion [8]. Interestingly, a recent study showed that incidence rates of SCC on sun exposed body sites correlated strongly with age, while the incidence rates of SCC on covered body sites did not increase as sharply with age [3]. However, incidence rates of SCC on covered body sites increased more rapidly with calendar time than those of sun exposed body sites.

The aim of our study was to confirm the different epidemiology of SCC incidence on sun exposed and covered body sites in the Dutch general population, in order to verify the need to further increase the awareness of SCCs on covered body sites among health care professionals.

METHODS

We used data of the Netherlands Cancer Registry (NCR). The NCR is based on all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnosis, haematology departments and radiotherapy institutions [9]. The following morphology codes (as specified in the International Classification of Diseases for Oncology (ICD-O-3) [10] combined with topography 'skin' were considered invasive cutaneous SCC: 8010, 8050-8084 (excluding 8077: intraepithelial neoplasia, 8080: Erythroplasia of Queyrat, 8081: Bowen disease, 8082: lympho-epithelial carcinoma) All patients with a first histological confirmed invasive primary SCC of the skin diagnosed between 1989 and 2008 were included (N=69,408) (i.e. patients with multiple primary SCC were counted only once). Information on the age distribution of the Dutch general population was obtained from Statistics Netherlands. Patients' age was categorized in tertiles: <70, 70-79 and ≥80 years. Incidence rates were standardised to the Standard European population to allow for international comparisons and time trends. Unstandardised age-specific incidence rates by 5-year age categories were used to study age-specific effects. For women, the head, neck, arms and legs were considered sun exposed sites [3]. For men, the legs were excluded from the sun exposed sites. Lesions on multifocal and unknown body sites were excluded (N=810). Estimated Annual Percentage Change (EAPC) was calculated by fitting a regression line to the natural logarithm of the rates, using the

calendar year as regressor variable (i.e. y=ax + b where y = ln(rate) and x = calendar year, then EAPC = 100 * (e^a – 1)).

The mean annual increase in absolute numbers of SCC was calculated by performing a linear regression with the absolute numbers of SCC as the dependent variable and calendar year as the independent variable. Regression models to calculate the mean annual increase and the EAPC were fit on two periods (males: 1989-2003 and 2003-2008, females: 1989-2002 and 2002-2008), because preliminary analyses showed that SCC incidence rates accelerated since 2003 for males and since 2002 for females. All the analyses were done separately for men and women. Statistical analyses were performed with SPSS 17.0 statistical software (SPSS inc., Chicago, IL, USA) and SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA). All statistical test were two-sided and considered significant at the $P < 0.05$ level.

RESULTS

The age-standardised incidence rates of SCC on sun exposed body sites increased from 20.6 per 100,000 inhabitants in 1989 to 30.6 per 100,000 inhabitants in 2008 for males and increased from 7.0 per 100,000 inhabitants to 17.7 per 100,000 inhabitants for females (Fig. 1). For covered body sites the incidence rates increased from 1.3 per 100,000 inhabitants in 1989 to 4.2 in 2008 for males and for females from 0.6 to 2.5 per 100,000 inhabitants. The EAPC of SCC incidence rates for the most recent period was 12.6% (95% CI: 11.1-14.2) for males and 14.1% (95% CI: 8.5-10.2) for females at covered body sites, while the EAPC of exposed body sites in this period was 6.4% (95% CI: 4.5-8.3) for males and 9.3% (95% CI: 8.5-10.2) for females.

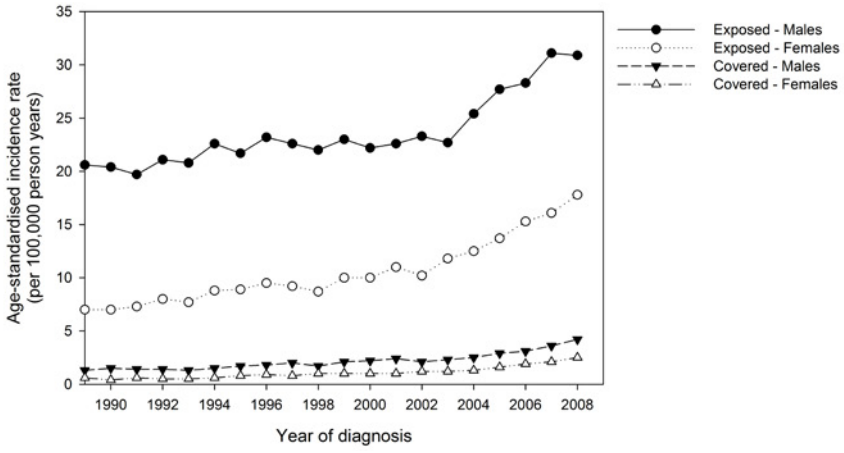

Figure 1: Age-standardised incidence rates (ESR) per 100,000 person years for cutaneous squamous cell carcinoma on sun exposed and covered body sites by sex.

Incidence rates of SCC on sun exposed body sites correlated strongly with age, in contrast to SCC on covered body sites (Fig. 2). The age-specific incidence rates increased with age and calendar year for both sexes demonstrating that age-specific incidence rates among the elderly as observed between 1989 and 1993 were observed among a much younger population between 2004 and 2008.

In table 2 the absolute number of newly diagnosed SCC patients as well as the age-standardised incidence rates (ESR) are shown by sex, period of diagnosis and age group. The largest percentage increase in incidence rates was observed among patients with SCC on covered body sites. In contrast, the largest increase in absolute number of newly diagnosed SCC patients per year were patients with SCC on sun exposed body sites. Although the relative increase in incidence rates of SCC on covered body sites reached levels up to 23.9%, the absolute number of newly diagnosed patients was 675 in 2008, compared to 5429 newly diagnosed patients with SCC on sun exposed body sites.

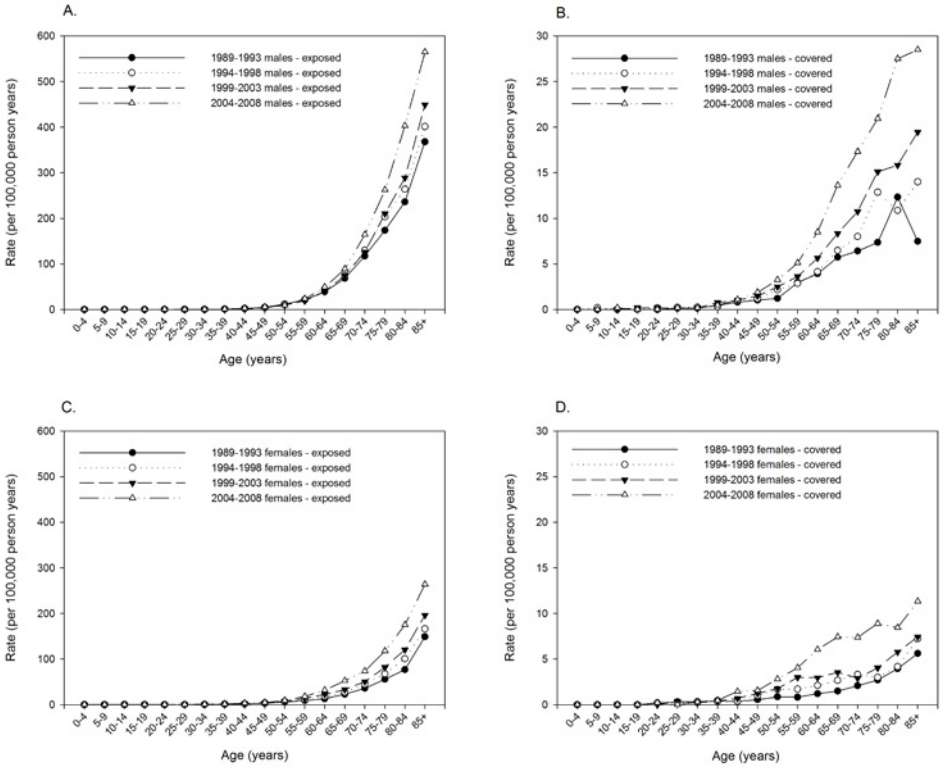

Figure 2: Age-specific incidence rates of cutaneous squamous cell carcinoma on exposed (a,c) and covered (b,d) body sites for males (a,b) and females (c,d). Please note that the figures have different y-axes (a and c are different from b and d).

Table 1: Number and age-standardised incidence rates of cutaneous SCC in the Netherlands

	N				Mean Annual Increase N (95% CI)				ESR (per 100,000 person years)				EAPC (95% CI)			
	1989-1993	1994-1998	1999-2003	2004-2008	Period 1[a]		Period 2[b]		1989-1993	1994-1998	1999-2003	2004-2008	Period 1[a]		Period 2[b]	
Males																
Sun Exposed																
<70	2495	2787	2873	3906	**7**	(4-10)	**57**	(44-69)	8.0	8.4	7.9	9.5	**-0.3**	(-0.9-0.3)	**5.1**	(3.1-7.2)
70-79	2520	3152	3493	4827	**19**	(15-23)	**77**	(58-95)	140.1	159.3	160.1	203.6	**1.3**	(0.7-1.9)	**6.7**	(4.2-9.3)
≥80	1930	2296	2806	4453	**17**	(15-19)	**92**	(81-103)	302.1	332.7	369.4	483.8	**1.9**	(1.5-2.3)	**7.4**	(5.3-9.5)
Covered																
<70	290	362	497	783	**4**	(3-5)	**19**	(13-25)	0.9	1.1	1.3	1.9	**3.8**	(3.0-4.6)	**10.6**	(7.2-14.2)
70-79	121	197	271	443	**3**	(2-4)	**13**	(11-15)	6.8	9.9	12.5	18.8	**5.3**	(2.5-8.3)	**15.5**	(13.5-17.5)
≥80	71	88	138	269	**1**	(-4-7)	**8**	(5-11)	9.9	12.4	17.7	28.0	**6.4**	(3.3-9.6)	**12.4**	(6.8-18.3)
Females																
Sun Exposed																
<70	1073	1375	1708	2733	**11**	(9-14)	**56**	(52-60)	3.2	3.9	4.6	6.6	**3.4**	(2.3-4.4)	**10.1**	(8.4-11.8)
70-79	1173	1547	1907	2777	**14**	(12-15)	**50**	(40-60)	43.8	54.1	63.2	91.4	**3.4**	(2.5-4.2)	**9.5**	(8.0-11.0)
≥80	1663	2204	2829	4357	**22**	(18-26)	**80**	(69-90)	112.8	133.3	158.3	219.2	**3.3**	(2.4-4.1)	**8.3**	(7.1-9.6)
Covered																
<70	111	211	311	580	**4**	(3-5)	**16**	(10-21)	0.3	0.6	0.8	1.4	**9.2**	(6.5-12.0)	**13.4**	(9.3-17.7)
70-79	62	89	100	238	**1**	(0-1)	**8**	(5-10)	2.3	3.2	3.3	8.0	**3.8**	(0.4-7.3)	**23.9**	(16.1-32.1)
≥80	72	94	119	197	**1**	(0-1)	**3**	(0-5)	4.8	5.7	6.6	9.9	**3.1**	(0.4-6.0)	**6.1**	(-0.2-12.7)

[a]1989-2003 for males and 1989-2002 for females, [b]2003-2008 for males and 2002-2008 for females

Abbreviations: N, number of cases; CI, confidence interval; EAPC, estimated annual percentage change; ESR, European standardized rate

Numbers in bold are the point estimates of the mean annual increase or the EAPC

DISCUSSION

Incidence rates of SCC on covered body sites showed large relative increases with calendar year, but were not as strongly dependent on age as incidence rates of SCC on sun exposed body sites. The age-dependent patterns and the overall EAPCs were comparable to those previously observed in Sweden [3]. A large EAPC of incidence rates of covered body sites (e.g., trunk) may point at increased prevalence of intermittent UV exposure of body parts that were previously less likely to be exposed (for example, by changes in tanning behaviour, UV exposure during holidays, leisure activities and sunbed use) [3,7]. Another explanation of an increase in the ratio of SCC on covered to non covered body sites may be the increased use of immunosuppressive drugs [11,12]. The amount of users of immunosuppressive drugs in the Netherlands increased from 25,400 users in 1994 to 101,640 users in 2008 [13] (personal communication). However, increased use of immunosuppressive drugs among organ transplant recipients probably leads to the same body site distribution of the first SCC compared to the general population [14,15]. The larger EAPCs on covered body sites are therefore not likely to be explained by the use of immunosuppressive drugs. Due to the smaller number of SCCs on covered body sites, this may have led to higher relative increases and thus higher EAPCs (Table 1).

It is also possible that the awareness of skin cancer in the general population and physicians improved resulting in an increase of total body skin examinations in patients at high risk of developing skin cancer. This would have resulted in more diagnosed SCC on covered body sites rather than real increases in SCC. The much larger increases in numbers of patients compared to relative increases in age-standardised incidence rates can be explained by population growth and population ageing during the studied period.

Conclusion

Although the majority of SCC develop at sun exposed body sites in elderly patients, the incidence rates of SCC among younger people and on covered body sites is increasing. This observation is emphasizing the increased need to perform full body skin examinations in people at high risk of developing cutaneous malignancies, such as solid organ transplant recipients, patients with a history of skin cancer or patients with extensive sun damaged skin.

Acknowledgements

We gratefully acknowledge Rob Verhoeven and his colleagues of the Netherlands Cancer Registry for providing data and the registration clerks for the dedicated data collection. We would like to thank Dr. Senada Koljenovic reviewing the selection of the morphology codes.

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Chapter 3

Burden of disease attributable to skin cancer

Chapter 3.1

Burden of disease due to cutaneous melanoma has increased in the Netherlands since 1991

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British Journal of Dermatology. Aug 2013; 169 (2): 389-97

ABSTRACT

Background: The burden of disease, describing loss of health and death due to a disease, has not been fully studied for melanoma in the general population over time.

Methods: Age- and gender-specific incidence data from all melanoma patients in the Netherlands between 1991 and 2010 were obtained from the Netherlands Cancer Registry. Melanoma-specific mortality and life expectancy data were obtained from Statistics Netherlands. Melanoma duration was calculated using the DISMOD software from the World Health Organisation. The Years of Life lived with Disability (YLD) and Years of Life Lost (YLL) due to melanoma were calculated using Dutch disability weights, incidence and mortality of melanoma and the life expectancy from the general population. The disability adjusted life years (DALY) was estimated by adding YLD and YLL.

Results: The world standardised incidence rates of melanoma have more than doubled for both men (7.1 per 100,000 inhabitants in 1991 to 17.0 in 2010) and women (9.4 per 100,000 inhabitants in 1991 to 19.8 in 2010). Likewise, the burden of melanoma to society increased rapidly. The YLD for men increased from 4,795 (1991 to 1994) to 12,441 and for women from 7,513 (1991-1994) to 16,544 (2007-2010). In 2007-2010 the total YLL due to melanoma was 30,651 for men and 26,244 for women compared to 17,238 and 16,900 in 1991-1994. The DALYs increased with 96% for men from 22,033 (1991-1994) to 43,092 (2007-2010) and increased with 75% for women from 24,475 (1991-1994) to 42,788 (2007-2010).

Conclusions: Melanoma is becoming a great burden to Dutch society.

Abbreviations:

YLD = Years of Life lived with Disability = number of incident cases x disability weight x average duration of the disease until remission or death

AYLD = Average Years of Life lived with Disability = YLD / number of incident cases

YLL = Years of Life Lost = number of deaths x standard life expectancy at age of death in years

AYLL = Average Years of Life Lost = YLL / number of deaths

YLM = Years Lived with Melanoma = number of incident cases x average duration of the disease until remission or death

INTRODUCTION

In the past three decades the incidence of melanoma has markedly increased in people of European ancestry. In 2010, melanoma was the 7th most common cancer in men and the 5th most common cancer in women in The Netherlands (a total of 4,665 new patients among 16.6 million inhabitants) [1]. Compared with most other malignancies, melanoma affects patients at a younger age and for the majority of melanoma patients survival rates are relatively good nowadays due to early detection [2-6]. This implies an increasing number of melanoma survivors who live with a cancer diagnosis and its social and psychological effects. They may utilize health care over a prolonged period of time for medical and psychological reasons related to their melanoma history, which can become great burden for the health care system.

The highest quality of life (QoL) impairment among melanoma patients is in the immediate period after diagnosis (diagnosis and treatment). The follow up phase can be associated with fear of recurrence and this psychological distress can interfere with screening recommendations [7]. Many patients receive more follow up than recommended [8]. The patients concerns should be recognized and improvements in information provision about recurrence risk may lead to lower levels of distress and less additional follow up visits.

Usually, the magnitude of a cancer problem is expressed in incidence and mortality rates and numbers of newly diagnosed cancer patients, as was also done for melanoma in the Netherlands up to 2008 [6]. However, the magnitude of the societal problem can also be expressed in a quite different way using Burden of Disease measures that measure the disease burden for individuals or populations. With these measures, the fatal as well as the non-fatal burden can be quantified and the duration of disease can be taken into account. The Burden of Disease measures reflect an improved estimation of the total burden for society and may therefore be used for research purposes, public health campaigns and for the allocation of limited health care resources [9]. The burden of a disease can be estimated by calculating the number of years of life lost (YLL), the number of years of life lived with disability (YLD) and Disability Adjusted Life Years (DALY) [9]. These additional measures are of key importance in estimating the burden of cancer types which occur in young patients and have a favorable prognosis.

Only a few studies have investigated the total burden of melanoma [10]. Melanoma mortality resulted in an average loss of 15 life years across different studies and countries [10]. Patients with metastatic melanoma lost on average 23 years [11]. Brochez and colleagues investigated the burden of melanoma in Belgium, expressed as years of potential life lost and showed that in those terms, melanoma was the second most important cancer of all adult-onset cancers [12]. In the United States the years of potential life lost due to melanoma was the highest for adult-onset cancers[13]. This burden underscores the need for continued research and access to funding for this disease [11]. The indirect cost due to morbidity and premature death were as high as over 3 billion dollar in the US, due to lost workdays, caregivers lost workdays, sick

leave, restricted activity days, etc. [10]. Only a few studies examined the changes in the burden over time and included the part of the population aged over 65. This population group is of increasing importance in many European countries as the elderly population is continuously growing.

In this study, the burden of melanoma was estimated by YLL, YLD and DALYs in the general population of The Netherlands and its trend over time between 1991 and 2010.

METHODS

Population

Age- and gender-specific data on newly diagnosed patients with melanoma (ICD-O codes: C44.0-C44.9) were obtained from the Netherlands Cancer Registry (NCR), which collects incidence and tumor data on all newly diagnosed cancers in the Netherlands from the regional comprehensive cancer centers since 1989 (i.e., only first melanoma's were used for this study). The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge, which accounts up to 8% of new cases, haematology departments and radiotherapy institutions. The quality of the data is high, due to thorough training of the administrators and computerised consistency checks at regional and national levels. Completeness in 1990 was estimated to be 98% on all cancers combined and 93% on skin cancer [14,15]. We used incidence data for 1991 to 2010. Annual data on age and gender of cancer deaths, population composition and life expectancies in the general population were obtained from Statistics Netherlands (CBS).

Study design

To estimate the burden of melanoma, we calculated Disability Adjusted Life Years (DALYs) by adding the number of Years of Life Lost (YLL) as a consequence of premature death due to melanoma plus the number of Years of Life lived with Disability (YLD) caused by melanoma per person. According to Murray et al. [16], one DALY represents the loss of one year of life lived in full health. The sum of these DALYs across the population, or the burden of disease, can be thought of as "a measure of the gap between the current health status and an ideal health situation in which the entire population lives to an advanced age, free of disease and disability"[16].

Statistical methods

All analyses were performed for 4-year periods and stratified for gender. World standardised incidence rates (WSR) were calculated by multiplying the age-specific incidence rates with standard World population data. Changes were evaluated by calculating the estimated an-

nual percentage change (EAPC). To calculate this, a regression line was fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y=ax+b$, where y=ln(rate) and x=calendar year, then EAPC=100 x (e^a -1). As there were no sudden changes in the incidence or mortality rates, the EAPC was calculated over the whole study period.

To estimate YLD, we multiplied the number of incident cases by the average duration a patient lives with melanoma in The Netherlands and a Dutch weighing factor that reflects the impact of melanoma on health related quality of life on a scale from 0 (perfect health) to 1 (death) [17]. Weight factors, also known as disability weights or health state preferences, dif-

Table 1: Duration and disability weights of each phase of disease.

		Good Prognosis[a]			Poor Prognosis[a]		
		Diagnosis/ Therapy	During Follow up	After Follow up	Diagnosis/ Therapy	Metastasis	Terminal
	Main analysis						
	Duration in years						
Stage at diagnosis:	No Metastasis	0.25	4.75	LE-5	0.25	2.50	0.25
	Lymph node metastasis	0.25	4.75	LE-5	0.25	2.50	0.25
	Distant metastasis	N.A.	N.A.	N.A.	0.25	2.50	0.25
	Disability weights						
Stage at diagnosis:	No Metastasis	0.19	0.19	0.03	0.19	0.81	0.93
	Lymph node metastasis	0.43	0.19	0.03	0.43	0.81	0.93
	Distant metastasis	N.A.	N.A.	N.A.	0.81	0.81	0.93
	Sensitivity analysis 1						
	Duration in years						
Stage at diagnosis:	No Metastasis	0.25	4.75	LE-5	0.25	**0.50**	0.25
	Lymph node metastasis	0.25	4.75	LE-5	0.25	**0.50**	0.25
	Distant metastasis	N.A.	N.A.	N.A.	0.25	**0.50**	0.25
	Disability weights						
Stage at diagnosis:	No Metastasis	0.19	0.19	0.03	0.19	0.81	0.93
	Lymph node metastasis	0.43	0.19	0.03	0.43	0.81	0.93
	Distant metastasis	N.A.	N.A.	N.A.	0.81	0.81	0.93
	Sensitivity analysis 2						
All at diagnosis:	*Duration in years*	0.25	4.75	LE-5	0.25	2.5	0.25
	WHO disability weights	**0.05**	**0.05**	0.03	**0.05**	**0.75**	**0.81**

[a]We assumed that the proportion of patients with a relative survival > 5 years had a good prognosis and the proportion of patients that do not survive the first 5 years after diagnosis had a poor prognosis. We also assumed a poor prognosis for all patients with distant metastasis at diagnosis, regardless of the 5-year relative survival estimates.

Bold numbers represent the changes in the sensitivity analyses compared to the main analysis

WHO, World Health Organization

Table 2: Incidence, mortality and burden of disease of Dutch melanoma patients, according to the period of diagnosis

	Men					Women				
	1991-1994	**1995-1998**	**1999-2002**	**2003-2006**	**2007-2010**	**1991-1994**	**1995-1998**	**199-2002**	**2003-2006**	**2007-2010**
Number of new melanoma patients	2,820	3,556	4,509	5,752	7,582	4,097	5,012	5,968	7,551	9297
Crude incidence rate*	9.4	11.6	14.3	17.9	23.3	13.3	16.0	18.5	23.0	27.9
Age standardised incidence rate*	7.4	8.8	10.5	12.6	15.4	10.1	11.8	13.5	16.2	19.0
Number of melanoma deaths	846	936	1,154	1,352	1,656	751	793	885	1,067	1,267
Crude mortality rate*	2.8	3.0	3.7	4.2	5.1	2.4	2.5	2.7	3.2	3.8
Age standardised mortality rate*	2.1	2.1	2.4	2.6	2.9	1.5	1.4	1.5	1.7	1.9
YLM	53,845	71,556	86,769	114.395	146,160	110,343	136,880	164,692	206,122	249,776
YLD[a]	4,795	6,008	7,506	9,575	12,441	7,513	9,125	10,833	13,588	16,544
YLL	17,238	18,131	21,860	25,210	30,651	16,900	17,350	17,998	21,686	26,244
DALYs[a] (YLD+YLL)	22,033	24,139	29,366	34,785	43,092	24,413	26,475	28,831	35,274	42,788
Age standardised YLD*	13	15	18	22	27	20	23	26	31	37
Age standardised YLL*	47	46	51	55	63	44	42	40	46	55
Age standardised DALYs*	60	61	69	77	90	63	65	67	77	92
AYLM	19.1	20.1	19.2	19.9	19.3	26.9	27.3	27.6	27.3	26.9
AYLD	1.7	1.7	1.7	1.7	1.6	1.8	1.8	1.8	1.8	1.8
AYLL	20.4	19.4	18.9	18.6	18.5	22.5	21.9	20.3	20.3	20.7
Sensitivity Analyses										
YLD[b]	4,378	5,483	6,840	8,725	11,320	7,240	8,791	10,436	13,085	15,924
DALYs[b]	21,616	23,614	28,700	33,935	41,971	24,140	26,141	28,434	34,771	42,168
YLD[c]	3,655	4,425	5,394	6,893	8,978	5,044	6,057	6,909	8,631	10,462
DALYs[c]	20,894	22,556	27,253	32,103	39,630	21,944	23,406	24,907	30,317	36,706

Source: Netherlands Cancer Registry and Statistics Netherlands

* = per 100 000 personyears of the world standard population

YLD: years lived with disability; YLM: years lived with melanoma; YLL: years of life lost; DALY: disability adjusted life years; AYLD: average years lived with disability; AYLM: average years lived with melanoma; AYLL: average years of life lost.

[a] Dutch disability weights and assumed on average 3 years survival of patients with a poor prognosis

[b] Dutch disability weights and assumed on average 1 year survival of patients with a poor prognosis

[c] World Health Organisation (WHO) disability weights and assumed on average 3 years survival of patients with a poor prognosis

fered by phase of disease and are described in Table 1. The WHO uses 0.05 (0 perfect health to 1 death) during therapy and follow up for patients with a good prognosis and 0.75 and 0.81 for patients with metastasis and terminal patients, respectively. Although the vast majority of patients are diagnosed at early stages with a good prognosis, over a third of melanoma patients experience considerable levels of anxiety, mainly during diagnosis and treatment [7]. Moreover, a proportion of melanoma survivors reported difficulty in obtaining a life insur-

ance or a mortgage [18]. For the aforementioned reasons, we believe that the disability weights used by the WHO do not fully capture the non-fatal disease burden of melanoma. Therefore, we used the higher Dutch disability weights (0.19, 0.43, 0.81 and 0.93) for our main analyses. Because, the Dutch disability weights differ by stage of disease, the number of patients with nodal and distant metastasis at diagnosis was estimated by using proportions from a previously published Dutch incidence data (i.e., 4.2% were diagnosed with nodal metastasis and 0.7% with distant metastasis) [6].

We used a follow up time of 5 years, according to the Dutch guideline [19]. We assumed that patients with a good prognosis survived beyond those 5 years and the patients with a poor prognosis survive on average 3 years after diagnosis. The 5-year relative survival was considered the proportion of patients with a good prognosis. These 5-year relative survival estimates by gender and nodal stage were obtained from Eisemann et al. [20]. We assumed that all patients with distant metastasis at diagnosis had a poor prognosis, regardless of their 5-year relative survival estimates. In contrast to the WHO, which assigns a weight factor of 0 after follow up, we assigned a weight factor of 0.03 after of follow up, because a third of cancer survivors in the Netherlands continue to experience problems with work, or problems with obtaining insurance and homeloans years after their diagnosis [18]. YLL corresponds to the number of deaths due to melanoma multiplied by the standard life expectancy in the general population at the age which death occurs as estimated by a standard life table [9]. The average years of life lost (AYLL) were calculated by dividing the YLL by the number of melanoma deaths. DALYs were calculated as the sum of the YLL due to premature mortality in the population and the YLD for incident cases of melanoma. To calculate the actual years that patients live with their melanoma, the Years Lived with Melanoma (YLM) were calculated by multiplying the number of melanoma patients with the duration of disease at the age of diagnosis. Melanoma disease duration was estimated using the DISMOD software [21]. Input variables used for DISMOD were age-specific incidence and mortality rates and we assumed no remission (i.e., rate was 0 for all ages). The average YLM (AYLM) was obtained by dividing the YLM by the number of melanoma patients.

Sensitvity Analyses

As the disability weights for patients with a poor prognosis are very high (i.e., 0.81 and 0.93), the assumption of an average survival of 3 years has a large impact on the total YLD and DALYs. Therefore, we performed a sensitivity analysis assuming 1 year survival for patients with a poor prognosis.

A second sensitivity analysis was performed using the WHO disability weights, because the Dutch disability weights are higher than those of the WHO [22]. Analyses were not stratified for stage at diagnosis, because the WHO has no separate weights for different stages at diagnosis. In these analyses, relative survival by age and gender was used to estimate the proportion of patients with a poor prognosis [2].

RESULTS

Incidence and mortality

The incidence of melanoma has more than doubled between 1991 and 2010 for both men and women (Table 2). Between 1991 and 1994, an annual average of 1,729 Dutch citizens was newly diagnosed with melanoma and this increased to 4,220 individuals per year in the period 2007-2010 (Table 2). The age standardised incidence rate for men increased from 7.4 per 100,000 inhabitants in 1991 to 15.4 in 2010. The age standardised incidence rate for women increased from 10.1 per 100,000 inhabitants to 19.0 during the same period. Age-specific incidence rates increased for each period of diagnosis (Fig. 1). The Estimated Annual Percentage Change (EAPC) in incidence rates was 4.7% (95% CI 4.3-5.1) for men and 4.1% (95% CI 3.7-4.5) for women. Age standardised mortality rates increased with 2.2 % (95% CI 1.8-2.6) annually from 3.0 per 100,000 male inhabitants in 1991-1994 to 4.4 in 2007-2010 and from 2.1 per 100,000 female inhabitants in 1991-1994 to 2.7 in 2007-2010, which equals an annual increase of 1.5% (95% CI 0.07-2.3). An increase of melanoma mortality was particularly observed for elderly (>65 years) with an increase from 7.8 to 17.4 per 100,000 personyears (WSR, EAPC 4.0, 95% CI 3.4-4.6). The mortality rate of young adults (<45 years) was low (0.4 per 100,000 in 2010) and remained stable over time. The mortality rate of middle aged persons (45-64 years) increased slowly with 1.2% (95% CI 0.6-1.8) annually from 4.2 to 4.7 per 100,000 person-years in 2010.

Years lived with Melanoma (YLM)

The Average Years Lived with Melanoma (AYLM), without adjustments for disability, remained stable during the study period for both sexes. Men lived on average 20 years with a melanoma and women 27 years (Table 2 and Figure 2). In contrast to the stable AYLM, the total years of

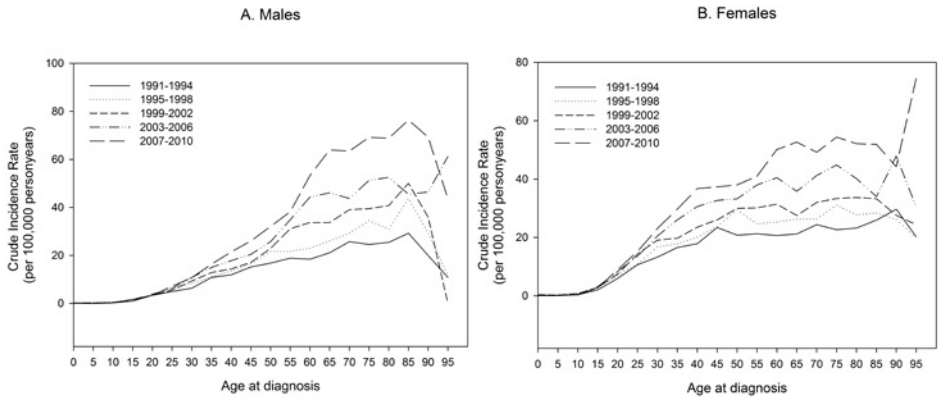

Figure 1: Incidence rates of cutaneous melanoma by age at diagnosis, 1991-2010 per 100,000 personyears for men (A) and women (B).

life lived with melanoma in the general population has rapidly increased. For men, a total of 146,160 life-years lived with melanoma in 2007-2010 was estimated compared to 53,845 years in 1991-1994. For women, the YLM rose from 110,343 to 249,776. (Table 2, Figure 2)

Years of life Lived with Disability (YLD)

The average number of years that a melanoma patient lived with melanoma, adjusted for disability due to melanoma was 1.7 years for men and 1.8 for women. (Table 2). The total YLD of melanoma in the general population increased rapidly. For men, the YLD increased from 4,795 (1991 to 1994) to 12,441 and for women from 7,513 (1991-1994) to 16,544 years (2007-2010).

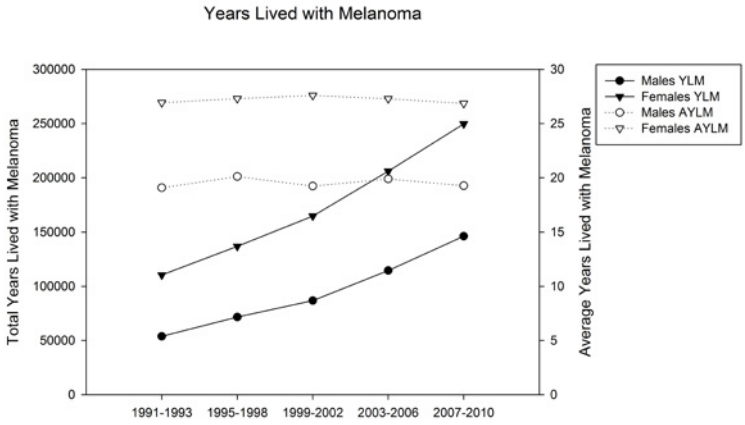

Figure 2: Years Lived with Melanoma (YLM) and Average Years Lived with Melanoma (AYLM) by period of diagnosis

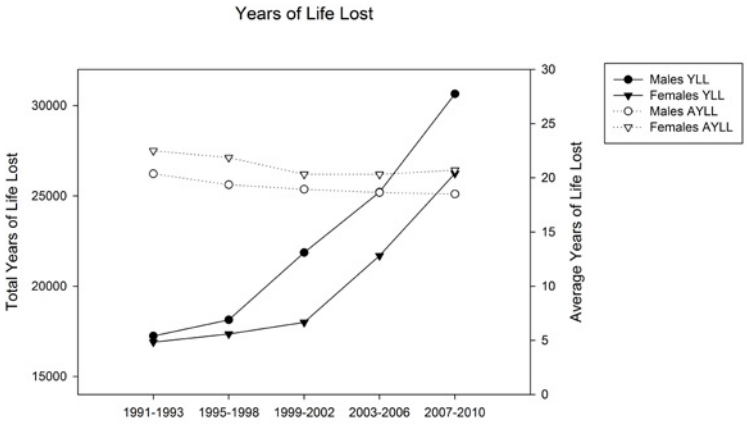

Figure 3: Years of Life Lost (YLL) and Average Years of Life Lost (AYLL) by period of diagnosis

Years of life lost (YLL)

In 1991-1994, a male melanoma patient dying from melanoma lost on average 20.4 life-years (AYLL) which decreased to 18.5 years in 2007-2010. For women the AYLL also decreased from 22.5 to 20.7 years (Table 2, Figure 3). However, the total YLL to melanoma in the Dutch population almost doubled for men and women during the 20 year study period. In 2007-2010 the total YLL for melanoma for men was 30,651 and 26,244 for women compared to 17,238 and 16,900 in 1991-1994 (Table 2).

Disability Adjusted Life Years (DALY)

The burden of melanoma as estimated by DALYs increased rapidly during the study period. The increase over the period 1991-2010 was steeper for men than women, with a 96% increase from 22,033 DALYs in 1991-1994 to 43,092 in 2007-2010 for men and a 75% increase from 24,475 DALYs to 42,788 during the same period for women.

Sensitvity analyses

In the first sensitivity analysis, we assumed 1 year survival for patients with a poor prognosis (Table 1). For men, this resulted in a 10% decrease in YLD and a 2 to 3% decrease in DALYs (Table 2). For women the influence of this assumption was smaller, with maximum difference of 4% in YLD and only a 1% difference in DALYs (Table 2).

In the second sensitivity analysis we estimated the impact of different weight factors (Table 1). Using the WHO disability weigths had a large impact on the estimated YLD and DALYs (Table 2). For men, this resulted in a difference of almost 30% in YLD and up to 8% difference in DALYs. For women, this resulted in a difference of almost 40% in YLD and 10 to 14% difference in DALYs.

DISCUSSION

The societal burden of melanoma increased since 1991. The fatal burden as well as the non-fatal burden contributed to this development, because both mortality rates and incidence rates increased. The increasing incidence of melanoma is an important development, but the high YLM and YLD for melanoma patients emphasizes the impact that melanoma has on health care. YLD and YLM are important indicators of burden of disease as they estimate the number of years patients might be in need for additional care (including psychological), whereas incidence rates merely indicate a rising trend in the number of patients that will require treatment and follow-up care. The high estimates of the burden of disease measures also illustrate that there is profit to be gained in the management of melanoma patients and its survivors. Improvement of cancer care and information provision may lead to lower levels of distress among the patients, improved quality of life and patient satisfaction [23,24].

The rate of increase of melanoma mortality in the Netherlands was slower than for incidence. Together with the increased relative survival, this pattern suggest a higher rate of early detection of melanomas [6]. Another possible explanation may be overdiagnosis (i.e., diagnosis of very slow growing tumors, that would never have progressed during the patient's life) or diagnostic drift (i.e., reclassification of what were previously found to be benign melanocytic nevi as truly malignant melanomas) [25,26]. The impact of these thin melanomas maybe less than the impact of thick melanomas on patients' lives. A population-based study among melanoma survivors (of which the majority had a thin melanoma), showed that the QoL does not differ from general population [27]. This suggests that the generic and cancer specific QoL questionnaires might not be sensitive enough for patients with predominantly low stage. The impact of melanoma is rather specific, such as anxiety of the deleterious effect of UV-light, problems with work, insurance or mortgage[7,18,27]. Unfortunately, there are no QoL instruments and disability weights specific for thin and thick melanomas. The WHO weights are lower than the Dutch weights and may resemble the disability weight of patients with predominantly thin melanomas better. Despite the predominance of thin melanomas, the burden of melanoma in terms of YLL increased considerably with more than 14,000 lost life years annually in 2007-2010. The high YLL is due to the fact that many patients are middle aged when diagnosed with their first melanoma, and most of those who die of melanoma die fairly soon after the diagnosis. The observed increases in mortality trends and incidence rates of thick melanoma are worrisome [6]. The YLD of patients with thick melanomas is probably higher than of those with thin melanomas. Furthermore, these trends in incidence and mortality rates will lead to an even higher YLL. Many studies on YLL due to melanoma only studied the population aged up to 65 or 75 years [10,12,28] to ascertain premature mortality in an occupational population (loss of productivity). This age restriction ignores non-fatal disease burden in the elderly, such as distress at time of diagnosis and during treatment, fear of recurrence and lifestyle changes, due to UV avoidance [7,27]. In order to be able to assess how long people are affected by a disease and not just during their occupational years, we did not apply any age restriction. The majority of melanoma patients are diagnosed at an age of 55-65 years and thereafter, the 10-year relative survival is 64% for males and above 90% for females [2]. Therefore, adopting a cut-off value of 65 years is likely to result in an underestimation of the YLL. Patients who died due to their melanoma, lost on average 20 life-years in our study, which is comparable to a recent US study, where an individual patient lost on average 20.4 years during a lifetime [13]. Despite the gradual decline in the numbers of life years lost per patient, which is attributable to a disproportional increase in mortality rates among the elderly, improving survival and a slightly higher age at diagnosis on average, the burden of melanoma to society rose sharply between 1991 and 2010, mostly due to increases in incidence rates. Primary prevention of melanoma is important to slow down the increasing amount of DALYs and especially non-fatal burden. Secondary prevention (i.e. early detection) of melanomas is important to decrease the fatal burden due to melanoma, especially among the elderly.

The low lifetime probability of an individual patient to die from his melanoma implies that most melanoma patients will live for many years after their diagnosis and probably die of other causes (AYLM ranging from 19 to 27 years). YLD was used to measure the non-fatal disease burden due to melanoma. However, the choice of disability weights had a large impact on the estimation of the YLD and DALYs. Soerjomataram et al. proposed a methodological framework to estimate the YLD for cancer [29]. For each cancer type specific disability weights for each disease state were proposed. The disability weights that were used in the methodological framework were only three studies (i.e. the Dutch, the WHO and the Victorian disability weights) [17,30,31]. Although the disability weights are key for estimating DALYs, there have not been many comprehensive studies with empirical determinations of them [32]. Disability weights were re-estimated for the global burden of disease study 2010. However, re-estimations for cancer were not included [33].

In the proposed methodological framework for cancer, the duration of each disease phase was equal for all countries, whilst melanoma-specific survival and guidelines for follow up care differ substantially across countries, ranging from one control visit to lifelong annual follow-up visits [19,34]. We also showed that the assumptions that were made for the duration of each phase of disease has a large impact on the total estimated YLD.

Duration of disease does not end at the last control visit. Psychological aspects, such as anxiety for recurrence, may persist longer than the recommended follow up time. This is reflected in the finding that Dutch melanoma patients, mainly with lower Breslow thickness, receive more follow up care than guideline recommendations [8]. Furthermore, the risk for a second primary melanoma remains elevated up to 20 years after diagnosis [35]. Considering the risk of recurrence, second primary cancer and the impact on patients' lives, melanoma may be regarded as a chronic disease. For this reason, we assigned a disability weight after 5 years of follow-up care (0.03), which resulted in higher DALY rates than those estimated for Europe and we calculated the YLM, without a disability weight [36]. Moreover, considering melanoma as a chronic disease also emphasizes the need for survivorship care plans, which aims at providing a cancer survivor with a summary of their course of treatment, management of late effects and strategies for health promotion. Providing accurate information may prevent anxiety, improve patients' satisfaction with care and possible reduce the overconsumption of health care, which is needed to reduce the substantial load on health care resources.

In conclusion, the burden of melanoma in the Netherlands is high and increasing substantially suggesting a need for health care policies to be adjusted in order to cope with this burden. Our research also shows that even though a disease has a good prognosis for most patients; it can be associated with a great burden to individual patients and society. In addition, there is a general need for an empirical estimation of disability weights and duration of disease.

Acknowledgements

We would like to thank the Netherlands Cancer Registry for their dedicated data collection.

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Chapter 3.2

Burden of disease due to keratinocytic cancer has increased in the Netherlands since 1989

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Submitted

ABSTRACT

Background: Keratinocytic cancer (KC) is the most common cancer among Caucasians.

Objective: To study time trends of the burden of disease attributable to KC in the Netherlands.

Methods: Data of all newly diagnosed KC patients (i.e. squamous cell carcinoma [SCC] and basal cell carcinoma [BCC]) was obtained from the population-based Netherlands Cancer Registry (NCR) and the Eindhoven Cancer Registry (ECR) (1989-2008). Population structure, nonmelanoma skin cancer (NMSC)-specific mortality data and life expectancy data were extracted from Statistics Netherlands. The disability adjusted life years (DALY) were the sum of the Years of Life lived with Disability (YLD) and the Years of Life Lost (YLL).

Results: The World Standardized Rate (WSR) of KC has doubled and was 103 and 94 per 100,000 person-years for males and females in 2004-2008, respectively. DALYs due to BCC increased by 124% and DALYs due to SCC increased by 66% since 1989-1993. KC accounted for a total loss of 19,913 DALYs (15,369 YLD and 4,544 YLL) between 2004 and 2008.

Limitations: Only the first KC was included in this study.

Conclusion: KC is a large burden to the Dutch society. Since incidence rates of KC are still increasing, the management becomes even more challenging.

Abbreviations:

YLD = Years of Life lived with Disability = number of incident cases x disability weight x average duration of the disease until remission or death
YLL = Years of Life Lost = number of deaths x standard life expectancy at age of death in years
DALY = Disability Adjusted Life Years = YLD + YLL
BCC = Basal Cell Carcinoma
SCC = Squamous Cell Carcinoma
KC = Keratinocytic Cancer = BCC + SCC
NMSC = Nonmelanoma Skin Cancer = BCC + SCC + all less common cutaneous malignancies, such as cutaneous lymphoma, Merkel cell carcinoma, Kaposi sarcoma etc.
WSR = World Standardized Rate

INTRODUCTION

Keratinocytic Cancer (KC) is the most common malignancy among both males and females in the Netherlands [1-3]. Although mortality due to KC is low, the diagnosis can be associated with a large burden for the individual patient and for the population. An individual patient may suffer from scars of excised facial tumors, fear recurrence, or they may be bothered by multiple actinic keratosis (AK) or KC [4,5]. The high incidence of KC is a strain to the health care system, because a large part of those patients should be regularly followed up for control or they present later during follow-up with a recurrence or a subsequent KC.

The magnitude of the KC burden in the Netherlands was expressed in incidence, survival, and mortality rates[2,6] However, the magnitude of the societal problem can also be expressed in burden of disease measures, as suggested by the World Health Organization (WHO). The Disability Adjusted Life Year (DALY) also takes related conditions into account (e.g. pain, psychological concerns) and is calculated by the sum of the Years of Life Lost (YLL) as a consequence of premature death due to NMSC and the number of Years of Life lived with Disability (YLD) caused by KC [7]. One DALY represents the loss of one year of life lived in full health[7].

One previous publication on DALYs was based on extrapolations and estimated that globally, 162,000 DALY's were lost in 2000 due to incident squamous cell carcinoma (SCC) and 58,000 due to incident basal cell carcinoma (BCC)[8]. To our knowledge, the time trends in burden of KC have never been estimated by YLL, YLD, DALYs in a population-based setting. In the Netherlands SCC is routinely registered nationwide and BCC is routinely registered by one population-based comprehensive cancer registry. We estimated the size of the burden of KC in the general Dutch population using these high quality population-based cancer registry data between 1989 and 2008.

METHODS

Population

Age- and gender-specific data on newly diagnosed patients with cutaneous SCC were obtained from the Netherlands Cancer Registry (NCR). Age- and gender-specific data on newly diagnosed patients with BCC and KC were obtained from the Eindhoven Cancer Registry (ECR), which is part of the NCR and the only regional comprehensive cancer center in the Netherlands that registers BCCs. The NCR collects incidence and tumor data on all newly diagnosed, histologically confirmed cancers in the Netherlands from the regional comprehensive cancer centers since 1989. The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA) [9]. Additional sources are the national registry of hospital discharge, which accounts up to 8% of new cases, haematology departments and radiotherapy institutions. The quality of the data is high, due

to thorough training of the administrators and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 98% on all cancers combined and 93% on skin cancer (excl. BCC) [9]. KC without histological diagnosis will not be registered in the cancer registry. However, only 7% of subsequent BCC were not histologically diagnosed, which indicates that completeness on first BCC is also at least 93%. Only the first SCC or the first BCC were included in this study. The following morphology codes combined with topography 'skin' were considered invasive cutaneous SCC: 8010, 8050-8084 (excluding 8077: intraepithelial neoplasia, 8080: Erythroplasia of Queyrat, 8081: Bowen disease, 8082: lymphoepithelial carcinoma) and invasive BCC: 8090-8110.

Annual data on age and gender of nonmelanoma skin cancer (NMSC) deaths (C44 of the International Classification of Disease [ICD]-10), population composition and life expectancies were obtained from Statistics Netherlands (CBS).

Approval of the Medical Ethics Committee is not needed for cancer registry data.. This research was conducted according the code of conduct for health research of the Dutch federation of scientific societies[10].

Statistical analyses

All analyses were performed for 5-year periods and stratified for sex. Age-standardized incidence rates were calculated by direct standardization according to the world standard population (WSR)[11]. Incidence rates of BCC obtained from the ECR were extrapolated to the Dutch population using the population composition from CBS. The 5-year relative survival estimates by age, gender, stage and period of diagnosis were calculated with traditional cohort-based relative survival analyses. Follow-up of vital status was calculated as the time from diagnosis to death or to end of follow-up on the 1st of February 2010. To analyze changes in age at diagnosis over time, linear regression analyses were performed.

To calculate YLD, the duration of each phase of the disease is multiplied with a Dutch disability weight, which differ by stage of disease (1.5% of male and 1.2% of female SCC patients had nodal or distant metastasis at diagnosis) (Figure 1) [12 2].

Duration of each disease phase was estimated using the Dutch guidelines and the relative survival of SCC [13,14]. According to the Dutch guideline follow-up is not recommended for patients with a single BCC (89% of all BCC patients) [3,13]. For SCC and multiple BCC, an annual follow-up visit during the first 5 years after diagnosis is recommended [14]. For SCC, the proportion of patients with a good prognosis was determined using the 5-year relative survival.

YLL corresponds to the number of deaths due to NMSC multiplied by the remaining life expectancy in the general population at the age at which death occurs as estimated by a standard life table, which was obtained from CBS. We assumed that all NMSC deaths were due to SCC. DALYs were calculated as the sum of the YLL and the YLD and age-standardized to the world standard population.

SCC and KC disease duration was estimated using the DISMOD software[15]. Input variables used for DISMOD were age-specific incidence and mortality rates and we assumed no remission (i.e., rate was 0 for all ages). The disease duration of BCC was equal to the life expectancy at age of diagnosis, because BCC is generally not associated with mortality.

Sensitivity analyses

In the first sensitivity analyses we assigned a weight factor to the remaining life expectancy after follow-up, because most KC occur on the face, which leads to visible scarring, fear of recurrence and subsequent KCs and may therefore affects patient's quality of life [4,5,16]. Based on clinical expertise (i.e. there are no empirical estimates of disability weights after follow-up) we assigned a weight factor of 0.03 to SCC and to BCC on the head and neck (61% of all BCC)

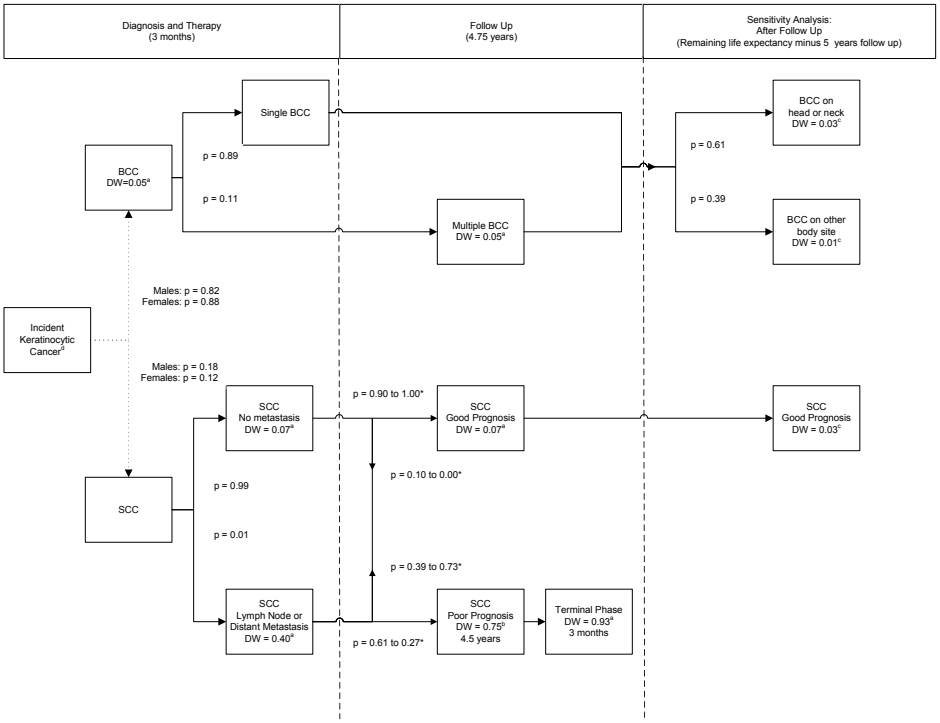

Figure 1: Keratinocytic cancer. Disease model

BCC, basal cell carcinoma; DW, disability weight; SCC, squamous cell carcinoma

[a]. Dutch weight

[b] WHO weight for metastasized disease

[c] assumed weights in this study

[d]The dotted line indicates that the proportion BCC and SCC was only used in the calculation of YLD for KC to assign the correct BCC- or SCC-specific weights to the patients. Separate incidence data was used for the calculation of YLD for BCC and SCC.

p = proportion of patients that will move to that phase of disease

*depending on relative survival according to sex, age, stage and period of diagnosis.

and 0.01 to BCC on other body sites [3]. In the second sensitivity analyses we assumed that 50% of all NMSC deaths were due SCC.

RESULTS

Incidence, survival and mortality

In 2008 more than 32,000 patients were newly diagnosed with KC in the Netherlands, compared to 12,918 in 1989 (Table 1). The age-standardized incidence rate of KC (WSR) has doubled for both males and females reaching 103 per 100,000 male inhabitants and 94 per 100,000 female inhabitants in 2008. The 5-year relative survival of males between 70 and 80 years remained 90% throughout the study period (Supplementary Table 1). For females of the same age the relative survival was 93% in 1989-1993 and 97% in 2004-2008. In 2004-2008, the relative survival for male SCC patients with a poor prognosis (stage III and IV) was 62% and 55% for females. The age-standardized mortality rate remained stable during the study period and was 0.3 per 100,000 person-years for males and 0.1 for females.

Burden of disease

The average age at BCC diagnosis for females decreased with 0.5 years per 10 calendar years (1989: 65.3, 2008: 64.8). For males the age at BCC and SCC diagnosis increased 1 year per 10 calendar years. The age at SCC diagnosis remained stable for females.

The average years of life, that a patient lived after SCC diagnosis was 10.9 for males and 12.8 for females (Table1). The average number of years, that a patient lived after BCC diagnosis increased from 17.7 to 18.8 years for males and from 21.6 to 23.9 years for females.

The YLD for both SCC and BCC increased rapidly during the study period. All YLD estimates in 2004-2008 have at least doubled since the first period (1989-1993). The age-standardized YLD rates for BCC also doubled during the study period. Other age-standardized YLD rates increased by 50%.

A male SCC patient, who died of SCC, lost on average 11.5 life years and a female patient lost on average 12.1 life years. On population level SCC was associated with an annual loss of almost 1,000 life years for males and females combined. The YLL remained relatively stable during the study period, which is in line with the stable mortality rate.

During the period of 2004-2008 KC accounted for 11,839 DALYs, corresponding to more than 5,000 DALYs annually in the Dutch population. DALYs due to BCC increased by 124% from 2,143 DALYs in 1989-1993 to 4,797 DALYs in 2004-2008. During the same period the DALYs due to SCC increased by 66% from 10,775 to 17,887.

Table 1: Incidence, mortality and burden of keratinocytic cancer in the Netherlands by sex and period of diagnosis.

	Males				Females			
	1989 -1993	1994 -1998	1999 -2003	2004 -2008	1989 -1993	1994 -1998	1999 -2003	2004 -2008
Number of new patients								
KC	33,176	39,140	48,325	69,229	31,271	38,760	48,376	70,140
BCC	27,353	32,336	40,675	59,754	27,492	34,266	43,103	62,951
SCC	7,509	8,951	10,199	14,897	4,217	5,587	7,049	10,998
Crude incidence rate per 100,000 person-years								
KC	89	102	122	171	82	99	120	170
BCC	74	84	103	148	72	87	107	153
SCC	20	23	26	37	11	14	18	27
World standardized incidence rate per 100,000 person-years (WSR)								
KC	67	72	81	103	50	58	69	94
BCC	55	60	69	90	45	53	63	86
SCC	14	15	16	20	5	6	7	10
Number of deaths[a]								
SCC	211	208	216	221	178	170	156	153
Crude mortality rate per 100,000 person-years								
SCC	0.6	0.5	0.5	0.5	0.5	0.4	0.4	0.4
World standardized mortality rate per 100,000 person-years (WSR)								
KC/SCC	0.3	0.3	0.3	0.3	0.1	0.2	0.1	0.1
Number of YLD								
KC	4,562	5,962	7,333	9,135	3,321	3,973	4,779	6,234
BCC	1,068	1,263	1,589	2,336	1,075	1,340	1,685	2,461
SCC	4,184	5,498	6,661	8,529	2,288	3,106	3,704	4,814
YLD per 100,000 person-years (WSR)								
KC	9	11	12	14	5	6	7	9
BCC	2	2	3	4	2	2	3	4
SCC	8	9	10	12	3	3	4	5
Number of YLL								
SCC	2,308	2,354	2,470	2,704	1,994	2,415	1,705	1,840
YLL per 100,000 person-years (WSR)								
SCC	5	4	4	4	3	4	2	2
Number of DALY								
KC	6,871	8,317	9,803	11,839	5,315	6,388	6,483	8,074
BCC	1,068	1,263	1,589	2,336	1,075	1,340	1,685	2,461
SCC	6,493	7,852	9,131	11,233	4,282	5,521	5,409	6,654
DALY per 100,000 person-years (WSR)								
KC	14	15	16	18	8	10	9	11
BCC	7	7	7	8	5	6	5	6
SCC	13	14	14	16	6	7	6	7

[a] all NMSC deaths were assumed to be due to SCC.

BCC; basal cell carcinoma, DALY; disability adjusted life years, KC; keratinocytic cancer, SCC; squamous cell carcinoma, WSR; world standardized rate, YLD; years of life lived with disability, YLL; years of life lost.

Sensitivity analyses

The assigned weight factor after follow-up resulted in an increase in DALY for KC with 200 to 400%. (Supplementary Table 2). This large difference was mainly due to a 10-fold increase in YLD due to BCC. Although the disability weights after follow-up were small (i.e. 0.01 or 0.03), they were taken into account for 20 to 25 years per patient (Table 1).

In the second sensitivity analyses we assumed that 50% (instead of 100%) of all NMSC deaths were due to SCC. This resulted in a maximum decrease of 23% in DALYs. The difference was smaller for more recent periods, due the small contribution of YLL to the total amount of DALYs.

DISCUSSION

The burden of disease due to KC has increased between 1989 and 2008. An increase in disease burden can be due to increasing incidence rates, increasing mortality rates or being diagnosed at a younger age. The increase in burden of KC was mainly due to the accelerating increase in incidence rates, which increased by 7 - 9% annually since 2002 [2,17]. Mortality rates remained stable during the study period. The years lived after KC diagnosis increased, but this was mainly due to the stable mortality rate and the increased life expectancy of the Dutch general population, which increased with 4.7 years for males and 2.4 years for females during the study period, while the age at diagnosis increased for males and decreased with only 0.5 years for females.

All newly diagnosed KC patients live on average 15 to 20 years after their first KC diagnosis during which many of those patients will be in need of additional health care to treat recurrences or subsequent KCs [18]. In our analyses only the first KC was considered, but within 5 years after diagnosis, 36% of all KC patients will develop a subsequent KC [18].

Due to many years that patients live after diagnosis and the high risk of recurrence and subsequent skin tumors, KC may also be regarded as a chronic disease. Five years follow-up is recommended in the Netherlands for SCC and high risk BCC patients (i.e. multiple BCC or BCC on ears, lips, nose, nasolabial fold or eye surroundings) [13]. However, many patients with a single BCC will also develop subsequent BCCs; 30% of patients with a first BCC will develop at least one subsequent BCC in the next five years [3]. Due to restricted health care resources it is impossible to provide all newly diagnosed BCC patients follow-up. Furthermore, incidence rates are increasing and do not seem to reach a plateau in the near future [2,6]. The absolute number of new BCC patients is estimated to exceed 55,000 in the Netherlands in 2020, which is an increase of almost 250% compared to the observed incidence in 2005 [6]. The number of new SCC patients will increase with the same percentage since 2005 to exceed 11,000 in 2020 [2]. As this will lead to an even higher burden for the health care system, KC patients may need a well-defined chronic disease management plan. For skin cancer, such a plan may

include patient information, tumor characteristics, treatment, prognosis, recommendations for surveillance of recurrence, health promotion such as avoidance of excessive sun-exposure and information about self-examination. For other tumor types, these disease management plans (survivorship care plans) improved the provision of information and lead to a better quality of life and reduced anxiety levels [19,20].

The number of DALYs as calculated in the main analyses may be an underestimation of the true number of DALYs, because KC may influence patient's life also after follow-up; patients may change their sun exposure behavior, worry about cosmetic outcome or may fear recurrence, subsequent tumors, cancer spreading or even mortality [4,5]. Given the high rate of recurrence and subsequent tumors and the increasing incidence rates among young adults, we feel that some disability after follow-up for control should be taken into account. The true number of DALYs loss due to KC probably lies somewhere midway between the main analyses and the sensitivity analyses; some patients will fear or have a subsequent KC or experience difficulties due to scars, while others will not.

We performed a similar study for melanoma in the Netherlands, which showed a higher loss of DALYs compared to Western-Europe (Netherlands: 90 (males) and 92 (females) DALYs per 100,000 person-years in 2007-2010, Western-Europe, 51 (males) and 43 (females) DALYs per 100,000 person-years) [21,22]. The impact of melanoma after follow-up contributed to this higher loss of DALYs [23-25].

In the Netherlands 35-40% of all dermatology claims to health insurance companies are related to skin cancer [26]. USA claims data shows, that NMSC is among the most costly cancers to treat [27]. It was estimated that almost 80 million dollars in the USA were lost each year due to lost working days or restricted activity days related to NMSC [28]. From economic evaluation of the SunSmart Program in Australia it was estimated that a skin cancer prevention program can restrict the loss of DALYs [29]. Although there appeared to be no effect on SCC, BCC incidence rates could decrease and result in a sufficient cost-effective intervention [29-31].

Strengths and limitations

A strengths of this study is the use of high quality population-based cancer registry data. The first SCC and BCC were routinely registered and the cancer registry was at least 93% complete on skin cancer (excl. BCC) [9]. The completeness on BCC is likely to be very high as well, because only 7% of subsequent BCC were not histologically confirmed, indicating that only a small proportion of first BCCs may have been missed [32]. A limitation of the study is the unknown proportion of patients with multiple or subsequent KC. The estimation of YLD was based on the first KC and assumptions about multiple KC at diagnosis were based on previous publications of the same population [3]. Subsequent KCs were not routinely registered in the cancer registry and could therefore not be taken into account in the analysis. This results in an underestimation of the true number of DALYs and was addressed in the sensitivity analysis.

Conclusion

The burden of KC accounts for a large burden on a population level, primarily due to the extremely high incidence rates. Since the incidence rates are still increasing, the management becomes even more challenging to address this high skin cancer burden.

Acknowledgements

We would like to thank the Netherlands Cancer Registry and the Eindhoven Cancer Registry for their dedicated data collection. We would like to thank Wilma J. Nusselder for critically reading the manuscript.

Supplementary Table 1: Five-year relative survival by sex, period of diagnosis, age and stage

	Males				Females			
	1989-1993	1994-1998	1999-2003	2004-2008	1989-1993	1994-1998	1999-2003	2004-2008
Age								
< 70 years	93%	92%	91%	94%	95%	94%	95%	97%
70-79 years	90%	89%	90%	90%	93%	93%	94%	97%
≥ 80 years	101%	97%	92%	97%	95%	94%	95%	98%
Stage								
I	95%	94%	94%	93%	98%	96%	97%	96%
II	80%	74%	74%	75%	80%	77%	77%	72%
III/IV	73%	61%	60%	62%	39%	49%	45%	55%

Supplementary Table 2: Sensitivity Analyses

	Males				Females			
	1989 -1993	1994 -1998	1999 -2003	2004 -2008	1989 -1993	1994 -1998	1999 -2003	2004 -2008
Assumption 1: Disability weight after follow up:								
Number of YLD								
KC	16,280	20,106	25,235	35,517	17,294	22,111	28,044	41,117
BCC	11,296	13,658	17,590	26,111	13,718	17,965	23,045	34,602
SCC	5,847	7,441	8,854	11,883	3,427	4,654	5,632	8,064
YLD per 100,000 person-years (WSR)								
KC	34	39	45	58	32	39	47	66
BCC	24	27	32	43	26	33	40	57
SCC	11	13	14	17	5	6	7	10
Number of DALY								
KC	18,588	22,460	27,704	38,221	19,288	24,526	29,749	42,956
BCC	11,296	13,658	17,590	26,111	13,718	17,965	23,045	34,602
SCC	8,155	9,795	11,324	14,587	5,421	7,069	7,337	9,904
DALY per 100,000 person-years (WSR)								
KC	39	43	49	62	35	43	50	68
BCC	24	27	32	43	26	33	40	57
SCC	16	18	18	21	8	10	9	12
Assumption 2: 50% of NMSC deaths due to SCC:								
Number of YLL								
SCC	1,154	1,177	1,235	1,352	997	1,207	852	920
YLL per 100,000 person-years (WSR)								
SCC	2	2	2	2	1	2	1	1
Number of DALY								
SCC	5,338	6,675	7,896	9,881	3,285	4,314	4,557	5,734
KC	5,717	7,139	8,568	10,487	4,318	5,181	5,631	7,154
DALY per 100,000 person-years (WSR)								
SCC	10	12	12	14	4	5	5	6
KC	11	13	14	16	7	8	8	10

BCC; basal cell carcinoma, DALY; disability adjusted life years, KC; keratinocytic cancer, SCC; squamous cell carcinoma, WSR; world standardized rate, YLD; years of life lived with disability, YLL; years of life lost.

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Chapter 4

Chemoprevention of skin cancer

Chapter 4.1

Chemoprevention for Keratinocytic (Pre)cancers: Balancing the Risks and Benefits

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Archives of Dermatology. May 2012; 148 (5): 638-40

四.一

Commentary on: Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial
Elmets CA, Viner JL, Pentland AP, et al J Natl Cancer Inst. 2010;102(24):1835-1844

Question: Can celecoxib reduce the incidence of actinic keratoses (AKs) and keratinocytic cancers?

Design: Randomized, double-blind, placebo-controlled phase 2-3 clinical trial.

Setting: Eight centers in the United States participated and included 240 patients from January 2001 to November 2006, when the Food and Drug Administration requested termination of this trial after the worldwide withdrawal of rofecoxib.

Patients: The study population comprised individuals 18 years or older with Fitzpatrick skin type I to III, with 10 to 40 AKs on the upper extremities, neck, face, and scalp at baseline and a previous histological diagnosis of a keratinocytic (pre)malignant neoplasm.

Intervention: Celecoxib (200 mg) or placebo twice daily.

Main Outcome Measure: The ratio of new AKs per patient at completion of the study to the number of AKs at randomization.

Exploratory Post Hoc Analysis: The mean cumulative number of keratinocytic skin cancers per patient.

Results: There was no difference in the incidence of AKs between the 2 groups at month 9 after randomization. The adjusted rate ratios for the celecoxib arm compared with the placebo arm were 0.41 (95% CI, 0.23-0.72) for keratinocytic skin cancers, 0.40 (95% CI, 0.18-0.93) for basal cell carcinomas (BCCs), and 0.42 (95% CI, 0.19-0.93) for squamous cell carcinomas (SCCs). Conclusion: Celecoxib might be effective for prevention of keratinocytic cancers but not for actinic keratoses.

COMMENT

To our knowledge, this is the first placebo-controlled randomized controlled trial (RCT) investigating the effect of a nonsteroidal anti-inflammatory drug (NSAID), celecoxib, on the development of AK[1]. In an exploratory analysis, this study also focuses on the effect of this drug on BCC and SCC incidence.

Experimental studies have demonstrated that cyclooxygenase (COX) expression, both the COX-1 and COX-2 isoform, is elevated in cutaneous (pre)malignant neoplasms[2]. In vitro studies also showed that COX-2 is upregulated in keratinocytes in response to UV exposure and that administration of a COX-2–specific NSAID reduced skin cancer risk in mice exposed to carcinogenic UV regimens[2]. Observational studies showed that use of NSAIDs reduced the risk of SCC and melanoma. An RCT showed that celecoxib significantly reduced the number of BCCs in patients with basal cell nevus syndrome[3-5]. In addition, topical diclofenac is used in the treatment of AK. In this study, Elmets et al[1] took the next step of the scientific ladder by testing the chemopreventive properties of an oral COX-2 inhibitor in an RCT in a population at high risk of developing keratinocytic (pre)malignant neoplasms (ie, patients having Fitzpatrick skin type III or less, with 10-40 AKs and a previous diagnosis of at least 1 AK and/or at least 1 BCC or SCC).

The number of new AKs at completion of the study as a percentage of those at baseline was chosen as a primary end point. This ratio was comparable in exposed and nonexposed groups at the end of the study. The primary outcome used in this study is relatively difficult to interpret for clinicians. Unfortunately, useful and easy-to-interpret measures, such as the number needed to treat (NNT; the number of patients needed to treat with celecoxib to prevent 1 BCC or SCC) cannot be calculated from the presented data.

The methodological advantage of focusing on an oncological precursor lesion (ie, as a proxy of cancer) is that the required sample size is usually smaller and the study duration shorter and, therefore, less costly. The disadvantage, however, is that the study will be underpowered to detect differences in the incidence of the cancer, which is the clinically relevant outcome. Although a 50% to 60% reduction in BCC and SCC incidence was observed among patients that had used celecoxib for 9 months, these results should be interpreted with caution because reducing BCC and SCC incidence was not included in the study objectives as registered in ClinicalTrials.gov (NCT00027976).

In the first experimental studies assessing the preventive effects of a drug, it is obvious to select populations at an extreme skin cancer risk (eg, patients with a prior skin cancer, xeroderma pigmentosum, nevus basal cell syndrome, or solid-organ transplant recipients)[6] because of the clinical relevance to these patient groups and the highest expected risk reduction. The potentially high-risk reduction implies that these first exploratory RCTs can be performed in a relatively small study population because sample size calculations are partly driven by the expected effect of the drug. If the study drug is (cost) effective in the high

risk populations, its chemoprophylactic properties can be tested in a much larger low-risk population. The required sample size in this study population should have been much larger to study the effects of celecoxib on BCC and SCC incidence because only a small fraction (1%) of AKs may progress to invasive SCC annually[7].

The rate ratios were analyzed at month 3, 6, 9, and 11, which seems fair for the primary end point but is not suitable for BCC and SCC because chemoprevention requires some time (in some cases up to 5 years or more) before it will effectively reduce cancer risk[3]. Moreover, by performing more than 15 analyses in addition to the primary objective, the likelihood that there is a significant finding by chance is considerable, since the P values of the post hoc analyses were not adjusted for multiple testing.

Concomitant use of aspirin (80 mg/d) was allowed during the study, which could have influenced the study results because 75 mg of aspirin seems to reduce cancer risk[8]. Although this misclassification bias of exposure is nondifferential (ie, aspirin users are probably equally distributed among the celecoxib and the placebo group), the proportion of patients using concomitant aspirin among treated and nontreated patients should have been reported. The use of sunscreen, which was allowed and recommended, should have been reported as well. This may have enhanced the effect of celecoxib if the celecoxib-treated patients were more likely to use sunscreen than the control patients.

Surprisingly, it took 8 US centers almost 5 years to include 240 patients. In total, 446 patients were screened during these 5 years (on average, approximately 11 patients were screened per center annually), which seems very low. To assess the generalizability of the study's findings and the size of selection bias, it would have been interesting to know to what extent the participants differed from the underlying population and to what extent the participants differed from the 183 screened subjects who did not meet the inclusion criteria.

The benefit from preventive therapy for cutaneous malignant neoplasms should outweigh the possible risks. This balance is influenced by many factors. Chemopreventive drugs require lifelong use because they do not have a sustainable pharmacological effect after discontinuation. Therefore, an optimal patient selection and the longterm safety of the drug are pivotal. Although adverse effects may occur in individual patients, the drug's safety profile should be acceptable on a population level. The importance of long-term drug safety is illustrated by the termination of this trial by the Food and Drug Administration because of an observed significant increase in cardiovascular thrombotic events in the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, in which patients received the COX-2-inhibitor rofecoxib to prevent adenomatous polyps[9]. For colorectal and especially keratinocytic cancers, the potential chemopreventive benefit was unlikely to outweigh the low but serious risk of cardiovascular adverse events of COX-2 inhibitors. Reducing celecoxib to once daily or using naproxen may reduce cardiovascular risks associated with NSAIDs. For some chemopreventive drugs, such as low-dose aspirin and statins, long-term safety has been established, and if these drugs show similar effectiveness in reducing skin cancer risk, they have a better risk-benefit ratio.

Ideally, the NNT and the number needed to harm, which is number of patients that should be exposed to the drug to cause 1 serious adverse event, are estimated to weigh the benefits and the risks of using a drug for chemoprevention.

Besides possible adverse effects, the chemopreventive drug may also have additional health benefits, which will substantially increase the net benefit of being exposed to such a drug. For example, low-dose aspirin has a positive effect on cardiovascular health and possibly increases survival in other types of cancers and is, therefore, more likely to result in a net benefit[10]. Therefore, low-dose aspirin would be a good candidate drug for future RCTs. Another way to maximize the net benefit is to select a subpopulation of patients who are likely to have the highest benefit of the chemoprophylactic effects of a drug. For keratinocytic cancers, it could be restricted to people with an increased SCC risk, to those with a history of several malignant neoplasms and/or extensive photodamaged skin, and to patients with specific genodermatoses or organ transplant recipients.

Bottom Line: Chemoprevention for cutaneous malignant neoplasms is an interesting strategy that needs to be explored further in observational and interventional studies that assess the risk-benefit ratio of the candidate drug.

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Chapter 4.2

Immortal time bias in time-to-event analyses: an example of β-blocker use on melanoma survival

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European Journal of Cancer. Aug 2013, accepted for publication (supplement)

四.二

ABSTRACT

Background: Drug exposure can be analysed as a time-fixed or as a time-varying covariate in time-to-event-analyses. In this example of β-blocker use and melanoma survival, we illustrate that incorrect use of time-fixed analysis of exposure leads to biased estimates.

Methods: Data from melanoma patients (N=791) included in both the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (RLS) was used. Associations between β-blocker use and melanoma survival were analyzed with a Cox proportional hazard model with time-fixed and time-varying definitions of exposure.

Results: In the incorrect time-fixed analyses, 253 person-years and 5 deaths were misclassified due to immortal time bias, which resulted in a 40% decreased death risk (adjusted hazard ratio [HR] 0.60, 95% confidence interval [CI]: 0.41-0.88) with β-blocker use for at least one year. After assigning these person-years correctly to the non-exposed in the time-varying analysis the adjusted HR was 0.86 (95% CI: 0.56-1.32). Assessment of exposure before start of follow up also showed no association (adjusted HR 0.86, 95% CI: 0.56-1.32). The risk of death was decreased by 13% with each additional year of β-blocker use in the time-fixed analyses. After controlling for immortal time bias with a time-varying definition of β-blocker duration, the adjusted HR for each year of β-blocker use was 1.01 (95% CI: 0.89-1.14).

Conclusion: Incorrect use of time-fixed analyses leads to biased risk estimates.

Impact: Time-fixed analyses of exposure before the start of follow up or time-varying analyses of exposure should be used in time-to-event-analyses to prevent bias towards beneficial drug effects.

INTRODUCTION

Use of β-blockers has been reported to be associated with a prolonged survival after diagnosis of several malignancies, such as melanoma [1,2] and breast cancer [3]. Exposure to β-blockers can be analysed as a time-fixed or a time-varying covariate in time-to-event analyses. The use of a time-fixed covariate assumes that exposure is measurable at baseline and remains constant over time. Changes in exposure status during follow up can be taken into account by using a time-varying covariate for exposure. Incorrect use of a time-fixed exposure variable in a Cox proportional hazard (PH) model, or other time-to-event models, can lead to biased estimates, due to immortal time bias [4,5 6,7].

We illustrate the differences of risk estimates between incorrect time-fixed and correct time-fixed or correct time-varying analyses of exposure using the association between β-blockers and melanoma survival as an example. In this example we defined long-term β-blocker users as those patients who used β-blockers for at least one year after melanoma diagnosis. Using it as a time-fixed covariate, this definition of exposure causes long-term β-blocker users to have a survival advantage of at least one year after diagnosis, in contrast to the unexposed group. The time period between diagnosis and one year exposure is called immortal time and this leads to an overestimation of beneficial drug effects [4,5]. The immortal time should be counted as unexposed follow up time in a time-dependent analysis. A time-fixed analysis of exposure is correct if long-term β-blocker use is assessed before the start of follow up [3]. Immortal time bias can also occur when duration of β-blocker use after diagnosis is analysed as if duration was already known at diagnosis [6,7]. In this case, with each additional year of β-blocker use the patient has a survival benefit by definition, because a patient has to be alive to gain years of exposure. One approach to prevent immortal time bias is a time-varying exposure definition.

METHODS

To assess the differences of risk estimates between these analyses we used data from the Eindhoven Cancer Registry (ECR) and the PHARMO record linkage system (RLS)[8]. Patients diagnosed with melanoma between January 1, 1998 and December 31, 2010, who were above 18 years old and lived in the coverage area of both the ECR and the PHARMO RLS were eligible (N=1,810) [8]. Vital status was updated through annual linkage with the Dutch Municipality Register until December 31, 2010.

Dispensings were selected based on the Anatomical Therapeutical Chemical (ATC) codes[9]. Dispensings starting with ATC code C07 were considered β-blocker dispensings. To calculate the duration of each dispensing, the amount of dispensed drug was divided by the number of pills prescribed per day, which was obtained from the label.

With the stpower cox function of STATA (StataCorp. 2011. College Station, TX: StataCorp LP), we calculated that at least 631 patients were needed to detect a hazard ratio (HR) of 0.80 with 80% power and an alpha-level of 0.05. Patients diagnosed with a thick melanoma (Breslow thickness>1mm) were included in the analyses (N=791). Patients were considered β-blocker users for at least one year if they used β-blockers for at least 270 days within a year after their first β-blocker prescription after diagnosis. This equals 3 dispensings of 90 days, allowing for 1 missing dispensing, due to e.g. hospitalization. β-blocker use for at least one year and duration of β-blocker use after diagnosis were analyzed as either a time-fixed or a time-dependent variable in Cox PH models. In the Cox PH model with the time-dependent duration variable, the number of cumulative days of β-blocker use of the subject with the event of interest is compared with the cumulative use of all other subjects at the same time point [10]. To illustrate a correct time-fixed analysis of exposure, β-blocker use for at least one year in the year before diagnosis was analysed as a time-fixed variable in a Cox PH model. This analysis was performed in a subgroup of patients with at least 1 year follow up in the PHARMO RLS before diagnosis (N=709). Variables which influence the HR with more than 10% in the age and sex-adjusted analyses were included in the multivariable model. Age and Breslow thickness were not linearly related to the LN(hazard) and therefore restricted cubic spline functions with 4 knots were included. The PH assumption was tested by calculating time-interval-specific hazard ratios. As the PH assumption was violated for duration, these analyses were stratified into time-periods with proportional hazards. Analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patients who used β-blockers after diagnosis were older than non-users but tumour characteristics did not differ (Table 2). In the incorrect time-fixed analyses, β-blocker use for at least one year after diagnosis was associated with a 40% reduction of the hazard on death (adjusted HR 0.60, 95% confidence interval [CI] 0.44-0.88) (Table 2). However, 253 person-years and 5 deaths were misclassified, which was corrected for in the time-dependent analyses, upon which β-blocker use for at least one year was not associated with decreased risk on death (adjusted HR 0.86, 95% CI 0.56-1.32). A correct time-fixed analysis of β-blocker use before diagnosis did not show an association with a prolonged survival either and resulted in exactly the same HR as obtained from the time-dependent analysis (Table 2).

Two years after diagnosis, the hazard of death was decreased by 13% with each additional year of β-blocker use in the incorrect time-fixed analyses (adjusted HR 0.89, 95% CI 0.80-0.89) (Table 2). In this analysis, duration of β-blocker exposure is modelled as if it was already known at baseline. When duration was analysed as a time-dependent variable, each additional year

Table 1: Patient characteristics

	Non-users	β-Blocker users[a]	p-value
N	567	224	
Follow up in years, median (IQR)	3.0 (1.2-5.6)	3.9 (2.0-6.9)	
Age in years, median (IQR)	57 (45-70)	67 (58-76)	<0.0001
Male sex, N (%)	295 (52.0)	112 (50.0)	0.61
Bodysite, N (%)			0.74
Head or Neck	90 (15.9)	35 (15.6)	
Trunc	212 (37.3)	75 (33.5)	
Upper limbs	155 (27.3)	66 (29.5)	
Lower Limbs	110 (19.4)	48 (21.4)	
Histological subtype, N (%)			0.54
Superficial Spreading Melanoma	273 (48.2)	114 (50.9)	
Nodular Melanoma	140 (24.7)	52 (23.2)	
Acral-Lentiginous Melanoma	6 (1.1)	1 (0.5)	
Lentigo Maligna Melanoma	7 (1.2)	6 (2.7)	
Other	141 (24.9)	51 (22.8)	
Breslow thickness in mm, median (IQR)	2.00 (1.35-3.00)	2.10 (1.43-3.90)	0.55
Nodal metastasis at diagnosis, N (%)	92 (16.2)	29 (13.0)	0.25
Distant metastasis at diagnosis, N (%)	15 (2.7)	2 (0.9)	0.17

Abbreviations: HR, hazard ratio; IQR, interquartile range; N, number

[a] Ever β-blocker use after diagnosis

of β-blocker use was no longer associated with a decreased hazard of death (adjusted HR 1.01, 95% CI 0.94-1.16) (Table 2).

DISCUSSION

Time-fixed analyses of exposure during follow up lead to biased estimates towards beneficial drug effects. Several approaches have been proposed to prevent immortal time bias in pharmacoepidemiological studies investigating drug exposure in time-to-event analyses [4,5,7]. Assessing exposure before start of follow up or a time-varying definition of exposure are approaches to gain robust and valid estimates.

Acknowledgements

We gratefully acknowledge our colleagues from the Eindhoven Cancer Registry and the PHARMO institute for drug outcomes research for their dedicated data collection, data processing and data linkage.

Table 2: Hazard ratios of all-cause mortality for β-blocker users vs. non-users

	Non-users	β-Blocker users
Incorrect Analyses		
β-blocker use during follow up as a time-fixed covariate		
β-blocker user for at least one year, N	654	137
Person-years	2565.0	647.7
All cause death (N,%)	153	33
Crude HR	1	0.86 (0.59-1.26)
Adjusted HR[b]	1	0.60 (0.41-0.88)
Duration of β-blocker use in years		
≤ 2 years after diagnosis		
Crude HR	1	0.59 (0.41-0.85)
Adjusted HR[b]	1	0.47 (0.32-0.68)
> 2 years after diagnosis		
Crude HR	1	0.93 (0.84-1.02)
Adjusted HR[b]	1	0.87 (0.78-0.98)
Correct Analyses		
β-blocker use before start of follow up as a time-fixed covariate		
β-blocker user for at least one year, N[a]	599	110
Person-years	2279.1	353.2
All cause death (N,%)	132	27
Crude HR	1	1.28 (0.85-1.94)
Adjusted HR[b]	1	0.86 (0.56-1.32)
β-blocker use during follow up as a time-varying covariate		
β-blocker user for at least one year, N	654	137
Person-years	2818.1	394.7
All cause death, N (%)	159	27
Crude HR	1	1.24 (0.81-1.88)
Adjusted HR[b]	1	0.86 (0.56-1.32)
Duration of β-blocker use in years		
≤ 2 years after diagnosis		
Crude HR	1	1.08 (0.69-1.70)
Adjusted HR[b]	1	0.75 (0.47-1.21)
> 2 years after diagnosis		
Crude HR	1	1.08 (0.96-1.22)
Adjusted HR	1	1.01 (0.89-1.14)

Abbreviations: HR, hazard ratio; N, number

[a] 82 patients were excluded from these analyses, due to a follow up time of less than 1 year before diagnosis.

[b] Covariates that were considered possible confounders were: age, sex, histological subtype, body site, nodal and distant metastasis at diagnosis and Breslow thickness. Final analyses were adjusted for age and sex.

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Chapter 4.3

Incident cancer risk after the start of aspirin use: results from a Dutch population-based cohort study of low dose aspirin users

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ABSTRACT

Observational and intervention studies suggest that low dose aspirin use may prevent cancer. The objective of this study was to investigate the protective effect of long term low dose aspirin use (≤ 100 mg daily) on cancer in general and site-specific cancer among low dose aspirin users in the Dutch general population.

We conducted a population-based cohort study with detailed information on aspirin exposure and cancer incidence. Only incident (new) low dose aspirin users, who were included in the linkage between PHARMO and the Eindhoven Cancer Registry (1998-2010) and free of cancer before the start of follow up were included. A Cox proportional hazard model with cumulative aspirin use as a time-varying determinant was used to obtain hazard ratios (HR).

Duration of aspirin use amongst 109,276 incident low dose aspirin users was not associated with a decreased risk of any of the site-specific cancers or cancer in general (adjusted HR per year of aspirin use for all cancers: 1.02, 95% confidence interval [CI] 1.00-1.04, HR of >6 years aspirin use compared to <2 years: 1.17, 95% CI 1.02-1.34). After adjusting for current and past aspirin use, 2-6 years of low dose aspirin use was associated with a reduced colorectal cancer risk compared to less than two years of aspirin use (adjusted HR 0.75, 95% CI 0.59-0.96). However, a clear dose-response relationship was not observed (adjusted HR >6 years aspirin use 0.95, 95% CI 0.60-1.49).

Our results do not support the primary prevention of cancer among long term aspirin users.

INTRODUCTION

Observational studies suggested that regular aspirin use may prevent cancer [1,2]. A meta-analysis of individual patient data of 51 randomized controlled cardiovascular trials including more than 70,000 individuals showed a reduction of cancer incidence (meta-odds ratio [OR] 0.71, 95% confidence interval [CI] 0.57-0.89) and mortality (OR 0.63, 95% CI 0.49-0.82), which became most apparent 5 years after randomization to daily aspirin [3]. However, these trials were primarily designed to assess prevention of cardiovascular events and prevention of cancer was assessed as a secondary endpoint. Long term follow up studies of these trials lacked statistical power to determine an effect of aspirin use on site-specific cancers and could only establish an effect on all cancers combined. Furthermore, trial participants are a highly selected group and therefore results cannot be extrapolated to the general population. The risk reduction of cancer mortality with aspirin use in real life appeared to be modest compared to the meta-analysis of trials (hazard ratio [HR] >5 years 0.84, 95% CI 0.75-0.95) [4]. The objective of this study was to investigate the possible protective effect of long term low dose aspirin use (≤ 100 mg daily) on the incidence of site-specific cancers in the Dutch general population. Because the protective effect of low dose aspirin became most apparent 5 years after randomization, we hypothesized that long term low dose aspirin users may have a lower cancer risk than short term users. Data from the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (RLS) were used to obtain high quality and complete information on low dose aspirin exposure (≤ 100 mg daily) of all new low dose aspirin users and cancer incidence over a period of 12 years [5].

METHODS

Setting

The coverage area of both the ECR and the PHARMO RLS includes more than one million Dutch citizens [5] Briefly, the ECR is a population-based cancer registry in the south of the Netherlands covering 2.4 million inhabitants. The ECR includes more than 95% of all newly diagnosed malignancies and is based on the automated pathological archive (PALGA), the national registry of hospital discharge diagnosis (LMR), haematology departments and radiotherapy institutions [6-8].

PHARMO RLS is a network of patient databases, which covers a demographic region of more than 3 million inhabitants including, among other things, community (out-patient) pharmacy data [8,9]. The community pharmacy database includes all pharmacy dispensed healthcare products on the Dutch market, prescribed by general practitioners or specialists, including aspirin dispensings. Over the counter (OTC) aspirin use was not included. Patients were followed over a long period of time; until they moved away from the ECR-PHARMO

catchment area, end of data collection of the specific community pharmacy, end of study period, or death, whichever occurred first. The date of death was obtained from the central bureau for genealogy (CBG), the local pharmacy or the hospital.

Patients

All citizens who lived in the ECR-PHARMO catchment area between 1 January 1998 and 31 December 2010 and were above 18 years were eligible (n=1,263,935, Figure 1). Participants were required to have a complete prescription history since the date of entry in PHARMO and at least 1 year of follow up to ascertain a new user design (n=1,233,205, Supplementary Figure 1) [10]. Participants with a low dose aspirin dispensing during the first year of follow up were considered prevalent users and were excluded from the main analyses (n=44,986). All incident (new) low dose aspirin users without cancer (excluding [excl] nonmelanoma skin cancer [NMSC]) before their first aspirin dispensing were included in the analysis (n=109,276). Patients with a NMSC diagnosis prior to their first aspirin dispense were excluded from the NMSC analyses.

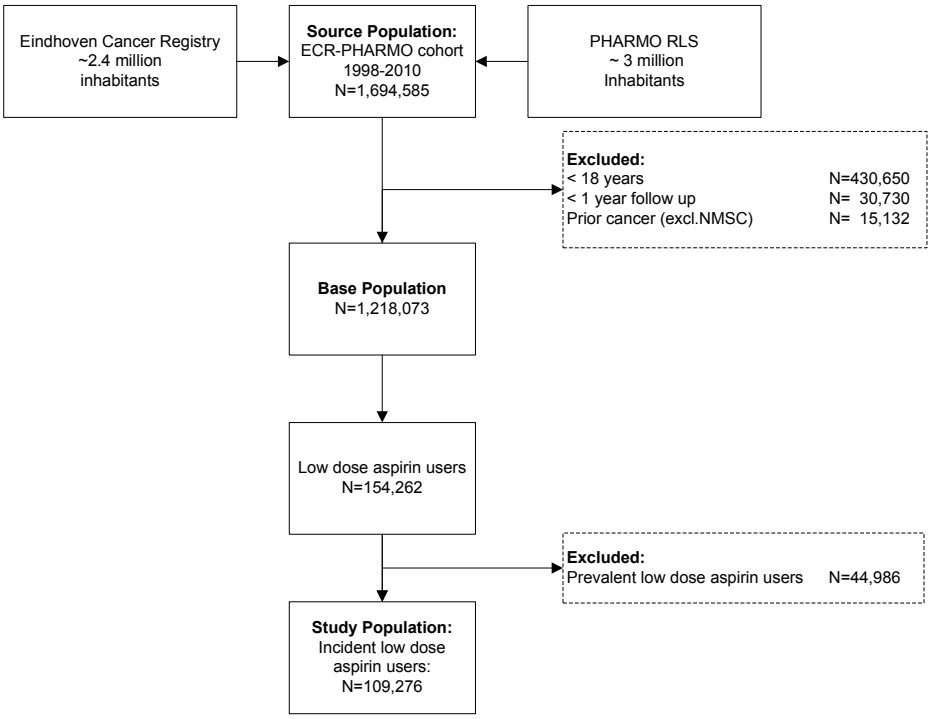


Figure 1: Flowchart: Only incident (new) low dose aspirin users from the ECR-PHARMO cohort who were above 18 years old, free of cancer and had at least 1 year follow up in the PHARMO record linkage system (RLS) were included in the main analysis. Prevalent low dose aspirin users were included in a sensitivity analysis.

Exposure to low dose aspirin

Dispensings were selected based on the Anatomical Therapeutic Chemical (ATC) codes of the World Health Organisation (WHO) collaborating centre for drug statistics methodology. Dispensings with full ATC codes; B01AC06, B01AC08 and B01AC30 were considered low dose aspirin dispensings (≤ 100 mg daily). To calculate the duration of each dispense, the amount of dispensed drug was divided by the amount prescribed per day, as defined in the pharmacy data.

Cancer as outcome

The invasive (grouped) cancers which were analysed in this study were cancer of the upper gastrointestinal (GI) tract (C15 and C16 of the International Classification of Disease 10 [ICD-10]), colorectal cancer (C18-C20), lung cancer (C33, C34), melanoma (C43), basal cell carcinoma (BCC) (C44) and other skin cancers (C44), breast cancer (C50), female genital cancer (C53-C56), prostate cancer (C61), urinary tract cancer (C64-C68) and lymphomas (C81-C88).

Covariates

Age at start of follow up, sex, co-medication use and comorbidities were considered potential confounders. As a proxy for comorbidities and the associated health care utilization we determined the unique number of dispensings (ATC codes) and the unique number of hospital discharge diagnosis (LMR) in the year previous to start of follow up [11,12]. Co-medication use which may influence risk of cancer was recorded for the year prior to start of follow up and included non-steroidal anti-inflammatory drugs (NSAID), statins, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, glucocorticoids and other immunosuppressive drugs (Supplementary Table 1).

Statistical analyses

The association between duration of low dose aspirin use and cancer was analysed by using a Cox proportional hazard (PH) model with cumulative drug use as a time-dependent covariate [13]. In these analyses the cumulative duration of aspirin use of the subject with the event of interest is compared with the cumulative duration of aspirin use of all other subjects at the same time point. Time since first aspirin dispensing was used as underlying timescale (Supplementary Figure 1).

A priori we decided that all analyses would be adjusted for age, sex, co-medication use and comorbidities. The linearity assumption was not met for age and therefore a restricted cubic spline function with 4 knots was included in the model for age. Final analyses were adjusted for unique number of ATC and LMR codes in the year prior to start of follow up (i.e. replacing ATC/LMR codes in the multivariable model for aforementioned co-medication use as binary variables (yes/no) resulted in similar results and the same conclusions). The correlation be-

tween the unique number of dispensings and hospitalizations was low (Pearsons correlation coefficient r = 0.22), indicating a low possibility of collinearity.

First, multivariable analyses were performed with duration of aspirin use as a continuous variable and a categorical variable (main analysis). Sensitivity analyses were performed to test if the main results were consistent with results obtained by alternative analysis strategies. Second, two lag time analyses were performed, discarding aspirin exposure one year or three years before diagnosis to control for a) misclassification of exposure time, due to the latency time, b) increased health care utilization before diagnosis, and c) reverse causation. Third, because in our models with cumulative exposure, no distinction was made between current use and past use, we adjusted the analyses for the number of days elapsed since last aspirin use. Fourth, prevalent aspirin users will include many compliant and long term users, who are particularly important for evaluating long term effects of aspirin use [14]. Excluding them may cause an overrepresentation of non-compliant and short term aspirin users in the main analyses. Therefore we included the prevalent users in a sensitivity analysis. Fifth, the reliability of recording of moving away from the ECR-PHARMO catchment area was unknown. Therefore patients were censored at the last date of any dispensing, because patient who pick up their dispensings did not move away and are most likely truly at risk in the analyses.

Finally, analyses were stratified by sex, age (<60, ≥ 60 years), number of unique dispensings (0, 1 or 2, >2) and number of unique hospitalizations (0, 1, >1) to assess the impact of effect modification. To check the PH assumption time interval specific HR were calculated. We observed no violation of the PH assumption. All analyses were performed using SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and considered significant at the $p < 0.05$ level.

RESULTS

The study population consisted of 109,276 incident low dose aspirin users with a median follow up time of 4.4 years (interquartile range [IQR] 2.0-7.0 years) since their first aspirin dispense (Table 1). The median age of low dose aspirin users was 69 (IQR: 49-69). Of all aspirin users, 12% had at least one hospital discharge diagnosis in the year before start of follow up and 72% used other medications. Most aspirin users used aspirin for six years or less. However, more than 14,000 people used low dose aspirin for more than six years. The daily low dose aspirin dose was ≥80 mg for 90.9% of all dispensings, ≤38 mg for 7.3% of all dispensings, and between 38 mg and 80 mg for 1.9% of all dispensings.

Each additional year of low dose of aspirin use was not associated with cancer risk among low dose aspirin users (adjusted HR per year of aspirin use for all cancers [excl. NMSC] 1.02, 95% CI 1.00-1.04) (Figure 2, Table 2). Long term aspirin users were not at decreased risk of cancer compared to short term users either (adjusted HR >6 years aspirin use for all cancers

Table 1: Patient characteristics

	New aspirin users	
N	109,276	
Males (N, %)	53,679	(49.1)
Females (N, %)	55,597	(50.9)
Age in years (Median, IQR)	59	(49-69)
Follow up in years since first aspirin dispense until death, end of study or lost to follow up (Median, IQR)	4.4	(2.0-7.0)
Reasons for end of follow up (N,%)		
Death	10,208	(9.3)
End of study	89,406	(81.8)
End of data collection of the pharmacy	7,826	(7.2)
Moved away from the ECR-PHARMO catchment area	1,836	(1.7)
Time since first aspirin dispense until first cancer diagnosis, excl. NMSC (N, %)		
< 2 years	1931	(1.8)
2 to 4 years	1356	(1.2)
4 to 6 years	1044	(1.0)
6 to 8 years	648	(0.6)
8 to 10 years	330	(0.3)
10 to 12 years	106	(0.1)
Duration of low dose aspirin use (N,%)		
< 2 years	57,197	(52.3)
2 to 4 years	22,806	(20.9)
4 to 6 years	14,661	(13.4)
6 to 8 years	8,608	(7.9)
> 8 years	6,004	(5.5)
Unique number of dispensings in the year before start of follow up (%)		
0	30,915	(28.3)
1 or 2	30,149	(27.6)
>2	48,212	(44.1)
Unique number of hospitalisation in the year before start of follow up (N, %)		
0	96,162	(88.0)
1	10,575	(9.7)
>1	2,539	(2.3)
Comedication in the year before start of follow up (N, %)		
NSAID users	31,011	(28.4)
Statin users	7,236	(6.6)
Immunosuppresive drug users	5,563	(5.1)
ACE inhibitor / AR blocker users	9,934	(9.1)
Estrogen users	9,279	(8.5)

In this table, aspirin users were not classified according to short term or long term use, because this definition of exposure is time-dependent

ACE angiotensin converting enzyme, AR angiotensin receptor, IQR interquartile range, NMSC nonmelanoma skin cancer, NSAID nonsteroidal anti inflammatory drugs

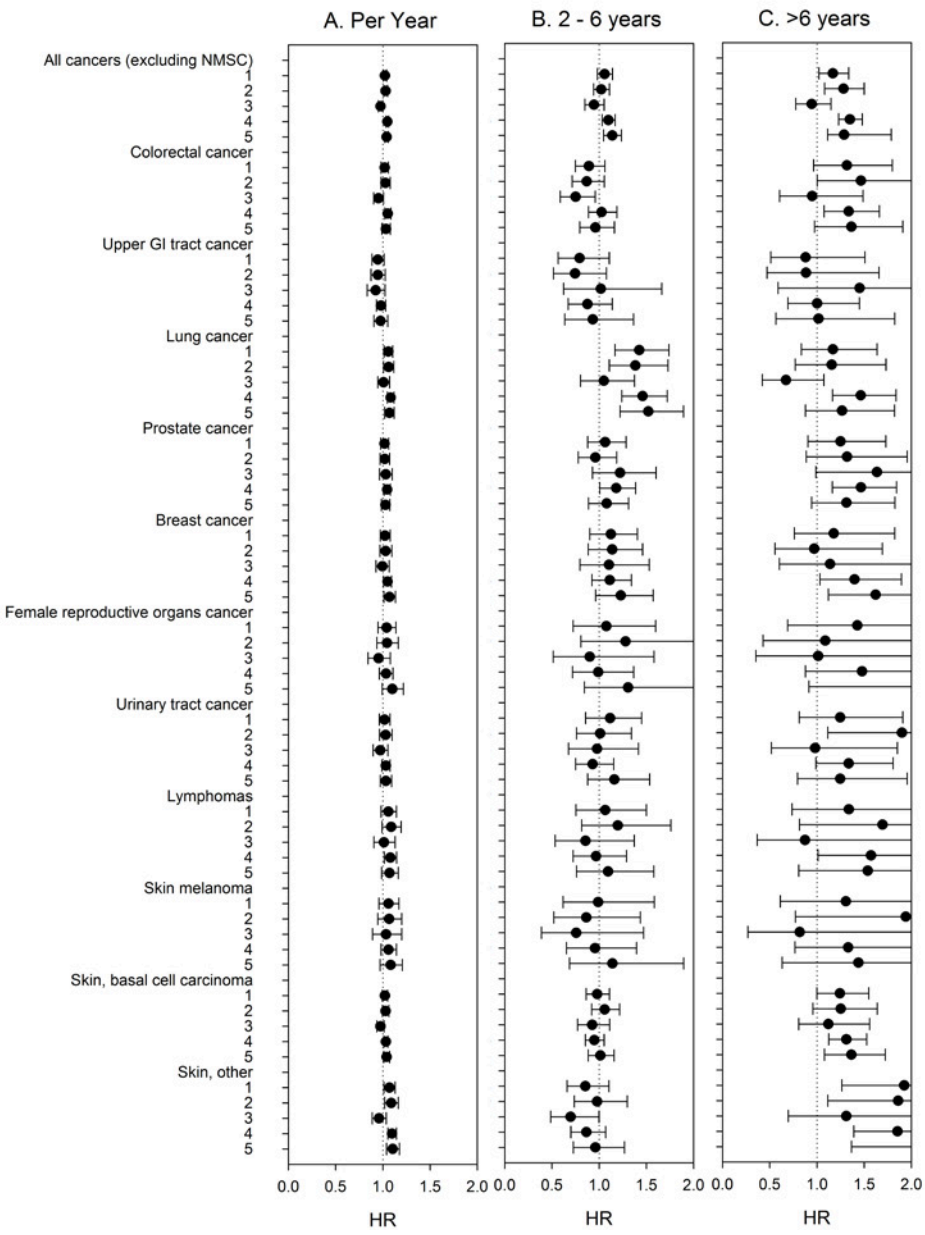


Figure 2: Hazard ratios of aspirin use for cancer risks: Hazard ratio's (HR) were calculated per year of aspirin use (A) and in categories of 2-6 years aspirin use (B) and >6 years aspirin use (C) compared to < 2 years aspirin use. For all cancers combined and each site-specific cancer four models were conducted. The multivariable model (1) was adjusted for age, sex, comorbidities and comedication use. A lag time of 1 year was included (2), analyses were adjusted for time since last use (3), prevalent users were included (4) and subjects were censored at the last date of any dispensing (5).

1.17, 95% CI 1.02-1.34). An inverse association was observed for upper GI tract cancer, although not statistically significant (adjusted HR per year of aspirin use 0.95 95% CI 0.88-1.01, adjusted HR >6 years aspirin use 0.88, 95% CI 0.51-1.51).

The HR per year of aspirin use for all site-specific cancers decreased after including time since last aspirin use in the model to adjust for the difference between past and current aspirin use (Figure 2, Supplementary Table 2). Discarding exposure during one or three years prior to diagnosis (the latent period of tumour development) did not change the conclusions (Figure 2, Supplementary Table 2). After adjusting for time since last use, two to six years of low dose aspirin use was associated with a reduced colorectal cancer risk compared to less than two years of aspirin use (adjusted HR 0.75, 95% CI 0.59-0.96). However, a clear dose-response relationship was not observed (adjusted HR >6 years aspirin use 0.95, 95% CI 0.60-1.49) (Figure 2, Supplementary Table 2). The non-significant inverse association for upper GI tract cancer disappeared after adjustment for time since last aspirin use (adjusted HR 2-6 years 1.02, 95% CI 0.62-1.66, adjusted HR >6 years 1.45, 95% CI 0.59-3.59). The number of long term aspirin users more than doubled after inclusion of prevalent aspirin users (34,168 prevalent and incident users compared to 14,771 incident users with >6 years aspirin use). However, including prevalent aspirin users did not result in a protective association of long term aspirin use compared to short term use (Figure 2, Supplementary Table 2). Censoring subjects at the date of the last dispense of any type of medication to control for possible missed moving out of the ECR-PHARMO catchment area, did not change the conclusions (Figure 2, Supplementary Table 2). Similar results were observed in analyses stratified for sex, age group, and number of unique dispensings and hospitalizations [data not shown].

DISCUSSION

Our results show, that long term aspirin use among low dose aspirin users may not prevent the incidence of cancer. Long term use among low dose aspirin users in the general population was not associated with a decreased risk of cancer in general or any site-specific cancer. After adjusting for current and past aspirin use, we observed a 25% risk reduction of colorectal cancer after two to six years of aspirin use compared to less than two years of aspirin use. A clear dose-response relationship was not observed with a longer duration of aspirin use. This may be due to the low number of long term incident aspirin users or to the low number of events in this category. We observed a non-significant modest inverse association between upper GI tract cancer and duration of aspirin use, which disappeared after adjusting for current and past aspirin use. This may indicate, that long term aspirin use appeared to be protective, because patients with gastric symptoms, who already have a higher risk of upper GI tract cancer, discontinue aspirin, whereas healthy patients continue aspirin use.

Table 2: Long term low dose aspirin use compared to short term use

			Duration of aspirin use									
			Per year		< 2 years		2 to 6 years			> 6 years		
	N[a]	Total number of events	Adjusted HR[b]	95% CI	Events	HR	Events	Adjusted HR[b]	95% CI	Events	Adjusted HR[b]	95% CI
All cancers (excluding NMSC)	109,276	5,415	1.02	(1.00- 1.04)	3,021	1	1,919	1.06	(0.98- 1.14)	475	1.17	(1.02- 1.34)
Colorectal cancer	109,276	972	1.02	(0.98- 1.06)	542	1	334	0.89	(0.75- 1.06)	96	1.32	(0.96- 1.80)
Upper GI tract cancer	109,276	268	0.95	(0.88- 1.01)	156	1	84	0.79	(0.57- 1.11)	28	0.88	(0.51- 1.51)
Lung cancer	109,276	915	1.06	(1.01- 1.10)	494	1	346	1.42	(1.17- 1.74)	75	1.17	(0.83- 1.64)
Prostate cancer	53,679	882	1.02	(0.98- 1.06)	451	1	338	1.06	(0.88- 1.29)	93	1.25	(0.90- 1.73)
Breast cancer	55,597	585	1.02	(0.97- 1.08)	348	1	200	1.12	(0.90- 1.40)	37	1.18	(0.76- 1.82)
Female genital cancer	55,597	188	1.04	(0.95- 1.14)	111	1	62	1.08	(0.72- 1.60)	15	1.43	(0.69- 2.95)
Urinary tract cancer	109,276	463	1.02	(0.96- 1.07)	241	1	172	1.12	(0.86- 1.45)	50	1.25	(0.81- 1.91)
Lymphoma	109,276	256	1.06	(0.98- 1.14)	136	1	94	1.06	(0.76- 1.50)	26	1.34	(0.74- 2.43)
Skin melanoma	109,276	142	1.06	(0.96- 1.17)	81	1	46	0.99	(0.62- 1.58)	15	1.31	(0.61- 2.79)
Skin, BCC	107,605	1,776	1.02	(0.99- 1.05)	932	1	663	0.98	(0.86- 1.11)	181	1.24	(1.00- 1.55)
Skin, other	107,605	445	1.02	(1.00- 1.04)	233	1	149	0.85	(0.66- 1.10)	63	1.92	(1.26- 2.93)

BCC, basal cell carcinoma, CI confidence interval, GI gastrointestinal, HR hazard ratio, NMSC nonmelanoma skin cancer

[a] Total number in the main analyses represents 109,276 incident low dose aspirin without cancer (excl. NMSC) before their first aspirin dispense (53,697 males and 55,597 females) An additional 1,671 subjects with NMSC before their first aspirin dispensing were excluded from the BCC and Skin/other analyses.

[b] Adjusted for age, sex, unique number of dispensings and unique number of hospitalizations in the year prior to start of follow up. In the sensitivity analyses

Results of other observational and intervention studies examining the association between aspirin use and cancer risk have been conflicting. A meta-analysis of individual patient data of 51 cardiovascular randomized controlled trials showed a reduction of cancer incidence 3 years after randomization to low dose aspirin (75-100 mg daily) in 6 trials including more than 30,000 individuals [3]. A pooled analysis of these 6 trials and 26 trials of daily aspirin of any dose did not show a clear effect on many site-specific cancers, such as cancer of the gastrointestinal tract. A statistically significant risk reduction was only observed for cancers of the female reproductive organs. A direct comparison between this study and our study is not possible, because our study included only aspirin users. Other differences between our study and the meta-analysis of individual patient data include the choice of study population (sample of the general population *vs.* selected trial participants), analysed treatment (dispensed drugs *vs.* scheduled treatment) and information of potential confounders (limited availability in automated health care databases *vs*. detailed information on an individual patient level). Other meta-analyses of observational studies on regular aspirin use and cancer risk showed a decreased risk of many site-specific cancers including colorectal cancer, esophageal and gastric cancer and other cancers of the digestive tract [1,2]. In the meta-analyses, modest risk reductions were observed for breast and prostate cancer [1,2]. Previous studies on lung cancer were inconclusive and no risk reduction was observed for pancreas, endometrium, ovary, bladder, and kidney cancer [1,2]. Analyses conducted in the vitamins and lifestyle (VITAL) study showed no association between low dose aspirin use and haematological malignancies either [15]. Observational studies of skin cancer and aspirin use also showed inconsistent results [12,16-18]. The protective findings in some of these studies may be due to the use of a time-fixed analysis of aspirin exposure. This analysis can produce a protective HR in a dataset where there is no association between exposure and outcome, while a time-dependent analysis of exposure results in a correct HR of 1 in the same dataset [19]. Data from the Nurses Health Study (NHS) was analysed with a time-dependent definition of aspirin exposure showing no risk reductions of squamous and basal cell carcinoma and even a slightly increased risk of melanoma [17].

Conflicting results were also seen in randomized controlled trials designed to assess cancer risk with regular aspirin use. The Cancer Prevention Programme (CaPP2) did not demonstrate a protective effect of aspirin (600 mg daily) in 1,000 Lynch syndrome patients on the development of colorectal carcinomas 4 years after randomization, but found a sudden risk reduction after a mean follow up of 4.5 years [20,21]. The Women's Health Study (WHS), (100 mg of alternate day aspirin) did not show an effect on cancer incidence after 10 years of follow up among almost 40,000 participants [22]. The lack of effect was hypothesized to be due to the low dose or low frequency of aspirin use. A recent analysis of posttrial follow-up revealed a delayed effect on colorectal cancer, but not on total cancer or any other site-specific cancer [23]. After a median follow up of 18 years, 53 fewer cancers and 48 fewer cardiovascular disease (CVD) cases occurred, but there was an increase of 193 gastrointestinal bleedings and 214

peptic ulcers. The risk-benefit ratio of aspirin use in a primary prevention setting remains controversial because of its modest effectiveness and risk of bleedings [24,25].

Ongoing trials focus on the risks and benefits of daily aspirin: the ASPrin in Reducing Events in the Elderly (ASPREE) trial for example examines if the benefits of aspirin (100 mg daily) outweigh the risks in healthy participants above 70 years. This trial can provide information about the possible extension of a disability-free life by using daily aspirin, which is a relevant primary endpoint to assess the risk-benefit ratio (NCT01038583) [26].

Future research may aim to identify biomarkers associated with a reduced cancer risk with aspirin use. Recently, a PIK3CA (the phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit alpha polypeptide) gene mutation was identified in colorectal cancer as a potential useful genetic marker to help target adjuvant treatment with aspirin more effectively [27]. Aspirin use among colorectal cancer patients with a mutation in the PIK3CA gene was associated with a 46% reduction in all-cause mortality and a 82% decrease in cancer related mortality [27]. Aspirin use was not associated with mortality in wild type cancers.

Strengths and Limitations

The strengths of this study include the large population-based sample and the detailed and high quality information on both aspirin use and cancer, limiting both selection and information bias. The validity of both exposure and outcome was high, because the cancer registry completeness exceeds 95%[7] and the PHARMO RLS has detailed information on dosage, duration and frequency of each dispensing during follow up [5]. Due to our study methodology, important biases in pharmacoepidemiology, such as immortal time bias[28,29], prevalent user bias[10], and lag time bias[12,16] were circumvented[13,30]. The limitations include the lack of information on OTC aspirin use and potential confounders. The non-differential misclassification of exposure due to OTC low dose aspirin use is likely to be minimal, because low dose aspirin for the indication 'platelet aggregation inhibition' is only available on prescription in the Netherlands. The proportion of high dose OTC aspirin use is unknown, which could have biased our results towards the null hypothesis. However, it has been shown that, pharmacy data can give valid associations even though a high proportion (25%) of the drugs are available OTC [31]. This suggests that the effect of missing high dose OTC aspirin may not be a large source of bias in the present study. Important confounders, such as use of other medications and comorbidities were included in our analysis. Other important confounders, such as smoking, overweight, alcohol use and other lifestyle factors were not available. This could have influenced our results, although we expected that this would have resulted in a too low HR, rather than towards no effect. In our analysis, adherent long term users were compared to those who discontinue aspirin use. A protective HR may be a result of the healthy adherer bias (i.e. adherence to the drug is associated with other healthy behaviors). Instead, we observed an increased cancer risk among long term users, which may indicated the opposite of the healthy adherer effect. An alternative explanation for our lack of a protective association

is an increased ascertainment of cancer among long term users, which could have biased our results towards the null. This is unlikely, because the specificity of the linkage in a random sample with at least one year follow up was as high as 99.5% [5]. In addition, an increased ascertainment of cancer among long term users could have been caused by short term users of which moving out of the ECR-PHARMO catchment area was not recorded. Therefore, we censored the subjects at the last date of any dispensing, but this did not alter the results. Aspirin users may have died prematurely, which resulted in a high number of short term users, but this could not be confirmed by an analysis of all-cause mortality (adjusted HR per additional year of low dose aspirin use 0.97, 95% CI: 0.96-0.98).

The negative findings of this study cannot be extrapolated to populations at high risk of developing cancer (e.g., patients with a history of cancer or patients with premalignant lesions, such as polyposis, Barett's esophagus, or actinic keratoses).

Conclusion

Long term aspirin use among low dose aspirin users was neither associated with a decreased risk of cancer in general, nor with a clear risk reduction of any site-specific cancer in the Dutch general population. Our results do not support the primary prevention of cancer among long term aspirin users. Ongoing clinical trials may provide information about the balance between risks and benefits of aspirin use among subgroups at higher risk for cancer.

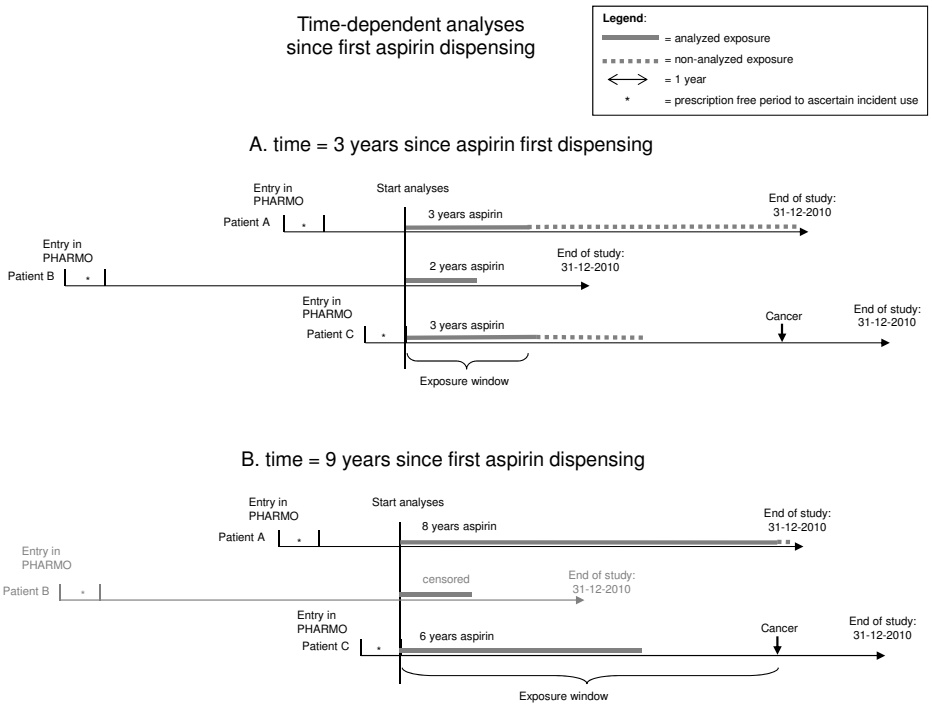
Acknowledgements

We would like to thank Mieke Aarts and her colleagues of the Eindhoven Cancer Registry for their dedicated data collection and linkage of the data. We would also gratefully acknowledge Huub Straatman and his colleagues from the PHARMO institute for drug outcomes research for their dedicated data collection, data processing and help with the SAS programming. We thank both the ECR and the PHARMO institute for drug outcomes research for the availability of their data on favorable terms. We would like to thank Emmilia Dowlatshahi and Satu Siiskonen for critically reading the manuscript.

Supplementary Table 1: ATC codes of comedication

Comedication	ATC code	Description
NSAIDs	M01A	Antiinflammatory and antirheumatic products, non steroids
	N02AB	Salicylic acid and derivates
	N02BB	Pyrazolones
Immunosuppresive drugs	H02AB	Corticosteroids for systemic use, plain - Glucocorticoids
	H02BX	Corticosteroids for systemic use, combinations
	L04A	Immunosuppressants
Statins	C10AA	HMG CoA reductase inhibitors, plain
	C10BA, C10BX	HMG CoA reductates inhibitors, combinations
ACE inhibitors en Angiotensin Receptor Blockers	C09A	ACE inhibitors, plain
	C09B	ACE inhibitors, combinations
	C09C	Angiotensin II antagonists, plain
	C09D	Angiotensin II antagonists, combinations
Estrogens	G03AA, G03AB	Hormonal contraceptives for systemic use – progestogens and estrogens, fixed and sequential preparations
	G03C	Estrogens
	G03F	Progestogens and Estrogens in combination
	G03HB01	Antiandrogens and estrogens
	G03XC	Selective estrogen receptor modulators

ACE, angiotensin converting enzyme; ATC, anatomical therapeutic chemical HMG coA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; NSAID, nonsteroidal anti-inflammatory drugs



Supplementary figure 1: Time-to-event analysis with aspirin use as time-dependent covariate: After entry in the PHARMO record linkage system (RLS) all patients with an aspirin dispensing within the first year were excluded to ascertain a new user design. Follow up started at the date of the first aspirin dispensing. Cumulative exposure was calculated at each time point. In this example patient A, B and C are all included in the risk set of an event at 3 years after the first aspirin dispensing (patient with event not shown) (A). Patient C is diagnosed with cancer 9 years after the first aspirin dispensing (B). The cumulative exposure of patient C at diagnosis is compared to the cumulative exposure in the same time period of all other cohort members still in follow up and event-free. Patient B was censored and not included in this risk set. In the lagged analyses exposure 1 year or 3 years before diagnosis was not taken into account.

Supplementary Table 2: Analyses of long term low dose aspirin use compared to short term use

			Duration of low dose aspirin use									
			Per year		< 2 years		2 to 6 years			> 6 years		
	N[a,b]	Total number of events	Adjusted HR[c]	95% CI	Events	HR	Events	Adjusted HR[c]	95% CI	Events	Adjusted HR[c]	95% CI
Main analyses + 1 year lagtime												
All cancers (excluding NMSC)	92,334	4,284	1.03	(1.01-1.05)	2,423	1	1,531	1.02	(0.94- 1.11)	330	1.28	(1.08- 1.50)
Colorectal cancer	93,028	784	1.03	(0.98- 1.08)	448	1	269	0.87	(0.71- 1.06)	67	1.46	(1.00- 2.14)
Upper GI tract cancer	93,138	213	0.95	(0.87- 1.03)	125	1	68	0.74	(0.52- 1.08)	20	0.88	(0.47- 1.66)
Lung cancer	93,047	712	1.06	(1.01- 1.12)	384	1	278	1.38	(1.11- 1.73)	50	1.16	(0.77- 1.73)
Prostate cancer	45,621	737	1.02	(0.97- 1.07)	415	1	258	0.96	(0.78- 1.18)	64	1.32	(0.89- 1.96)
Breast cancer	47,321	471	1.03	(0.97- 1.09)	290	1	160	1.14	(0.89- 1.46)	21	0.97	(0.56- 1.69)
Female genital cancer	47,390	145	1.04	(0.94- 1.16)	85	1	52	1.28	(0.81- 2.03)	8	1.09	(0.43- 2.75)
Urinary tract cancer	93,102	371	1.03	(0.96- 1.10)	191	1	141	1.01	(0.76- 1.34)	39	1.90	(1.11- 3.24)
Lymphoma	93,129	204	1.09	(0.99- 1.19)	106	1	79	1.20	(0.81- 1.76)	19	1.69	(0.82- 3.52)
Skin melanoma	93,154	115	1.07	(0.95- 1.20)	65	1	38	0.86	(0.52- 1.44)	12	1.94	(0.77- 4.88)
Skin, BCC	91,583	1,502	1.03	(0.99- 1.06)	811	1	574	1.06	(0.92- 1.22)	117	1.25	(0.96- 1.64)
Skin, other	91,776	379	1.09	(1.02- 1.16)	204	1	135	0.98	(0.74- 1.30)	40	1.86	(1.11- 3.11)
Main analyses + 3 years lagtime												
All cancers (excluding NMSC)	68,961	2,731	1.02	(0.99- 1.05)	1,687	1	948	1.06	(0.95- 1.18)	96	1.06	(0.80- 1.40)
Colorectal cancer	70,256	508	1.02	(0.95- 1.09)	313	1	177	1.09	(0.84- 1.41)	18	0.94	(0.50- 1.78)
Upper GI tract cancer	70,492	140	0.93	(0.83- 1.05)	88	1	43	0.64	(0.41- 1.00)	9	1.08	(0.39- 3.01)
Lung cancer	70,345	441	1.04	(0.96- 1.12)	264	1	161	1.11	(0.84- 1.46)	16	1.09	(0.55- 2.16)
Prostate cancer	34,586	460	1.00	(0.93- 1.07)	284	1	161	0.95	(0.72- 1.24)	15	0.81	(0.40- 1.63)
Breast cancer	35,426	286	1.04	(0.95- 1.14)	186	1	93	1.30	(0.93- 1.83)	7	0.88	(0.35- 2.25)
Female genital cancer	35,595	90	1.09	(0.92- 1.29)	60	1	27	1.08	(0.58- 2.01)	3	1.54	(0.31- 7.67)
Urinary tract cancer	70,423	257	1.03	(0.94- 1.14)	149	1	97	1.06	(0.75- 1.50)	11	1.22	(0.52- 2.88)
Lymphoma	70,474	139	1.12	(0.97- 1.29)	88	1	44	1.35	(0.78- 2.33)	7	1.45	(0.47- 4.45)

Supplementary Table 2: (Continued)

			Duration of low dose aspirin use									
			Per year		< 2 years		2 to 6 years			> 6 years		
	N[a,b]	Total number of events	Adjusted HR[c]	95% CI	Events	HR	Events	Adjusted HR[c]	95% CI	Events	Adjusted HR[c]	95% CI
Skin melanoma	70,507	76	1.11	(0.92- 1.32)	46	1	25	0.83	(0.45- 1.53)	5	5.03	(0.87- 28)
Skin, BCC	69,060	1,015	1.04	(0.99- 1.09)	613	1	357	1.11	(0.92- 1.32)	45	1.64	(1.06- 2.55)
Skin, other	69,489	254	1.13	(1.02- 1.26)	135	1	109	1.57	(1.09- 2.24)	10	1.07	(0.47- 2.41)
Main analyses + time since last use												
All cancers (excluding NMSC)	109,276	5,415	0.98	(0.95 - 1.00)	3,021	1	1,919	0.95	(0.85-1.05)	475	0.94	(0.78-1.15)
Colorectal cancer	109,276	972	0.95	(0.90- 1.01)	542	1	334	0.75	(0.59-0.96)	96	0.95	(0.60-1.49)
Upper GI tract cancer	109,276	268	0.92	(0.83- 1.02)	156	1	84	1.02	(0.62-1.66)	28	1.45	(0.59-3.59)
Lung cancer	109,276	915	1.01	(0.95- 1.07)	494	1	346	1.05	(0.80-1.37)	75	0.67	(0.42-1.07)
Prostate cancer	53,679	882	1.03	(0.97- 1.10)	451	1	338	1.22	(0.93-1.60)	93	1.63	(0.99-2.70)
Breast cancer	55,597	585	0.99	(0.93- 1.07)	348	1	200	1.10	(0.80-1.53)	37	1.14	(0.60-2.15)
Female genital cancer	55,597	188	0.95	(0.84- 1.08)	111	1	62	0.90	(0.51-1.58)	15	1.01	(0.35-2.91)
Urinary tract cancer	109,276	463	0.97	(0.90- 1.05)	241	1	172	0.98	(0.68-1.42)	50	0.98	(0.52-1.85)
Lymphoma	109,276	256	1.01	(0.91- 1.13)	136	1	94	0.86	(0.53-1.37)	26	0.87	(0.37-2.07)
Skin melanoma	109,276	142	1.03	(0.89- 1.20)	81	1	46	0.76	(0.39-1.47)	15	0.82	(0.27-2.48)
Skin, BCC	107,605	1,776	0.97	(0.94- 1.01)	932	1	663	0.93	(0.77-1.11)	181	1.12	(0.81-1.56)
Skin, other	107,605	445	0.96	(0.89- 1.03)	233	1	149	0.70	(0.49-1.00)	63	1.31	(0.70-2.46)
Main analyses + including prevalent users												
All cancers (excluding NMSC)	154,262	9,456	1.05	(1.03 -1.06)	4,124	1	3,773	1.10	(1.03 -1.17)	1,559	1.35	(1.23 -1.48)
Colorectal cancer	154,262	1,679	1.05	(1.02 -1.08)	718	1	617	1.03	(0.89 -1.19)	287	1.34	(1.08 -1.66)
Upper GI tract cancer	154,262	481	0.98	(0.93 -1.03)	202	1	187	0.88	(0.67 -1.14)	92	1.00	(0.69 -1.45)
Lung cancer	154,262	1,675	1.08	(1.05 -1.12)	685	1	705	1.46	(1.24 -1.72)	285	1.46	(1.17 -1.84)
Prostate cancer	78,902	1,627	1.05	(1.01 -1.08)	649	1	687	1.18	(1.01 -1.39)	291	1.46	(1.16 -1.84)
Breast cancer	75,360	933	1.05	(1.01 -1.09)	461	1	357	1.11	(0.92 -1.34)	115	1.40	(1.03 -1.90)

Supplementary Table 2: (Continued)

			Duration of low dose aspirin use									
			Per year		< 2 years		2 to 6 years			> 6 years		
	N[a,b]	Total number of events	Adjusted HR[c]	95% CI	Events	HR	Events	Adjusted HR[c]	95% CI	Events	Adjusted HR[c]	95% CI
Female genital cancer	75,360	309	1.03	(0.96-1.11)	154	1	112	0.99	(0.72-1.37)	43	1.48	(0.88-2.48)
Urinary tract cancer	154,262	794	1.03	(0.99-1.08)	334	1	301	0.93	(0.75-1.15)	159	1.34	(0.99-1.81)
Lymphoma	154,262	427	1.08	(1.01-1.15)	184	1	165	0.97	(0.72-1.29)	78	1.57	(1.01-2.44)
Skin melanoma	154,262	241	1.06	(0.98-1.14)	106	1	91	0.96	(0.65-1.40)	44	1.33	(0.77-2.31)
Skin, BCC	152,244	3,081	1.03	(1.01-1.05)	1,261	1	1,241	0.95	(0.86-1.05)	579	1.31	(1.12-1.53)
Skin, other	152,244	829	1.10	(1.05-1.14)	333	1	285	0.86	(0.70-1.07)	211	1.85	(1.39-2.47)
All cancers (excluding NMSC)	109,276	4795	1.04	(1.02- 1.06)	2,664	1	1,703	1.14	(1.05- 1.24)	428	1.29	(1.11- 1.79)
Colorectal cancer	109,276	854	1.03	(0.99- 1.08)	474	1	297	0.96	(0.79- 1.16)	83	1.36	(0.97- 1.91)
Upper GI tract cancer	109,276	227	0.98	(0.91- 1.05)	130	1	71	0.93	(0.64- 1.36)	26	1.02	(0.57- 1.82)
Lung cancer	109,276	803	1.07	(1.02- 1.12)	437	1	300	1.52	(1.22- 1.89)	66	1.27	(0.88- 1.82)
Prostate cancer	53,679	840	1.03	(0.98- 1.07)	430	1	319	1.08	(0.89- 1.31)	91	1.31	(0.94- 1.83)
Breast cancer	55,597	514	1.07	(1.01- 1.13)	305	1	173	1.23	(0.96- 1.57)	36	1.62	(1.12- 2.59)
Female genital cancer	55,597	168	1.10	(0.99- 1.22)	96	1	58	1.31	(0.85- 2.02)	14	2.05	(0.92- 4.57)
Urinary tract cancer	109,276	419	1.03	(0.97- 1.09)	217	1	157	1.16	(0.88- 1.53)	45	1.25	(0.79- 1.96)
Lymphoma	109,276	233	1.07	(0.99- 1.16)	124	1	85	1.09	(0.76- 1.58)	24	1.54	(0.81- 2.93)
Skin melanoma	109,276	129	1.08	(0.97- 1.21)	72	1	44	1.14	(0.69- 1.90)	13	1.44	(0.63- 3.28)
Skin, BCC	107,605	1613	1.04	(1.01- 1.07)	853	1	595	1.01	(0.89- 1.16)	165	1.36	(1.08- 1.72)
Skin, other	107,605	398	1.10	(1.04- 1.17)	203	1	137	0.96	(0.73- 1.27)	58	2.14	(1.36- 3.35)

BCC, basal cell carcinoma, CI confidence interval, GI gastrointestinal, HR hazard ratio, NMSC nonmelanoma skin cancer

[a] Total number in the analyses represents 109,276 incident low dose aspirin without cancer (excl. NMSC) before their first aspirin dispense (53,697 males and 55,597 females) An additional 1,671 subjects with NMSC before their first aspirin dispensing were excluded from the BCC and Skin, other analyses.

[b] Total number in the analyses represents 154,262 incident and prevalent low dose aspirin without cancer (excl. NMSC) before their first aspirin dispense (78,902 males and 75,360 females) An additional 2,018 subjects with NMSC before their first aspirin dispensing were excluded from the BCC and Skin/other analyses.

[c] Adjusted for age, sex, unique number of dispensings and unique number of hospitalizations in the year prior to start of follow up.

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Chapter 4.4

Non-steroidal anti-inflammatory drug use is not associated with keratinocytic cancer risk: results from a Dutch population-based cohort study

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Submitted

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ABSTRACT

Introduction: Preclinical and experimental studies show that cyclooxygenase (COX) inhibition by non-steroidal anti-inflammatory drugs (NSAIDs) may reduce the incidence of keratinocytic cancers. The objective of this study was to study the association between NSAIDs and incidence of keratinocytic cancers in the Dutch general population

Methods: All patients aged >18 years included in the linkage between the population-based PHARMO record linkage system (RLS) and the Eindhoven cancer registry (ECR) were included. Date of diagnosis of the first cutaneous squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) were obtained from the ECR. Date of dispense, duration, dose and type of NSAID of each NSAID dispense were obtained from the pharmacy database. Cox proportional hazard models with NSAID exposure as time-dependent covariate were used to calculate hazard ratios (HR) of BCC or SCC incidence with NSAID use (at least >1 year) compared to no use and short term use.

Results: This study included more than 40,000 NSAID users (at least >1 year) and 1.2 million non-users or short term users. Among all participants, 14,078 participants were newly diagnosed with BCC and 2,335 with SCC. Duration of NSAID exposure was not associated with an increased or decreased risk on SCC and BCC (adjusted HR per year NSAID use : SCC 0.96 95 % CI 0.89-1.04; adjusted HR BCC 0.94 95% CI 0.88-1.01). Comparable HR were observed after stratification for age and immunosuppressive drug use. Average defined daily dose (DDD) since first NSAID dispense did not modify the effect of NSAID duration.

Discussion: Prescription NSAID use was not associated with a decreased risk on either SCC or BCC in the Dutch general population.

INTRODUCTION

Skin cancer is becoming a large societal burden, with increasing incidence rates and, in 2010, already over 40,000 newly diagnosed patients in the Netherlands among 16 million inhabitants [1,2]. The incidence of keratinocytic cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]) increases steeply with 8 to 9% per year [2,3].

At least 36% of all keratinocytic cancer patients will develop one or more subsequent keratinocytic cancers [4,5]. Chemoprevention may be an alternative strategy to reduce the incidence of skin cancer among high risk individuals. Non-steroidal anti-inflammatory drugs (NSAIDs) are good candidates, because they may prevent other cancers as well [6]. NSAIDs inhibit the cyclooxygenase (COX) enzymes, which promote carcinogenesis in many cancers, including keratinocytic cancer [7]. COX inhibition may reduce the incidence of keratinocytic cancer [7-9]. Moreover, topical diclofenac (a NSAID) is approved for the treatment of actinic keratosis (AK), a precancerous lesion of SCC [10].

In this study we investigated whether duration of prescribed NSAID use (at least >1 year) was associated with a decreased incidence of skin cancer in the general population using a large and detailed community pharmacy database linked to a high quality population-based cancer registry.

METHODS

Setting

The study population included more than one million Dutch citizens who lived in the coverage area of both the Eindhoven cancer registry (ECR) and the PHARMO record linkage system (RLS)[11]. Briefly, the ECR is a population-based cancer registry in the South of the Netherlands covering 2.4 million inhabitants. The ECR is based on the automated pathological archive (PALGA), the national registry of hospital discharge diagnosis (LMR), hematology departments and radiotherapy institutions [12,13]. The ECR includes more than 98% of all newly diagnosed malignancies and more than 93% of all newly diagnosed skin cancers (SCC and melanoma)[14]. Completeness on newly diagnosed BCC is likely to be equal. A prior study in the ECR catchment area found that only 7% of subsequent BCC is not histologically confirmed [15]. As histology is more likely confirmed for first primary skin cancers, we expect that the histological confirmation of the first BCC is also at least 93%. PHARMO RLS is a network of patient databases, which covers a demographic region of more than 3 million inhabitants including community (out-patient) pharmacy data[11,13]. The community pharmacy database includes all pharmacy dispensed healthcare products on the Dutch market, prescribed by general practitioners or specialists, including NSAID dispensings. Over the counter (OTC) NSAID use is not included. Patients were followed over a long period of time; until they moved away from the

ECR-PHARMO catchment area, end of data collection of the specific community pharmacy, end of study period, or death, whichever occurred first. The date of death was obtained from the central bureau for genealogy (CBG), the local pharmacy or the hospital.

Study population

All citizens who lived in the ECR-PHARMO catchment area between 1 January 1998 and 31 December 2010 and were above 18 years were eligible (n=1,269,056). Participants were required to have a complete prescription history since the date of entry in PHARMO and at least 1 year of follow up to determine covariates (n=1,238,326). Patients with a record of invasive cancer (incl. nonmelanoma skin cancer [NMSC]) in the ECR or with a hospital discharge diagnosis for cancer or chemotherapy prior to 1998 were excluded (n=8,107). Patients above 100 years old at cohort entry were excluded (n=398) as registration may be less reliable in the very old.

Exposure to NSAIDs

Dispensings were selected based on the Anatomical Therapeutic Chemical (ATC) codes of the World Health Organization (WHO) collaborating centre for drug statistics methodology. Dispensings starting with 'M01A' or 'N02BB' were considered NSAIDs. Aspirin dispensings (ATC codes: B01AC06, B01AC08, B01AC30, N02BA01, N02BA15, N02BA51 and N02BA65) were considered NSAID dispensings, if the daily dosage was above 100 mg. Aspirin dispensings ≤100 mg were considered low dose aspirin dispensing for cardioprotection and were investigated as possible chemopreventive drug in a previous study [16]. To calculate the duration of each dispense, the number of dispensed pills was divided by the number of pills prescribed per day, as defined in the pharmacy data.

Keratinocytic cancer as outcome

The following morphology codes of the International Classification of Disease for Oncology (ICD-O3) combined with topography 'skin' were considered invasive cutaneous SCC: 8010, 8050-8084 (excluding 8077: intraepithelial neoplasia, 8080: Erythroplasia of Queyrat, 8081: Bowen disease, 8082: lympho-epithelial carcinoma). Morphology codes 8090 to 8110 combined with topography 'skin' were considered BCC. Date of diagnosis and stage (Tumour Lymph Node Metastasis (TNM) classification) were obtained from the medical records.

Covariates

Sex, socio-economic status, number of comorbidities and comedication use were considered potential confounders. An indicator of socio-economic status developed by Statistics Netherlands was used and categorized according to quintiles ranging from 1 (low) to 5 (high) [17]. As a proxy for comorbidities and the associated health care utilization the unique number of hospital discharge diagnosis (LMR) in the past year was determined [18,19]. The cumulative dura-

tion of frequently used comedication which may influence risk of skin cancer was determined and included low dose aspirin, statins, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), photosensitizing drugs and immunosuppressive drugs (Supplementary Table 1) [20-24].

Statistical analyses

We restricted the analyses to NSAID use for more than 1 year in order to differentiate between the "true" long term NSAID users and incidental NSAID users. The association between NSAID use (>1 year) and skin cancer was analysed by using a Cox proportional hazard (PH) model with cumulative drug use as a continues time-dependent covariate.[25] Age was used as underlying timescale because the risk of BCC and SCC is known to depend on age.

The relevant exposure window or an induction period for BCC and SCC is unknown. Therefore, we analysed NSAID exposure during different time periods with different lag times using age- and gender-adjusted models (Supplementary table 2) and chose the best fitting model based on Akaike's Information Criterion (AIC) for the final analyses. Duration of NSAID use with a lag time of 3 years was observed to be the best fitted model for SCC. The minimal AIC could not be determined in the BCC analyses. As conclusions did not differ between different exposure windows, the same exposure window as for SCC was chosen as a final model.

Those covariates (possible confounders) that changed the estimate by more than 10% in the bivariable analyses were included in the final model as time-dependent covariates. In addition, average DDD was included in the multivariable model as a time-dependent variable to assess the impact of duration independent of daily dose. Average DDD was calculated at each time point by dividing the cumulative DDD by the number of days since first NSAID dispense.

To check the PH assumption interaction terms with age (time scale) were tested. The PH assumption for BCC, but not SCC, was violated and therefore we calculated age-specific HR for BCC (< 70 years and ≥ 70 years). Interaction terms with NSAID duration and sex, average DDD and immunosuppressive drug use were included in the model to assess the impact of effect modification. Interaction between NSAID duration and immunosuppressive drug use was observed to be statistically significant for SCC and therefore we calculated separate HR for immunosuppressive drug users and non-users. All other interaction terms were not statistically significant.

Based on the earlier literature on different types of NSAIDs and the skin cancer risk, COX-2 inhibitors and photosensitizing NSAIDs were analysed as a separate group [8,9,24,26] (ATC codes: Supplementary Table 1). The low number of events among people who used COX-2 inhibitors for more than one year (14 SCC and 43 BCC), resulted in a lack of statistical power and therefore we do not show these results. In addition, as many studies suggest an effect of NSAID use of several years, we also provided a HR for more than 4 years of NSAID use. To address the possibility of ascertainment bias (i.e. NSAID users may more likely to be diagnosed

Table 1: Descriptives of NSAID users (>1 year) and the reference group (no use or < 1 year NSAID use)

	Reference (No NSAID use or < 1 year)		NSAID users(≥ 1 year)		p-value
N	1,186,830		42,973		
PATIENT CHARACTERISTICS					
Male sex (N, %)	548,278	(46)	14,910	(35)	< 0.001
Age at cohort entry (mean, SD)	44.8	(17.3)	56.1	(15.2)	< 0.001
Duration of follow up in years (mean, SD)	8.8	(3.4)	10.1	(2.6)	
Socio-economic status (N,%)					
low	151,713	(13)	5,042	(12)	< 0.001
low to average	230,441	(19)	10,346	(24)	
average	166,078	(14)	6,691	(16)	
average to high	281,718	(23)	9,589	(22)	
high	309,862	(26)	9,458	(22)	
unknown	47,018	(4)	1,847	(4)	
Unique number of hospital discharge diagnosis in the year prior to cohort entry					
0	1,088,278	(92)	35,787	(83)	< 0.001
1	80,744	(7)	5,563	(13)	
>1	17,808	(2)	1,623	(4)	
Comedication use during follow up (N, %)					
ACE inhibitors / angiotensin receptor blockers	179,625	(15)	16,279	(38)	< 0.001
Immunosuppressive drugs	8,839	(0.7)	4,311	(10)	< 0.001
Low dose aspirin (≤100mg daily)	143,964	(12)	13,939	(32)	< 0.001
Photosensitizing drugs	490,502	(41)	35,013	(82)	< 0.001
Statins	163,684	(14)	14,529	(34)	< 0.001
KERATINOCYTIC CANCER					
SCC (N, %)	2,158	(0.2)	177	(0.4)	< 0.001
BCC (N, %)	13,103	(1.1)	975	(2.3)	< 0.001
Age at skin cancer diagnosis (mean, SD)					
SCC	73.0	(11.8)	73.9	(11.0)	0.34
BCC	64.9	(12.4)	70.1	(11.5)	< 0.001
NSAID USE					
Cumulative duration during follow up (N,%)					
1 to 2 years			22,651	(52)	
2 to 4 years			12,695	(30)	
> 4 years			7,627	(18)	
Average DDD during follow up (N,%)					
< 1 DDD			9,590	(22)	
1 DDD			7,818	(18)	
> 1 DDD			25,565	(60)	

Abbreviations: ACE Angiotensin Converting Enzyme; BCC Basal Cell Carcinoma; SCC Squamous Cell Carcinoma

with KC than non-users) a sensitivity analysis was performed in NSAID users, comparing long term NSAID use (> 1 year) to short term NSAID use (≤ 1 year). All analyses were performed using SAS 9.2 statistical software (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and considered significant at the $p < 0.05$ level.

RESULTS

Study population

This study included more than 40,000 NSAID users (>1 year) and almost 1.2 million non-users or short term users (Table 1). Among all participants, 14,078 participants were newly diagnosed with BCC and 2,335 with SCC during follow-up. NSAID users were older and were more likely to be female and had a lower socio-economic status. The health care consumption was higher among NSAID users as indicated by the unique number of hospital discharge diagnosis and comedication use. More than 20,000 participants used NSAIDs for more than 2 years and more than 7,600 used NSAIDs for over 4 years. The average daily dosage of most NSAID users was above the DDD as recommended by the WHO for its main indication (analgesics). The study sample included 6,100 COX-2 inhibitor users (> 1 year) and 26,815 users of photosensitizing NSAIDs (> 1 year).

NSAIDs and SCC

The age and sex adjusted HR showed an increased risk of SCC with each additional year of NSAID use among people who have been exposed to NSAIDs for one year or more (Table 2). After adjusting for potential confounders, duration of NSAID use was no longer associated with SCC risk (adjusted HR per year NSAID use: 0.96 95 % CI 0.89-1.04). The HR of SCC differed between immunosuppressive drug users and non-users (Table 2). Immunosuppressive drug use was associated with a longer duration of NSAID use (3.5 years NSAID use compared to 2.5 years NSAID use, $p<0.001$). The correlation between duration of NSAID use and Immunosuppressive drug use was low (Pearsons $r = 0.18$), indicating that the increased risk per year of NSAID use was not due to a longer duration of immunosuppressive drug use.

NSAIDS and BCC

Among people who have been exposed to NSAIDs for one year or more, each additional year did not reduce the risk of BCC (adjusted HR per year NSAID use: HR 0.94 95% CI 0.88-1.01) (Table 2). Separate HR were estimated for young (<70 years) and elderly (≥70 years) to take the non-proportional hazards into account, but this stratification did not alter the estimates (Table 2).

Sensitivity analysis

Duration of photosensitizing NSAID use was not associated with an increased risk on SCC or BCC (HR per year photosensitizing NSAID use: SCC 0.94, 95% CI 0.85-1.04; HR BCC 1.00 95% CI 0.97-1.03).

NSAID use of four years or more was not associated either with a decreased risk of SCC or BCC (adjusted HR SCC 0.89 95% CI 0.53-1.51, adjusted HR BCC 0.87 95% CI 0.0.64-1.18),

Table 2: HR of keratinocytic cancer per year NSAID use

		Events in exposure group (N)	Sex adjusted HR (95% CI)[e]		Multivariable adjusted HR (95% CI)[e,f]	
SCC						
N in analyses:	1229338					
Total events:	2335					
Reference:	No use or < 1 year use		1		1	
Duration in years of:	*amongst:*					
All NSAIDs	All subjects[a]	71	1.10	(1.04 -1.15)	0.96	(0.89 -1.04)
All NSAIDs	Immunosuppresive drug non-users[b,g]	44	1.13	(1.04 -1.22)	1.00	(0.92 -1.09)
All NSAIDs	Immunosuppresive drug users[b,g]	27	1.29	(1.12 -1.49)	1.20	(1.04 -1.40)
Photosensitizing NSAIDs	All subjects[d]	48	1.12	(1.02 -1.23)	0.94	(0.85 -1.04)
BCC						
N in analyses:	1229315					
Total events:	14078					
Reference:	No use or < 1 year use		1		1	
Duration in years of:	*amongst:*					
All NSAIDs	All subjects[a]	286	1.06	(1.03 -1.08)	0.94	(0.88 -1.01)
All NSAIDs	subjects < 70 years[c]	109	1.06	(0.99 -1.13)	0.99	(0.94 -1.04)
All NSAIDs	subjects ≥ 70 years[c]	177	1.10	(1.05 -1.15)	0.94	(0.88 -1.01)
Photosensitizing NSAIDs	All subjects[d]	210	1.09	(1.04 -1.14)	1.00	(0.97 -1.03)

Abbreviations: BCC, Basal Cell Carcinoma; CI, Confidence Interval; HR, Hazard Ratio; N, Number; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; SCC, Squamous Cell Carcinoma

[a]Main analysis

[b]Stratified HR because of statistical interaction

[c]Stratified HR because of non-proportional hazards

[d]Sensitivity analysis

[e]Age was the timescale of the Cox proportional hazards regression.

[f]Adjusted for sex and time-dependent for: average DDD, unique number of hospitalization in the last year , duration of ACE inhibitors / angiotensin receptor blockers, immunosuppressive drugs, low dose aspirin (≤100mg daily), photosensitizing drugs and statins.

[g]To avoid overadjustment, duration of immunosuppressive drugs was not included in this multivariable model because of stratification on this variable

although the number of events among patients with more than 4 years of NSAID use was limited (14 SCC and 43 BCC). To control for the possibility of ascertainment bias of BCC and SCC among NSAID users, the association was also assessed in NSAID users. The HR was comparable to the main analysis (adjusted HR SCC 0.95 95% CI: 0.87-1.02; adjusted HR BCC 0.96, 95% CI: 0.92-1.00).

DISCUSSION

Our findings suggest that NSAID exposure does not reduce the incidence of keratinocytic cancer in the general population. NSAIDs are thought to interfere with the carcinogenesis of keratinocytic cancer by inhibiting the cyclooxygenase (COX) enzymes[7]. In the early phase of tumor development, COX-2 derived prostaglandines may stimulate proangiogenic factors, such as VEGF [27]. This suggests that NSAIDs may be an effective chemopreventive drug. Our results show, however, that in a population-based setting prescribed NSAID use was not associated with a decreased keratinocytic cancer risk. The possible protective effect was not masked by an increased risk due to possible photosensitization, as both photosensitizing NSAIDs were not associated with an increased risk of keratinocytic cancer. We observed an increased HR for SCC with NSAID use among immunosuppressive drug users. The correlation between duration of NSAID use and immunosuppressive drug use was low,indicating that it is unlikely that this increased risk was caused by an increased duration of NSAID use among long term immunosuppressive drug users. The increased risk may as well represent a change finding, caused by the low number of events in this stratified analysis (27 SCC amongst immunosuppressive drug users).

Our null results are similar to the findings of other observational studies, but contradict other epidemiological study results [28-31]. In the Nurses Health Study (NHS,) self-reported NSAID use (including OTC use) had no effect on melanoma, SCC and BCC development in relation to frequency, current or past use and duration of use of NSAIDS [30]. In the VATTC trial prescribed NSAID use was assessed among patients at high risk for developing keratinocytic cancer (at least 2 keratinocytic cancers in the face or ears in the past 5 years) [31] and showed no effect on the incidence of subsequent keratinocytic cancers. Moreover, the analyses were repeated with a time-fixed exposure covariate and a simulated null dataset, without a relation between outcome and exposure and observed that a time-fixed analyses of exposure could produce a spurious protective HR. This emphasizes the importance of a time-dependent analysis of exposure to prevent immortal time bias [32].

In contrast to our results, a decreased risk on skin cancer was found in other observational studies [33-35]. In a large population-based case-control study in Denmark, a decreased risk of SCC and melanoma but not for BCC was observed among ever users of NSAID [34]. The completeness of the cancer registry data on SCC and BCC in this study was only 60%. Due to

information bias, the HR may have been biased towards a protective association, if reporting of keratinocytic cancer was less likely among NSAID users, potentially because clinicians considered the reporting of other comorbidities more important among NSAID users. Results from two double-blinded randomized controlled trials showed that the use of celecoxib may reduce keratinocytic cancer size and incidence among high risk individuals (patients with a genetic predisposition or with multiple AKs) [8,9]. We could not assess the association between use of selective COX-2 inhibitors and keratinocytic cancer in the general population due to the low number of events amongst COX-2 inhibitor users (n=14). Aspirin is the most well-known NSAID and may reduce the incidence of many cancer types. In a prior ECR-PHARMO cohort study, we observed among more than 100,000 new low dose aspirin users (≤ 100 mg daily) no decreased risk of cancer in general or any of the site-specific cancers including melanoma, BCC and SCC [16].

An alternative explanation for the observed lack of a protective association is an increased ascertainment of skin cancer among NSAID users, which could have biased our results towards a HR of one. This is unlikely, because the specificity of the linkage in a random sample with at least one year follow up was as high as 99.5% [11]. In addition, assessment of the association in NSAID users only resulted in the same HR. Due to the observational design, our null findings could also be a result of residual confounding. We were able to adjust the analyses for important confounders, such concomitant medication use, health care utilization and socio-economic status. However, information on life style, behavioral factors and ultraviolet (UV) exposure were not available. If increased UV exposure was more likely among NSAID users, this could have resulted in too high HR. We deemed confounding by sun exposure unlikely to be a large source of bias as other observational studies in which risk estimates were adjusted for sun exposure also showed null results [28-31].

Strengths and limitations

The strengths of this study include the population-based setting, high-quality and complete cancer registry and pharmacy data, which facilitated a detailed and time-dependent analysis of duration, dosage, timing and type of NSAID exposure. All BCC and SCC in this study were histologically confirmed. The completeness of the cancer registry on skin cancer was estimated to be 93% [14,15]. The limitations of this study include the lack of information on OTC use and information on UV exposure. Non-differential misclassification of NSAID use, due to OTC use may have biased our results towards the null results. We attempted to reduce this bias by focusing on NSAID use for more than one year as this is more likely to be on prescription. Pharmacy data can give valid risk estimates of drugs, which are also available OTC, if the OTC prevalence in the population is 25% or lower [36]. We deemed it unlikely that the prevalence of OTC NSAID use for more than one year is higher than 25%, although no estimates of OTC NSAID use in the Netherlands are available. In addition, Asagari et al. observed that neither prescribed NSAIDs nor OTC NSAIDs were associated with a decreased SCC risk [29].

Further chemoprevention research should focus on populations, which are more likely to respond to NSAID use or should focus on more potent NSAIDs. The VATTC trial included a high-risk population (history of at least 2 KC), but also failed to show an effect of NSAIDs in general [31]. Other trials in high risk individuals using celecoxib did show an effect, suggesting that a high risk population may be served by using selective COX-2 inhibitors [8,9]. For SCC it was observed, that a possible protective effect of aspirin may be greater in tumors with PTCH loss or altered p53 [33]. Chemoprevention of recurrence or subsequent keratinocytic cancer (i.e. secondary prevention) may be more effective in patients with PTCH loss or p53 alterations. Future research should aim to identify tumor or patient characteristics to target chemoprevention to a subpopulation of patients, which are most likely to respond the preventative therapy.

Conclusion

NSAIDs do not seem to be effective chemopreventive drugs for keratinocytic cancer in the general population. Our results do not rule out the possibility that specific types of NSAIDs may be effective as secondary prevention intervention in high risk populations, such as patients with multiple AKs or priors keratinocytic cancers. Further research on NSAIDs should focus on high risk individuals and specific types of NSAIDs.

Acknowledgements

We thank both the Eindhoven Cancer Registry (ECR) and the PHARMO institute for drug outcomes research for their dedicated data collection and the availability of their data on favorable terms.

Supplementary Table 1: ATC codes

Medication	ATC code	Description
Comedication		
Photosensitizing drugs		Cardiac drugs
	C01BD01	Amiodarone
	C01BA01, C01BA51, C01BA71	Quinidine (and combinations)
	C08CA	Calcium antagonists Dihydropyridine derivates
		Antidiabetics
	A10BB, A10BC	Sulfonylurea derivates used in diabetes mellitus
		Antipsychotica
	N05AD01	Haloperidol
	N05AA01	Chlorpromazine
	N05AA, N05AB, N05AC	phenothiazines
		Antibiotics
	J01AA	Tetracyclines
	J01MA	Fluoroquinolones
	J01EB, J01EC, J01ED, J01EE, A07AB	Sulfonamides (and combinations (EE))
		Antimalarial drugs
	P01BA	aminoquinoline
	P01BC	methanolquinolines
		Diuretica
	C03C, C03EB	High-ceiling diuretics and combinations
	C03A, C07B, C07D, C03AE	Thiazides en combinaties
	C03DB01	Amiloride
	C03DA01	Spironolactone
Immunosuppresive drugs	L04A	Immunosuppressants
Statins	C10AA	HMG CoA reductase inhibitors, plain
	C10BA, C10BX	HMG CoA reductates inhibitors, combinations
ACE inhibitors en Angiotensin Receptor Blockers	C09A	ACE inhibitors, plain
	C09B	ACE inhibitors, combinations
	C09C	Angiotensin II antagonists, plain
	C09D	Angiotensin II antagonists, combinations
Low dose Aspirin	(B01AC06, B01AC08, B01AC30, N01BA01, N01BA15, N01BA51, N01BA65) AND daily dosage <100 mg	Aspirin

Supplementary Table 1: (Continued)

Medication	ATC code	Description
Type of NSAID		
COX-2 inhibitors	M01AH	COX-2 inhibitors
Photosensitizing NSAIDs		
	M01AA01	Phenylbutazone
	M01AB01	Indometacin
	M01AB02	Sulindac
	M01AB05	Diclofenac
	M01AC01	Piroxicam
	M01AE	Propionic acid derivates
	M01AG01	Mefenamic acid
	M01AX01	Nabumetone
	N02BA11	Diflunisal

ACE, angiotensin converting enzyme; ATC, anatomical therapeutic chemical HMG coA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; NSAID, nonsteroidal anti-inflammatory drugs

Supplementary Table 2: Timing of NSAID exposure

	SCC			BCC		
		N:	1,229,338		N:	1,229,315
		Events:	2,335		Events:	14,078
	Events in exposure category (N)	HR[a]	95% CI	Events in exposure category (N)	HR[a]	95% CI
0-12 years before diagnosis (all cumulative exposure)	121	1.10	(1.04 -1.15)	536	1.06	(1.03 -1.08)
0 - 4 years before diagnosis	76	1.08	(0.98 -1.19)	353	1.06	(1.01 -1.11)
4 - 8 years before diagnosis	42	1.19	(1.04 -1.35)	174	1.10	(1.03 -1.17)
8 - 12 years before diagnosis	17	1.45	(1.19 -1.76)	57	1.23	(1.09 -1.38)
1 year lagtime	101	1.11	(1.05 -1.17)	446	1.07	(1.04 -1.10)
2 years lagtime	85	1.13	(1.06 -1.20)	371	1.08	(1.04 -1.11)
3 years lagtime	71	**1.15**	**(1.08 -1.24)**	286	1.08	(1.04 -1.13)
4 years lagtime	56	1.18	(1.08 -1.28)	223	1.09	(1.05 -1.15)
5 years lagtime	41	1.20	(1.09 -1.33)	161	1.10	(1.04 -1.17)

Abbreviations: AIC Akaike's Information Criterium; BCC Basal Cell Carcinoma; CI, Confidence Interval; HR, Hazard Ratio; N, Number; SCC, Squamous Cell Carcinoma

Numbers in bold represent the minimal AIC.

[a] Age was the timescale of the Cox proportional hazard regression and analyses were adjusted for sex

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Chapter 4.5

β-blocker use and all-cause mortality of melanoma patients: results from a population-based Dutch cohort study

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European Journal of Cancer. Aug 2013, accepted for publication

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ABSTRACT

Background: Results from preclinical and observational studies suggest that β-adrenoreceptor inhibition might influence disease progression of melanoma.

Patients and methods: Patients ≥18 years with cutaneous melanoma (Breslow thickness >1 mm) registered in the Eindhoven Cancer Registry between January 1, 1998 and December 31, 2010, who were also registered with PHARMO record linkage system (RLS), were eligible. Randomly selected patients using β-blockers from PHARMO record linkage system (RLS) matched on age and gender served as a control cohort. Adjusted time-dependent and time-fixed Cox proportional hazard models were employed to estimate the hazard ratio of all-cause mortality. 5-year relative survival rates for all-cause mortality were calculated to estimate disease specific survival.

Results: 203 of 709 eligible patients used β-blockers after melanoma diagnosis. The use of β-blockers was not associated with the risk of dying (adjusted HR 0.82, 95% CI 0.55-1.24). Neither duration of exposure nor β-blocker dosage showed significant influence on survival. 5-year relative survival for β-blocker users was lower than in non-users amongst melanoma patients (80.9% and 83.7%, respectively) but higher among the β-blocker control group compared to the general population (101.4%).

Conclusion: Our results do not show a statistically significant impact of β-blocker exposure on overall survival of melanoma patients, regardless of the timing, duration or dosage of β-blocker use.

INTRODUCTION

With the development of immunomodulating drugs and targeted therapies for metastastic melanoma, treatment options for disseminated melanoma have finally emerged [1-4]. However, only a small subset of patients responds to the immune modifiers, not all patients harbour mutations that are (yet) targetable and secondary resistance is a problem. Alternative pathways as starting points for the suppression of melanoma progression therefore need to be investigated.

Observational studies showed a protective effect of incidental use of β-blockers, a widely used substance class for the treatment of primarily cardiovascular diseases, for the progression of several cancers [5-9]. Animal models of ovarian and breast cancer suggest that activation of β-adrenergic receptors can influence the growth and dissemination of tumour cells [10,11]. The presence of β-adrenoreceptors on primary and metastatic melanoma cell lines has been confirmed [12] and putative modes of β-blocker action include inhibition of angiogenesis via down-regulation of VEGF [13] and reduced expression of MMP2 and 9 [12], inhibition of migratory activity in carcinoma cells [14] and induction of apoptosis [15].

Two recent independent studies demonstrated reduced disease progression [8] and increased survival time [5] for melanoma patients with β-blocker use. One study was based on a very small number of patients (30 β-blocker users, 91 untreated patients) leading to limited statistical power [8]. The larger study used only pre-diagnostic exposure data (intention-to-treat analysis) [5], whereas one may expect β-blockers to influence the metastatic process also after diagnosis. Total duration and daily dosage of β-blocker exposure was not considered in either study and β-blocker exposure during follow-up was investigated as a time-fixed covariate possibly introducing an immortal-time bias in the smaller study [8].

We found these initial findings intriguing and decided to investigate the effect of β-blockers on overall survival in melanoma patients in a large population-based cohort study in the Netherlands using data from the Eindhoven Cancer Registry (ECR) and the PHARMO Record Linkage System (RLS). We hypothesized that β-blocker use after melanoma diagnosis would result in improved survival. Sensitivity analyses using different exposure definitions were conducted to assess the effect of timing of β-blocker use.

PATIENTS AND METHODS

Setting

Data from the linkage between the ECR and the PHARMO RLS was used to obtain high quality and complete information on β-blocker exposure and melanoma diagnosis [16]. Briefly, the ECR is a population-based cancer registry in the South of the Netherlands covering 2.4 million inhabitants. The ECR includes more than 95% of all newly diagnosed malignancies [17] and is

based on pathology reports and patients´ medical records and encompasses comprehensive tumour details, patient characteristics, comorbidities at diagnosis and treatment received directly after diagnosis. Vital status until December 31, 2010 was available through linkage with the Dutch municipal records.

PHARMO RLS is a network for patient databases covering a demographic region of three million inhabitants [16]. The central patient database is linked to more than ten databases [18] and includes e.g. community pharmacy data (out-patients only). The community pharmacy database includes all pharmacy dispensed healthcare products on the Dutch market prescribed by medical practitioners. Previous studies demonstrated that drug dispensing records in PHARMO RLS are virtually complete with regard to prescription drugs [19,20]. The overlapping PHARMO-ECR catchment area includes one million inhabitants. Patients were followed either until they moved away from the PHARMO-ECR catchment area, end of data collection of the specific community pharmacy or end of study or death, whichever occurred first.

Study population

Data of patients ≥18 years registered in the ECR with a diagnosis of invasive melanoma between January 1, 1998 and December 31, 2010 who were also registered in PHARMO RLS at the time of melanoma diagnosis were retrieved (N=1,810).

As information on the cause of death was not available and as tumour progression and subsequently melanoma-specific death is rare among patients with thin primary melanomas (≤ 1mm) [21], we included only patients with thick melanomas (>1mm, n=791). Patients were divided into categories using Breslow tumour thickness (1.01-2.0mm, 2.01–4.0mm and >4.0 mm).

To correct for the different survival of β-blocker users compared to the general population, a control cohort of 1210 randomly selected β-blocker users of the PHARMO RLS cohort matched on age, gender and index date in a 1:10 ratio to the melanoma patients with β-blocker use was constructed. The date of melanoma diagnosis was assigned to the matched controls and used as their index date (i.e. the date of melanoma diagnosis of the melanoma patient had to be within the follow-up time in PHARMO RLS of the matched control). The date of death of the matched β-blocker users was obtained from the central bureau for genealogy, the local pharmacy or the hospital.

Patients and controls were required to have at least one year of follow-up with PHARMO RLS prior to melanoma diagnosis or index date, respectively, to determine potential confounders and drug exposure in the year prior to diagnosis. Study follow-up began with the date of melanoma diagnosis in the melanoma cohort and with the index date for the matched cohort.

Definition of β-blocker use

Dispensings with the anatomical therapeutical chemical (ATC) code group C07 of the WHO Collaborating Centre for Drug Statistics Methodology (Table 1) were considered β-blocker dis-

pensings. β-blockers are classified as β1-selective or non-selective $\beta_1/_2$-antagonists depending on their affinity to the β-adrenoreceptor subtypes. The majority of β-blockers prescribed for cardiovascular diseases nowadays are β1-selective. The duration of each dispense was calculated by dividing the amount of dispensed drug by the number of pills prescribed per day as defined in the pharmacy data. In case of overlap of two dispensings, the number of overlapping days was added to the dispensing duration of the second dispensing. The defined daily dose system (DDD) of the WHO [22] was used to compare the dosage of different types of β-blockers. To calculate the DDD equivalent used by an individual patient, the amount of pills dispensed was multiplied by the corresponding dosage per pill and divided by the DDD.

Potential confounders

Age at diagnosis, gender, tumour specific data and comorbidities were considered potential confounders (s. Table 2). The number of distinct medication classes dispensed (unique ATC codes) and unique hospital admissions in the year prior to diagnosis as a proxy of general morbidity as well as a proxy of health-care- and pharmacy-seeking behaviour were also considered potential confounders [23]. All covariables are listed in Table 2.

Analyses were stratified by the different covariables for potential interaction. None of these covariables showed significant statistical interaction with β-blocker use and were therefore not considered effect modifiers.

Table 1: ATC codes of all dispensed β-blockers

Drug name	ATC code	Non selective	β_1 selective	Number of dispensings	% of total
Acebutolol	C07AB04		X	80	1.3
Atenolol	C07AB03		X	1469	23.4
Bisoprolol	C07AB07		X	973	15.5
Carvedilol	C07AG02	X		24	0.4
Celiprolol	C07AB08		X	0	0.0
Labetalol	C07AG01	X		71	1.1
Metoprolol	C07AB02		X	2645	42.1
Nebivolol	C07AB12		X	101	1.6
Oxprenolol	C07AA02	X		49	0.8
Pindolol	C07AA03	X		88	1.4
Propranolol	C07AA05	X		184	2.9
Sotalol	C07AA07	X		599	9.5
Total				6283	100.0

Frequency and ATC codes of β-blocker types dispensed for all β-blocker patients after melanoma diagnosis (83.9% β_1-selective). ATC C07 stands for β-blocking agents used for cardiovascular diseases.

Abbreviations

ATC, Anatomical Therapeutic Chemical classification system.

Table 2: Patiënt and tumour characteristics

Characteristics	Ever β-blocker user after diagnosis (*N*=203)[a]	non-users (*N* =506)[b]	*p*[c]
Gender			0.92
Male	106 (52.2%)	262 (51.8%)	
Female	97 (47.8%)	244 (48.2%)	
Age[d]			
Years, median (IQR)	67 (59-77)	59 (46-71)	<0.001
Time of FU			
Years, median (IQR)	3.7 (1.9-6.2)	2.8 (1.2-5.2)	0.002
Number of deaths			
N (%)	50 (24.6%)	109 (21.5%)	0.37
Histological subtype			
SSM	104 (51.2%)	244 (48.2%)	0.42
NMM	48 (23.6%)	129 (25.5%)	
LMM	6 (3.0%)	6 (1.2%)	
ALM	1 (0.5%)	6 (1.2%)	
Others	44 (21.7%)	121 (23.9%)	
Body site of the melanoma			
Head and neck	33 (16.3%)	78 (15.4%)	0.89
Trunk	70 (34.5%)	186 (36.8%)	
Upper extremity	44 (21.7%)	99 (19.6%)	
Lower extremity	56 (27.6%)	143 (28.3%)	
Tumour thickness			
>=1,01 and <= 2	99 (48.8%)	271 (53.6%)	0.15
>=2,01 and <=4	61 (30.0%)	158 (31.2%)	
>=4,01	43 (21.2%)	77 (15.2%)	
Nodal metastases[d]			
N (%)	25 (12.3%)	79 (15.6%)	0.26
Distant metastases[d]			
N (%)	2 (1.0%)	13 (2.6%)	0.25
Comorbidities[d]			
N (%)	119 (58.6%)	148 (29.2%)	<0.001
Hypertension	64 (31.5%)	51 (10.1%)	<0.001
Heart diseases	55 (27.1%)	42 (8.3%)	<0.001
Cancer	34 (16.7%)	55 (10.9%)	0.08
Stroke	12 (5.9%)	6 (1.2%)	0.001
Diabetes	11 (5.4%)	31 (6.1%)	0.38
Lung diseases	7 (3.4%)	27 (5.3%)	0.20
Gastrointestinal diseases	6 (3.0%)	9 (1.8%)	0.29

Table 2: (Continued)

Characteristics	Ever β-blocker user after diagnosis (*N*=203)[a]	non-users (*N* =506)[b]	*p*[c]
Unique hospitalizations[e]			
no admissions	157 (77.3%)	437 (86.4%)	0.01
1 admission	35 (17.2%)	51 (10.1%)	
>1 admission	11 (5.4%)	18 (3.6%)	
Unique ATC codes[e]			
0 ATC codes	12 (5.9%)	100 (19.8%)	<0.001
1-3 ATC codes	58 (28.6%)	208 (41.1%)	
>3 ATC codes	133 (65.5%)	198 (39.1%)	

Abbreviations

ATC, Anatomical Therapeutic Chemical classification system; FU, follow-up; IQR, interquartile range; *N*, total number of patients.

[a]Patients who filled in a β-blocker dispensing after diagnosis of melanoma.

[b]No dispensings for β-blocker filled in after diagnosis of melanoma.

[c]*p*-values based on 2-sided x2 test or Fisher´s exact test for categorical variables, 2-sided t-test for numerical values.

[d]At the time of initial melanoma diagnosis.

[e]In the year prior to diagnosis.

Statistical analysis

X^2-tests and Fisher´s exact tests were used to test for differences between categorical variables, for continuous variables a Student´s *t*-test was used. The association between β-blocker use and melanoma survival was analysed by using a Cox proportional hazard (PH) model. We calculated that at least 631 patients were needed to detect a hazard ratio (HR) of 0.80 with 80% power and an alpha-level of 0.05 (stpower cox function of STATA [StataCorp. 2011. College Station, TX: StataCorp LP]),

β-blocker use (binary variable: β-blocker user yes/no) was analysed as a time-dependent variable with time since diagnosis as the underlying timescale. In this analysis, patients were considered β-blocker users from the time of first β-blocker dispense and non-users before their first dispense. If the patients had filled in a β-blocker dispensing within 90 days prior to melanoma diagnosis and used β-blockers at the time of melanoma diagnosis, they were classified as β-blocker users since time=0. Duration and dosage of β-blocker were analysed by using a Cox PH model with cumulative drug use as a time-varying determinant [24]. In these analyses, the number of cumulative days of β-blocker use of the subject with the event of interest is compared with the cumulative β-blocker use of all other subjects at the same time point. To check the PH-assumption, time interval specific hazard ratios (HR) were calculated, showing that the PH-assumption was violated for duration only. We therefore stratified the duration analyses into time-periods with PH.

As gender and age are strongly associated with melanoma survival differences [25], and are also related with β-blocker use, all analyses were adjusted for age and sex. Variables which

influenced the age and sex-adjusted HR by more than 10% were considered potential confounders, but none of the variables met this criterion.

To be able to address the excess mortality due to melanoma in the absence of cause of death information, we used five year relative survival rates for all-cause mortality. These were calculated as the absolute survival rate divided by the expected survival rate in the period of diagnosis from the general population with the same sex and age structure [26,27]. They were calculated independently for the melanoma patients with and without β-blocker use as well as for a control cohort (randomly selected β-blocker users from PHARMO-RLS) allowing comparisons between the two melanoma groups as well as the control cohort and the general population. To prevent immortal time bias of chronic β-blocker use after diagnosis, chronic β-blocker use was assessed before diagnosis [28]. Patients with ≥ two dispensings within one year prior to melanoma diagnosis and β-blocker use at the time of melanoma diagnosis were considered chronic β-blocker users in the relative survival analyses.

All statistical tests were two-sided with a rejection of the null hypothesis at $p<0.05$. Analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA) and SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Sensitivity Analyses

Sensitivity analyses were conducted to examine how a different exposure definition (before melanoma diagnosis and before and after melanoma diagnosis) influences the observed HR of the main analysis. In these exploratory analyses, β-blocker use was analysed as a time-fixed variable.

In the first sensitivity analysis, chronic β-blocker use was defined as a minimum of two dispensings within one year prior to melanoma diagnosis and β-blocker use at the time of melanoma diagnosis. The second sensitivity analysis comprised patients with a minimum of three dispensings within the year preceding melanoma diagnosis and 6 months after, β-blockers had to be dispensed at least twice before melanoma diagnosis and once after. In this analysis, patients with <6 months follow-up in PHARMO RLS after diagnosis were excluded to prevent bias.

RESULTS

Study population

Of the 709 eligible melanoma patients who were registered with ECR-PHARMO RLS, 203 (28.6%) used β-blockers after melanoma diagnosis (Figure 1, Table 2).

Compared with the non-users, β-blocker users were significantly older (67 years vs. 59 years, $p<0.001$) and had a significantly longer follow-up time (median of 3.7 years, interquartile range [IQR] 1.9-6.2 vs. median of 2.8 years, IQR 1.2-5.2; $p=0.002$). Neither tumour thickness

nor nodal or distant metastasis status differed significantly between groups (Table 2). As expected, comorbidities were more prevalent in the β-blocker user group (58.6% vs. 29.2%, p<0.001) and β-blocker users had a higher number of unique hospitalizations (p=0.01) and unique ATC codes (p<0.001).

Patient and tumour characteristics of the cohorts used for the two sensitivity analyses were very similar and presented in supplementary table S1.

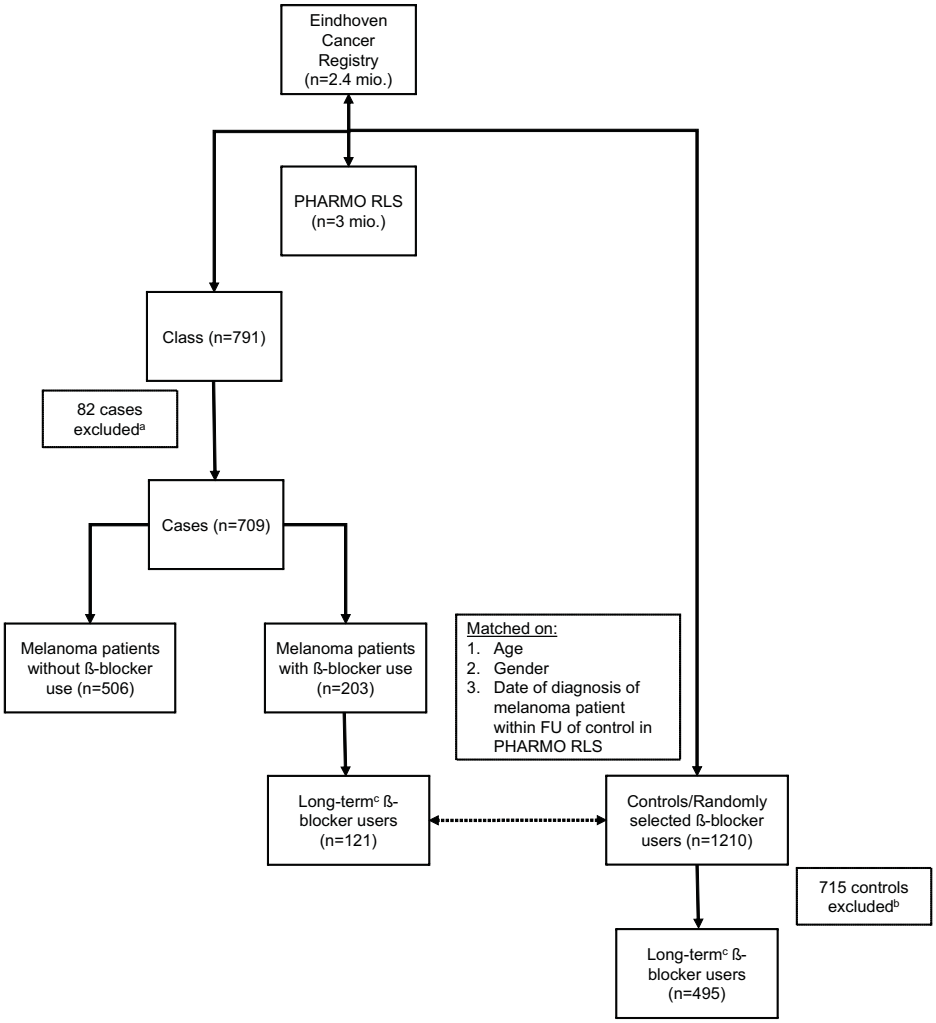

Figure 1: Study population selection and matching.

[c]≥2 β-blocker dispensings in the year prior to and β-blocker use at the time of melanoma diagnosis.

Abbreviations

ECR, Eindhoven Cancer Registry; FU, follow-up; RLS, Record Linkage System.

Of the 1210 individuals selected as matched controls, 495 met the inclusion criteria (one year follow up prior to index date, ≥two β-blocker dispensings and use at time of index date).

β-blocker use and hazard ratios (HR) of all-cause death

Metoprolol (42.1%) was the most often prescribed β-blocker in all patients, 83.9% of all dispensed β-blockers were β_1-selective.

β-blocker use was not significantly associated with a reduction of the hazard of death in the time-dependent analysis (adjusted HR 0.82, 95% CI 0.55-1.24), (Table 3). In the time-fixed analyses (sensitivity analyses), HR for the crude data as well as the adjusted data yielded similar results (sensitivity analysis 1: HR 0.85, 95% CI 0.57-1.28; sensitivity analysis 2: HR 0.89, 95% CI 0.58-1.36).

Neither the duration of β-blocker exposure nor the amount of cumulative DDDs changed the HR significantly (Table 4). However, a trend for a decreased hazard of death was seen with increasing amounts of DDDs.

Relative survival analyses

The 5-year crude survival of melanoma patients was higher for non-users than for β-blocker users (74.0% vs. 67.3%) as expected due to the older age of the β–blocker user group. However, also 5-year relative survival, which takes age and gender adjustments into account, was in favour of non-users, albeit differences were small and non-significant (83.7% vs. 80.9%, p=0.47, Table 5). For the matched controls (randomly selected β-blocker users), the 5-year relative survival rate was marginally above that of the general population with the same age and sex structure (101.4%; 95% CI 95.2-107.6).

Table 3: Cox proportional hazard ratios (HR) for all-cause mortality for the β-blocker users

	Crude HR	95% CI	Adjusted HR[d]	95% CI
Non-user	1		1	
β-blocker user after melanoma diagnosis (time-dependent) (*N*=203)[a]	1.28	0.86-1.90	0.82	0.55-1.24
Sensitivity Analysis 1: Chronic β-blocker user before diagnosis (time-fixed) (*N*=120)[b]	1.30	0.87-1.93	0.85	0.57-1.28
Sensitivity analysis 2 Chronic β-blocker user before and after diagnosis (time-fixed) (*N*=113)[c]	1.33	0.88-2.01	0.89	0.58-1.36

Abbreviations

CI, confidence interval; HR, hazard ratio.

[a]β-blocker dispensing within 90 days to melanoma diagnosis and use at time of melanoma diagnosis and/or β-blocker use after diagnosis. Time-dependent analysis.

[b]Min. 2 dispensings for β-blocker within 1 year prior to melanoma diagnosis and use at time of melanoma diagnosis. Time-fixed analysis.

[c]Min. 2 prescriptions for β-blocker within 1 year prior to melanoma diagnosis and min. 1 dispensing within 6 months after melanoma diagnosis. Time-fixed analysis.

[d]Only adjusted for age and sex as no other variable showed to be an effect modifier or confounder.

DISCUSSION

Our results do not show a statistically significant impact of β-blocker exposure on overall survival of melanoma patients, regardless of the timing, duration or dosage of β-blocker use. However, the direction of the main results (HR 0.82 (95% CI 0.51-1.24) was consistent with the Danish findings [5].

Epidemiological and preclinical studies have associated activation of β-adrenergic signalling and release of the adrenergic neurotransmitters epinephrine and norepinephrine with cancer progression and promotion of metastasis [29]. These findings led to pharmacoepidemiological studies investigating the association between the use of β-adrenergic blocking agents and disease progression in several cancers. Especially in breast cancer, a reduced risk of metastasis development and breast-cancer specific mortality has been described [9].

Table 4: Cox proportional hazard ratios (HR) for all-cause mortality for duration and dose of β-blocker use after melanoma diagnosis

	Crude HR	95% CI	Adjusted HR[a]	95% CI
DURATION				
HR per additional year of BB use				
Non-user	1		1	
0-2 years after melanoma diagnosis	1.11	0.96-1.79	0.78	0.48-1.27
>2 years after melanoma diagnosis	1.06	0.92-1.22	0.96	0.82-1.11
HR per exposure category				
0-2 years after melanoma diagnosis				
Non-user	1		1	
0-2 years	1.13	0.68-1.87	0.77	0.46-1.28
>2 years	n.a.		n.a.	
>2 years after melanoma diagnosis				
Non-user	1		1	
0-2 years	1.92	1.17-3.13	1.33	0.81-2.19
>2 years	1.49	0.56-3.95	1.00	0.38-2.68
DOSAGE				
Non-user	1		1	
HR per additional 100 DDD	1	0.99-1.01	1	0.98-1.01
HR per DDD category				
Non-user	1		1	
1-600 DDD	1.79	1.13-2.84	1.30	0.81-2.09
601-2000 DDD	1.55	0.95-2.54	0.95	0.58-1.58
>2000 DDD	0.89	0.45-1.79	0.66	0.32-1.32

Abbreviations

CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; n.a., not applicable.

[a]Only adjusted for age and sex as no other variable showed to be a confounder

Table 5: 5-year crude and relative survival rates for β-blocker users, non-users and the matched control cohort

	5-year crude survival (%)	95% CI	p^a	5-year relative survival (%)	95% CI	p^a
Melanoma patients[b]						
β-blocker user (*N*=120)	67.3	56.3-78.6	Referent	80.9	76.0-85.6	Referent
Non-user (*N*=589)	74.0	69.6-78.8	0.20	83.7	70.5-96.9	0.47
Matched control cohort[c]						
β-blocker user (*N*=495)	79.6	74.8-84.4	n.a.	101.4	95.2-107.6	n.a.

Abbreviations: CI, confidence interval; n.a., not applicable.

[a]Log-rank test for crude survival, set-test for proportions for relative survival.

[b]Chronic β-blocker users. Min. 2 dispensings for β-blocker within 1 year prior to melanoma diagnosis and use at time of melanoma diagnosis.

[c]Control cohort of β-blocker users without melanoma diagnosis matched on age and gender.

Phase II clinical trials assessing the safety and efficacy of β-blockers in colorectal and ovarian cancers are underway (NCT00888797, NCT01308944).

In melanoma cell lines, catecholamines were shown to enhance the secretion of VEGF, MMP-2 and MMP-9 [12,30] and to upregulate the expression of interleukins (IL) 8 and 6 [12] thus promoting angiogenesis and metastasis. As β-adrenoreceptors are present on primary and metastatic melanoma cells [12] and as propranolol, a non-selective β-blocker, was shown to inhibit norepinephrine-dependent stimulation of VEGF, IL-8 and IL-6 gene expression, a beneficial effect of β-blockers has also been hypothesized in melanoma.

To this stage, however, it is still unknown how the *in vitro*-findings can be translated into the *in vivo*-situation. There is no consensus on the timing, duration or dosage of the β-blocker needed to exert an antitumoural effect should such an effect exist. This is reflected by the different definitions of β-blocker use employed in the various studies. In the Danish study, patients were termed β-blocker users if they used β-blockers prior to tumour diagnosis [5], in the Italian study only if β-blockers were used after diagnosis [8]. We considered β-blocker use >1 year prior to melanoma diagnosis as well as a very short duration (<90 days) of β-blocker exposure unlikely to have a significant effect on tumour progression. Different exposure timings were accounted for in our study by using different definitions of β-blocker exposure in the main and sensitivity analyses, none of which were significantly associated with a decreased risk of death with very similar adjusted HR ranging from 0.82-0.89 (Table 3).

Immortal-time bias can occur when drug exposure, which varies during follow up, is treated in the analyses as if all drug exposure during follow up was already known at diagnosis [28,31]. This might explain why a protective effect of β-blocker use after melanoma diagnosis was found in the Italian study [8].

We tried to assess for dosage by using DDDs and stratifying into different exposure groups. There was no linear relationship with dosage, the HR improved with larger amounts of cumulative DDDs (>2000 DDD) but did not reach statistical significance. It is possible that the β-blocker dosage needed for an antitumoural effect is higher than the dosage given for car-

dioprotection. The number of β-blocker users with these high cumulative dosages may have been too small in our sample to find a significant effect. However, if such high cumulative dosages are needed for a protective effect on melanoma progression, their clinical usefulness is very limited. Previous studies [5,8] in melanoma patients did not consider dosage therefore no comparisons can be made.

The results of the 5-year survival analyses support our findings; the relative survival rate of β-blocker users with melanoma was even slightly lower than of the non-users with melanoma (80.9% vs. 83.7%, respectively). In comparison, the matched cohort of randomly selected β-blocker users without melanoma had a relative survival superior to the general population (101.4%). This is in concordance with previous studies, which showed that β-blockers in general improve overall survival, most likely because of their cardioprotective effects [32].

This study has several strengths. It is based on prospectively collected data from two large, nationally representative and linked cancer- and prescribing-databases. Detailed information on patient demographics, patient outcomes, tumour characteristics and, importantly, dose, duration and timing of β-blocker exposure was available from these databases. Several limitations have to be mentioned. Firstly, the cause of death was unknown, therefore only all-cause mortality could be assessed. However, if only melanoma-related deaths are evaluated there is always a risk of omitting deaths due to melanoma if e.g. no cause of death was documented or another cause of death was wrongly assumed. Additionally, with the inclusion of a matched cohort of randomly selected patients who used β-blockers, we were able to demonstrate that relative survival of β-blocker users is better than the general age- and gender-matched population, the lower 5-year survival rate in melanoma patients with β-blocker use can therefore not solely be attributed to an increased death risk due to the cardiovascular comorbidities. Lastly, one has to discuss the relevance of improved melanoma-specific survival if it doesn´t result in an overall survival benefit as was seen in the Danish study [5].

Some preclinical studies suggest that non-selective β-blockers exert greater effects in breast and ovarian cancer cell lines than β_1-selective agents [10,33]. Due to the low dispensing rate of non-selective β-blockers, we could not investigate the effect of β_1-selective versus non-selective $\beta_{1/2}$-antagonists. As neither metoprolol nor atenolol, the most commonly prescribed β-blockers, are totally β_1-specific and both partially inhibit β_2-adrenergic receptors as well [34], we did not expect a great difference between the two groups. Additionally, melanoma cell lines express both β_1- and β_2-receptors [12]. It is possible, however, that similar to the different mutation patterns there are differences in the expression of β-adrenergic receptors in the melanoma subtypes resulting in different effects of the β-blockers.

The study was non-randomized; residual confounding can therefore not be excluded.

In conclusion, our data did not show a significant beneficial effect of β-adrenergic inhibiting drugs on survival of melanoma patients. Epidemiological studies with even larger patient numbers or a meta-analysis of smaller, comparable datasets, are required to have enough power for investigating the effect of large cumulative dosages as well as selective versus non-

selective β-blockers and should focus on determining the timing and the dosage of β-blocker susceptibility of melanoma cells. A possible approach would be to pool data from different countries, which also have access to linked cancer and pharmacological registries to achieve higher patient numbers. In our view, the currently available data is not sufficiently convincing to justify randomized clinical trials in melanoma patients as was proposed recently [35].

Acknowledgements

We would like to thank Mieke Aarts and her colleagues from the Eindhoven Cancer Registry and Josine Kuiper and her colleagues from the PHARMO RLS for their dedicated data collection, data processing and data linkage.

Table S1- Supplemental table (online only): Patient and tumour characteristics of the 2 sensitivity analysis divided by different β-blocker treatment status.

Characteristics	β-blocker user cohort 2 Chronic user before diagnosis (*N*=120)[a]	non-users (*N*=589)[b]	*p*[c]	β-blocker user cohort 3 Chronic user before and after diagnosis (*N*=113)[d]	non-users (*N*=533)[b]	*p*[c]
Gender			0.46			0.46
Male	66 (55.0%)	302 (51.3%)		62 (54.9%)	272 (51.0%)	
Female	54 (45.0%)	287 (48.7%)		51 (45.1%)	261 (49.0%)	
Age at index date						
Years, median (IQR)	70 (63-79)	59 (47-71)	<0.001	69 (72-80)	58 (46-71)	<0.001
Time of FU						
Years, median (IQR)	2.5 (1.2-4.7)	3.2 (1.4-5.6)	0.03	2.8 (1.4-4.6)	3.6 (1.8-6.0)	0.002
Number of deaths						
N (%)	30 (25.0%)	129 (21.9%)	0.46	28 (24.8%)	119 (22.3%)	0.57
Histological subtype						
SSM	58 (48.3%)	290 (49.2%)	0.23	54 (47.8%)	259 (48.6%)	0.26
NMM	35 (29.2%)	142 (24.1%)		32 (28.3%)	127 (23.8%)	
LMM	4 (3.3%)	8 (1.4%)		4 (3.5%)	7 (1.3%)	
ALM	0 (0.0%)	7 (1.2%)		0 (0.0%)	6 (1.1%)	
Others	23 (19.2%)	142 (24.1%)		23 (20.4%)	134 (25.1%)	
Body site of the melanoma						
Head and neck	21 (17.5%)	90 (15.3%)	0.87	20 (17.7%)	75 (14.1%)	0.74
Trunk	40 (33.3%)	216 (36.7%)		37 (32.7%)	196 (36.8%)	
Upper extremity	25 (20.8%)	118 (20.0%)		23 (20.4%)	105 (19.7%)	
Lower extremity	34 (28.3%)	165 (28.0%)		33 (29.2%)	157 (29.5%)	
Tumour thickness						
>=1,01 and <= 2	57 (47.5%)	313 (53.1%)	0.46	53 (46.9%)	282 (52.9%)	0.22
>=2,01 and <=4	39 (32.5%)	180 (30.6%)		35 (31.0%)	168 (31.5%)	
>=4,01	24 (20.0%)	96 (16.3%)		25 (22.1%)	83 (15.6%)	

Table S1- Supplemental table (online only): (Continued)

Characteristics	β-blocker user cohort 2 Chronic user before diagnosis (*N*=120)[a]	non-users (*N*=589)[b]	*p*[c]	β-blocker user cohort 3 Chronic user before and after diagnosis (*N*=113)[d]	non-users (*N*=533)[b]	*p*[c]
Nodal metastases						
N (%)	14 (11.7%)	90 (15.3%)	0.31	10 (8.8%)	84 (15.8%)	0.06
Distant metastases						
N (%)	1 (0.8%)	14 (2.4%)	0.49	1 (0.9%)	8 (1.5%)	1.00
Comorbidities						
N (%)	87 (72.5%)	180 (30.6%)	<0.001	79 (69.9%)	157 (29.5%)	<0.001
Hypertension	46 (38.3%)	69 (11.7%)	<0.001	43 (38.1%)	57 (10.7%)	<0.001
Heart diseases	46 (38.3%)	51 (8.7%)	<0.001	45 (39.8%)	44 (8.3%)	<0.001
Cancer	27 (22.5%)	62 (10.5%)	<0.001	25 (22.1%)	54 (10.1%)	0.001
Stroke	9 (7.5%)	9 (1.5%)	<0.001	9 (8.0%)	9 (1.7%)	<0.001
Diabetes	7 (5.8%)	35 (5.9%)	0.03	6 (5.3%)	30 (5.6%)	0.05
Lung diseases	3 (2.5%)	31 (5.3%)	0.01	3 (2.7%)	29 (5.4%)	0.02
Gastrointestinal diseases	4 (3.3%)	11 (1.9%)	0.02	4 (3.5%)	8 (1.5%)	0.02
Unique hospitalizations[e]						
no admissions	91 (75.8%)	503 (85.4%)	0.03	83 (73.5%)	458 (85.9%)	0.001
1 admission	20 (16.7%)	66 (11.2%)		20 (17.7%)	59 (11.1%)	
>1 admission	9 (7.5%)	20 (3.4%)		10 (8.8%)	16 (3.0%)	
Unique ATC codes[e]						
0 ATC codes	1 (0.8%)	111 (18.8%)	<0.001	1 (0.9%)	102 (19.1%)	<0.001
1-3 ATC codes	24 (20.0%)	242 (41.1%)		23 (20.4%)	222 (41.7%)	
>3 ATC codes	95 (79.2%)	236 (40.1%)		89 (78.8%)	209 (39.2%)	

Abbreviations

ATC, Anatomical Therapeutic Chemical classification system; FU, follow-up; IQR, interquartile range; N, total number of patients.

[a]Min. 2 dispensings for β-blocker within 1 year prior to melanoma diagnosis and use at time of melanoma diagnosis.

[b]No dispensing for β-blocker or only short term use.

[c]p-values based on 2-sided x2 test or Fisher´s exact test for categorical variables, 2-sided t-test for numerical values.

[d]Min. 2 dispensings for β-blocker within 1 year prior to melanoma diagnosis and min. 1 dispensing within 6 months after melanoma diagnosis. Time-fixed analysis.

[e]In the year prior to diagnosis.

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Chapter 5

General discussion

GENERAL DISCUSSION

The main aims of this thesis were (1) to describe the incidence, mortality and survival of melanoma and squamous cell carcinoma (SCC) in the Netherlands; (2) to estimate the burden of disease attributable to skin cancer in the Netherlands and (3) to investigate if chemoprevention can help to reduce the burden of skin cancer in the Netherlands. In this chapter I will discuss the main findings, their interpretations, strengths and limitations and future perspectives.

EPIDEMIOLOGY OF SKIN CANCER IN THE NETHERLANDS

The age-standardised incidence rates of melanoma, SCC and basal cell carcinoma (BCC) are increasing with 4% to 9% each year, as is described in chapter 2 for melanoma and SCC and was previously described for BCC by Flohil et al. [1-3]. Since the years 2002-2003, rate of increase of incidence of SCC and BCC have accelerated. Before 2002 they increased by 1 to 4% per year and since 2002 by 7 to 9% per year. There are several potential underlying causes of these accelerations. First, they may be artificial increases, being a result of an increase in completeness of the cancer registry resulting in more keratinocytic cancers being registered, rather than the real incidence having augmented. Although this may have influenced incidence rates somewhat, it is unlikely to be the cause of the large increases, because the completeness of the cancer registry on skin cancer was already 93% in 1994 [4]. Any improvement in the completeness of the registry must have been small and is unlikely to have resulted in such strong, and persisting accelerations in incidence rates. Second, an increase in awareness of skin cancer among the general population and among physicians due to skin cancer prevention campaigns may have led to an increase in skin check-ups and full body examinations, resulting in more existing skin cancers being diagnosed. This is consistent with an increase of keratinocytic cancers on the trunk, although this was not observed for women with SCC [1,3]. Third, with the introduction of a shift towards a production-driven health care system in the Netherlands, since 2006 physicians may be more likely to surgically treat skin cancer resulting in histological confirmation of the diagnosis and therefore higher numbers in the cancer registry. Fourth, an increased use of immunosuppressive drugs may have contributed to the increase in incidence rates as these drugs are known to increase skin cancer risk and the number of immunosuppressive drug users in the Netherlands increased from 25,400 users in 1994 to 101,640 users in 2008 [5] (personal communication). However, this would have resulted in a larger impact on SCC incidence rates than on BCC incidence rates, because in patients receiving immunosuppression the expected ratio of SCC:BCC (1:4) is reversed and we observed similar accelerations for both BCC and SCC [6]. It is therefore unlikely that the use of immunosuppressive drugs was the main cause of both the increase in BCC and SCC.

Finally, a delayed effect of increased sun exposure of the population will result in increased incidence of melanoma, BCC and SCC. This is the most likely explanation for the observed trends. Since the 1950 the amount of leisure time and number of holidays increased. Simultaneously, holidays to sunny destinations became more affordable [7]. In addition, sun bed use gained popularity since 1990. All these factors contributed to an increase in cumulative and intermittent sun exposure. The largest relative increases in incidence rates were observed on covered body sites, which may point at increased prevalence of exposure to ultraviolet (UV) radiation on body parts that were previously less likely to be exposed (chapter 2.3).

There is debate on whether or not the observed increases in melanoma incidence rates are real or a reflection of overdiagnosis [8,9]. A clear definition of overdiagnosis is pivotal in this debate. Diagnosing a lesions with microscopic features of melanoma, but that would never have progressed or progressed so slow that the patient dies before the cancer would have become symptomatic is called overdiagnosis [9,10], whereas inappropriately diagnosing lesions as malignant is misdiagnosis, rather than overdiagnosis [10].

Overdiagnosis is a well-known and problematic phenomenon in cancer screening. Cancer screening studies showed that cancer incidence rates are proportionally related to the amount of effort placed on detecting cancer [9,10]. In 2005 Welch published an ecological study, based on Northern American data, in which he observed that the biopsy rate of skin lesions increased by 2.5 fold and the melanoma incidence with 2.4 folds, whereas melanoma mortality remained stable [11]. Such a pattern is suggestive of overdiagnosis (Figure 1). However, since this is an ecological study, the reasons for biopsy were unknown and may have been unrelated to melanoma, but because of suspicion of BCC, SCC or another cutaneous problem. Ecological fallacy may have occured because the observed association is not assessed at an individual level, but deduced from the group level [12].

Diagnostic drift may also have contributed to possible overdiagnosis. Frangos et al showed that lesions that were diagnosed 20 years ago as dysplastic nevi and that were re-examined

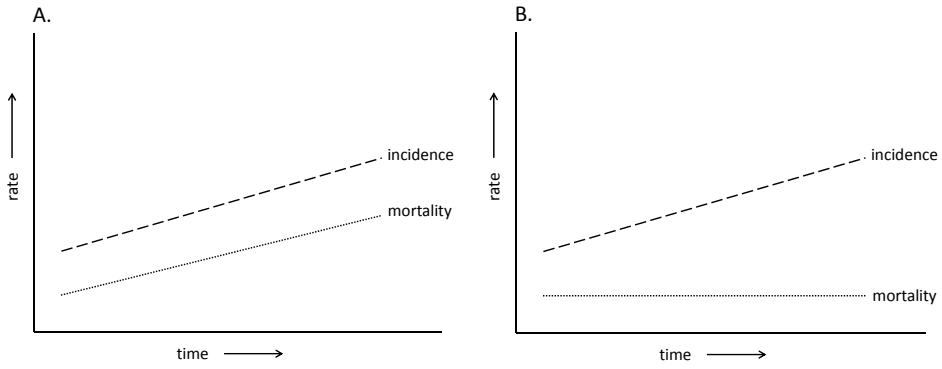

Figure 1: Overdiagnosis of cancer. The pattern of incidence and mortality rates of figure 1A suggest a true increase in disease and the pattern of figure 1B suggests overdiagnosis.

in 2008-2009 were more frequently classified as thin superficial spreading melanomas by the original dermatolopathologist compared to 20 years ago [13]. It should be noted, that the distinction between the histopathological diagnosis of true malignant melanoma and other benign melanocytic nevi may be very difficult, which is reflected in the discordance in histopathological diagnosis among experts [14]. Melanocytes migrate in the embryonic phase from the neural crest to the dermis, from which they migrate to the epidermis. From a diagnostic slide it is difficult to judge if melanocytes migrate from the epidermis to the dermis (possibly invasive melanoma) or from the dermis to the epidermis (regular melanocyte migration). Anxiety to not miss a melanoma that might eventually result in metastasis and death may have resulted in a tendency to assign the diagnosis of malignancy in cases that are difficult to interpret [15]. To avoid the negative consequences of a potential underdiagnosis, clinicians and dermatopathologists may have become more conservative without fully taking the consequences for the patient into account. The overdiagnosis of melanoma can have a severe negative impact on quality of life, such as anxiety, behavioral changes, problems with obtaining insurance and other problems that come with the diagnosis 'cancer' [16-18].

Overdiagnosis in populations can be recognized through increasing incidence rates, especially of early stage tumors, accompanied with stable mortality rates (Figure 1) [9]. In the Netherlands, there is no strong indication for overdiagnosis in these terms[2]. Both incidence rates of thick melanomas and melanoma mortality rates increased, which was most prominent in the elderly. The increased death rates among the elderly (>65 years) may reflect higher cumulative lifetime ultraviolet exposure, late stage at diagnosis, poor access to medical care or undertreatment [19]. Overdiagnosis can also result in an improvement in survival statistics. The detection of more slow growing tumors results in a prolonged survival time, which is called length time bias [20]. This phenomenon may have contributed to the increase in 10-year relative survival in the Netherlands between 1989 and 2008, because during the study period there were no significant changes in treatment. In conclusion, a large part of the thin melanomas is probably a result of overdiagnosis, but given the increase in thick melanomas and melanoma mortality, the melanoma epidemic in the Netherlands seems to be real.

BURDEN OF SKIN CANCER IN THE NETHERLANDS

The burden of a disease in a population is not fully described by incidence and mortality rates alone. The health related quality of life (HRQoL) of a disease may be influenced by the psychological impact, disability caused by the disease or related complaints. This is especially important for diseases with a long duration and chronic diseases. To compare the disease burden between different diseases the World Health Organization (WHO) has developed the Disability Adjusted Life Year (DALY). The DALY describes the fatal and non-fatal disease burden and is calculated by the sum of the Years of Life Lost (YLL) and the Years of Life lived

with Disability (YLD). These burden of disease measures may be used for the prioritization of research and the allocation of limited health care resources. A close relative of the DALY is the Quality-Adjusted Life Year (QALY), which is a measure of health improvement, rather than loss of health. The QALY is a valuation of health benefit and was developed for cost-effective analysis to compare different health care interventions to maximize population health when resources are scarce [21].

In chapter 3 of this thesis I described that the disease burden of both melanoma and keratinocytic cancer in terms of DALYs has increased during the last twenty years. Measuring the YLL is of key importance in estimating the burden of melanoma, as melanoma occurs at relatively young ages (median age: 53 years) compared to most other cancers [22]. A patient who dies due to melanoma lost on average 20 life years, making melanoma the second most important cancer in terms of YLL [23]. This type of burden measures give a completely different view on the disease than mortality rates do, which are quite low for melanoma (i.e. 4 per 100,000 person-years in the Netherlands [European standardized rate]). Therefore, for fatal cancers YLL is a very useful measure. We applied the DALY concept to keratinocytic cancers, but death from keratinocytic cancer is rare and therefore the larger number of DALYs is mainly driven by disability (YLD). YLD takes related conditions, such as pain, disability and psychological concerns, and the duration of the disease into account, which is important for chronic diseases. Both keratinocytic cancer and melanoma can be regarded as chronic diseases. Melanoma patients experience problems many years after diagnosis and follow up, regarding anxiety, work and obtaining insurance [16,18]. keratinocytic cancer patients have a persistently increased risk of developing multiple keratinocytic cancers [24-26]. Consequently, keratinocytic cancer patients may fear recurrence, subsequent tumors or suffer from scars for the rest of their lives. For the aforementioned reasons we included a disability weight also for periods long after follow up. However, the qualitative and quantitative impact of keratinocytic cancer on patient's lives is largely unknown. It was found that HRQoL of keratinocytic cancer patient measured with generic questionnaires was comparable to that of the general population and preliminary concluded that keratinocytic cancer may cause little handicap [27]. It may also indicate that the impact of keratinocytic cancer is very specific, such as anxiety for UV exposure and a psychological impact due to cosmetic disfigurement, issues that are not picked up by the frequently used instruments. The recently developed skin cancer quality of life impact tool (SCQOLIT), assesses quality of life in so-called nonmetastatic skin cancer patients and focuses on specific issues, such as UV exposure, bothering by scarring or disfigurement, anxiety for dying of skin cancer and if patients received enough information to recognize a subsequent skin cancer [28]. This may be a useful tool to capture the specific burden of keratinocytic cancer. A major flaw of this questionnaire is the use of multiple issues and questions combined in one item, which makes the interpretation of the results difficult. The skin cancer index is easier to interpret, but lacks information about UV-related issues [29]. Therefore, our group is currently developing a new questionnaire for quality of life of

keratinocytic cancer. Using this questionnaire a better insight in the individual burden of the disease can hopefully be gained. On a patient-level, health care can be improved by identifying those patients that will be in need of additional health care. For example, patients that feel that they need more information to recognize new skin cancer can be provided an extra follow up visit to enhance information provision. This may lead to less anxiety, improved patient satisfaction and quality of life.

The information obtained from the questionnaire on the proportion of patients who suffer from their scars, who are not bothered by them at all, or who are anxious about possible recurrence or subsequent tumors may be used to improve our disease model. In our analyses we assigned a disability weight after follow up either to all patients or to nobody. If the proportion of patients which experience problems after follow up and their characteristics are known, our disease model can be improved by assigning a disability weight to only those patient with a reduced HRQoL. Unfortunately, there are no empirical estimates of disability weights for estimating the disease burden after follow up. Moreover, the widely used disability weights are based on only three studies (i.e., the Dutch, the WHO and the Victorian disability weights) [30-32]. The Dutch disability weights were estimated by a panel of three physicians and panel of lay persons [33]. For the Global Burden of Disease (GBD) study 2010 disability weights were re-estimated for a subset of all diseases, using face to face or telephone surveys among 13,000 individuals in five different countries and an open-access web-based survey among 16,000 individuals [34]. This is a much better way to estimate disability weights than using a small group of experts and only one lay panel. A future study should re-estimate the disability weights for cancer in a similar way as for the GBD 2010. Moreover, in such a study new disability weights should also be estimated for cancer survivors. The health states identified by keratinocytic cancer specific HRQoL questionnaires may be used to estimate new disability weights for melanoma and keratinocytic cancer during and after follow up. A combination of new empirically estimated disability weights and a known number of patients who experience reduced HRQoL, will result in a better estimation of the true number of DALYs in the population.

The large number of skin cancer patients also result in a substantial societal burden in terms of finances and burden on the health care system. In the Netherlands 35-40% of all dermatology claims to health insurance companies are related to skin cancer [35]. The costs of skin cancer can be expressed in direct costs (i.e. health care costs of detection, treatment and follow up) and indirect costs (.e. loss of productivity occurring as a result of an individual's inability to work on account of the disease). USA claims data showed that the treatment costs of nonmelanoma skin cancer (NMSC) are comparable to those for lung, colorectal and breast cancer [36]. It was estimated that almost 80 million dollars in the USA were lost each year due to lost working days or restricted activity days related to NMSC [37]. A study in Sweden on both direct and indirect costs of skin cancer showed that outpatient care was the main cost driver accounting for 42% of total costs [38]. Due to the large number of patients (>43,000 new

patients in the Netherlands in 2010), of which a large part needs follow up or will return to medical care because of subsequent tumors, it is likely that outpatient care also accounts for the largest proportion of the total costs of skin cancer in the Netherlands. Many melanoma patients receive more follow up than recommended in the Dutch guideline, indicating that patients may be anxious and they or their health professionals would like them to have an annual skin check by a professional for re-assurance [39].

CHEMOPREVENTION OF SKIN CANCER

Prevention is needed to reduce the skin cancer burden. Preventive measures should be effective, safe, cost-efficient and easy to implement. Three levels of prevention can be distinguished in public health [40]. The aim of primary prevention is to prevent skin cancer development. Primary prevention campaigns aimed at informing the general population about the deleterious effect of excessive UV exposure, but so far have not proven very effective in inversing the increasing trends in the Netherlands. The Dutch Cancer Society (KWF) started to inform people about the risk of skin cancer associated with sun exposure since 1998. However, knowledge about health is not enough to change people's behavior. In a clinical setting, the term secondary prevention is used to indicate the prevention of second events after experiencing a first event. In public health, the aim of secondary prevention is to detect and treat skin cancer in an early stage. Secondary prevention from a public health perspective includes screening to detect primary skin cancers. There is an ongoing debate about skin cancer screening at a population level. There is uncertainty about whether skin cancer screening meets the screening prerequisites as defined by Wilson and Junger [41]. Arguments against screening include, the uncertainty about the cost-effectiveness and the uncertainty about the reduction in mortality, because screening would most likely detect more slow growing tumors and not the fast-growing aggressive tumors. As mortality of skin cancer in the Netherlands is quite low, it is questionable if organized mass screening would manage to substantially lower the mortality. At the same time it will result in more skin cancers being diagnosed and needing treatment, increasing the burden on the healthcare system. Tertiary prevention aims to slow down disease progression among patients already diagnosed with the disease.

As primary prevention campaigns do not seem to be effective so far in the Netherlands, and the cost-effectiveness and other prerequisites of skin cancer screening remain unclear, alternative prevention strategies for a large group of people should be explored. Chemoprevention may be an alternative way to help prevent subsequent skin cancers (table 1). An example is the use of acitretine to prevent skin cancer in patients with a history of multiple SCC and to a lesser extent BCC, such as organ transplant recipients, who are at high risk of developing many skin cancers. However, the use of acitretine is limited, due to the low

Table 1: (Hypothetical) application of Acitretine and other chemopreventive drugs.

Application of Chemoprevention in different levels of prevention					
Level of chemoprevention	Definition	Acitretine	Low dose Aspirin	NSAIDs	β-blockers
Primary chemoprevention	Prevent the development of skin cancer	-	-(-)	-(-)	-
Secondary chemoprevention	Prevent subsequent skin cancers	+	+	+	+
Tertiary chemoprevention	Prevent or slow down metastatic process	-	-	-	+(-)

Signs between brackets indicate the recommendations obtained from the studies in this thesis.

tolerability [42]. The ideal candidate drug has an excellent safety profile and has other health benefits in addition to the prevention of skin cancer. Therefore, low dose aspirin may be an good candidate drug. The safety profile is extremely important, especially when considering a chemopreventive drug for the prevention of keratinocytic cancer, because the mortality is low.

In this thesis we searched for an indication of chemopreventive properties of aspirin and Non-Steroidal Anti-Inflammatory Drugs (NSAID) in a population-based setting using routinely collected data obtained from the linkage between the PHARMO Record Linkage System (RLS) and the Eindhoven Cancer Registry (ECR)[43]. In case of an observed benefit in an average risk population, the risk:benefit balance is likely to be in favour of the drug in a clinical setting, which is the prevention of subsequent skin cancers among high risk patients. This could be subsequently tested in a randomized controlled trial. Null results in a population-based setting may indicate that there is a lack of efficacy or that the chemopreventive drug can only achieve efficacy in a subgroup of patients or in patients with certain tumor characteristics.

NSAIDs, like cyclooxygenase (COX)-2 inhibitors may be used to prevent skin cancer in high risk populations, such as patients with multiple Actinic Keratosis (AK). NSAIDs are administered in high dosages, which may cause gastrointestinal adverse effects, such as gastric ulcers. Prevention of cancer may also be achieved with aspirin in lower dosages, but this may cause bleedings. Both NSAIDs and low dose aspirin are therefore not suitable for the primary prevention of cancer. An inverse association between low dose aspirin use and cancer in the general population may broaden its indications, such as the use in a primary prevention setting in cardiovascular disease, where the benefits do not outweigh the risks [44]. Aspirin may also slow down cancer progression and may therefore also be used in a tertiary prevention setting for colorectal cancer, but there is no association between melanoma mortality and aspirin use [45-48]. The use of β-blockers is tertiary chemoprevention, as the use of them may slow down cancer progression and may therefore prevent metastasis and death from melanoma [49,50].

Low dose aspirin and skin cancer incidence

Low dose aspirin is a good candidate drug for chemoprevention. It has been on the market for a long period of time and has a well-known safety profile. Low dose aspirin is widely used as

secondary prevention for cardiovascular diseases (CVD). The risk:benefit balance of aspirin for the secondary prevention of cardiovascular events is well established [51,52], but the net benefit for primary prevention of cardiovascular events is uncertain due to the increase in major bleeds [44]. The current trials on primary prevention do not justify the use of daily aspirin in all apparently healthy individuals. Ongoing primary prevention trials in participants at higher risk due to diabetes (ASCEND[53] and ACCEPT-D[54]), advanced age (ASPREE[55]) and a cluster of risk factors (ARRIVE[56]) may help to assess the risk:benefit balance in these groups. Although protocol amendments are needed to prospectively collect information about cancer during follow up and afterwards [57]. In addition, aspirin use may prevent incidence of several types of cancer, which may put the risk:benefit balance in favor for the prevention of skin cancer [46,58]. Most knowledge about cancer prevention of aspirin comes from long term follow up from these cardiovascular trials [46]. In a meta-analysis of Randomized Controlled Trials (RCT) of daily aspirin use the risk and the benefits were both studied [46]. Among six cardiovascular primary prevention trials the possible cancer risk reduction was studied, taking into account the risk on vascular death, non-vascular death, major vascular events and major extracranial bleeds [46]. Unfortunately, a major flaw of this meta-analysis is that the two largest primary prevention trials (Women's Health Study[59] and Physician's Health Study[60]) in which there was no effect on cancer were excluded from the analysis, because aspirin was administered on alternate days instead of daily. The rationale behind this was the 48h dosage interval, which may have resulted in inadequate platelet inhibition compared to daily use, given the short half-life of aspirin (~20 min) and the individual variability in the recovery rate of platelet COX-1 activity [61]. Long term follow up of these RCTs lacked statistical power to determine an effect on site-specific cancer [46]. Moreover, trial participants are highly selected and results cannot be extrapolated to the general population. We therefore studied cancer incidence amongst long term aspirin users in the general population in chapter 4.3. Using data from the ECR-PHARMO cohort we had detailed information on both exposure and outcome. In addition, we used time-dependent analyses of exposure to prevent time-related biases. A limitation of our study was that long term aspirin users could not be compared non-users, due to differences in cancer risk factors for which we could not adjust as we had no such data on lifestyle and behavioral factors. As low dose aspirin use is expected to decrease cancer risk after at least 3 years of cumulative use we compared long term use to short term use [46]. We did not observe a decreased risk on cancer in general or site specific cancer. Our results do not support the use of low dose aspirin in a primary prevention setting to prevent cancer.

Maybe, aspirin use should be targeted more efficiently to a subgroup, particularly susceptible to the efficacy of aspirin use. Recently, a PIK3A gene mutation (the phosphatidylinositol-4,5-bisphosphonate 3-kinase, catalytic subunit alpha polypeptide gene) was identified in colorectal cancer as a potential useful genetic marker to help target adjuvant treatment with aspirin more effectively. In a normal cell activation of phosphatidylinositol 3-kinase (PI3K) results in an upregulation of prostaglandine E which inhibits apoptosis. COX-2 contributes

to this process of cell survival by also increasing prostaglandine E. Of all CRC patients, 15% to 20% carries a mutation in the PI3K pathway. These patients may particularly benefit from aspirin use as both the COX-2 and PI3K pathway of PGE are blocked and apoptosis is no longer inhibited. Indeed, aspirin use among colorectal cancer patients with a mutation in the PIK3CA gene was associated with a 46% reduction in all-cause mortality and a 82% decrease in cancer related mortality [48]. Aspirin use was not associated with mortality in wild type cancers.

Future research should aim to identify patient and tumor characteristics which increase the efficacy of potential chemopreventive drugs in skin cancer, which may help to target chemoprevention to those patients, who are most likely to respond to therapy. For SCC it was observed, that a possible protective effect of aspirin may be larger in tumors with Patched loss or altered p53 [62]. Maybe tertiary prevention of subsequent tumors or prevention of recurrence may be effective with aspirin in patients with Patched loss or p53 alterations.

NSAIDs and keratinocytic cancer incidence

Increased COX-2 signalling may be causally related to the development of keratinocytic cancer [63]. NSAIDs are administrated in high dosages and inhibit COX-2 systemically and may therefore be a more potent chemopreventive drug than low dose aspirin. A disadvantage of NSAID use is the increased risk of gastrointestinal complications, such as ulcers. NSAIDs are frequently prescribed in combination with proton pump inhibitors to protect the gastric mucosa, because COX-1 is inhibited by NSAIDs, but should be expressed constitutively to maintain the gastric mucosa [63]. Selective COX-2 inhibitors were developed to potentially reduce gastrointestinal problems, but maintain the analgesic effect. Unfortunately, rofecoxib was withdrawed worldwide after termination of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial by the Food and Drug Administration (FDA), because of an observed significant increase in cardiovascular thrombotic events [64]. There is no need to explain that these side effect are unacceptable when considering chemoprevention of non-fatal skin cancer. During the same period the FDA requested termination of a trial on chemoprevention of AK by celecoxib, due to the withdrawal of rofecoxib [65]. A reduced incidence of BCC and SCC was observed among participants assigned to celecoxib, although the reduction in number of AK was the primary endpoint of this study. To study the possible inverse association between the use NSAIDs, selective COX-2 inhibitors and skin cancer in the general population, we used data from the ECR-PHARMO cohort. We restricted our study to NSAID use for more than one year, because NSAIDs are available over the counter (OTC) and people without a NSAID prescription are as likely to have used OTC NSAIDs. Long term NSAID use for analgesic use amongst rheumatic patients for example, is more likely to be on prescription. In our study, as described in chapter 4.4, we observed no reduced incidence of keratinocytic cancer among people who used NSAIDs for more than one year. In addition, a recent meta-analysis on melanoma and NSAIDs also failed to show a protective effect [66]. Therefore we conclude that

NSAIDs are not likely to reduce the skin cancer incidence in an average risk population. Our results do not exclude the possibility that they might be effective in a high risk population, such as that of the celecoxib trial. However, the results in high risk populations are controversial as well [67].

β-Blockers and melanoma survival

Stress can be a cofactor in the progression of cancer, which may be mediated by the catecholamine stress hormones (epinephrine and norepinephrine) which bind to the β-adrenergic receptor. Norepinephrine signalling was also found to be of importance for progression of melanoma *in vitro* [68]. Two epidemiological studies showed an effect of β-blocker use on melanoma survival [49,69]. However, one study was underpowered for its objective and was not adequately analysed, causing a survival advantage for the long term β-blocker users due to the definition of exposure [69,70]. A larger population-based study showed an effect on all-cause mortality and disease specific mortality [49]. However, β-blocker use was studied before diagnosis to simulate an intention to treat analysis and duration of β-blocker use after diagnosis was therefore not taken into account. Using data from the ECR-PHARMO cohort allowed us to study the use of β-blockers before and after melanoma diagnosis, taking duration and dosage into account (chapter 4.5). Our results did not show a statistically significant impact of β-blocker use on all-cause mortality among melanoma patients, although the direction was consistent (HR 0.82) with the Danish study which showed a protective effect on all-cause mortality and melanoma-specific mortality [49]. It is known from breast cancer research and preclinical studies that non-selective β-blockers reduce cancer-specific mortality as a result of β_2-adrenergic receptor antagonism [71,72]. It is possible that the Danish study included a larger proportion of non-selective β-blocker users, and therefore managed to reach statistical significance. The dispensing rate of non-selective β-blockers was low in our study (16% of all β-blocker dispensings). Phase II clinical trials are underway to assess the safety and efficacy of β-blockers as adjuvant therapy for colorectal, breast and ovarian cancer [73] (NCT00888797, NCT01308944, NCT01847001), but the currently available results for melanoma are not sufficiently convincing to justify a RCT in melanoma patients. Before such a trial would be justified, an analysis of large cohort of melanoma patients using non-selective β-blockers is needed. Expansion of the ECR-PHARMO cohort to the entire Dutch population may not even be enough, just like in the Scandinavian countries, because the number of non-selective β-blocker users is low [71]. Pooling data from different routinely collected databases may be needed to gain sufficient power.

Alternatively, tumor characteristics which indicate the efficacy of β-blocker use on melanoma survival should be identified. It was found that β-blockers are particularly associated with improved relapse free survival in patients with triple negative breast cancer (estrogen receptor negative, progesterone receptor negative and HER2 negative) [50]. Patients with triple negative breast cancer have a higher prevalence of abdominal obesity and metabolic syn-

drome, which has been linked to disregulation of the sympathetic nerve system. Moreover, triple negative breast cancer is associated with an higher expression of β-adrenergic receptors, making this tumors more susceptible to β-blocker therapy. Future research may aim to identify a melanoma subtype with an increased expression of β-adrenergic receptors or to identify genetic differences between patients with regard to β-adrenergic signaling. For example, small nucleotide polymorphisms (SNPs) in endogenous release of norepinephrine may lead to an elevated tone of norepinephrine, which may lead to the identification of increased susceptibility of response to adjuvant β-blocker therapy.

METHODOLOGICAL CONSIDERATIONS IN CHEMOPREVENTION RESEARCH

In this thesis, we did not observe any benefit of low dose aspirin or NSAIDs in the general population regarding the primary prevention of skin cancer. There are not many other candidate drugs with a favourable risk:benefit balance to prevent skin cancer in the general population, with the exception of statins, which are widely used to lower cholesterol and have an excellent safety profile. Use of statins has been associated with a reduced Breslow thickness, which is an important indicator of melanoma prognosis [74].

However, before we proceed to focus on other medications it is more important to improve the research methods. Larger sample sizes are needed in order to reach sufficient statistical power within subgroups of users. Our sample included more than 100,000 low dose aspirin users and more than 40,000 long NSAID users (>1 year NSAID use), but the low number of very long term users (>5 years) in combination with a rare event, such as melanoma, still resulted in a lack of statistical power. A larger sample size is also needed to investigate the effect of non-selective β-blockers on the progression of melanoma, because they are not as frequently prescribed as the β_1-adrenergic receptor selective β-blockers. Caution is needed when increasing samples sizes. If extremely large sample sizes are needed to reach a statistically significant result, the clinical relevance of this result is questionable. In this perspective, it may be helpful to calculate the number needed to treat (NNT), which is the number of patients that should be treated to prevent one skin cancer. Together with the number needed to harm (NNH), a careful consideration of both the risks and the benefits can be made altogether.

Larger sample sizes will not solve all problems when evaluating drug effects in a non-clinical trial setting [75]. A study with a large sample size but without proper design and analysis may result in highly significant but false associations between drug use and cancer. A small sample size study with adequate design and adjustment for all possible confounding factors may yield non-significant but correct results. On the other hand, regional and national databases of routinely collected data contain large quantities of health information, usually covering whole populations and often collected data over a prolonged period of time [76]. It

is important to overcome methodological difficulties to make optimal use of such valuable data sources. The use of such routinely collected databases is an efficient and cost-effective way to answer key questions. International consortia may be needed to efficiently study specific subgroups of which the sample size in a single database would be too small. In genetic research, such consortia were set up among multiple cohort studies to facilitate genome wide association (GWA) study meta-analyses and replication. However, use of these data resources leads to specific challenges for researchers. The use of this available routine data is increasing, but the strengths, limitations and biases are unclear. Currently, a guideline for the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) is under development [77]. This will be and extension of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, addressing specific issues, such as record linkage methodology, to enhance the transparency of reporting this type of studies. Furthermore, the guideline could help researchers to review and improve areas of methodological concern, thereby improving this research field. The field of pharmacoepidemiology has historically focused primarily on adverse drug effects [78]. The aim of chemoprevention research is the opposite: to identify unintended beneficial effects in contrast to unintended adverse effects. This type of research entail other types of bias compared to the traditional pharmacoepidemiology setting and may require different methods of design and analysis. Several types of bias may lead to incorrect protective associations between long term use of (preventive) medication and cancer, such as immortal time bias (duration of exposure is treated as if already known at baseline), protophatic bias (initiation of drug exposure is a result of undiagnosed cancer) and the healthy user and healthy adherer bias (initiation or adherence to the drug is associated with other healthy behaviors) [70,78,79]. In addition, the precise timing, duration and dosage of the chemopreventive drug are unknown. Several statistical methods have been proposed to identify the correct lag time or the timing of effective drug exposure [80,81]. These methods should be applied in future research.

The question raises if chemoprevention may only be adequately investigated by RCTs, because of the methodological difficulties. A chemoprevention RCT for cancer will require a very long follow up time and extremely large numbers. A possibility is to restrict the trial to high risk participants in which an effect can be observed in a limited amount of time, such as patients with multiple AK or Xeroderma Pigmentosum (XP), but this will seriously limit the generalizability of the results to a broader population. An example is the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) trial, in which the efficacy of topical tretinoin was assessed to prevent subsequent keratinocytic cancers among 1131 participants with at least two prior keratinocytic cancers during a follow up time of up to 5.5 years [82].

Observational studies have the advantages of including a broad population of people and a larger sample size. A well-conducted observational research can be equally valid as a RCT, if the study is restricted to topics in which exposure allocation is unrelated to the outcome (e.g. adverse effects), and includes only participants in whom allocation of exposure

is random (e.g. radiation for left or right sided breast cancer) or is restricted to people who do not have any risk factors of which residual confounding is possible [83]. These are very stringent, unrealistic restrictions, regarding the association between medication use and cancer incidence, because allocation of exposure (prescription of medication) is never random in pharmacoepidemiology.

The most important limitation of our observational population-based study was the lack of important potential confounders. As it is not feasible to obtain this information for each of the approximately 4 million PHARMO participants, one could think of a construction of an equivalent of the Charlson Comorbidity Index for lifestyle, based on type and pattern of medication use. It would be useful to quantify how the lifestyle or other behavioral factors differ between long term preventive therapy users (low dose aspirin users/statin users), non-users and participants who discontinue preventive drug therapy. Statin users are known to be more likely to receive preventive services (e.g. Prostate Specific Antigen (PSA) screening, mammography and influenza vaccination) [84] and to have a decreased risk of many outcomes, which are unlikely to be related to statin use, but a rather a result of risk avoiding behavior. This is illustrated by the observation that statin users have a decreased risk of car accidents [85]. On the contrary, a recent study in Denmark found no evidence of a healthier lifestyle of statin users [86]. Instead, statin users appeared less healthy than other persons. There was no indication of a healthy adherer effect. Although long term use was defined in this Danish study as at least one year and it would also be useful to know the lifestyle of patients who adhere to the medication for at least 5 years as protective effects are usually observed after a longer duration than one year. In addition, the lifestyle profile among statin users may differ between countries, due to the differences in prescribing behavior of the physicians. Insight in the complex social and behavioral factors would certainly improve the validity of observational research.

In addition to quantifying the amount of uncontrolled confounding, identification of high-quality data-analysis methods of routinely collected data for chemoprevention research is warranted. Two pharmacoepidemiological consortia aim to identify limitations of current methods in the field of pharmacoepidemiology and to develop methodological standards for pharmacovigilance studies (i.e. Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium [PROTECT] and Observational Medical Outcomes Partnership [OMOP]) [87,88]. One of the goals of the OMOP project is to study the performance of observational analysis methods to identify true risks using large volumes of electronic health care data for drug safety surveillance [87]. They observed that there is a substantial chance of identifying false positive associations at traditional levels of statistical significance with a range of methods currently accepted as standard for pharmacoepidemiology evaluation (e.g. inception cohort studies, self-controlled case series and case control design) [89]. The false positive rate might also be higher than the expected 5% for unintended beneficial effects, but in hypothesis-driven chemoprevention research additional evidence of the association

is provided by its temporality, a biological plausible mechanism and a dose-response relation among other prerequisites for causality [90]. It is important to identify reliable statistical methods to analyse routinely collected data for chemoprevention research and to recognize how choices for the database, design and analysis can influence study results.

CONCLUSION

The skin cancer incidence rates are increasing in the Netherlands and do not seem to reach a plateau in the near future. I am convinced that at least a part of the skin cancer epidemic is real, considering the rise in all three common skin cancers, the increase in melanoma mortality and increase in melanoma incidence among all Breslow thicknesses. The increase in mortality rates is a worrying trend as patients who die due to melanoma lose on average 20 life years. The majority of the patients with skin cancer will live 20 to 25 years after their initial diagnosis, in which they may be in need of additional health care for subsequent tumors, recurrences or psychological care. This illustrates that skin cancer is both a large personal and societal burden. I explored the possibility of chemoprevention as an alternative to reduce skin cancer incidence and mortality. I did not find risk-reducing effects of low dose aspirin and NSAIDs. This may indicate that either NSAIDs and low dose aspirin are not effective in reducing (skin) cancer or that efficacy may only be achieved in a subpopulation of patients. Larger datasets are needed to allow specific subgroup analysis in high risk populations. Future research should identify molecular or genetically different subtypes of BCC, SCC and melanoma or identify genetically predisposed patients to predict the efficacy of the chemopreventive drug. I recommend to start consortia to study specific subgroups, quantification of uncontrolled confounding and identification of high-quality methods of analysis to move the field of chemoprevention research in automatically collected databases forward, as this is a highly valuable source of information. Identification of a chemopreventive drug using these automatically collected databases may lead to an application in a clinical setting.

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Summary


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Chapter 1 is a general introduction to this thesis. The incidence of skin cancer is increasing in the Netherlands, like in many other countries. Sun exposure is a well-known risk factor, but primary prevention campaigns to reduce sun exposure seem to fail. Therefore chemoprevention might be an alternative to prevent skin cancer. In this thesis the epidemiology and burden of disease due to skin cancer in the Netherlands is described. The possibility of the use of chemopreventive drugs to prevent (skin) cancer incidence or prolong melanoma survival is investigated.

In **Chapter 2.1** I describe the epidemiology of cutaneous melanoma in the Netherlands. Data on all melanoma patients in the Netherlands between 1989 and 2008 was obtained from the Netherlands Cancer Registry (NCR). Mortality data was obtained from Statistics Netherlands (CBS). Like in most other countries, the incidence rate of melanoma has increased since 1989 by 4% each year. In 2008, more than 4000 people were diagnosed with melanoma in the Netherlands. The relative survival has improved and most likely reflects an artificial prolonged survival time caused by early diagnosis, because no major improvements in treatment were introduced during the study period. Unlike many other countries, in which mortality rates remained stable, the mortality rates of melanoma in the Netherlands increased as well by 2.3% annually. Because in many countries only incidence of thin melanomas increased and mortality rates remained stable, it was suggested that the increase in incidence represented overdiagnosis, which is an increased in diagnosis of cancer that would never had progressed or progressed very slowly. Because in the Netherlands the incidence of thick melanomas and mortality increased as well, I believe that the increase in melanoma incidence represents a real increase in disease occurrence and is not merely due to overdiagnosis.

In **Chapter 2.2** I describe the epidemiology of cutaneous squamous cell carcinoma (SCC) in the Netherlands. For this population-based study we used data from the NCR and CBS. In 2008, 6158 patients were newly diagnosed with cutaneous SCC. This corresponds to an European Standardised Rate (ESR) of 35.4 per 100,000 person-years for males and 20.5 per 100,000 person-years for females. The incidence rates of SCC increased since 1989, but since 2002 the incidence rates increased even more rapidly by 7% for males and 9% for females. This sudden increase in incidence rates was also observed for BCC in the Netherlands, but not for melanoma. The most likely explanation for this sudden increase in a delayed effect of cumulative sun exposure among the elderly. The 5-year relative survival of SCC remained high and stable during the study period (92% for females and 95% for males). The SCC mortality rate was low (0.5 per 100,000 person-years) and decreased by 1.9% annually.

In **Chapter 2.3** I differentiate between the epidemiology of SCC on sun exposed and covered body sites. SCCs on sun exposed body sites showed the largest absolute increase and were strongly associated with age. On the contrary, incidence of SCC on covered body sites

showed the largest relative increase and was weakly age-dependent. This pattern may reflect an increase in sun exposure on body sites that were previously unexposed (e.g. trunk) or may be due to the fourfold increase in immunosuppressive drug use in the Netherlands which is associated with a strongly increased SCC risk (RR up to 100-fold). The relatively large increase on SCC on covered body sites emphasizes the need for full body examination of patients who present with an SCC (mostly on visible body sites, such as the face).

The burden of disease attributable to cutaneous melanoma is described in **Chapter 3.1.** The World Health Organisation (WHO) has developed the Disability Adjusted Life Year (DALY), which is a measure of loss of healthy life years in a population and is obtained by the sum of the Years of Life lived with Disability (YLD) and the Years of Life Lost (YLL). The DALY also takes duration of disease into account as well as related conditions, such as pain and psychological concerns. Data on melanoma incidence was obtained from the NCR and data on melanoma mortality was obtained from CBS. The duration of disease was calculated by imputing the incidence, mortality and remission rates into the DISMOD software. Since 1991 the loss of DALYs has increased and reached an annual loss of more than 21,000 DALYs. Both YLL and YLD contributed to this increase. For an individual patient this means that on average patients live 19 to 27 years after melanoma diagnosis and patients who die due to melanoma loss on average 20 life years. After melanoma diagnosis, patients may be in need of additional health care, may experience problems with work or obtaining an insurance. Our results show that even though a disease has a good prognosis for most patients, it can be associated with a great burden to an individual patient and society.

In **Chapter 3.2** I describe the burden of disease due to keratinocytic cancer in the Dutch population. Data on SCC incidence was obtained from the NCR. BCC incidence was obtained from the comprehensive cancer center south (Eindhoven Cancer Registry [ECR]) and extrapolated to the Dutch population. Data on nonmelanoma skin cancer mortality (NMSC) was obtained from CBS. The duration of SCC was calculated by imputing the incidence, mortality and remission rates into the DISMOD software. The life expectancy at time of BCC diagnosis was considered the disease duration as mortality due to BCC is extremely rare. The burden of keratinocytic cancer has also increased during the past twenty years. The annual loss was estimated to be between 5,000 and 20,000 DALYs, depending on the assumed burden after follow up. The loss of DALYs was mainly driven by YLD. After follow up patients may be in need of additional health care for treatment of subsequent keratinocytic cancer, patients may fear or develop recurrences or subsequent keratinocytic cancer or they may not be satisfied with the cosmetic outcome. There are no disability weight for the period after follow up and the exact impact on quality of life after keratinocytic cancer diagnosis is unknown, which makes it difficult to estimate the loss of DALYs in the population. The extremely large incidence rates

cause a large burden on a population level. Since incidence rates are increasing by 6 to 9% annually, the management becomes even more challenging.

In **Chapter 4.1** I comment on clinical considerations when conducting chemoprevention research. Drugs used for chemoprevention are likely to be taken lifelong and should therefore have a favorable safety profile. Drugs used for chemoprevention of keratinocytic cancer should cause no or extremely minimal side-effects to put the risk:benefit balance in favor of the drug. Ideally the drug has additional health benefits, such as the prevention of cardiovascular events or other prevention of other cancers. Investigating the potential chemopreventive effect of candidate drugs is most efficient in patients at high risk, such as patients with actinic keratosis (AK), because the net benefit is expected to be large.

In **Chapter 4.2** is described how incorrect analysis of exposure during follow up may lead to biased risk estimates in survival analysis. β-Blocker use after melanoma diagnosis was used as an example. Duration of exposure is not measurable at the start of follow up. Treating duration of exposure as if it was already known at baseline leads to immortal time bias. That is, patients with a long duration of exposure have to be alive for a prolonged period of time to gain the exposure. This will always result in a protective effect of long term drug use with regard to the event of interest. Immortal time bias can be easily avoided by determining exposure status before the start of follow up or using a time-varying definition of exposure.

In **Chapter 4.3** I used data from the linkage between the ECR and the PHARMO record linkage system (RLS) to investigate the possible protective effect of low dose aspirin (< 100 mg daily) on cancer in general and many site-specific cancers. The ECR is a population-based cancer registry in the southern part of the Netherlands. The PHARMO RLS is a network of patient-centered databases containing, amongst other things, a community pharmacy database. The combination of these databases provided detailed information on both outcome and exposure. Cox proportional hazard models with a time-dependent covariate for exposure were used to calculate the hazard ratios. As I was not able to correct for all differences in cancer risk factors between aspirin users and non-users, I decided to perform the analyses in aspirin users only. Prior studies showed that short term aspirin use does not affect cancer risk, therefore I hypothesized that cancer risk among long term aspirin users would be lower compared to short term aspirin users. Duration of low dose aspirin use did not affect cancer risk (HR all cancers per year of aspirin use 1.02 95% CI: 1.00-1.04). Long term aspirin use (>6 years) was not associated with a decreased cancer risk in general or any site specific cancer (HR all cancers 1.17 95% CI: 1.02-1.34). I concluded that low dose aspirin use in a population at average risk for cancer is not recommended in a primary prevention setting. Our results do not exclude the possibility that low dose aspirin may be effective in patients at high risk for developing cancer.

In **Chapter 4.4** I examined the association between long term use of non-steroidal anti-inflammatory drugs (NSAIDs) and keratinocytic cancer. For this study, data from the linkage between the ECR and the PHARMO RLS was obtained. NSAIDs are also available over the counter (OTC) and are therefore not completely captured in the community pharmacy database of the PHARMO RLS. OTC use is most likely to be intermittent and short term use. Therefore we focused in this study on NSAID use of one year or more. Hazard ratios of NSAID use (>1 year) compared to short term or no use were calculated using Cox proportional hazard models with NSAID use as time-dependent covariate. Duration of NSAID was not associated with a decreased SCC or BCC risk (HR per year NSAID use: BCC 0.94, 0.88-1.01 HR SCC 0.96: 0.89-1.04). Average defined daily dose (DDD) did not modify the effect of NSAID duration (p for interaction BCC 0.77, SCC 0.55). Some NSAIDs have been reported to be photosensitizing, which may mask a potential beneficial effect of other non-photosensitizing NSAIDs. Therefore, photosensitizing NSAIDs and COX-2 inhibitiors were analysed as a separate group, but they were also not associated BCC or SCC risk. COX-2 inhibitors have been reported to be more potent chemopreventive drugs, but the number of events among COX-2 users was too low to perform separate analyses. I concluded that duration of NSAID use is not associated with a decreased keratinocytic cancer risk in a population at average risk.

In **Chapter 4.5** I describe a population-based cohort study among melanoma patients to investigate a possible beneficial effect of β-blocker use on melanoma progression. Melanoma cells express the β2-adrenergic receptors, which facilitate cancer metastasis in response to stress hormones. β-Blockers may therefore slow down melanoma progression. Data of the ECR-PHARMO cohort was used to retrieve exposure to β-blockers of all newly diagnosed patients with a thick melanoma (>1 mm) between 1998 and 2010. In our study, use of β-blockers before and after melanoma diagnosis was not associated with a beneficial effect on all-cause mortality (HR 0.82, 95% CI 0.55-1.24). The relative survival was calculated as a proxy for disease specific survival, but this was also equal between β-blocker users and non-users (80.9% for β-blocker users and 83.7% for non-users). Most patients used β1-selective β-blockers, whilst non-selective β-blockers may be more effective. This could not be examined, due to the low number of non-selective β-blocker users in our study and a larger study is required.

In **Chapter 5** I discuss the results of this thesis, indicate the strength and limitations and provide recommendations for future research. Several factors may have contributed to the observed increase in skin cancer incidence, of which an increased sun exposure is the most likely explanation. In addition to incidence and mortality rates, the burden of skin cancer in the population can be described by YLL, YLD and DALYs. In order to make a more accurate estimation of the total burden in the population, a re-estimation of the disability weights and the development of disability weights for the period after follow up is needed. On an individual level of disease burden, the impact of keratinocytic cancer on patients life's should

be investigated in more depth. Aspirin and NSAIDs were not found to reduce skin cancer incidence and use of β-blockers did not prolong melanoma survival. Further research should focus on more potent chemopreventive drug classes (e.g. non-selective β-blockers), subgroups of patients more likely to respond to the chemopreventive drug (genetic predisposed individuals, patient with multiple Aktinic Keratosis [AK] or possibly identification of tumor characteristics which predict efficacy of the chemopreventive drug). In addition, chemoprevention research in automatically collected databases comes with specific methodological challenges. The development of the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement is a good first step to improve reporting of these type of studies and to help identifying specific caveats.

Samenvatting

Hoofdstuk 1 is een algemene inleiding voor dit proefschrift. Net als in veel andere landen, neemt de incidentie van huidkanker in Nederland toe. Alhoewel blootstelling aan ultraviolet (UV) straling een bekende risicofactor is, lijken primaire preventie campagnes tot nu toe geen effect te hebben. Chemopreventie zou een alternatieve manier kunnen zijn om huidkanker te voorkomen. In dit proefschrift wordt de epidemiologie en de ziektelast van huidkanker in Nederland beschreven. Daarnaast wordt onderzocht of het gebruik van chemopreventieve medicatie huidkanker kan voorkomen of de overleving bij melanoom kan verbeteren.

In **hoofdstuk 2.1** wordt de epidemiologie van het cutane melanoom in Nederland beschreven. Data van alle patiënten met een eerste melanoom tussen 1989 en 2008 werd verkregen van de Nederlandse Kankerregistatie (NKR). Mortaliteitsdata werd verkregen van het Centraal Bureau voor de Statistiek (CBS). Zoals in de meeste andere landen, nam ook in Nederland de incidentie toe met zo'n 4% per jaar. In 2008 werden meer dan 4000 mensen gediagnosticeerd met een eerste melanoom. De relatieve overleving is verbeterd, maar dit wordt waarschijnlijk veroorzaakt door de vroege opsporing van het melanoom, want tussen 1989 en 2008 zijn er geen grote vooruitgangen geboekt voor de behandeling van het melanoom. In tegenstelling tot de meeste andere landen, waar de mortaliteit stabiel bleef, nam de mortaliteit in Nederlands juist toe met 2,3% per jaar. Er werd gesuggereerd dat de toegenomen incidentie is ontstaan door overdiagnose, omdat er veel dunne melanomen werden gediagnosticeerd en de mortaliteit vaak stabiel bleef. Overdiagnose is de diagnose van tumoren die nooit verder zullen groeien of zo langzaam groeien, dat de patiënt overlijdt aan een andere doodsoorzaak voordat de tumor symptomatisch wordt. In Nederland nam zowel de incidentie van dikke melanomen als de mortaliteit toe en daarom denk ik dat de toegenomen incidentie een echte toename in het aantal ziektegevallen weergeeft en dat het niet alleen te wijten is aan overdiagnosticering.

In **hoofdstuk 2.2** wordt de epidemiologie van het plaveiselcelcarcinoom (PCC) van de huid in Nederland beschreven. Voor deze studie werd weer gebruik gemaakt van de data van de NKR en het CBS. In 2008 werden 6158 patiënten gediagnosticeerd met een eerste PCC. Dit komt overeen met een leeftijdsgestandariseerd incidentiecijfer (European Standardised Rate [ESR]) van 35,4 per 100.000 persoonsjaren voor mannen en 20,5 per 100.000 persoonsjaren voor vrouwen. Sinds 1989 is de incidentie van PCC toegenomen en sinds 2002 neemt het steeds sneller toe, met 7% voor mannen en 9% voor vrouwen. Deze plotselinge toename werd in Nederland ook voor het basaalcelcarcinoom (BCC) waargenomen, maar niet voor het melanoom. De meest waarschijnlijke verklaring voor deze toename is, dat dit een effect is van de toename in de cumulatieve zonblootstelling van ouderen tijdens eerdere periodes in hun leven. De relatieve overleving van het PCC bleef hoog en stabiel tussen 1989 en 2008 (92% voor vrouwen en 95% voor mannen). De sterfte was laag (ESR: 0,5 per 100.000 persoonsjaren) en nam met 1,9% per jaar af.

In **hoofdstuk 2.3** wordt onderscheid gemaakt tussen de epidemiologie van PCC op zonblootgestelde en bedekte lichaamsdelen. De grootste absolute toename werd gezien bij PCC op de zonblootgestelde lichaamsdelen en de toename was sterk afhankelijk van de leeftijd. In tegenstelling tot de incidentie van PCC op zonblootgestelde lichaamsdelen, werd bij PCC op bedekte lichaamsdelen de grootste relatieve toename gezien. Deze toename was ook veel minder afhankelijk van de leeftijd. Dit patroon kan een weerspiegeling zijn van de toegenomen zonblootstelling op lichaamsdelen die vroeger bedekt bleven, zoals de romp. Maar het kan ook een gevolg zijn van de verviervoudiging van het gebruik van immunosuppressiva, hetgeen een 100 maal verhoogt risico geeft op PCC. De relatieve toename van PCC op bedekte lichaamsdelen benadrukt het belang van onderzoek van het gehele lichaam van patiënten die met een eerste PCC gediagnosticeerd worden. Deze bevinden zich namelijk vaak op de meest zichtbare plaatsen, zoals in het gezicht.

De ziektelast van het melanoom in de Nederlandse populatie wordt beschreven in **hoofdstuk 3.1**. De Wereld Gezondheidsorganisatie (World Health Organization [WHO]) heeft een maat ontwikkeld om het verlies in gezonde levensjaren in een populatie te beschrijven. Dit is de Disability Adjusted Life Year (DALY) welke wordt berekend door het aantal Years of Life Lost (YLL) en het aantal Years of Life lived with Disability (YLD) bij elkaar op te tellen. De duur van de ziekte en gerelateerde klachten, zoals pijn en psychologische klachten worden meegenomen bij de berekening van het aantal DALYs. Data over de incidentie van het melanoom werd weer verkregen via de NKR en de sterfte van het CBS. De duur van de ziekte werd berekend door de incidentie, de mortaliteit en de remissie in te voeren in de DISMOD software. Het verlies van DALYs in de Nederlandse populatie is sinds 1991 sterk toegenomen en in 2010 gingen 21.000 gezonde levensjaren verloren door het melanoom. Zowel een toename in YLD als YLL heeft hiertoe bijgedragen. Dit betekent dat een individuele patiënt gemiddeld 19 tot 27 jaar leeft na de diagnose. Gedurende deze periode kan een patiënt extra zorg nodig hebben, problemen ervaren op het werk of bij het verkrijgen van een verzekering of een hypotheek. Een patiënt die sterft door een melanoom verliest gemiddeld 20 levensjaren. Alhoewel de meeste patiënten met een melanoom een goede prognose hebben, laten deze resultaten zien dat de diagnose melanoom een behoorlijke last kan zijn voor de patiënt en de populatie.

In **hoofdstuk 3.2** word de ziektelast beschreven van BCC en PCC in de Nederlandse populatie. Voor dit onderzoek werd incidentie data van PCC van het NKR gebruikt. Incidentie data van BCC werd verkregen van het Integraal Kankercentrum Zuid (IKZ) en geëxtrapoleerd naar de Nederlandse populatie. Sterftecijfers van nietmelanoom-huidkanker (NMHK) werden verkregen via het CBS. De ziekteduur van PCC werd berekend door de incidentie, de sterfte en de remissie in te voeren in de DISMOD software. De levensverwachting op de leeftijd van de BCC diagnose werd gebruikt als de duur van de ziekte, omdat sterfte door een BCC extreem zeldzaam is. De ziektelast door BCC en PCC is de laatste 20 jaar ook toegenomen. Het

verlies in aantal gezonde levensjaren ligt tussen de 5.000 en 20.000 DALYs, afhankelijk van de aannames over de ziektelast na follow up. Het verlies van DALYs door BCC en PCC wordt voornamelijk gedreven door het verlies van YLD. Na follow up kunnen patiënten extra zorg nodig hebben voor de behandeling van recidieven, meerdere huidtumoren, angst hebben voor het ontwikkelen van nieuwe huidtumoren of ontevreden zijn over het cosmetische resultaat van de behandeling. Er zijn helaas geen disability weights voor de periode na follow up en de exacte impact op de kwaliteit van leven is ook niet bekend. Dit maakt het moeilijk om een nauwkeurige schatting te maken van het verlies van het aantal DALYs in de populatie. De zeer hoge incidentiecijfers veroorzaken een grote last op populatie niveau. Omdat de incidentiecijfers met 6 tot 9% per jaar toenemen wordt de behandeling van deze grote groep patiënten een behoorlijke uitdaging.

In **hoofdstuk 4.1** worden klinische overwegingen besproken die van belang zijn bij chemopreventie onderzoek. Chemopreventieve medicatie moet hoogstwaarschijnlijk levenslang gebruikt worden. Daarom is het belangrijk dat het gebruik van deze medicatie veilig is. Zeker voor de preventie van BCC en PCC, dat geassocieerd is met een zeer lage mortaliteit, is het belangrijk dat de medicatie geen of bijzonder weinig bijwerkingen geeft. Idealiter heeft de medicatie ook nog andere gezondheidseffecten, zoals de preventie van andere kankers. Chemopreventie onderzoek is het meest efficiënt bij patiënten met een hoog risico op huidkanker, zoals patiënten met actinische keratose (AK), omdat in deze patiëntengroep de nettowinst het grootst is.

In **hoofdstuk 4.2** wordt beschreven hoe een incorrecte analyse van medicatiegebruik tijdens follow up kan resulteren in onjuiste schattingen van het relatief risico in overlevingsanalyses. Het gebruik van β-blokkers na melanoom diagnose werd gebruikt als voorbeeld. De duur van de medicatie is niet te meten aan het begin van de follow up. Wanneer duur van de medicatie behandeld wordt in de analyse alsof dit aan het begin van de follow up al bekend was, ontstaat een immortal time bias. Dit resulteert altijd in een te laag relatief risico op de uitkomst door gebruik van de medicatie op lange termijn. Immortal time bias kan gemakkelijk worden voorkomen door gebruik van de medicatie te bepalen voor het begin van de follow up of door gebruik te maken van een tijdsafhankelijke definitie van medicatiegebruik in de analyse.

In **hoofdstuk 4.3** wordt data van de koppeling tussen het IKZ en het PHARMO Record Linkage System [RLS] gebruikt om de associatie tussen het gebruik van lage dosis aspirine (<100 mg per dag) en alle kankers te onderzoeken. IKZ is een populatie-gebaseerde kankerregistratie in het zuiden van Nederland. PHARMO RLS is een netwerk van patiënt-gecentraliseerde databases, dat onder andere een database bevat met alle recepten die zijn opgehaald in de openbare apotheek. Hierdoor is nauwkeurige informatie over het gebruik van aspirine

en diagnose van kanker beschikbaar. Cox proportionele hazard (PH) modellen met een tijdsafhankelijke definitie van aspirine gebruik werden gebruikt om de hazard ratio's (HR) te berekenen. De analyse werd beperkt tot de aspirine gebruikers, omdat het niet mogelijk was om de analyse aan te passen voor de vele mogelijke confounders. Uit eerdere studies is gebleken dat aspirine gebruikers pas na enkele jaren een verlaagd risico op kanker hebben. Onze hypothese was, dat het risico op kanker bij lange termijn aspirine gebruikers lager is dan bij mensen die aspirine slechts voor een korte periode gebruiken. De duur van lage dosis aspirine had geen effect op het risico op kanker (HR per jaar aspirine gebruik voor alle kankers 1.02, 95% betrouwbaarheidsinterval [BI]: 1.00-1.04). Lange termijn aspirine gebruik (>6 jaar) was ook niet geassocieerd met een verlaagd risico op kanker ten opzichte van korte termijn gebruik (<2 jaar) (HR per jaar aspirine gebruik voor alle kankers 1,17 95% BI 1,02-1,34). Hieruit concludeer ik dat gebruik van lage dosis aspirine als primaire preventie van kanker in de algemene populatie niet effectief is. Deze resultaten sluiten niet uit, dat lage dosis aspirine effectief kan zijn voor mensen met een hoog risico op kanker.

In **hoofdstuk 4.4** onderzoeken we de associatie tussen pijnstillers (Non-Steroidal Anti-Inflammatory Drugs [NSAIDs]) en BCC en PCC. Voor deze studie werd weer gebruik gemaakt van de data van de koppeling tussen IKZ en PHARMO RLS. NSAIDs zijn ook verkrijgbaar zonder recept en zijn daarvoor niet allemaal geregistreerd in PHARMO RLS. Het gebruik zonder recept is waarschijnlijk intermitterend en kortdurend. Daarom werd in deze studie alleen het langdurige gebruik (> 1 jaar) van NSAIDs onderzocht. HR's voor langdurig NSAID gebruik werden berekend door middel van Cox PH modellen met NSAID gebruik als tijdsafhankelijke variabele. Duur van NSAID gebruik was niet geassocieerd met een verlaagd risico op BCC en PCC (HR per jaar NSAID gebruik voor BCC 0,94, 95% BI: 0,88-1,01 HR PCC 0,96 95% BI: 0,89-1,04). De dagelijkse dosis had geen invloed op het effect van de duur van NSAID gebruik (p voor interactie BCC 0,77, SCC 0,55). Een fotosensibiliserend effect is beschreven voor een aantal NSAIDs. Dit kan een beschermend effect van NSAIDs maskeren. Daarom werden zowel de fotosensibiliserende NSAIDs als aparte groep geanalyseerd, maar het was niet geassocieerd met een verlaagd risico op BCC of PCC. Verder zijn de selectieve cyclooxygenase (COX)-2 remmers waarschijnlijk de meeste effectieve NSAID, maar heet aantal BCC en PCC bij COX-2 gebruikers was te laag voor een betrouwbare analyse. Langdurig NSAID gebruik is niet geassocieerd met een verlaagd risico op BCC en PCC in de algemene populatie.

In **hoofdstuk 4.5** wordt een populatie-gebaseerde cohort studie beschreven van patiënten met een dik melanoom (> 1 mm) om het effect van β-blokkers op de progressie van het melanoom te onderzoeken. De β_2-adrenoreceptor op melanoomcellen wordt geactiveerd door stress hormonen en kan van belang zijn bij metastasering. β-Blokkers zouden de metastasering kunnen vertragen of voorkomen. Data van het gebruik van β-blokkers bij alle patiënten met een eerste melanoom boven de 1 mm tussen 1998 en 2010 werd verkregen via de kop-

peling tussen IKZ en PHARMO RLS. Het gebruik van β-blokkers voor en na de diagnose van het melanoom was niet geassocieerd met een gunstig effect op de overleving (HR 0,82, 95% BI 0,55-1,24). De relatieve overleving, als een benadering van de ziekte-specifieke overleving, was gelijk tussen β-blokker gebruikers en niet-gebruikers (80,9% voor β-blokker gebruikers and 83,7% voor de niet-gebruikers). De meeste patiënten gebruikten β_1-adrenoreceptor-specifieke β-blokkers, terwijl niet-selectieve β-blokkers waarschijnlijk effectiever zijn om metastasering te voorkomen. Dit kon helaas niet worden onderzocht, vanwege het lage aantal gebruikers van niet-selectieve β-blokkers in de onderzoekspopulatie van onze studie. Een grotere studie is nodig om het mogelijke effect van niet-selectieve β-blokkers te kunnen onderzoeken.

In **hoofdstuk 5** worden de resultaten van dit proefschrift besproken en geïnterpreteerd. De sterke en zwakke punten worden besproken en er worden aanbevelingen gedaan voor verder onderzoek. Verschillende factoren hebben bijgedragen aan de toename van de incidentie van huidkanker, waarvan een toegenomen blootstelling aan UV straling waarschijnlijk de belangrijkste verklaring is. Naast de incidentie en de mortaliteit kan de ziektelast in een populatie ook worden beschreven door YLD, YLL en DALYs. Om betere schattingen te kunnen maken van de totale ziektelast in de populatie is het nodig dat de disability weights opnieuw worden bepaald en dat er nieuwe gewichten worden ontwikkeld voor de periode na follow up. Hiervoor moet eerst de impact van BCC en PCC op individueel niveau verder worden onderzocht. Langdurig gebruik van lage dosis aspirine en NSAIDs lijken het risico op (huid) kanker niet te verlagen en ook het gebruik van β-blokkers lijkt geen effect te hebben op de overleving van het melanoom. Verder onderzoek zou beperkt moeten worden tot medicatie die mogelijk effectiever is (zoals bijvoorbeeld niet-selectieve β-blokkers) en op patiëntengroepen die het meeste baat kunnen hebben bij chemopreventie (bijv. patiënten met een genetische predispositie, patiënten met meerdere Aktinische Keratose (AK) of de mogelijke identificatie van tumor en patiënt karakteristieken die voorspellend zijn voor de response van de patiënt). Daarnaast zijn er specifieke methodologische problemen bij chemopreventie onderzoek in geautomatiseerde gezondheidszorg databases. De ontwikkeling van de REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement is een goede eerste stap om de rapportage te verbeteren en specifieke valkuilen te identificeren.

List of publications

PUBLICATIONS IN THIS THESIS

L.M. Hollestein, S.A.W. van den Akker, T. Nijsten, H.E. Karim-Kos, J.W.W. Coebergh and E. de Vries Trends of cutaneous melanoma in The Netherlands: increasing incidence rates among all Breslow thickness categories and rising mortality rates since 1989. *Ann Oncol*. Feb 2012; 23 (2): 524-30

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Dankwoord


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DANKWOORD

Promotie onderzoek doe je niet alleen en daarom wil ik een aantal mensen bedanken. Allereerst wil ik Tom bedanken. Hij is superbelangrijk voor mij en ik vind het zielig als hij pas achteraan komt te staan.

Lieve Tom, dankjewel, dat je er altijd voor me bent. Je bent er voor me als ik vrolijk thuis kom, wanneer ik weer één of andere leuke analyse heb geprogrammeerd, maar je bent er ook voor me als ik chagrijnig thuis kom, omdat die stomme analyses weer niet willen lukken. Ik ben ontzettend trots op je en ik ben blij voor je dat je nu ook elke dag vrolijk naar je werk toe gaat.

Daarnaast ben ik vooral Tamar en Esther veel dank verschuldigd. Voor het vertrouwen dat zij mij gegeven hebben, voor alle mogelijkheden om mezelf verder te ontwikkelen en omdat ik simpelweg de leukste baan ter wereld van hen gekregen heb!

Beste Tamar, ik had me geen betere promotor kunnen wensen. Terwijl ik door de SPSS/SAS/R bomen soms het bos niet meer zag, bleef jij altijd de grote lijnen van het onderzoek zien. Ik heb veel bewondering voor hoe je alle onderzoekers begeleid en voor al je expertise op die verschillende onderzoeksgebieden. Ondanks je drukke schema, weet je toch altijd even tijd voor mij te maken. Daar heb ik veel waardering voor.

Beste Esther, al heel snel werd ik 'Esther de tweede' genoemd bij de Dermatologie en dat beschouw ik als een heel groot compliment. Ik heb veel profijt gehad van al je ervaring en je netwerk van internationale contacten. Ik ben erg blij voor je dat je het IARC project in Colombia kon gaan doen, maar ik mis je gezelligheid en onze overleg-momentjes bij de Derma. Ik vind het ontzettend leuk, dat je de halve wereld over bent gereisd om bij mijn verdediging te kunnen zijn!

Ik wil iedereen bij PHARMO bedanken. Het was ontzettend leuk, om een paar dagen per week bij jullie te werken. Ik heb ontzettend veel geleerd. Jullie zijn een goed team! Beste Myrthe, je was een goede begeleider. Het is leuk om zo af en toe nog even telefonische te sparren over epidemiologische problemen. Ik vind het erg leuk dat je in mijn commissie plaats wilt nemen.

Ook wil ik graag alle mensen van het IKZ bedanken. Het is ontzettend fijn om met jullie samen te werken. Mieke, je bent altijd supersnel met het toesturen van comments of data. Ik vind het erg leuk, dat ook jij in mijn commissie zit.

Beste Jan-Willem Coebergh, Bruno Stricker en Martino Neumann, hartelijk dank voor het plaatsnemen in de kleine commissie en het doorlezen (en goedkeuren!) van mijn proefschrift. Beste Bruno en Jan-Willem, hartelijk dank, dat ik mocht aansluiten bij jullie onderzoeksgroep.

Beste Ron en Erik, hartelijk dank voor de fijne samenwerking. Ondanks de lange tijd en vele moeite dat het kostte om het aspirine artikel te publiceren, bleven jullie de vorderingen volgen. In het vervolg kan ik beter geen 'one size fits all approach' toepassen, maar zal ik op zoek moeten naar de juiste schoenmaat!

Beste Alexander van Akkooi, hartelijk dank dat je vandaag in mijn commissie plaats wilt nemen.

Alle co-auteurs wil ik ook hartelijk bedanken voor jullie inzet en de fijne samenwerking.

Dear Elisabeth, thank you for our collaboration. I enjoyed working with you and I will visit you very soon in Germany. I am looking forward to working on future projects with you and Dirk Schadendorf.

Beste Theo Stijnen, hartelijk dank voor het beantwoorden van al mijn statistiek vragen. Wat jammer, dat de Masterspecialisatie Statistical Science er nog niet was voor biomedische wetenschappen toen ik in Leiden studeerde!

Beste Ewout Steyerberg en Yvonne Vergouwe, ook al staan de projecten waar ik met jullie samen aan heb gewerkt niet in mijn proefschrift, ik wil jullie toch bedanken voor de samenwerking. Het is fijn om met al mijn vragen over predictiemodellen bij jullie terecht te kunnen.

Beste Dennis en Vincent, bij Generation R is mijn enthousiasme voor de klinische epidemiologie begonnen. Hartelijk dank voor de ontzettend leuke afstudeerstage.

Beste Enes, Robert, Sophie, Cynthia, Emmilia, Joris, Leonie, Satu, Merel en Shmaila. Best jammer, dat ik geen 10 paranimfen kon vragen. Vooral dankzij jullie ga ik elke dag met veel plezier naar mijn werk. Ook al is het heel erg ouderwets, maar ik vind het hartstikke gezellig, dat jullie nog regelmatig met mij praten, omdat ik alles via de whatsapp mis!
Beste Satu, bedankt dat je mijn paranimf wil zijn. We hebben maar aan één artikel samengewerkt in dit proefschrift, maar dat moeten we écht veranderen. Ik hoop dat we nog veel nerdie-projecten samen kunnen doen. Ik zal 1-5-15, vast vrij houden voor jouw promotie (dat is wel zo leuk na 11-11-11 en 11-12-13)!
Beste Leonie, dankjewel dat je mijn paranimf wil zijn. Bedankt, dat je altijd zo vrolijk, behulpzaam en geïnteresseerd bent. Gelukkig staat de analyse-pc bij jullie, dan heb ik een goede

reden om even gezellig een kletspraatje te maken. Heel veel succes met het afronden van je promotie!
Alle andere onderzoekers van de Dermatologie wil ik ook bedanken voor de ontzettend fijne sfeer. Ik veel geleerd van al jullie vragen. Het is mede dankzij jullie dat ik kan promoveren.

Het is inmiddels een traditie op de afdeling Dermatologie, dat je in het begin steeds naar een werkplek op zoek bent. Het voordeel van zo vaak verhuizen, is dat ik veel verschillende gezellige roomies tegen ben gekomen (o.a., Cynthia, Sophie, Robert, Enes, Emmilia, Imke, Anne-Roos, Petra, Michelle, Satu, Esther, Luba en Shmaila).

Lieve vrienden, heel erg bedankt voor de gezellige etentjes, filmavondjes, picknicks, vakanties, avondjes bankhangen, (hard)looptrainingen, derde kerstdagen, etc. Dat is namelijk heel erg belangrijk om het promoveren vol te kunnen houden!

Lieve vrienden van Hashi (of onze derde familie), heel erg bedankt voor alle gezellige trainingen en kletspraatjes aan de Hashi-bar! Nu dit proefschrift af is, wordt het toch wel eens tijd om mijn zwarte band te gaan halen?! (Als mijn lieve uke ten minste tijd heeft?)

Lieve Joop en Joop Jr., heel erg bedankt voor de interesse die jullie altijd in mijn werk tonen en het werk dat jullie ons uit handen nemen, bijvoorbeeld wanneer we zelf niet hoefden te koken, als we het druk hadden en gezellig bij jullie konden aanschuiven. Ook vandaag denk ik aan Lidy. Ze zou vast erg trots zijn geweest zijn en de hele buurt verteld hebben over mijn promotie.
Lieve Tonnie, je bent ontzettend lief voor ons geweest. Ik had af en toe moeite om te ontspannen tijdens de afronding van dit proefschrift, maar als we gezellig een dagje naar Den Bosch gingen had ik daar helemaal geen moeite mee!

Lieve papa en mama, dankjewel voor alles. Dat zeg ik, omdat deze paar bladzijden te kort zijn om alles op te schrijven, maar ik ga het toch proberen (goh, wat lijk ik toch op mijn moeder). Dankzij jullie heb ik altijd eerst mijn huiswerk gemaakt, terwijl ik eigenlijk iets leukers wilde gaan doen. En dankzij jullie kon ik gaan studeren (en zelfs nog een keer van studie veranderen). Dankjewel dat jullie er altijd voor me zijn en zoveel voor me doen.

Lieve Myrna, jij leerde me dat er meer is in het leven dan alleen maar studeren. En dat er meer soorten schoenen zijn dan Ecco's en meer soorten tassen dan Eastpaks. Alhoewel we in veel opzichten van elkaar verschillen, lijken we soms toch ook heel veel op elkaar. Ik vind het supergezellig dat jij en Julien nu onze overburen zijn. Hopelijk vinden jullie dat ook.

Lieve Erwin, (sorry, dat je nu achteraan staat?!) mijn kleine broertje, die inmiddels al veel groter is dan ik. Je bent een volhouder. Ik ben hartstikke trots op je en ik vond het supergaaf om bij je propedeuse-uitreiking te zijn. En ik ben vast dubbel zo trots als je studie straks af is. Zet 'm op!

Curriculum Vitae

Loes Hollestein werd geboren op 4 juli 1984 in Rotterdam. Zij en haar man, Tom Zandwijk, haalden in 2002 hun VWO diploma aan de christelijke scholengemeenschap 'Het Farel College' in Ridderkerk. Daarna studeerde zij twee jaar aan de pedagogische academie voor het basis onderwijs (pabo) van de Hogeschool Rotterdam in Dordrecht. In 2004 begon zij aan de studie biomedische wetenschappen in Leiden. Haar afstudeeronderzoek deed zij op de afdeling epidemiologie bij Generation R, waarbij ze echo vetmetingen bij kinderen valideerde met behulp van computed tomography (CT)-scans als gouden standaard. In 2010 studeerde ze af in de educatie richting van de master biomedische wetenschappen en haalde zij haar eerstegraads lesbevoegdheid voor biologie in het voortgezet onderwijs bij het Interfacultair Centrum voor Lerarenopleiding, Onderwijsontwikkeling en Nascholing (ICLON). In 2010 begon zij aan haar proefschrift bij de afdeling Dermatologie in het Erasmus Medisch Centrum onder leiding van Prof.Dr. Tamar Nijsten en Dr. Esther de Vries. Na de afronding van haar proefschrift zal ze werkzaam blijven bij de afdeling Dermatologie als onderzoeker.

PhD Portfolio Summary

PHD PORTFOLIO SUMMARY

Name PhD student:	Louisette Maria Hollestein
Erasmus MC Department:	Dermatology
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD-period:	March 2010 – December 2012
Promotor:	Prof.dr. T.E.C. Nijsten
Supervisor:	Dr. E. de Vries

	Year	Workload (hours/ECTS)
1. PhD training		
General courses		
Master's degree clinical epidemiology, NIHES	2010-2012	
Principles of research in medicine	2010	0.7 ECTS
Clinical decision analysis	2010	0.7 ECTS
Methods of public health research	2010	0.7 ECTS
Markers and prognostic research	2010	0.7 ECTS
Clinical trials	2010	0.7 ECTS
Pharmaco-epidemiology	2010	0.7 ECTS
Classical methods for data-analysis	2010	5.7 ECTS
Modern statistical analysis	2010	4.3 ECTS
Principles of genetic epidemiology	2011	0.7 ECTS
Cohort studies	2011	0.7 ECTS
Primary and secondary prevention research	2011	0.7 ECTS
Study Design	2011	4.3 ECTS
Clinical epidemiology	2011	5.7 ECTS
Methodological topics in epidemiologic research	2011	1.4 ECTS
Cancer epidemiology	2012	1.4 ECTS
Meta-analysis	2012	0.7 ECTS
Basis regelgeving klinisch onderzoek (BROK)	2010	22 hours
Specific Courses		
Courses for the quantitative researcher	2010	1.4 ECTS
Advanced topics of clinical trials	2012	1.4 ECTS
Repeated measurements	2012	1.4 ECTS
Missing values in clinical research	2012	0.7 ECTS
Workshops		
Advanced workshop on cancer survival methodology London School of Hygiene and Tropical Medicine	2011	16 hours

Presentations		
Oral		
'NSAIDs may prevent melanoma' 12e Wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, Nederland	2010	1 ECTS
'Cutaneous SCC in the Netherlands: trends in incidence, survival and mortality 1989-2008' 41st Annual meeting of the European Society for Dermatological Research (ESDR), Barcelona, Spain	2011	1 ECTS
'NSAIDs and low dose aspirin may prevent melanoma and keratinocytic cancers' 13e Wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, Nederland	2012	1 ECTS
'Aspirin and risk of BCC: a population-based linkage study' 6th International Congress on Dermato-epidemiology (IDEA), Malmö, Sweden	2012	1 ECTS
'Epidemiology of melanoma in the Netherlands' Symposium Melanoom, Werkgroep Immunologie Nederland voor Oncologie (WIN-O) , Zeist, The Netherlands	2012	1 ECTS
'Burden of disease due to melanoma increased in the Netherlands since 1991' Melanoma group meeting of the European Organisation for Research and Treatment on Cancer (EORTC), Paris, France	2013	1 ECTS
'Low dose aspirin use is not associated with a decreased skin cancer risk: a population-based cohort study among 1.2 million Dutch inhabitants' 6th International Investigative Dermatology (IID) meeting, Edinburgh, Scotland	2013	1 ECTS
Poster		
'Burden of keratinocytic cancer in the Netherlands' 14e Wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, Nederland	2013	1 ECTS
'Burden of disease due to skin cancer increased in the Netherlands' 8th World Congress of Melanoma, Hamburg, Germany	2013	1 ECTS
International Conferences		
6th Meeting of the European Association of Dermato Oncology (EADO), Athens, Greece	2010	1 ECTS
41st meeting of the European Society of Dermatologic Research (ESDR), Barcelona, Spain	2011	1 ECTS
7th International Congress on Dermato-Epidemiology (IDEA), Malmö, Sweden	2012	1 ECTS
6th International Investigative Dermatology (IID) meeting, Edinburgh, Scotland	2013	1 ECTS
Melanoma group meeting of the European Organisation for Research and Treatment on Cancer (EORTC), Paris, France	2013	1 ECTS
8th World Congress of Melanoma, Hamburg, Germany	2013	1 ECTS
National Conferences		
12e Wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, Nederland	2011	1 ECTS
13e Wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, Nederland	2012	1 ECTS
14e Wetenschappelijke jaarvergadering van de Nederlandse Vereniging voor Experimentele Dermatologie (NVED), Lunteren, Nederland	2013	1 ECTS

Other		
Integraal kankercentrum Nederland (IKNL) Thema avond: alle risicofactoren voor huidkanker nog eens op een rij, Leiden, The Netherlands	2011	2 hours
Integraal kankercentrum Nederland (IKNL) Thema avond: Nieuwe ontwikkelingen binnen de diagnostiek en behandeling van het maligne melanoom, Leiden, The Netherlands	2011	2 hours
Symposium Melanoom, Werkgroep Immunologie Nederland voor Oncologie (WIN-O) , Zeist, The Netherlands	2012	8 hours
PhD day, Rotterdam, The Netherlands	2012	6 hours
SPA II: Oncologie in de parel van de Ardennen, Spa, Belgium	2012	1 ECTS
Methodologie van Patiëntgebonden onderzoek en Voorbereiding van subsidieaanvragen, Centrum van Patiëntgebonden Onderzoek (CPO), Rotterdam, The Netherlands	2013	6 hours
2. Teaching		
Practical 'Introduction SPSS ' EADV/ESDR Summer Research Course: Clinical Research and Epidemiology	2012	1 ECTS
Supervising research meetings at the department of Dermatology	2010	2 ECTS
Supervising master's thesis of Marlieke Vos, Erasmus University, Rotterdam 'Aspirin use and melanoma survival'	2013	2 ECTS
Occasional Reviewer for:		
British Journal of Dermatology		
Journal of Investigative Dermatology		
International Journal of Cancer		
European Journal of Cancer		

Printing of this thesis was financially supported by: Integraal Kankercentrum Zuid, Pharmo Institute, N.V., Leo Pharma B.V., Pfizer B.V., Roche, Fagron, Abbvie B.V., Chipsoft, Spirig Benelux (Galderma Benelux), Eucerin.