Sunscreen use, indoor tanning and risk of melanoma among Norwegian women

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The highest activity a human being can attain is learning for understanding, because to understand is to be free.

Baruch Spinoza

Summary

Cutaneous melanoma is a major public health challenge with rising incidence rates in most western countries. Exposure to ultraviolet (UV) radiation is the main cause of cutaneous melanoma. The most important UV exposure is sunlight, and sunscreen use is a routine advice for skin cancer prevention, especially for intentional sun exposure such as sunbathing. Sunscreen use protects against sunburn and squamous cell carcinoma of the skin, however, the question regarding if sunscreen use prevents melanoma remains open and controversial. Indoor tanning has become popular in recent decades also among teens and young adults. Indoor tanning was recently classified as carcinogenic to humans but the association between indoor tanning and melanoma is still uncertain, with more evidence for exposure before age 35. Public health consequences of melanoma are increasingly important and more knowledge is needed for effective melanoma prevention.

This thesis investigated sunscreen use and sunburn in relation to demographic and phenotypic characteristics, trend of sunscreen use between 1997and 2007, and the association between sunscreen use, including sun protection factor (SPF), and melanoma and the attributable fraction of melanoma related to sunscreen use. Moreover, this thesis aimed to study the association between indoor tanning and melanoma risk including dose-response, age at first use and age at melanoma diagnosis. Data from the Norwegian Women and Cancer Study (NOWAC) was used, which is a large population-based prospective study, established in 1991, with a long and complete follow-up through 2012, and is representative of the Norwegian female population.

Sunscreen use was increasing from 1997 to 2007 with a tendency to use sunscreens with higher SPF. However, sunburn was an issue and had not decreased over this time period. Moreover, use of sunscreen with SPF≥15 was not common among Norwegian women. The prospective NOWAC data support the hypothesis that during intentional sunbathing SPF≥15 sunscreen use can reduce melanoma risk compared to use of SPF<15 sunscreen. The findings of this thesis suggest that use of sunscreen with SPF≥15 by all women aged 40–75 might lead to an 18% drop in melanoma incidence in 10 years. Furthermore, the findings of this thesis provide strong supporting evidence on the strength of the association, dose-response, and temporality of the association between indoor tanning and melanoma risk, and the hypothesis of a higher vulnerability to harmful effects of indoor tanning before 35 years of age.

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Abbreviations

AM	Acreal melanoma
CI	Confidence interval
EPIC	European Prospective Investigation into Cancer and Nutrition
EU	European Union
HR	Hazard ratio
IARC	International Agency for Research on Cancer
ICD	International classification of disease
LM	Lentigo maligna melanoma
MED	Minimal erythema dose
NM	Nodular melanoma
NOWAC	Norwegian Women and Cancer Study
OR	Odds ratio
PAF	Population attributable fraction
PF	Prevented fraction
PPD	Persistent pigment darkening
PR	Prevalence ratio
RR	Relative risk
SCC	Squamous cell carcinoma
SPF	Sun protection factor
SSM	Superficial spreading melanoma
UV	Ultraviolet

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1. Introduction

Cutaneous melanoma (hereafter termed melanoma) is the most lethal form of skin cancer and a major public health challenge in white populations. Melanoma incidence has increased faster than any other cancer among many white populations during the past decades. It is estimated that there were 230 000 new cases of melanoma worldwide and 55 000 deaths attributed to it in 2012 (1), with 22 000 of those deaths in Europe (2-4). Additionally, melanoma was responsible for 1 169 000 years of life lost in 2010 worldwide (5). Norway has one of the highest incidence rates of melanoma in the world, and incidence rates have increased 28% and 29% among men and women, respectively, from the previous 5-year (2005–2009) to the most recent period (2010–2014) (6).

Both solar and artificial ultraviolet (UV) radiation are classified by the International Agency for Research on Cancer (IARC) as carcinogenetic to humans (7). Solar radiation is the most important environmental risk factor for melanoma (8, 9). However, the association is complex. While epidemiological studies have found no positive association between chronic sun exposure (continuous exposure mainly due to occupational exposure) and risk of melanoma (10), intermittent exposure (short and intense exposure mainly due to sunbathing, vacations in sunny climates or outdoor recreations) and history of sunburns, which is a predictor of intermittent exposure, increase the risk of melanoma substantially (10-13). Sunscreens are recommended alongside clothing and shade to protect skin from harmful effects of solar radiation (14, 15). If applied properly, sunscreen can decrease the risk of actinic keratosis (16) and squamous cell carcinoma (SCC) (17). However, epidemiological studies on sunscreen use and risk of sunburn have inconsistent results, with some studies indicating a higher risk of sunburn among sunscreen users (18, 19). Moreover, the association between sunscreen use and risk of melanoma is still controversial. Some studies found a decreased risk of melanoma among sunscreen users (20-23), while others found no association (24) or higher risk of melanoma among sunscreen users (25-28). Behavioural patterns of sunscreen use seem to play an important role in the paradoxical findings regarding sunscreen use and risk of sunburn and melanoma (29, 30). Indoor tanning, another behavioural risk factor for melanoma, has been very popular in many western countries since the early 1980s (31), and thus has become an important source of UV exposure. Several epidemiological studies investigated the association between indoor tanning and risk of melanoma, and the

summary estimates from meta-analyses showed a positive association (32-34). However, the body of evidence is mainly from case-control studies, and high-quality evidence is still scarce.

The purpose of this thesis was to study sunscreen use and sunburn in relation to demographic and phenotypic characteristics and to investigate the association between sunscreen use, including sun protection factor (SPF), and melanoma and the attributable fraction of melanoma related to sunscreen use. Moreover, this thesis aimed to study the association between indoor tanning and melanoma risk including dose-response, age at first use and age at melanoma diagnosis.

This thesis used data from the Norwegian Women and Cancer Study (NOWAC) [Kvinner og Kreft]. NOWAC is a large population-based prospective study established in 1991, with a long and complete follow-up, and is representative of the Norwegian female population (35).

The background section of this thesis will review the scientific literature on melanoma, its epidemiology and risk factors, with more focus on risk factors as related to the aims of the thesis.

2. Background

2.1 Cutaneous melanoma

Melanoma is a generic term for a malignancy derived from pigment-producing cells (melanocytes), which are located primarily in the skin (cutaneous), but also found in the respiratory tract, gastrointestinal tract, genitourinary tract (mucosal), or eyes (ocular or uveal) (36). For the purpose of this thesis, we use the term "melanoma" for the cutaneous melanoma. Melanoma is the most lethal form of skin cancer. Although it is responsible for only 4% of all skin cancers, 80% of the skin cancer deaths are due to melanoma (37).

Melanoma is classified into four clinical subtypes, and different pathways of carcinogenicity have been suggested for each subtype (38-40):

1. Superficial spreading melanoma (SSM) is the most commonly occurring subtype of melanoma, accounting for 60–80% of all diagnosed melanomas. SSM is associated with intermittent sun exposure and tends to begin in pre-existing nevi. It occur more commonly on the trunk and lower limbs, and have a radial growth pattern.
2. Lentigo maligna melanoma (LM) is slow growing, occurring usually on the chronically sun-exposed skin such as the face, head, and neck. It is diagnosed mainly in the seventh decade of life and comprises 5–15% of melanomas.
3. Nodular melanoma (NM) may arise on any skin site and usually presents as a rapidly growing lump, which can be non-pigmented and ulcerated. NM is characterized by rapid vertical growth, contrary to SSM. Even though NM represents 10–30% of all melanomas, it counts for 50% of thick melanomas (thickness > 2.0 mm).
4. Acreal melanoma (AM) starts as a slowly enlarging asymmetric brown-black macule, on the palms, soles, or under the nail. AM accounts for less than 10% of all melanomas, but tends to have a worse prognosis compared with other subtypes.

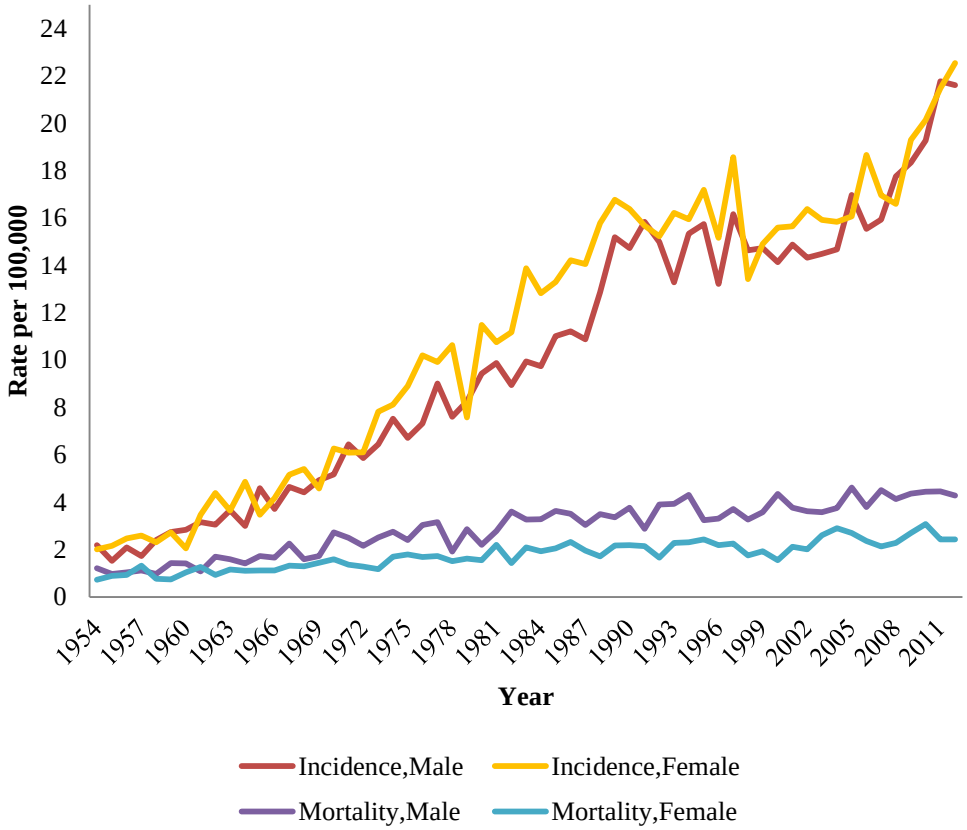
2.2 Epidemiology

2.2.1 Incidence and mortality

In 2012, more than 230 000 new cases and 55 000 individuals were estimated to die from melanoma globally (1). Melanoma incidence has increased faster than any other cancer in many western countries in the past decades (2, 41). In the USA, the age-

adjusted incidence rate has risen from 8 and 9 per 100 000 among women and men, respectively, in 1975 to 24 and 35 per 100 000 among women and men, respectively in 2010 (42). An individual dying from a melanoma loses an average of 20 years of potential life (43, 44). Total treatment cost of melanoma is estimated as $3.3 billion annually in the USA (45). In Norway, melanoma has developed from being a very rare disease in the 1950s, with age-adjusted incidence rate less than 3 in 1954–1958, to the fourth most common cancer type, with 37 and 42 cases per 100 000 among women and men, respectively, in 2014 (6, 46). Norway has the highest mortality rate due to melanoma in Europe (3) and the mortality rate has increased during the past decades (Figure 1).

Figure 1. Melanoma incidence and mortality between 1954–2012 among women and men in Norway (source: NORDCAN; 27/1/2016).



2.2.2. Risk factors

The causal carcinogenic mechanism of melanoma is complex, and an individual´s risk depends upon phenotypic characteristics, genetic factors, UV exposure, behavioural factors, and the interactions between them.

a) Phenotypic characteristics

Nevi

Number and type (i.e. common or atypical) of nevi, also known as moles, are one of the well-known risk factors for melanoma. Nevi are benign lesions, which are composed of melanocytes. Several epidemiological studies and their summary estimates in the meta-analyses (12, 47) have shown that the number of common nevi is an important risk factor for melanoma. In the most recent meta-analysis, individuals with ≥50 common nevi had more than double the risk of developing melanoma compared with individuals with <10 nevi, and 27% of the melanomas were attributed to having ≥50 common nevi on the body (48). Moreover, there is a strong dose-response association between the number of common nevi and melanoma risk, and individuals with ≥150 common nevi on their body are at more than 12 times higher risk of developing melanoma than individuals with <10 nevi (48).

Atypical (also known as dysplastic or asymmetric) nevi are also associated with higher risk of melanoma. Individuals with ≥7 atypical nevi larger than 5mm on their leg were at 5 times higher risk of melanoma (49). It is estimated that about 25% of melanomas are attributed to the presence of one or more atypical nevi (48).

The role of nevi in melanoma development is complex and still not fully understood. The expression and development of a nevus are also complex and are related to both genetic and environmental factors and their interaction (42).The number of nevi is shown to be associated with UV exposure (50, 51) and a twin study found that both age and sun exposure mediate the contribution of genetic factors in the expression of nevi (52). Two different pathways for melanoma are suggested, known as the “divergent pathway” hypothesis (53): 1) Individuals with a low propensity for melanocytic proliferation require regular sun exposure to develop melanoma and are more likely to develop melanoma on sun-exposed body sites such as the face, head or neck. This pathway is called “chronic sun exposure” and requires high cumulative exposure to the sun for

development. 2) Individuals with a large number of nevi have an inherently high propensity for melanocytic proliferation and require modest sun exposure in order to develop melanoma. This group is more likely to be diagnosed with melanoma on body sites with large numbers of nevi such as the trunk. This pathway is called "nevous pathway" and tends to develop earlier in life (in the middle decades) compared with "chronic sun exposure" melanomas(53). Some epidemiological studies support this hypothesis (54-56).

Other pigmentation factors

The major phenotypic characteristics that are established melanoma risk factors are fair skin colour, skin sensitivity to sun exposure (i.e. skin that freckles after sun exposure, burns easily and unable to acquire tan), and hair and eye colour. Melanoma is rare in dark-skinned populations (57). Two meta-analyses showed that both fair skin and high freckle density were independent risk factors, which each of them approximately doubled melanoma risk (58, 59). The Norwegian-Swedish Women lifestyle and Health cohort study (49) found an increased risk of melanoma among individuals with skin sensitivity to sun exposure. The summary estimate of thirty-seven case-control studies showed an increased risk of melanoma among individuals with light hair and eye colour (59). In the NOWAC study (which population partially overlaps with the Norwegian-Swedish Women lifestyle and Health cohort study), eye colour was not associated with melanoma risk, while hair colour was: blond- and red-haired women had more than two and three times higher risk of melanoma, respectively (49). It is argued that the association between hair and eye colour and risk of melanoma might not be causal and only due to their collinearity with skin colour and sensitivity. However, as hair and eye colour are less prone to misclassification or recall bias, they may be the most accurate measure of skin sensitivity in fair skin populations such as Norway (49, 60).

b) Genetic risk factors

Approximately 5% of all melanomas occur in a familial setting with two or more first-degree relatives affected (61). A meta-analysis of fourteen case-control studies found a 74% increased risk of melanoma associated with a family history of melanoma in first-degree relatives (relative risk [RR]=1.74, 95% confidence interval [CI]: 1.63–1.95) (59). However, it is not clear whether this association is due to shared genetic factors, environmental factors, or both. The discovery of melanoma susceptibility genes is

important in the understanding of melanoma causal pathways and treatment, as well as developing precise prediction tools to identify high-risk groups (42).

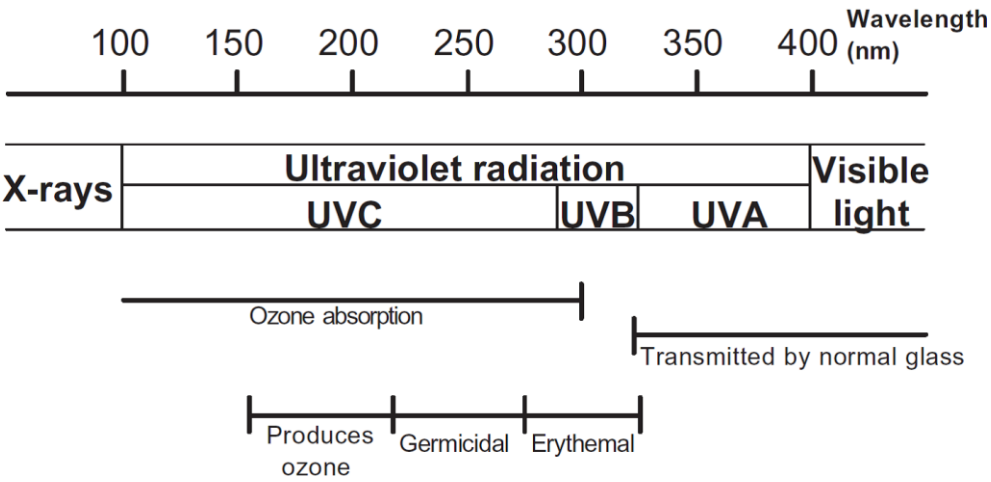
c) Environmental factors

UV radiation from both sun exposure and indoor tanning is the most important and the only easily modifiable risk factor for melanoma. Several studies have linked sun exposure and indoor tanning to melanoma risk (10, 32), but the association is complex, and differs for intermittent, chronic and total exposure (the sum of chronic and intermittent exposure). Indoor tanning was classified as carcinogenic to human by International Agency for Research on Cancer (IARC) in 2009 (7); however, the conclusion of the expert group doing the evaluation was based mainly on the evidence from case-control studies (33). Since UV exposure and protection is the focus of this thesis, this topic will be discussed in more depth in the following sections.

2.3 Sun exposure

Sun exposure is the major cause of melanoma and more than 90% of melanoma in Australia, Canada, UK, Nordic countries, and the USA is attributed to sun exposure (62-66). Solar radiation consists of a continuous spectrum of electromagnetic radiation and can be divided into three main ranges of wavelengths: UV, visible, and infrared (8).

Figure 2. UV radiation spectrum. From Matsumura and Ananthaswamy (8).



UV radiation is also divided into three parts (Figure 2): UVA (320–400 nm), UVB (280–320nm) and UVC (100–280nm). Both UVA and UVB might play important roles in the carcinogenesis of melanoma. UVB can cause DNA damage and gene mutation (67). The

consequence is sunburn, inflammation, and a tanning response in human skin. UVB also has immunosuppressive effects and plays a role in skin aging (8, 68). UVA, which penetrates more deeply into the skin, contributes substantially to skin aging, also known as photo-aging. Until recently scientists believed that it was less dangerous than UVB, but studies over the past two decades revealed that UVA also has immunosuppressive and carcinogenic effects (69).

UV exposure from midday sun consists of 95% UVA and 5% UVB. Almost all UVC and most of UVB is blocked by stratospheric ozone. The UVA and UVB that reach the earth surface depends on several factors including time of day, season, geographical latitude and altitude, clouds, surface reflection, and air pollution. The sun is the major source of human exposure to UV radiation and has important biological consequences (8, 70, 71). Due to the limited penetration of UV (up to 1 mm), the main biological effects of UV exposure is limited to the skin and eyes. The effects of UV radiation on skin can be divided into two categories: acute and chronic. Acute effects include sunburn, tanning, and vitamin D production. Skin cancers and photo-aging are the main consequences of chronic exposure (71). In epidemiological studies, individual sun exposure is mainly estimated by semi-quantitative questionnaires, which do not provide detailed information on the wavelength and dose of exposure. Moreover, the UV dose in a given skin area depends on several factors, including clothing, occupation, and amount of outdoor activities (72). Several case-control and some cohort studies have investigated the association between sun exposure and risk of melanoma. These studies demonstrate the complex interplay between sun exposure and melanoma risk (10, 49, 60, 73).

Intermittent, chronic, and total exposure

The body of the evidence from epidemiological studies indicates a likely causal association between sun exposure and melanoma risk (42). However, the association is complex (74). Several case-control and cohort studies have investigated the association between sun exposure and melanoma risk and meta-analyses of these studies consistently showed that intermittent sun exposure is strongly associated with melanoma risk (10, 11, 75). Chronic sun exposure has shown to be unrelated or negatively associated with risk of melanoma (10). Total sun exposure has found to be positively associated with an increased risk of melanoma, however, the association is weaker than that intermittent sun exposure (10, 11). History of sunburn, which is the biological response to acute sun

exposure and is an indicator of intermittent sun exposure, is positively associated with melanoma risk in epidemiological studies (10, 49, 60). The association between sunburns and melanoma risk is stronger and more consistent than for intermittent sun exposure (10, 12). One possible explanation for the inconsistency of association between cumulative and intermittent sun exposure and melanoma risk in epidemiological studies might be recall bias: sunburn is easier to recall, and reflects both sun exposure and individuals' sun sensitivity and behaviour. In a meta-analysis of more than 50 studies, the summary estimate for the highest compared to the lowest category was RR=2.0 (95% CI 1.7 to 2.4) for sunburn, RR=1.6 (95% CI 1.3 to 2.0) for intermittent sun exposure, RR=1.0 (95% CI 0.9 to 1.0) for chronic sun exposure, and RR=1.3 (95% CI 1.0 to 1.8) for total sun exposure (10). The protection by epithelial thickening and tanning of the skin after sun exposure might explain the weak association between chronic sun exposure and risk of melanoma in epidemiological studies(10). The risk of melanoma related to sun exposure differs also by the anatomic site (42). Chronic sun exposure is associated with head and neck melanoma and older age at diagnosis, while, melanomas on the extremities and trunk has been linked to intermittent sun exposure and younger age at diagnosis (56, 76). This suggests different causal pathways and supports the divergent pathway hypothesis (77).

Since sun exposure is the most preventable cause of melanoma and other skin cancers, primary prevention programmes in many countries have been implemented to improve public awareness about the harmful effect of overexposure to the sun, and to promote sun protection behaviours (14). Overexposure to the sun can be modified through several practices, including minimising outdoor activities during midday, wearing sun-protective clothing and applying sunscreen. Sunscreen is the most popular way of sun protection in many populations (78) including Norway (79), however, there have been controversies regarding its effectiveness in melanoma prevention (80-82). The next session of this thesis part is devoted to these controversies given the available scientific evidence.

2.4 Sunscreens

Sunscreens are products with chemical UV absorbers or physical blockers, designed to prevent the sun's UV radiation from reaching the skin (83). The ingredients can be divided into UVB, UVA, or broadband absorbers (84). Sunscreens have been available since the 1930s, and in recent decades, the sunscreen industry has focused on increasing the Sun protection factor (SPF). In the early 1990s, most of the sunscreen products had

SPFs less than 10 and only UVB protection, but by the year 2000 sunscreen with SPF of 15 and higher became available (85).

Sun protection factor (SPF)

SPF is the capacity of a sunscreen to protect the skin from erythema after UV exposure, and mainly shows the protection from UVB (86). In order to measure the biological effects of UV radiation, a minimal erythema dose (MED) is defined, which is a minimal exposure to UV radiation that is sufficient to cause erythema with well-defined borders 16 to 24 hours after irradiation (87). MED is used to measure the SPF of sunscreens. The standard dose for SPF testing is 2 mg of sunscreen per cm^2 of skin. SPF is defined as (86):

$$SPF = \frac{MED\ with\ the\ tested\ sunscreen}{MED\ without\ sunscreen}$$

For example, SPF 15 means that 1/15th of the burning radiation will reach the skin if sunscreen is applied evenly at a dosage of 2 mg^2 of skin. SPF does not assess the degree of UVA protection (88). Measuring UVA protection in sunscreens is challenging because UVA causes less erythema than UVB. Currently, there is no generally accepted standard method for measuring UVA protection by sunscreens. The most common methods used for UVA measurement are in vivo tests for persistent pigment darkening (PPD) and critical wavelengths assessed by spectrophotometry (86). The PPD testing protocol is similar to the SPF test. The major points of the PPD protocol include a) the use of skin that is capable of yielding a pigment response, b) a filter that allows a UVA emission spectrum from 320 to 400 nm to be obtained without UVB and visible light, c) multiple-incremental doses (25% progression) of UVA with and without sunscreen protection, and d) observation of pigment response 2 to 24 hours after the end of UVA exposure (89).

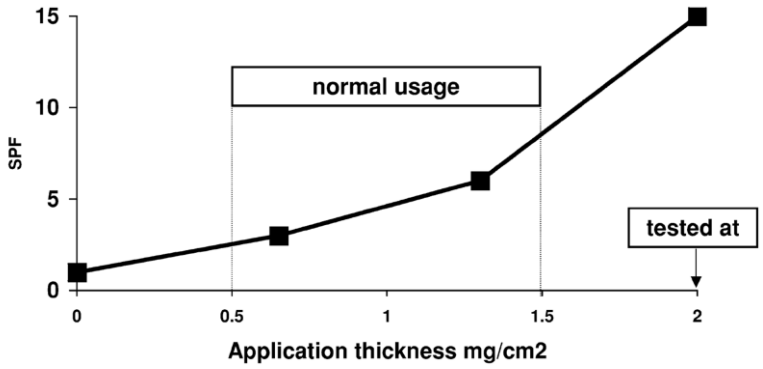
Recent research and governmental regulations have focused on UVA protection, and in the last decade, broad-spectrum sunscreens provide UVA protection proportional to the UVB protection (84, 90). According to the European Union (EU) recommendations, sunscreen products have to attain a minimum level of UVA protection at least one-third of the labelled SPF (84, 91). In 2012, the FDA determined that broad-spectrum sunscreens with SPF 15 or higher could be marketed as reducing the risk of skin cancer (92). An ideal sunscreen should provide high protection against both UVB and UVA,

should be waterproof, sweat-proof, photo-stable, cosmetically acceptable, and non-toxic (86).

Sunscreen failure

In an ideal situation, sunscreen with SPF 15 or higher is adequate to prevent sunburn for all day exposure (85). However, epidemiological studies have found paradoxical results, with a higher prevalence of sunburn among sunscreen users (18, 19, 93, 94). This paradox may be explained by the behavioural pattern of sunscreen users (29, 30, 95). People usually apply sunscreens much less than the recommended amount, typically between 0.5–1.5 mg per square centimetre of skin (96-98). Application thickness has an important effect on the protection; and most users achieve only 20 to 50% of the expected protection from the label of the product (Figure 3) (78, 85).

Figure 3. Variation in SPF with a thickness of application in normal usage of sunscreen labelled SPF15. From Diffey (78).



Moreover, people usually do not apply sunscreen evenly to the skin in different parts of the body (99). Areas such as ears, neck and feet may be forgotten, re-application every two hours or after perspiring or swimming may be neglected (100-102). In addition, many people use sunscreen to prolong the time spent in the sun. A health conscious attitude towards sun exposure and a desire for safe tanning may motivate people to use sunscreen, but also increase their sun exposure time, which may cause unwanted sunburns (103). Using sunscreen with high SPF has been associated with a longer duration of recreational sun exposure and an increased prevalence of sunburn in several epidemiological studies (19, 104, 105).

Sunscreen and melanoma risk

The application of sunscreen can decrease the risk of SCC (17), actinic keratosis (16), and nevi in children (106), but the scientific evidence that sunscreen prevents melanoma is still controversial (80, 107). To date, all observational studies on the association between sunscreens and melanoma risk have been case-control studies, mostly conducted before the year 2000. Some of these studies found a decreased risk of melanoma among sunscreen users (20-23), while others found no association (24) or a higher risk of melanoma among sunscreen users (25-28). These studies were criticized for lack of adjustment for potential confounding variables, and almost all were conducted before high SPF sunscreens were available on the market. Two meta-analyses on all data published between 1966 and 2003 found no effect of sunscreens on melanoma risk (108, 109). In the single case-control study published after the two meta-analyses, routine sunscreen use decreased melanoma risk (21).

The Nambour Skin Cancer Prevention Trial (20) is the only randomized control trial that studied the association between sunscreen use and risk of melanoma. This trial was conducted among adults in Australia, i.e. an area with high ambient solar radiation and with a population with high awareness of sun-related melanoma risk. The study participants were randomly assigned to sunscreen intervention or control group. The intervention group was given a free, unlimited supply of broad-spectrum sunscreen with an SPF=16 and control participants followed their usual sunscreen use practices, without being provided free sunscreen. Even though regular use of sunscreen with SPF=16 reduced the risk of melanoma (hazard ratio[HR]=0.50; 95% CI: 0.24 to 1.02; P=0.051), the results of this trial are unlikely to be generalizable to the white populations in Europe and other more temperate locations (107). Pattern and intensity of sun exposure in Australia differ from those in Northern Europe, where high levels of sun exposure occur mainly during sunbathing in the summer or sunbathing vacations abroad. In these intentional sun exposure sessions, large skin areas are uncovered and exposed to the sun to acquire a tan. Moreover, people do not have access to free unlimited supplies of sunscreen, and when using it, may apply less than the recommended amount and neglect reapplying (82). Thus, to date, the effectiveness of sunscreens in preventing melanoma in sun exposure situations outside Australia has not been demonstrated (82).

2.5 Indoor tanning

Aside from sun exposure, the use of indoor tanning devices (e.g. sunbeds) is the most important source of UV radiation, especially UVA (110, 111). Indoor tanning exists since the 1970s, and became popular in Western countries in the early 1980s (111, 112). It is frequently used in Northern Europe and in the USA, in particular by young women (31). There are large differences in the composition of UV wavelengths from indoor tanning devices and the sun. Prior to the 1980s, tanning devices emitted higher UVB radiation (280–315 nm) than natural sunlight, while UVA radiation (315–400 nm) was lower (111, 113). Risk of combustion and concern about skin cancer risks associated with UVB radiation in the 1980s resulted in the dose of UVA to UVB radiation in sunbeds being increased by the manufacturers of indoor tanning devices (111). UVA radiation was not considered to pose a similar skin cancer risk as UVB radiation. UVA is 1000 times weaker than UVB in causing erythema, and UVA radiation primarily makes an immediate tan that fades quickly. UVB is necessary to achieve a long lasting tan. Since the 1990s, the fluorescent tubes in the sunbeds mainly emit a combination of UVA and UVB radiation (111, 114).

The UV radiation types and doses from sun exposure and artificial tanning devices differ substantially. The intensity of UVA to cause skin reddening is 500–1000 times lower than UVB. Thus, before getting a high dose of UVA from the sun the skin would become severely burnt by the UVB. However, tanning devices provide a higher dose of UVA to UVB radiation. Spectral UVA irradiance from Norwegian sunbeds is 3–26 times higher than from the summer sun in Oslo, Norway (111). The UV exposure in modern sunbeds is higher than summer midday sun in the Mediterranean Sea (70, 110, 114, 115), and often higher than the limits allowed by safety regulations (111, 116). Compared to outdoor activities in which 15–50% of the body is exposed, 95–100% of the body is exposed in a sunbed (42). In a meta-analysis of the most recent international data, past-year prevalence of indoor tanning was 18% (95% CI, 12.2–24.1%) in adults and 45% (95%CI, 9.4–81.0%) in university students (31). In a Norwegian survey from 2014, use of indoor tanning in the year before the interview occurred amongst 16% of subjects >18 years, and twice as many women than men used indoor tanning (79). Indoor tanners are characterized by their lack of knowledge about harmful effects of indoor tanning, and tend to live unhealthier lifestyles (117).

Indoor tanning and melanoma risk

Several case-control studies and a few cohort studies have investigated indoor tanning in relation to melanoma, and a positive association was found in most of the studies (33). In 2009, the IARC classified indoor tanning devices as carcinogenic to humans (group 1 carcinogen) (7). The most recent meta-analysis (2014) of 31 studies estimated that ever-users of indoor tanning had a 16% higher risk of melanoma than nonusers (odds ratio [OR]=1.16, 95% CI 1.05–1.28) (33). In addition, a suggestive dose-response effect was observed, with a 34% increased risk of lifetime exposure to more than 10 tanning sessions compared with never use (OR=1.34, 95% CI 1.05–1.71) (33).

A meta-analysis by IARC in 2006 showed a higher melanoma risk associated with younger age at initiation of indoor tanning (≤35years old) and suggested a greater susceptibility to harmful effects of indoor tanning during youth (34). However, in some studies (117, 118), but not all (119), younger age at initiation was a predictor of higher cumulative exposure, and frequent indoor tanners started to use tanning devices before age 30 years. Thus, it is not clear whether higher risk of melanoma in young age is due to higher susceptibility to UV radiation exposure or higher cumulative UV radiation exposure.

Since randomised controlled trials (RCTs) are not ethical for investigating the association between indoor tanning and melanoma risk, prospective cohort studies provide the most reliable evidence of a causal association (114). So far, the body of evidence is mainly limited to case-control studies, and evidence from prospective cohort studies is scarce. Although the current published data indicate a clear association between indoor tanning and melanoma risk, these data can be confounded by the lack of accurate measurement of duration and dose of UV radiation exposure, biases due to study design, and lack of proper control for concurrent sun exposure and host phenotype (114).

3. Aims of thesis

3.1 General aim

The main aim of this thesis was to study sunscreen use and sunburn in relation to demographic and phenotypic characteristics and to investigate the association between sunscreen use, including SPF, and melanoma and the attributable fraction of melanoma related to sunscreen use. Moreover, this thesis aimed to study the association between indoor tanning and melanoma risk in adult Norwegian women.

3.2 Specific aims

More specifically the aims were to examine the following in the NOWAC cohort:

- Patterns of sunscreen use according to demographic and phenotypic characteristics, sun exposure, and sunburn experience, and the trend of sunscreen use and sunburns from 1997 to 2007 (paper I).

- Melanoma risk in relation to use of high SPF (≥15) versus low SPF (<15) sunscreens, and to estimate population attributable fraction (PAF) of melanoma related to sunscreen use (paper II).

- The association between indoor tanning and melanoma risk including dose-response, duration of use, age of indoor tanning initiation and age at melanoma diagnosis. (paper III).

4. **Materials and methods**

4.1 Study design and population

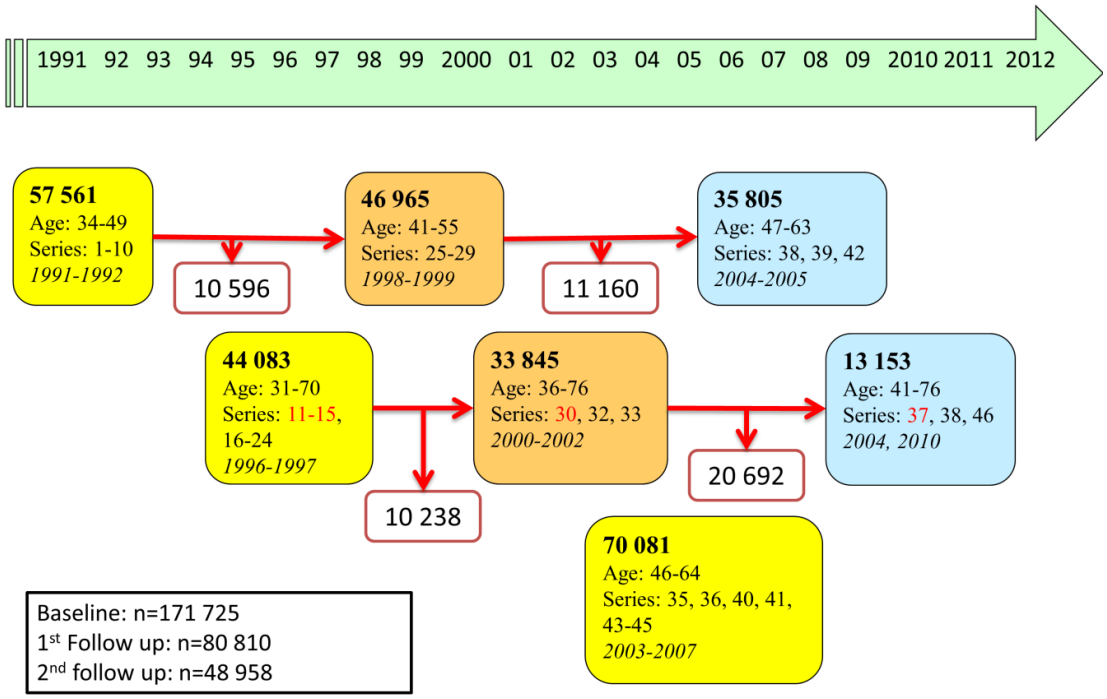
The Norwegian Women and Cancer Study (NOWAC)

This thesis is based on data from NOWAC, a national-wide population-based prospective cohort study established in 1991. NOWAC was primarily designed to study risk factors for different cancer types (120). The questionnaires including a wide range of exposures such as hormones use, dietary intake, host susceptibility factors and UV exposure. Several articles have been published on breast cancer (121, 122), skin cancers (49, 60) and other cancers and diseases (123-125). NOWAC partially included in the Norwegian-Swedish Women's Lifestyle and Health Cohort Study (60) and the European Prospective Investigation into Cancer and Nutrition (EPIC) (126, 127).

The NOWAC study population was selected by a random sampling of women from the National Population Register. From 1991 to 1997, a total of 179 387 women aged 30–70 years were invited to participate, and 101 644 returned an 8-page questionnaire (response rate 57%) (35). Due to practical and financial limitations and aims to do methodological sub-studies, the enrolment procedure was divided into 24 different series of questionnaire over 7 years (35)(Figure 4). NOWAC is a representative of the Norwegian female population (35). Thus, it is possible to estimate RRs and PAFs of cancers in relation to putative risk factors.

All NOWAC participants who had answered their baseline questionnaire in 1991 to 1997 were invited to answer the first follow-up questionnaire between 1998–2002. 80 810 women responded (response rate 81%). The second follow-up questionnaire was planned to be sent every 10–11 years after the first questionnaire, and started to be answered in 2003 for those women enrolled in 1991–1997. By the end of 2012, 48 958 women had responded (120). The size of the cohort increased during 2003–2007 by additional invitation of 130 577 women born between 1943–1957, of whom 70 081 (48%) enrolled and responded to 7 different series of questionnaire (Figure 4). All NOWAC participants were born between 1943–1966, and approximately one-third of all Norwegian women born between 1943–1957 have been enrolled in the NOWAC (Figure 5).

Figure 4. Baseline, first, and second follow-up questionnaires in the Norwegian Women and Cancer Study (NOWAC) until the end of follow-up on December 31, 2012. Baseline questionnaires with number of participants are in yellow, first follow-up questionnaires in orange, second follow-up questionnaires in blue, and non-respondents in white boxes. Series of questionnaires with no information on sun exposure/host factors are in red numbers.

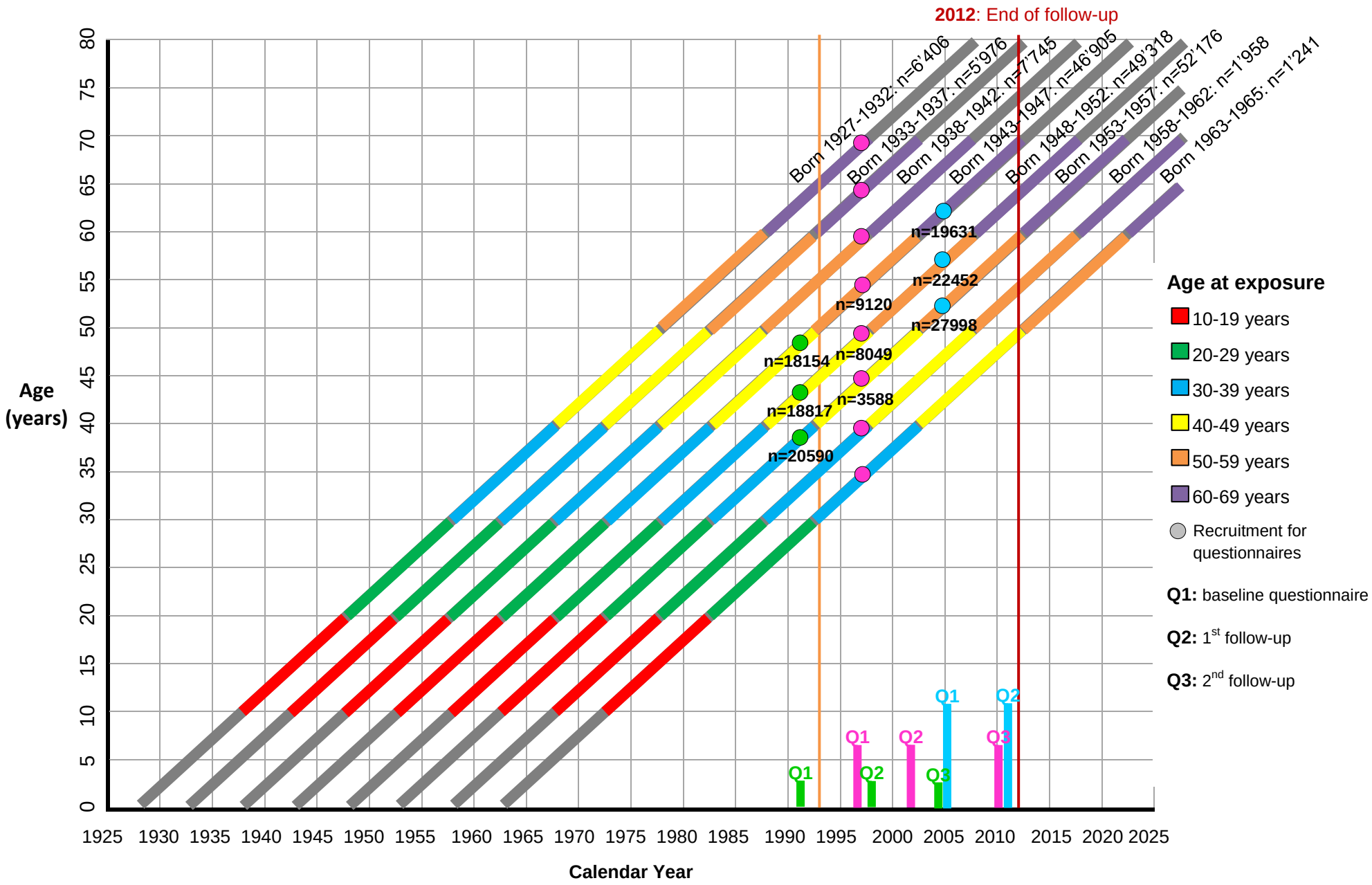


Sampling procedures

All Norwegian residents have a unique 11-digit number incorporating birth date and gender. Information about changes in name, address, and vital status (alive, dead or emigrated) are continuously updated based on mandatory registration and notifications to the registry. The sampling was carried out at the Division of Sample Surveys at Statistics Norway, using a drawing register from which women were randomly sampled (35).

Invited women received a common letter of introduction, a photo booklet, and a health- and lifestyle questionnaire. Examples of an original printed baseline and follow-up questionnaires in Norwegian and an English translated version are included in Appendices I, II and III. Updated information about the NOWAC study is available on the website: https://site.uit.no/nowac/.

Figure 5. The Norwegian Women and Cancer Study (NOWAC) study sample by birth cohort (n=171 725).

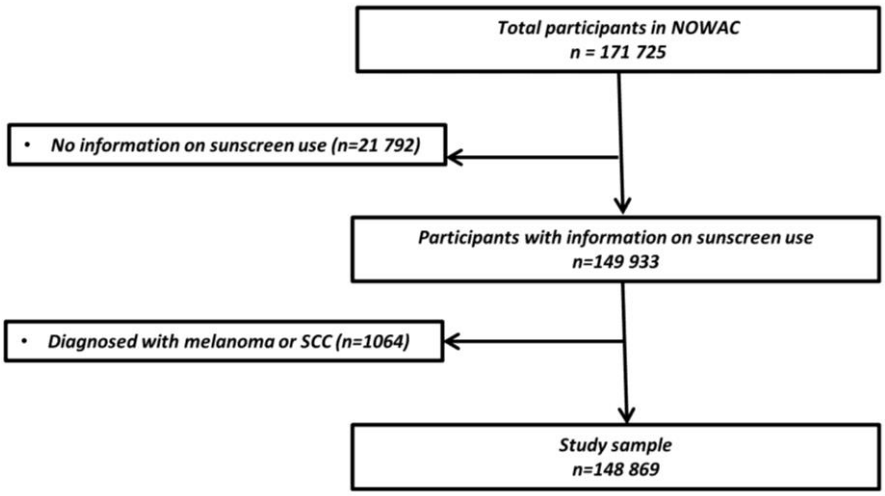


4.2 Study samples

Paper I

Using NOWAC, we described a) patterns of sunscreen use according to demographic and phenotypic characteristics, sun exposure, and sunburn experience; and b) trends of sunscreen use and sunburns from 1997 to 2007. Most of the NOWAC participants answered sunscreen questions for the first time in their baseline or first follow-up questionnaire between 1997 and 2007. The study sample consisted of 149 933 NOWAC women who answered at least one of the questions about sunscreen use in either of these questionnaires. We excluded 1064 women with SCC diagnosed before or at the time of answering the initial questions about sunscreen use. Thus, the final study sample comprised 148 869 women (Figure 6).

Figure 6. Illustration of the study sample in paper I.

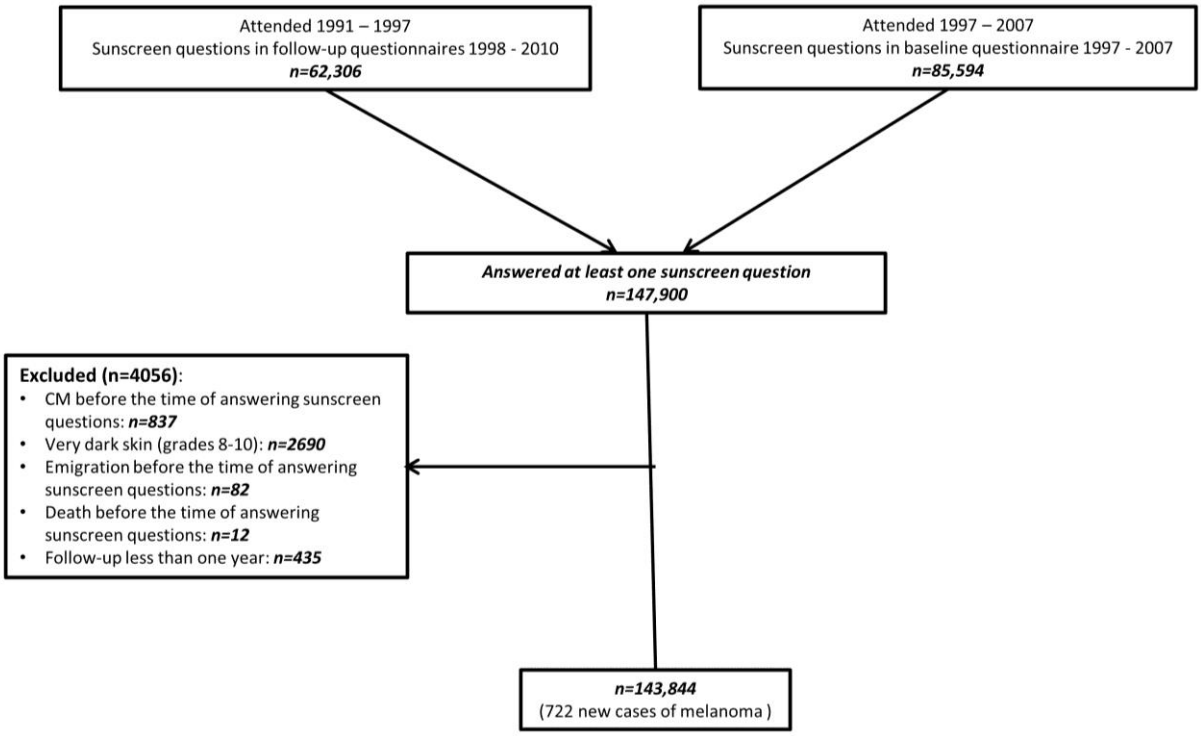


Paper II

We estimated melanoma risk in relation to use of high versus low SPF sunscreens and calculated PAF of melanoma related to sunscreen use. A total of 147 900 women answered the questions about sunscreen use in Norway or other northern locations (referred to as in high latitudes in the paper) and southern latitudes (referred to as in low latitudes in the paper) at least once. In this paper, we did not use information on sunscreen use at Easter holidays, and as a result, the total number in this paper is slightly lower than the first paper. The reason for not using the information on sunscreen use at Easter holidays was the high variability in sunscreen use in different years. The date of Easter varies up to a month in different years, which affects the sunscreen use due to differences in the weather conditions. Moreover, not all people expose themselves to the sun during

the Easter holidays. We excluded 837 women diagnosed with melanoma prior to answering the sunscreen questions, 2 690 women with very dark brown to black skin (grades 8–10 of the skin colour scale used in NOWAC; see below), 94 women who had emigrated or died before the sunscreen questions were returned, and 435 women with follow-up time <1 year. The final study sample included 143 844 women who answered questions about sunscreen use either in their baseline questionnaire during 1997–2007 at age 45–70 years, or in their follow-up questionnaires during 1998–2010 at age 40–75 years (Figure 7).

Figure 7. Illustration of study sample in paper II.

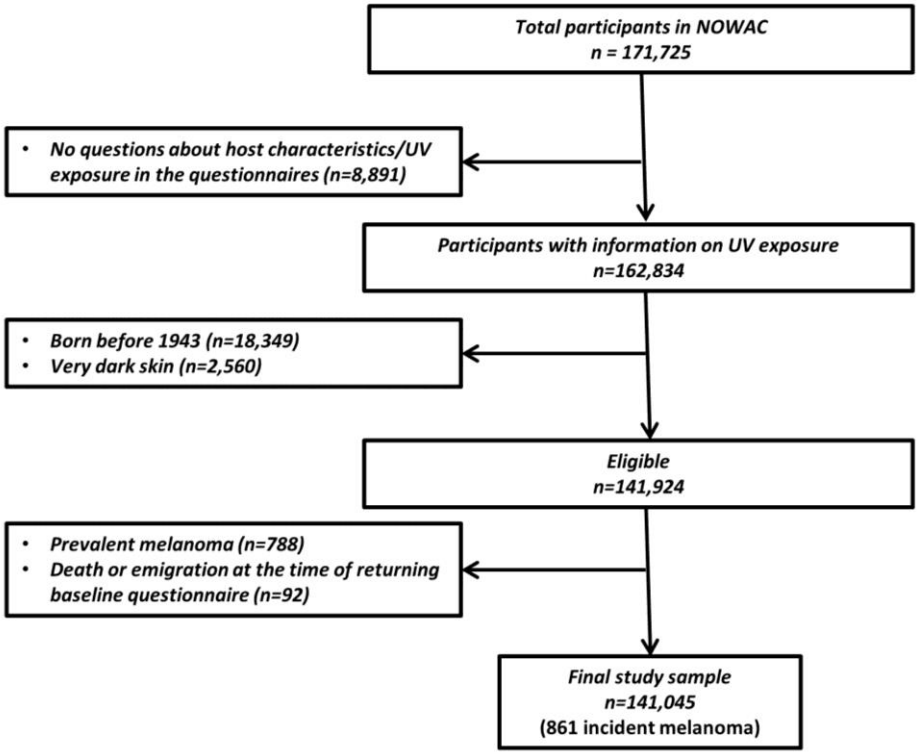


Paper III

We estimated melanoma risk and age at melanoma diagnosis according to age at initiation and cumulative use of indoor tanning. Among 171 725 participants in NOWAC, phenotypic characteristics and UV exposure were collected for 162 834 women (born in 1927–1957) at baseline (Figure 6). We excluded 18 349 women born in 1927–1942 that lived most of their life prior to the availability of any indoor tanning devices (as the first

whole body sunbed came on the marked in 1972 in Norway) (111), and 2560 participants with very dark skin as measured by a colour scale (grades 8–10). Thus, 141 924 women born in 1943–1957 were available for investigating the association between indoor tanning and risk of melanoma. We further excluded 788 participants with prevalent melanoma, and 92 who died or emigrated before the date of returning the questionnaire. Thus, the final study sample comprised 141 045 women (Figure 8).

Figure 8. Illustration of study sample in paper III



4.3. Data collection

Sunscreen use

The questions about sunscreen use in NOWAC are (Table 1):

- Use of sunscreen on three different occasions (at Easter holidays, in Norway or abroad but not in southern latitudes, and in sunbathing vacations in southern latitudes), with a check box for each occasion. From 2002, a check box was added to the questionnaires for "never".
- The SPF of the sunscreens used on these occasions at the time of questionnaire answering and 10 years previously to the answer of the questionnaire (separate answers), with open responses for each occasion. In a minority of the questionnaire series, pre-defined SPF categories (1–4, 5–9, 10–14, 15–29 and ≥30) were used.
- The brand of sunscreen used, with a check box for each brand.

Questions about sunscreen use were added from 1997, and most of those (81%) who enrolled in 1991–1997 answered sunscreen questions for the first time in their first follow-up questionnaire in 1998–2010. Information on sunscreen use was updated during follow-up questionnaires.

Sun exposure

The NOWAC participants reported their history of severe sunburns per year that resulted in pain or blisters and subsequent skin peeling (never, 1, 2–3, 4–5, ≥6 times/year) in childhood (0–9 years), adolescence (10–19 years), and in adulthood (Tables 1 and 2). The average number of weeks per year spent on sunbathing vacations (never, 1, 2–3, 4–6, ≥7 weeks/year) in southern latitudes (typically Southern European countries with latitude <45° such as Spain or Greece) or within Norway or outside southern latitudes were reported for the same age-periods. The question regarding sunbathing vacations was later divided into two: one concerning northern latitudes, and the other southern latitudes (Table 1).

Indoor tanning

NOWAC participants were asked to report the average use of an indoor tanning device as never, rarely, 1, 2, 3–4 times per month, or >1 time per week, in childhood (0–9 years), adolescence (10–19 years), and adulthood (Table 2). Information on indoor tanning was updated through follow-up questionnaires.

Phenotypic characteristics

The participants reported hair colour (dark brown/black, brown, blond/yellow, red) and eye colour (brown, grey/green, blue). Approximately half the participants also answered questions about skin reaction to acute sun exposure at the beginning of the summer (turns brown without becoming red, turns red, red with pain, red with pain and blisters), and skin reaction after repeated sun exposure (turns deep brown, brown, light brown, never turns brown). These two questions were later replaced by the question on untanned skin colour, which was recorded by a 1×9-cm colour scale graded from 1 (very fair) to 10 (dark brown). Information on the number of regular symmetric nevi (0, 1–10, 11–50, ≥50) and asymmetric nevi >5 mm on the legs from toes to groin (0, 1, 2–3, 4–6, 7–12, 13–24, ≥25; A photo booklet that was included with the questionnaire provided colour pictures with three examples of asymmetric nevi), and freckling after sunbathing (yes, no) was also collected from 1997 (Table 1).

Other covariates

Information on education (in years), height (cm), weight (kg), and place of residence were collected in the baseline questionnaire.

Reproducibility

One study was conducted in 2002 to assess the test-retest reproducibility of self-reported melanoma risk factors in NOWAC (Table 1) (128). The overall reproducibility of the questions was acceptable and not affected by age, education, or skin colour (128).

Table 1. Overview of UV exposure and phenotypic variables with the corresponding question in the questionnaire (translated into English) and reliability coefficients in the NOWAC study

Variable	Response options	Question	Reliability coefficients (95%CI)[a]	Series No.	No.
Sunscreen use[b,c]	One check box for each occasion	When do you use sunscreen?		22–29, 32, 33, 35, 36, 38–46	147 900
		- at Easter	0.64 (0.60–0.68)[d]		
		- in Norway or outside southern latitudes	0.54 (0.49–0.58)[d]		
		- on sunbathing vacations to southern latitudes	0.74 (0.71–0.78)[d]		
Sun protection factor (SPF)	Open responses for each occasion in most of the questionnaires, and pre-defined options as 1–4, 5–9, 10–14, 15–29, ⩾30 in a few questionnaires.	What sun protection factor do you use at these times?		22–29, 32, 33, 35, 36, 38–46	147 900
		- at Easter	0.76 (0.73–0.79)[d]		
		- in Norway or outside southern latitudes	0.69 (0.65–0.72)[d]		
		- on sunbathing vacations to southern latitudes	0.73 (0.69–0.77)[d]		
Sunscreen brands	One check box for each brand and open responses for the corresponding SPF	Which brand of sunscreens do you use? Indicate SPF if you remember		22–29, 32, 33, 35, 36, 38–46	147 900
Sunburns	Never, ⩽1, 2–3, 4–5, ⩾6 per year	How many times per year have you been burned by the sun resulting in pain or blisters with subsequent peeling?	0.49 (0.45–0.53)[e]	1–10, 16–29, 32, 33, 35, 36, 38–46	162 834
Sunbathing in Southern latitudes	Never, ⩽1, 2–3, 4–5[f], ⩾7 weeks per year	How many weeks on average per year have you been sunbathing vacation to southern latitudes?	0.71 (0.68–0.74)[e]	1–10, 16–29, 32, 33, 35, 36, 38–46	162 834
Sunbathing in Northern latitudes	Never, ⩽1, 2–3, 4–5[f], ⩾7 weeks per year	How many weeks on average per year have you been sunbathing in Norway or outside southern latitudes?	0.47 (0.44–0.51)[e]	1–10, 16–29, 32, 33, 35, 36, 38–46	162 834
Hair colour	Dark brown/black, brown, blond, red	What is your hair colour?		1–10, 16–29, 32, 33, 35, 36, 38–46	162 834
Eye colour	Brown, grey/green/mix, blue	What is your eye colour?		1–10, 16–29, 32, 33, 35, 36, 38–46	162 834
Skin reaction to acute sun exposure[g]	A tan without redness, red, red with pain, red with pain and blisters	How your skin react to heavy (acute) sun exposure at the beginning of the summer?		1–10, 16–24, 26	77 650
Skin reaction to chronic sun exposure[g]	A deep tan, a normal tan, a light tan, no tan	How your skin react to repeated and long-lasting sun exposure?		1–10, 16–24, 26	77 650
Skin colour[b]	a 1×9-cm colour scale graded from 1 (very fair) to 10 (dark brown)	Scale your untanned skin colour.	0.59 (0.55–0.63)[e]	22–29, 32, 33, 35, 36, 38–46	147 900
Freckling	Yes/no	Do you freckle when sunbathing?	0.77 (0.74–0.81)[e]	22–29, 32, 33, 35, 36, 38–46	147 900
Asymmetric nevi	0, 1, 2–3, 4–6, 7–12, 13–24, ⩾25	How many irregular moles larger than 5 mm do you have in total on both legs (from toes to groin)?		1–10, 16–29, 32, 33, 35, 36, 38–45	162 834
Symmetric nevi	0, 1–10, 11–50, >50	How many small regular moles do you have in total on both legs (from toes to groin)?		22–24, 26, 27	26 400
Solarium use	Never, rarely, 1/month, 2/month, 3–4/month, ⩾1/week	How often have you tanned yourself in a solarium?	0.70 (0.67–0.73)[e]	1–10, 16–29, 32, 33, 35, 36, 38–46	162 834

[a]From Veierød et al. 2008.(128)
[b]This question was added to the baseline and follow-up questionnaires from 1997.
[c]The option "never" was added from 2002.
[d]Spearman correlation coefficient with 95% CI.
[e]Kappa or weighted kappa with 95% CI.
[f]Misprint in the questionnaire: fourth response category should have been "4–6" and not "4–5".
[g]This question was replaced by the question about skin colour and freckling when sunbathing from 1997/1998.

Table 2. Age and year intervals in questions about sunburns, sunbathing vacations and indoor tanning in different series of questionnaire dispatches in the NOWAC study.

Series number	Age-/calendar year intervals	Age range	No.
Baseline questionnaire			
1–10	<10, 10–19, 20–29, 30–39, 40–49	34–49	57 561
36, 40, 41, 43, 44, 45	<10, 10–19, 20–29, 30–39, ≥40	47–64	56 140
19–24	<10, 10–19, 20–44, ≥45	41–70	34 681
35	<10, 10–19, 20–29, 30–44, ≥45	46–61	13 941
16	<10, 10–19, 20–49, ≥50	50–69	511
11–15, 17,18	n.a.[a]	31–69	8 891
Total			171 725
First follow-up			
25, 27, 28, 29	1991–1994, 1995–1998	41–55	46 965
32, 33	1997–2001	46–76	28 499
30	n.a.[a]	36–49	5 346
Total			80 810
Second follow-up			
38	<10, 10–19, 20–29, 30–39, 40–49, ≥50	41–76	1431
39, 42	40–49, ≥50	47–63	34 659
46	2002–2010	54–68	8623
37	n.a.[a]	40–53	4245
Total			48 958

[a]No questions about phenotypic characteristics/UV exposure in the questionnaire. n.a.: not available

4.4. Record linkages and follow-up information in NOWAC

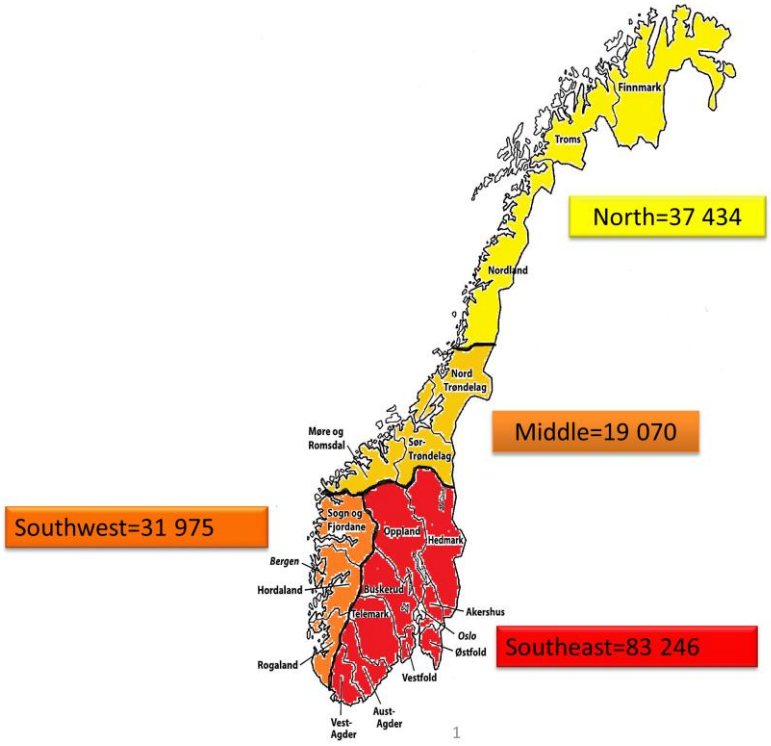
The 11-digit person number is used by all official registries in Norway and enables linkage with the Cancer Registry of Norway for follow-up of cancer incidence and vital status (alive, emigrated or dead) until December 31, 2012. The information on cancer from the Cancer Registry of Norway have been estimated to be almost complete for solid tumours (6). Melanoma is registered according to the international classification of disease, Seventh Edition (ICD-7; codes 190.0–190.9), and 99.9% of melanomas are morphologically verified (6). The Cancer Registry is regularly linked with the Norwegian Population Register for information on vital status.

4.5. Definition of variables and categorization

For each paper in this thesis, we used slightly different samples and variables from the NOWAC study. Thus, definitions and categorisations of some variables differ between papers I-III. For instance, in both papers II and III, cumulative number of sunburns and sunbathing vacations were calculated similarly, and were categorised into tertiles based on the distribution in the baseline questionnaire. However, in paper II, baseline was defined as the questionnaire when the participants answered the sunscreen questions,

which was first follow-up questionnaire for about half of study sample. Thus, the cut-offs for these variables are different in these two papers. We categorised region of residence (latitudes 58º-70º) based on the average ambient UV radiation hours (129) as highest (Southeast Norway), medium (Southwest Norway), medium-low (Central Norway), and low (Northern Norway) in all three papers (Figure 9).

Figure 9. Number of participants in the NOWAC study according to place of residence



Paper I

In this paper, we used data on sunscreen use a) at Easter holidays, in Norway or abroad but not in southern latitudes, b) and in sunbathing vacations in southern latitudes. We used information from the baseline questionnaires for those enrolled from 1997, and first follow-up questionnaire for those enrolled in 1991–1996, as well as the SPF of sunscreen used on these occasions. For the analysis of sunscreen use in southern latitudes, we confined our sample to those who had spent at least one week on sunbathing vacation in southern latitudes in their adulthood (age ≥20 years). The following categories of

exposure were created: skin colour: pale (grade 1–3), olive (grade 4–7), and dark skin (grade 8–10); education: ≤7 years, 8–10 years, 11–13 years, 14–16 years, and ≥17 years; presence of large asymmetric nevi on legs: 0, 1 and ≥2; type of SPF: <15 and ≥15. Age was defined as the age when answering the questionnaire with questions on sunscreen use, and was categorised as 40–49, 50–59, and ≥60 years. All NOWAC women were born in 1927–1966, and birth cohort was categorised as 1927–1936, 1937–1946, 1947–1956, and 1957–1966.

Paper II

For the purpose of this paper, we used data on sunscreen use in northern and southern latitudes (high and low latitudes, respectively) and the reported SPF for the corresponding occasion. Participants were classified as nonusers of sunscreen if they did not indicate sunscreen use or if they recorded zero to the SPF question for the corresponding occasion. Other participants were classified as SPF<15 or SPF≥15 users according to their answers. In categorizing sunscreen use in both high and low latitudes according to SPF, we had 9 combinations, which we categorized into 4 groups as: nonusers in both occasions, sunscreen use with SPF<15 in only one occasion, sunscreen use with SPF<15 in both occasions, and sunscreen use with SPF≥15 on at least one occasion. The majority of the participants in the latter group (78%) were those who used sunscreen with SPF<15 in high latitudes and SPF≥15 in low latitudes or SPF≥15 in both locations. To obtain cumulative number of sunburns, the observed frequencies in all age-periods were multiplied by the number of years for the given period, summed and categorised as none, lowest (1–29 sunburns), middle (30–53 sunburns), and highest tertile (≥54 sunburns). Cumulative number of weeks on sunbathing vacation was calculated in the same way and categorised as none, lowest (1–100 weeks), middle (101–180 weeks), and highest tertile (≥181 weeks). For those participants who explicitly answered questions about sunbathing in low latitudes, cumulative number of weeks sunbathing in low latitudes was calculated similarly and categorised as: none, lowest (1–29 weeks), middle (30–62 weeks), and highest tertile (≥63 weeks). Indoor tanning was categorised as never and ever. Untanned skin colour was recorded by a 1×9-cm colour scale graded from 1 (very fair) to 10 (very dark brown; very dark (8–10) were excluded from the study), and was categorised as dark (grades 6–7), medium (4–5) and light (1–3). The participants reported their hair colour (dark brown/black, brown, blond/yellow, red), freckling after sunbathing (yes, no) and

number of asymmetric nevi >5 mm on the legs (0, 1, 2–3, 4–6, 7–12, 13–24, ≥25; categorised as 0, 1, ≥2).

Paper III

We created five variables to describe the exposure to indoor tanning: cumulative number of indoor tanning sessions, ever/never use, duration of use (never, <10 years and ≥10 years), current use (yes or no in the most recent age-period), and age of indoor tanning initiation (never, <30 years, ≥30 years; excluding a sub-sample of women who were asked about indoor tanning between ages 20-44; n=12,358). To calculate the cumulative number of indoor tanning sessions, the observed frequencies for all age-periods starting from age 10 were converted to yearly amount (never=0, rarely=1, 1/month=12, 2/month=24, 3–4/month=42, and >1/week=60 per year) and multiplied by the number of years for the given period, summed and categorized as never, lowest (≤14 sessions), medium (15–30 sessions), and highest tertile (≥31 sessions). Since very few reported indoor tanning before age 10 (<1%) and many did not answer the question for indoor tanning before age 10, we did not include this period in the calculation. Women with missing information in one age-period or more were considered missing, and multiple imputations were used to impute missing values. Number of years of education categorised as ≤10, 11–13, and ≥14 years. Host factors included untanned skin colour, hair colour (black/dark brown, brown, blond/yellow, red), freckling when sunbathing (yes, no), and number of asymmetric nevi >5 mm on the legs (0, 1, 2–3, 4–6, 7–12, 13–24, ≥25; categorized as 0, 1, ≥2). Untanned skin colour was categorised as dark (grades 6–7), medium (4–5) and light (1–3). Cumulative number of sunburns was calculated in the same way as cumulative number of indoor tanning sessions but including age-period <10 years, and categorized as none, lowest (≤30 sunburns), medium (31–51 sunburns), and highest tertile (≥52 sunburns). Cumulative number of weeks on sunbathing vacations was calculated in the same way and categorised as none, lowest (≤46 weeks), medium (47–87 weeks), and highest tertile (≥88 weeks). Finally, we calculated cumulative number of indoor and outdoor tanning sessions by summing tertiles of cumulative number of indoor tanning sessions and cumulative sunbathing vacations (score from 0–6) and categorising it into four categories (1=lowest to 4=highest).

Information on indoor tanning, sunburns, and sunbathing vacations were updated through the follow-up questionnaires.

4.6 Statistical analyses

The statistical analytical approaches varied according to the study designs in the different papers, and are fully explained in the papers. In brief, in papers II and III, the linear trend was assessed by modelling the exposure as a continuous variable and testing the significance in the model using a likelihood ratio test. We used a likelihood ratio test for multiplicative interaction, comparing models with and without interaction terms. Test of statistical significance was two sided for all the analyses. In paper I, $P<0.01$, and in papers II and III $P<0.05$ were considered statistically significant. All statistical analyses were conducted in STATA versions 13 and 14 (Statacorp, Texas, USA).

Paper I

We examined the association between sunscreen use and personal characteristics. Because of the high prevalence of the outcome, a generalized linear regression with a log link and binomial distribution (log-binomial regression) was used (130) (*binreg* function in Stata) (131), and prevalence ratios (PRs) and 99% CIs were calculated. Where applicable, analyses were adjusted for age and/or calendar year when answering the sunscreen questions. Log-binomial regression was also used in the analysis of the association between sunburn and sunscreen use at Easter holiday, in northern and southern latitudes, and also to determine the effect of the calendar year on sunscreen use while adjusting for age and birth-cohort. To examine the effect of the calendar year on sunscreen use, calendar year was categorised as 1997–1998, 2002–2004 and 2005–2007. Trend of sunscreen use and current sunburn were plotted for the same samples that were used in the multivariable analyses.

Paper II

We studied the association between sunscreen use and risk of melanoma. Cox regression was used with age as the time scale and stratified by calendar year of answering questionnaires, calculating HRs and 95% CIs. Entry time was age of answering the sunscreen questions for the first time, and exit time, the age of melanoma diagnosis, emigration, death, or the end of follow-up, December 13, 2012, whichever occurred first. Sunscreen use was modeled using only the information recorded at baseline, and as a time-dependent variable using updated information from follow-up. We used age as the time-scale (132) and models were stratified by calendar year when answering the questionnaires to adjust for both age and calendar year. We further adjusted for hair colour, freckling when sunbathing and ambient UV of residence, and cumulative number

of sunburns and weeks on sunbathing, and indoor tanning. Additional adjustment for education and skin colour did not change the results. In all models, cumulative number of sunburns and sunbathing vacations were modeled as time-dependent by updating information from the follow-up questionnaires. Interaction effects between sunscreen use and hair colour (light/dark), sunburn (never/ever), sunbathing vacations (never/ever) and freckling (yes, no) were evaluated using the likelihood ratio test. PAF for melanoma associated with sunscreen use was estimated.

Paper III

We investigated the association between indoor tanning and risk of melanoma. Poisson regression analysis with age as the time scale was used to estimate RR with 95% CI. Person-years were calculated from the date of the return of the baseline questionnaire to the date of melanoma diagnosis, emigration, death, or end of follow-up, December 31, 2012, whichever occurred first. Cumulative use, ever use, duration of use and current use of indoor tanning, as well as cumulative sunburn and sunbathing, were included as time-varying variables in the Poisson regression analyses. We also examined site-specific risk for trunk and extremities related to indoor tanning (but not head/neck due to few cases). All analyses were adjusted for attained age (5-year intervals), birth-cohort (1943–1947, 1948–1952, 1953–1957) and calendar year of inclusion (1991–1992, 1997–1998, 2004–2007), since calendar year of indoor tanning exposure may influence the level of UV exposure (133). We further adjusted for ambient UV of residence, hair colour, cumulative sunburns, and sunbathing vacations. Additional adjustment for skin colour and freckling when sunbathing did not change the results. Interaction effects between cumulative indoor tanning and duration of use (<10, ≥10 years), age at initiation (<30, ≥30 years), sunburn (never, low, medium/high), sunbathing (never, low, medium/high), birth-cohort, freckling, hair colour (dark, light), and year at inclusion were tested. Linear regression analysis was used to study age at diagnosis in relation to age at initiation of indoor tanning, adjusting for birth-cohort, year of inclusion, hair colour, cumulative number of sunburn and sunbathing vacations. In all models, cumulative indoor tanning, cumulative number of sunburns and sunbathing vacations were modeled as time-dependent by updating information from the follow-up questionnaires

Population attributable Fraction (PAF)

Quantification of the impact of an exposure on an outcome at a population level is a fundamental public health concern. In epidemiological studies, the strength of association between an exposure and an outcome is usually reported as RRs or ORs. However, these measures of association do not take into account the importance of prevalence of the risk factor in the population (134). PAF is a measure that takes into account both the strength of association between the risk factor and the outcome and the prevalence of the risk factor in the population (134). PAF is defined as the proportion of outcome in a given population that would theoretically have been reduced if none of the individuals has been exposed to the risk factor (135). Originally PAF was formulated for a single dichotomous risk factor (136), but it has been expanded for multiple, categorical or continuous risk factors and study designs (135).

In the definition of PAF, a causal relationship between the risk factor and the outcome is assumed and the outcome occurrence is assumed to be higher in the exposed group. In this case, the PAF varies between zero and one, and is often presented as a percentage. However, if the exposure is protective, the outcome occurrence would be higher in an unexposed group and PAF would be negative. The analogous measure to PAF proposed for this situation is Preventable fraction (PF), which is the proportion of outcome that could be reduced if it was possible to expose all the population to this preventive factor (137). The relationship between PAF and PF was presented as (138):

$$1-PF=1/(1-PAF)$$

PAF for a protective factor can be made positive by reversing the coding of exposure to that the exposed group to the protective factor is labelled as the reference level and the unexposed group as the exposed group (139).

In this thesis, PAF of melanoma in relation to sunscreen use was calculated using *punafcc* function in stata (140). The function uses the formula by Samuelsen and Eide, which is developed for the estimation of PAF in cohort studies, and properly takes into account the follow-up time (141). We defined women who reported sunscreen use with SPF≥15 as unexposed in the formula, and calculated PAF for four scenarios: 1) what if the total population of women would have used sunscreen with SPF≥15 during the study period, 2) what if all women with blond/red hair would have used sunscreen with SPF≥15 during the study period, 3) what if all women who reported freckling after sunbathing would have used sunscreen with SPF≥15 during the study period, and 4) what if all women who

used sunscreen with SPF<15 would have used sunscreen with SPF≥15 during the study period. Adjusted time-dependent HRs was used to calculate the PAFs.

Missing values and imputation methods

Missing data are a common and challenging problem in the statistical analysis of epidemiological studies. There are different ways of dealing with missing data. Multiple imputation is a method with wide application in recent years (142). The key to this method is that under assumed missingness patterns (assuming missing completely at random or missing at random), we can obtain a valid estimate for missing data from the observed data. Thus, multiple imputation is valid if the missing covariate information is not influenced by any unmeasured characteristics (143).

In the data analysis of papers II and III, multiple imputation with chained equations was used (144). Approximately 20% and 15% of the observations had missing information on one or more covariates in the multivariable analyses in papers II and III, respectively. Ten and 15 datasets were imputed in these papers II and III, respectively, to evaluate the influence of missing information on the estimates. The imputation models included all covariates in the multivariable models.

The number of imputations was based on the reproducibility argument, which considers the Monte Carlo error of the results, to be confident that a repeat analysis of the same data would produce essentially the same results (145, 146). The estimates, CIs, and P values were similar in the results from 5 and 10 imputations in paper II, and 10 and 15 imputations in paper III.

4.7 Ethical and legal aspects

The letter of introduction informed the NOWAC women about the purpose of the study, and the right to withdraw from the study at any time. For exposure updates, the letter also explained why the women had been contacted again. On all questionnaires there is a request for written informed consent to participate in the study. The NOWAC study has been approved by the Regional Ethic Committee of North-Norway and the Norwegian Data Inspectorate, including the collection and storage of questionnaire information and biological samples. The women gave informed consent for later linkage to the Cancer Registry of Norway, and the register of death certificates in Statistics Norway. In addition, the participants have given consent for additional written contact (35).

5. Results

5.1 Paper I

Ghiasvand R, Lund E, Edvardsen K, Weiderpass E, Veierød MB. *Prevalence and trends of sunscreen use and sunburn among Norwegian women.*

The mean age when answering the questionnaire was 53 years (range 41–75 years). Sixty-five percent of the women (n=96 852) used sunscreen at Easter holiday, 73% (n=109 213) in Norway, and 87% (n=71 011) in sunbathing vacations in southern latitudes. Sunscreen with SPF ≥15 was used by 25 156 (18%) at Easter holiday, 18 118 (13%) in Norway and 22 678 (30%) in southern latitudes.

The prevalence of sunscreen use increased from 1997–2007, and this increase was associated with age and birth-cohort. There was a significant interaction between age and year when answering the questionnaire ($p_{interaction}<0.001$). The difference in sunscreen use between age-groups was greater in 1997–2003 and prevalence of sunscreen use was much higher in the oldest age-group in 2004–2007 as compared to 1997–2003. Sunscreen use was more common among women with pale or olive skin colour than among dark-skinned women.

In 1997, 40% did not use sunscreen at Easter holiday, and quite similar (38%) in 2007, whereas, using sunscreen with SPF≥15 at Easter holiday increased from 11% in 1997 to 26% in 2007. From 1997 to 2007, no use of sunscreen in Norway decreased from 35% to 21%. Using sunscreen with SPF≥15 increased from 7% in 1997 to 25% in 2007.

In 1997, 39% and in 2007, 46% reported ≥1 sunburns per year in the recent decade ($P_{trend}=0.001$). Women who experienced ≥4 sunburns per year during adolescence reported more sunscreen use in adulthood than never sunburned women ($PR_{Easter}=1.54$, 99% CI: 1.30–1.83; $PR_{Norway}=1.49$, 99% CI: 1.20–1.84; $PR_{southern\ latitudes}=1.37$, 99% CI: 1.14–1.65). Moreover, in the multivariable analysis, those who experienced sunburn almost once a year were less likely to use sunscreen with SPF≥15 compared with those who never experienced sunburn.

5.2 Paper II

Ghiasvand R, Weiderpass E, Green AC, Lund E, Veierød MB. *Sunscreen use and subsequent melanoma risk: a population-based cohort study*

The mean follow-up of 10.7 years (range 1.0–15.6 years) comprised 1 532 247 person-years of follow-up, during which 722 cases of melanoma were diagnosed. Mean ages at the start of follow-up and diagnosis were 53 years (range 40–75 years) and 60 years (range 42–83 years), respectively. The lower limb was the most common site of melanoma (n=266), followed by the trunk (n=249), upper limb (n=118), head and neck (n=49), and multiple sites (n=40). The majority of cases were superficial spreading melanoma (56%), followed by nodular melanoma (15%).

Sunscreen users were more likely to be in the youngest age groups, live in areas with high ambient UV radiation, have higher education, light skin colour, blond or red hair, and to freckle when sunbathing ($p<0.001$) as well as to report significantly more sunburns and bathing vacations, and indoor tanning ($p<0.001$). Moreover, compared to nonusers, sunscreen users with a history of sunburn tended to have a higher risk of melanoma, while sunscreen users with no history of sunburn tended to have a lower risk of melanoma.

In the analysis of sunscreen use according to SPF, SPF<15 sunscreen was defined as the reference category due to the heterogeneity of the pattern of sun exposure between sunscreen users and nonusers. Using SPF≥15 sunscreen on at least one occasion was associated with significantly decreased melanoma risk compared to consistently using SPF<15 (time-dependent model, HR=0.67, 95% CI: 0.53–0.83). Similarly, in sub-analysis of sunscreen use in low latitudes, SPF≥15 was associated with significantly decreased melanoma risk compared to SPF<15. As expected, non-use of sunscreen was associated with decreased melanoma risk compared to consistent use of SPF<15 sunscreen. Sensitivity analysis by additional adjustment for skin reaction after both acute and chronic sun exposure yielded similar results. Results of multiple imputation analyses did not provide evidence that bias due to missing data influenced the associations examined.

The estimated PAF for melanoma associated with use of SPF≥15 sunscreens for the total population of women aged 40–75 years was 18% (95% CI: 4%–30%), rising to 21% (95% CI: 3%–35%) in blond/red-haired women. Among women who used sunscreen with SPF<15, the estimated PAF for changing to SPF≥15 sunscreens was 33% (95% CI: 16%–46%).

5.3 Paper III

Ghiasvand R, Rueegg CS, Weiderpass E, Green AC, Lund E, Veierød MB. *Indoor tanning and melanoma risk: long-term evidence from a prospective population-based cohort study.*

Mean age at study entry was 48 years (range 34–64) and mean age at diagnosis 56 years (range 34–69). The lower limb was the most common site of melanoma (n=343), followed by trunk (n=303), upper limb (n=116), head and neck (n=52).

Ever use of indoor tanning devices was reported by 70% of the participants. Indoor tanning was more common among women in the younger birth-cohorts, women with fewer years of education and light skin colour, and among those who reported a higher cumulative number of sunbathing vacations.

Melanoma risk increased significantly with cumulative use (P_{trend}=0.006; adjusted RR=1.32, 95% CI: 1.08–1.63 for the highest tertile had the highest risk compared to never use). Ever-users of indoor tanning devices had a significantly higher risk of melanoma than never-users (adjusted RR=1.24, 95% CI: 1.05–1.46). Compared with those who reported no current use of indoor tanning devices, current users were at a significantly higher risk of melanoma (adjusted RR=1.21, 95% CI: 1.05–1.40).

We found an increased risk of melanoma for women with age at initiation <30 years compared to never users (adjusted RR=1.34, 95% CI: 1.05–1.66), with a significantly higher melanoma risk among those with age at initiation <30 years ($P_{interaction}$=0.02). A highly significant trend in risk of melanoma with increasing cumulative indoor and outdoor UV exposure was observed (P_{trend}<0.001).

Mean age at diagnosis was significantly lower for both those with age at initiation of indoor tanning <30 years and ≥30 years compared to never-users, with 2.2 years (95% CI 0.9–3.4) lower among women who started indoor tanning <30 years and 1.2 years (95% CI 0.2–2.1) lower among women started at ≥30 years of age.

6. Discussion

6.1 Discussion of the main findings

Sunscreen use and sunburn among adult Norwegian women

In this first population-based study in Norway, we assessed the prevalence of sunburn and sunscreen use and the associated factors among Norwegian women. Sunscreen use was associated with age, education, skin color, skin sensitivity and the number of nevi on legs or arms, which is consistent with previous studies (147, 148). Using sunscreen with SPF≥15 did not appear to decrease the likelihood of having had two or more sunburns per year. This result is in concordance with other studies that reported no association (19, 29), although some found a higher risk of sunburn among sunscreen users (18, 93, 149) and some found an indication of the opposite (150). We did not have detailed information about sunscreen application, but earlier studies found that those paradoxical results (i.e. failure to prevent sunburn) are the consequence of using sunscreens inappropriately, such as using less than the defined amounts of sunscreen, neglecting re-application after perspiring or swimming, and not applying to the whole exposed areas (101, 102). In addition, many people use sunscreen to prolong the time spent in the sun in their recreational activities (18, 93). On the other hand, women who experienced several sunburns in childhood or adolescence in our study tended to use more sunscreen with SPF≥15 in adulthood. Some case-control studies found an increased risk of melanoma among sunscreen users (108), which have been criticized due to possible design limitations and confounding, such as confounding by indication (21, 151). This higher probability of sunscreen use among women who experienced several sunburns in their childhood or adolescence might be another explanation for this relation, as sunburn is a risk factor for melanoma.

Sunscreen use is recommended as the third best strategy (after avoiding the midday sun and wearing protective clothing) and adjunct to the other forms of sun protection (152). However, sunscreen use is the most frequently used sun protection behavior (14). Our results suggest that even though many Norwegian women did use sunscreen, very few of them used the recommended SPF≥15. Sunscreen use among women has had an increasing trend from 1997 to 2007 in Norway. However, this increase has not been accompanied by a decrease in sunburn. Since there is no reduction in sunburn, we would not expect a decrease in the incidence of skin cancer, and there is evidence of a continuous increase in the incidence rate of melanoma and SCC among Norwegian

women aged ≥40 years (2, 6, 46). High prevalence of sunburn suggests that not only sunscreen, but also the other sun protection methods are not common or well used.

Sunscreen use and risk of melanoma

We prospectively studied the effect of sunscreen use on melanoma risk. We found that women who reported using sunscreen with SPF≥15 were at a 30% reduced risk of melanoma compared to those who reported using sunscreen with SPF<15. Moreover, according to our estimates, melanoma incidence among adult women (aged 40–75) in Norway could potentially decrease by 18%, if all were to use SPF≥15 sunscreen for about 10 years (average follow-up in our study).

In the only randomized trial on sunscreen use and risk of melanoma (Nambour trial) (20), 1621 participants were randomly assigned to sunscreen intervention and given a free, unlimited supply of broad-spectrum sunscreen with an SPF=16 and control participants followed usual sunscreen practices. It showed that regular use of sunscreen with SPF=16 can reduce the risk of melanoma (11 versus 22 melanomas; HR=0.50, 95% CI: 0.24–1.02). There are two main differences between our study and the Nambour trial. First, the trial was conducted in a tropical area where people are willing to protect their skin against the sun and their sun exposure is mainly nonintentional, unlike the Norwegians and other European and North American populations where people intentionally expose large parts of their body to the high levels of UV during the summer (82). A national survey in Australia in 2010/2011 found that more than 70% of Australian adults no longer prefer a suntan (153). In contrary, a Norwegian survey in 2014 found that 74% of the respondents agreed with the statement "I sunbathe to get tan" (79). Second, sunscreen use in practice is different from a trial setting. In real life, people do not have access to a free unlimited supply of sunscreen and tend to use much less than the recommended amount and neglect reapplying. However, in agreement with the result of the Nambour trial, our findings suggest that using sunscreen with SPF≥15 may decrease the risk of melanoma in real life and in intentional sun exposure circumstances. A recent large case-control study that assessed the association between sunscreen use and risk of melanoma found a decreased risk of melanoma among those reporting frequent routine use of sunscreen for two decades compared to nonusers (21).

We used SPF<15 as the referent since the nonusers of sunscreen were a small group and had different sun exposure compared to sunscreen users. Sunscreen is the most popular

sun-protection method in many populations (154) including Norway (79). In 2007, 81% of NOWAC women reported using sunscreen in Norway or other high latitudes and 91% reported use in low latitudes.18 Nonusers were more likely to live in low ambient UV locations, and to report no sunbathing vacations, no sunburns and never use of indoor tanning devices. Thus, it was not surprising to find lower melanoma risk for nonusers compared to consistent users of SPF<15 sunscreen.

We used SPF<15 as the referent since the nonusers of sunscreen were a small group and had different sun exposure compared to sunscreen users. Sunscreen is the most popular sun-protection method in many populations (154) including Norway (79). In 2007, 81% of NOWAC women reported using sunscreen in Norway or other high latitudes and 91% reported use in low latitudes (155). Nonusers were more likely to live in low ambient UV locations, and to report no sunbathing vacations, no sunburns and never use of indoor tanning devices. Thus, it was not surprising to find lower melanoma risk for nonusers compared to consistent users of SPF<15 sunscreen.

We found that general use of SPF≥15 sunscreen for the average of 10 years (average follow-up in this study) could potentially reduce melanoma incidence among women aged 40–75 years by 18%, or by up to 33% among SPF<15 sunscreen users if they switched to SPF≥15 sunscreen. Among those with light hair colour (blond/red) and those who freckling after sunbathing who use sunscreen with SPF<15, risk of melanoma reduces about 40%, if they change to sunscreen with SPF≥15. In 2010, about 28% of Australians reported daily sunscreen use and it estimated that about 14% of melanoma incidence prevented by sunscreen use (156). We previously showed that in our study population, using sunscreen in both high and low latitudes had an increasing trend between 1997 and 2007, however, majority of women were using sunscreen with SPF<15. In 2007, only 25% of women were using sunscreen with SPF≥15 in high latitudes and 45% in sunbathing vacations in low latitudes and less than 5% reported using sunscreen with SPF≥30 (155). The upward trend of using broad-spectrum high SPF sunscreens along with improvement in application has the potential to decrease the incidence of melanoma and lower its burden in the coming years.

Indoor tanning and risk of melanoma

We found a significant dose-response association between melanoma risk and cumulative number of indoor tanning sessions. Moreover, longer duration of use, current use and

younger age at initiation of indoor tanning was significantly associated with a higher risk of melanoma. Importantly, indoor tanning was associated with younger age at melanoma diagnosis. These associations remained significant after controlling for potential confounders including age, birth-cohort, ambient UV of residence, hair colour, skin colour, and cumulative number of sunburns and sunbathing vacations.

We found a 32% increased risk of melanoma for cumulative use of >30 sessions and risk was 53% higher for those with ≥480 sessions (e.g. once a week or more for 10 years) compared to never use. Our findings support the evidence from the two recent meta-analyses (32, 33). Two cohort studies found a non-/borderline significant increased risk of melanoma among indoor tanners, however, they did not have detailed information on indoor tanning and the sample sizes were quite small (157, 158). This study is the first prospective cohort that investigated cumulative indoor tanning during several decades of life, current use, age at initiation, and the average age at melanoma diagnosis.

Indoor tanning was significantly associated with younger age at diagnosis, with a two-year decrease in mean age at diagnosis among patients who started indoor tanning <30 years of age. While this is the first study to examine the association between indoor tanning and mean age at melanoma diagnosis, a case-control study found a significant association between indoor tanning and early-onset melanoma, and those with >10 lifetime sessions of indoor tanning were at a significantly higher chance of being diagnosed with melanoma before age 30 (119). The minimum age at inclusion in our study was 34 and we excluded melanomas diagnosed before inclusion, thus, the difference in the average age at diagnosis for indoor tanners compared to never-users is likely to be larger than our estimates. Considering high prevalence of indoor tanning among young people, this finding has important implications for public health. It shows that indoor tanning increases the burden of melanoma not only by increasing the incidence, but also by decreasing the age at onset. Globally, it is estimated that 1,169,000 years of life were lost due to melanoma in 2010 (5), and a person dying from melanoma loses an average of 20 years of potential life (43).

In Norway, the first whole-body tanning model became available in 1972, and indoor tanning became popular during the 1980s (111). Thus, most of our study cohort (born in 1943–57) did not have access to sunbeds during their adolescence. The prevalence of indoor tanning was high among the participants, with 70% reporting ever tanning indoors,

but the cumulative number of sessions was quite low and two-thirds of the indoor tanners reported ≤30 sessions. The proportion of indoor tanners with age at initiation <30 years was about 20% in our study, with an increasing trend in the younger cohorts. According to a recent Norwegian survey 35% of respondents aged 18–24 years reported indoor tanning in the past year (79) and a recent meta-analysis reported indoor tanning among 55% of university students, with 43% during the past year and a significant increasing trend over time (31). At the same time, a recent systematic review found a trend toward significantly higher UV radiation measured in modern indoor tanning devices in recent years in Europe, and this UV radiation is higher than from natural sun (110). Therefore, younger generations are exposed to a higher dose of artificial UV and the negative impact of indoor tanning is expected to be higher, compared to women in our study cohort.

In 1983, Norway implemented the first regulations on indoor tanning devices, and tanning devices with the UVB-rich lamps were replaced by devices with the UVA-rich fluorescent lamps (111). Thus, in our study, older birth-cohorts were more exposed to UVB-rich tanning devices and younger birth-cohorts were mainly exposed to newer, UVA-rich devices. However, we found no interaction in the association between indoor tanning and risk of melanoma by birth-cohort, which is in line with the evidence from other studies that newer tanning devices are as hazardous as the older ones (113, 158, 159). Indoor tanners were more likely to have a light skin colour and they reported a higher cumulative number of sunbathing vacations, which is in line with the findings from previous studies on the characteristics of indoor tanners (117, 118).

The meta-analysis by the IARC in 2006 found higher melanoma risk associated with younger age at initiation (≤35years) and suggested a greater susceptibility to harmful effects of indoor tanning during youth (34). However, younger age at initiation is shown to be a predictor of higher cumulative exposure in some studies, but not in all (119), and two recent case-control studies found no higher risk of melanoma related to a younger age at initiation (160, 161). Frequent indoor tanners often initiate indoor tanning before age 30 (117, 118). However, a higher risk of melanoma for initiation <30 years compared to initiation ≥30 in our study provides supporting evidence of higher susceptibility during youth and young adulthood.

6.2 Methodological considerations

The main strength of our studies included in this thesis is a large cohort with well-characterized and prospective data collection. Moreover, having detailed exposure information across several decades of life, complete follow-up through high-quality national registries, and a large number of melanoma cases are all strengths of the second and third papers, which made them among the most reliable evidence on sunscreen use and indoor tanning related to the risk of melanoma presently available. However, several methodological considerations must be taken into account with regard to the interpretation of epidemiological findings. The validity of a study is considered in terms of three important aspects, including the choice of statistical methods, internal validity (whether the effect estimates are biased due to the way the data is collected, analysed and interpreted), and external validity (whether the results from the study may apply or be generalized to populations or groups outside the study sample) (162). In the following, these aspects and their potential consequences on the interpretation of our findings will be discussed.

6.2.1 Statistical methods

Regression models

The papers included in this thesis used multivariable regression models to estimate relevant measures of association after adjusting for potential confounding. In paper I a generalized linear regression with a log link and binomial distribution (log-binomial regression) was used (130)and PRs (163) for sunscreen use were calculated. Logistic regression is the most popular regression model for binary data, and for rare outcomes the ORs approximate the RRs and PRs. However, sunscreen use was a common outcome, and in cases of common outcomes ORs overestimate the PRs (130). Moreover, the interpretation of PR is more intuitive especially in the presence of confounders and easier to communicate with a general audience (163).

Papers II and III were analysed prospectively, using Cox proportional hazard models and Poisson models, respectively. When using a Cox proportional hazard model a key assumption is proportional hazards. We tested proportionality assumption using Nelson-Aalen plots for a graphical picture and then analysis of Schoenfield residuals (164). We used Poisson regression in paper III, since it allows for more flexible modelling of how covariates act on the hazards (164).

Identification of effect modification

The homogeneity of effect is an underlying assumption when reporting common estimates. Since there are distinctions among statistical, biologic and public health concepts of interaction, it is important to emphasize that evaluation of effect modification in this thesis was based on the statistical concept (statistical interaction) (135, 165). Moreover, statistical interaction is scale dependent, and in this thesis, we evaluated the effect modification on the multiplicative/relative scale (135). The primary method used to evaluate effect modification was to add product terms in the multivariable regression model and test the significance by the likelihood ratio test. When there was a modification effect (i.e. sunburn in the association between ever-use of sunscreen and risk of melanoma in paper II, and age at initiation in the association between cumulative indoor tanning and risk of melanoma), stratum- specific estimates for each level of effect modifier were reported.

Handling missing data

In the analysis of papers II and III, multiple imputation with chained equations (144) was used to evaluate the influence of missing data. The multiple imputation method assumes that the pattern of missing data is completely random or only depends on the observed covariates and not on any unobserved data. If the pattern of missing data is completely at random, then the complete cases are a random sample and both estimates from the complete case and multiple imputation are unbiased and similar. If the pattern of missing data is at random, then the complete cases are not random sample. In this case, complete case analysis gives biased and multiple imputation gives unbiased estimates. If missingness is not at random (i.e. the pattern of missing data depends on unmeasured data), then both estimates from complete case analysis and multiple imputation might be biased (143). The measures of association obtained by complete cases analyses and multiple imputation in this thesis yielded similar estimates, suggesting missing completely at random. However, we cannot completely exclude the possibility of biased estimates from both complete case analyses and multiple imputation due to unmeasured data.

6.2.2 Internal validity

Even though RCTs are considered the gold standard for providing reliable evidence, they face important ethical and logistical constraints, and they usually only focus on highly selected samples and outcomes. Since melanoma is a rare disease and experimenting sunscreen use and indoor tanning on humans has ethical and logistical issues, cohort

studies provide the most reliable evidence. Prospective cohort studies, similar to RCTs, follow the participants and compare the outcome in groups that did and did not receive the exposure (in this thesis, sunscreen use and indoor tanning). The main difference between these two designs is that the allocation of participants in cohort studies is not by chance. Thus, confounding might influence the internal validity of cohort studies. Moreover, selection bias and information bias can affect the internal validity of cohort studies. In the following, these three main sources of bias and their possible effects on the results in this thesis will be discussed.

6.2.2.1 Selection bias

Selection bias happens if the selection of subjects is associated with the exposure and the outcome, or in the other words, the association between the exposure and the outcome is different for those who participate compare to all eligible subjects including non-participants (135). In NOWAC, eligible women were randomly selected from a national registry, which minimise the sampling error. However, the proportion of women who returned the questionnaires can be a source of selection bias. The response rate of about 60% in NOWAC can be a hazard to its validity, however, comparing three variables (number of children, oral contraceptive use, and years of school) among responders and non-responders showed no significant difference. In the study of the non-responders, the main reasons for not participating were "not enough time to fill out the questionnaire" (17%), "too personal questions" (22%), "worried about data security in scientific studies" (29%), and "other reasons" including forgotten about the questionnaire, lack of interest, and lost the questionnaire (35, 120). We do not think any of these reasons had a strong association with our exposures of interest or covariates studied in this thesis. Moreover, the cumulative age-specific rates for all cancers in 1999 for the age group 40–74 years in NOWAC and the national rates from the Cancer Registry of Norway were identical (35). Therefore, selection bias does not seem to influence the findings in this thesis greatly.

6.2.2.2 Information bias

Information bias is an important source of bias in epidemiological studies, which arise from measurement error in a quantitative variable or misclassification of a categorical variables (exposure, outcome, and/or confounders) in a study (166). Information bias can occur in many ways including recall bias, instrument error, interviewer/detection bias, or other sources of measurement errors. Measurement error that does not depend on any other variables is called non-differential measurement error or misclassification (135).

Measurement error that depends on values of other variables is called differential measurement error or misclassification (135). In the following, different sources of information bias in relation to the papers in this thesis will be discussed.

Recall bias

Recall bias is a measurement error due to differences in accuracy or completeness of recall to memory of past events or experiences (166). Recall bias is an important source of differential misclassification in case-control studies. However, in cohort studies, where the information gathers prospectively and before the occurrence of an outcome, recall bias is less likely to influence the results. We excluded participants with melanoma diagnosed before or at the time of answering the questionnaires, and all information was assessed before melanoma diagnosis to minimize the risk of recall bias.

Outcome misclassification

Outcome misclassification is an important source of misclassification bias in many cohort studies and clinical trials. Outcome misclassification occurs when there is a systematic difference between groups concerning outcome diagnosis/detection. Since NOWAC is linked to the Cancer Registry of Norway, a high-quality national registry with 99.9% of melanomas morphologically verified (6), misclassification of outcome is not likely to pose any problem in the findings reported in this thesis.

Exposure misclassification

Information about the exposures of interest (sunscreen use, sunburns, sunbathing vacations and indoor tanning) and covariates were measured by self-report, because it is the only feasible type of measure for large cohort studies. Misclassification of exposure is almost inevitable, but both validity and reproducibility of exposure should be established to be able to estimate the effect of misclassification. We have no information on the validity, but the reproducibility for some of the variables including main variables of interest was examined (Table 1), which a measure of random within-person error in the exposures.

The reproducibility for the SPF of the sunscreens used in Norway or outside southern latitudes and in vacation to southern latitudes were 0.69 and 0.73, respectively (Table 1). Overall, the reproducibility of sunscreen information was good and not related to age, education or skin colour, suggesting non-differential misclassification. The validity of self-reported sunscreen use has shown to be as good as objective measures (167, 168).

Measurement of the history of sunburns and sunbathing and indoor tanning, especially for childhood and adolescence, can be prone to recall error. The reproducibility of indoor tanning and sunbathing vacations to southern latitudes was good (0.70 and 0.71, respectively), but fairly low for sunburns (0.49) and sunbathing in Norway or other northern latitudes (0.47) (128). The reproducibility estimates are similar to the estimates from other studies (169, 170). It has found that self-reported sun exposure produces a valid measure of exposure to solar UV radiation (171).

Covariate misclassification

The reproducibility was good for freckling when sunbathing (0.77), and number of regular symmetric nevi (0.65), but lower for skin colour (0.59) (129).

In conclusion, the reliability of exposures was fair to good, which indicates some degree of non-differential misclassification in the findings of this thesis. Non-differential misclassification of an independent dichotomous exposure always cause underestimation of the association and dilute the association between the exposure and outcome toward the null (135). However, non-differentiality does not guarantee bias toward the null, as categorizing continuous or collapsing categorical exposure variable into fewer categories can change a non-differential misclassification to differential. In addition, non-differential misclassification of exposure or outcome with more than two categories can lead to bias away from null, or if the errors in a variable depend on errors in the other variables, i.e. correlated non-differential misclassification (135, 172). Furthermore, misclassification of confounders decreases the ability to control them in the analysis and cause bias due to residual confounding. The complexity of the simultaneous misclassifications of exposures and confounders and their correlations makes it impossible to predict the size and the direction of bias.

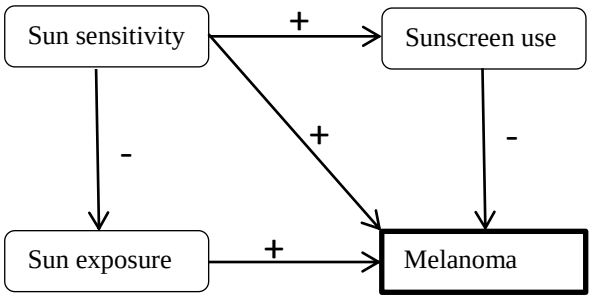
6.2.2.3 Confounding

A confounder is a factor that is associated with both exposure and outcome, but is not the effect of outcome and not on the causal pathway between exposure and the outcome (135). Random allocation in randomised trials means that the groups being compared are expected to be similar in terms of both measured and unmeasured confounders. However, in cohort studies, confounding is a major potential source of bias. Thus, it is important to identify and measure potential confounders and to assess their distribution and influences

on the associations under study. The most important known confounders of the association between sun exposure and risk of melanoma are host characteristics, especially skin sensitivity to sun (173). In addition, host characteristics and sun exposure are important potential confounders for the associations between both sunscreen and indoor tanning and risk of melanoma. Fortunately, as described in the method section, information on potential confounders has been collected in NOWAC. Our approach was to use prior knowledge and directed acyclic graphs to distinguish a set of minimally sufficient variables to adjust for through the multivariable analysis.

Individuals with sensitive skin to sun exposure, i.e. those with light skin, blond/red hair colour and skin that burn easily in the sun, are at higher risk of melanoma. These individuals, because of their skin sensitivity, might tend to avoid sun or use sunscreen and other methods of sun protection. Thus, these characteristics negatively confound the association between sun exposure and risk of melanoma and positively confound the association between sunscreen use (or other sun protective methods) and risk of melanoma, and weakening the real associations (Figure 10). Hair colour is the most accurate measure of skin sensitivity in our population (49, 60) and was an important proxy of sun sensitivity in the analyses in this thesis. In the study of the association between sunscreen use and risk of melanoma, we also adjusted for freckling when sunbathing. Further adjustment for skin colour did not change the estimates.

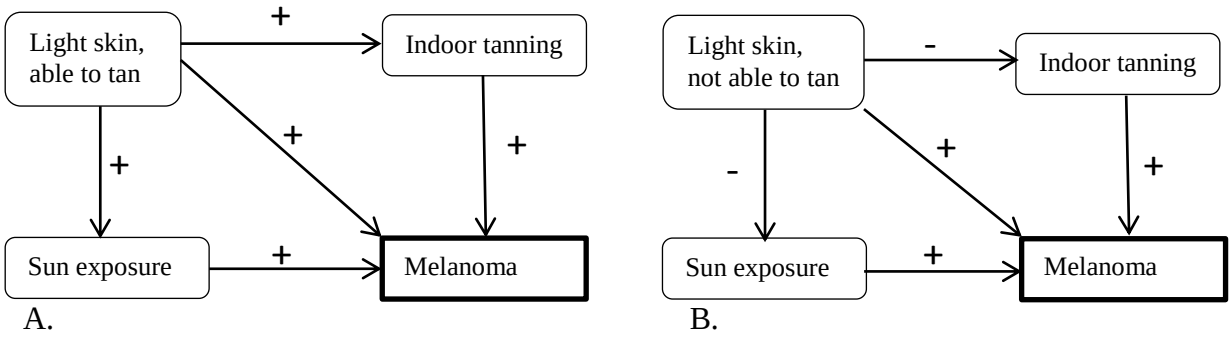
Figure 10. Representation of confounding effect of sun sensitivity on the association between sunscreen use and risk of melanoma.



The role of host factors as confounders of the association between indoor tanning and risk of melanoma is more complicated. Indoor tanners are usually young people with light

skin whose skin has the ability to tan, and they tend to sunbathe (117). Thus, these characteristics positively confounding the association between indoor tanning and melanoma and not adjusting for them might cause overestimation of the association. On the other hand, light-skinned people with skin, which is unable to develop a tan usually avoid both the sun and artificial UV exposure. These characteristics negatively confound the association between indoor tanning and melanoma and might cause underestimation of the association (Figure 11). In paper III, we adjusted for hair colour, sunbathing and sunburns, and additional adjustment for skin colour and freckling when sunbathing did not change the estimates.

Figure 11. Representation of confounding effect of sun sensitivity on the association between indoor tanning and risk of melanoma.



The quality of sunscreens and their ability to protect skin against the sun has improved during the past decades (174, 175). In addition, the public health knowledge about skin cancer and the importance of skin protection has improved over time. Thus, in the analyses of sunscreen use, we adjusted for both calendar year and birth-cohort. Similarly, we adjusted for both calendar year and birth-cohort in the analysis of indoor tanning and melanoma risk because the participants in different birth-cohorts were exposed to different devices. Also, the calendar year of indoor tanning exposure may influence the level of UV exposure (133). Moreover, we adjusted for age by adding it as a variable into the Poisson regression model, or by using it as the time-scale in the Cox regression models.

<u>Unmeasured/residual confounding</u>

Residual confounding is confounding that remains after adjustment for the all measured confounders (162). In the analysis of sunscreen use and melanoma, we did not have information on other methods of sun protection. Thus, it is reasonable to assume that use of other methods of sun protection was not related to the SPF of sunscreen and, therefore, did not affect estimates among sunscreen users. However, nonusers of sunscreen may have had a greater tendency to use other, more efficient methods of sun protection like protective clothing, which might explain part of their reduced melanoma risk compared to SPF<15 sunscreen users. Moreover, we did not have information about total UV exposure, including the time the participants spent in the sun for gardening, running, sailing or other outdoor activities. However, sunbathing activity is a good measure of intermittent sun exposure (176), and sunburn is also a good indicator of sun exposure, taking into account of the intensity of exposure, skin sensitivity, and protective factors (173). As mentioned before, error in measuring confounders, especially sun exposure, might introduce residual confounding and influence the results in this thesis to some degree.

6.2.2.4 External validity

Participants in NOWAC are representative of women born between 1927–1966 in Norway (35). Thus, all our risk estimates and attributable fractions can be generalized to the Norwegian women in the same birth-cohorts. The efficiency of sunscreen depends on both the quality of sunscreens and proper use. Newer sunscreens of high quality with higher SPF, and changes in the attitude and behaviour about sun protection in younger generations over time can increase the efficiency of sunscreens in protecting against sun exposure. Thus, our results on sunscreen use and risk of melanoma should only be generalised to the other generations and populations with caution, if at all. Moreover, our results might not be generalizable to men, since gender is associated with sunscreen use, with a lower frequency in men (147, 150, 177).

Similarly, our findings on indoor tanning and risk of melanoma should be generalized with considerations. Most of our study population (born between 1943–57) did not have access to sunbeds during their adolescence. The prevalence of indoor tanning was high among the participants, with 70% reported ever tanned indoors, but the cumulative number of sessions was quite low and for two-thirds of indoor tanners was ≤30 sessions. The proportion of indoor tanners with age at initiation <30 years was about 20% in our study, with an increasing trend in the younger cohorts. According to a recent Norwegian survey 35% of respondents aged 18–24 years reported indoor tanning in the past year (79)

and a recent meta-analysis reported indoor tanning among 55% of university students, with 43% during the past year, and a significant increasing trend over time (31). On the other hand, a recent systematic review found a time trend toward significantly higher UV measured in modern indoor tanning devices in recent years in Europe, which is higher than from natural sun light (110). Therefore, the young generations are exposed to a higher dose of artificial UV and the negative impact of indoor tanning is expected to be higher, compared to women in our study sample.

6.3 Conclusion

- Sunscreen use increased from 1997 to 2007 with a tendency to use sunscreens with higher SPF. However, sunburn was an issue and had not decreased over the study time. Moreover, use of sunscreen with SPF≥15 was not common among Norwegian women.

- The prospective NOWAC data support the hypothesis that during intentional sunbathing SPF≥15 sunscreen use might reduce melanoma risk compared to use of SPF<15 sunscreen. Our findings suggest that use of sunscreen with SPF≥15 by all women aged 40–75 could potentially lead to an 18% drop in melanoma incidence in 10 years.

- Our findings provide strong supporting evidence on the strength of the association, dose-response, and temporality of the association between indoor tanning and melanoma risk and support the hypothesis of a higher vulnerability to harmful effects of indoor tanning before 35 years of age.

6.4 Public health implications

Since the mid-1950s, the incidence of melanoma has increased almost 11-fold among men and 10-fold among women (6). The Norwegian Cancer Society started sun protection campaigns in 1991 (in the media, pharmacies, nurseries, and general practice), before the Easter holiday and before summer. Current recommendations are to avoid the

sun during midday, prevent sunburn, use protective clothing, use sunscreen with SPF≥15, and avoid indoor tanning, in the order mentioned (178). We are not advocating any changes to these recommendations. Our study provides supporting evidence for the last two recommendations. The high prevalence of sunburn in our study suggests that not only sunscreen, but also other methods of sun protection, are not common or well used. The increasing trend of melanoma incidence rates indicates the need for a more intensive action. Our findings suggest that sunscreen might protect melanoma even during intentional sunbathing. However, it is important to educate the public how they should use sunscreens properly and how much sunscreen should be applied by simple methods such as a handful of sunscreen for the whole body (178) or the teaspoon rule of sunscreen (179, 180). Even though sunscreen with SPF=15 is sufficient to protect the skin against erythema and sunburn if used properly, it has been suggested that sunscreens with higher SPF might provide better protection when applied at the typically used amounts (between 0.5 to 1 mg/cm^2 instead of 2 mg/cm^2) (99, 181).

In the third paper, we found a significant dose-response association between melanoma risk and cumulative number of indoor tanning sessions. Moreover, a longer duration of use and younger age at initiation of indoor tanning was significantly associated with a higher risk of melanoma. Importantly, indoor tanning was associated with a younger age at melanoma diagnosis. Indoor tanning is still popular in Norway, in spite of recommendations by the Cancer Society (178). In 2012, the Ministry of Health and Care Services banned access to sunbeds for individuals younger than 18 years in Norway. However, about 90% of tanning facilities in Norway are unattended, i.e. the customers decide and control their own tanning sessions (182). Indoor tanning is still popular among young adults, and 35% of participants aged 15–24 years surveyed in 2014 reported indoor tanning in the past 12 months (178). Our findings on the association between indoor tanning and risk of melanoma indicate that to restraint the current increasing trend of melanoma in Norway, efforts need to be accelerated and expanded beyond the recommendations from the Cancer Society, and bans on access to minors. Commercial indoor tanning was completely banned in Brazil and Australia in 2009 and 2014, respectively (183).

6.5 Future research directions

There is still a lot that we do not know about melanoma. Melanoma is a heterogeneous disease, differing according to anatomic site, histological subtype, and thickness at

diagnosis. It is likely that these clinical differences reflect different aetiologies (77, 184). Refined prevention strategies are essential to cut the rise in melanoma incidence. The pattern and amount of UV required causing melanoma depends upon the phenotypic characteristics and the anatomic site of melanocytes, which suggests multiple causal pathways. Melanoma thickness at the time of diagnosis is strongly associated with the histopathological subtype, where NM and AM are detected at significantly more advanced stages than SSC and LM. Breslow thickness is the most important prognostic factor, however, our understanding of risk factors for melanoma with different histological subtypes and Breslow thicknesses is limited. NOWAC can contribute greatly in providing valid evidence on the anatomic site of melanoma in relation to UV exposure, phenotypic factors, and age, and identify important baseline characteristics and exposures of women subsequently diagnosed with thick versus thin melanoma, and among different histopathological subtypes.

Finding from a few epidemiological studies are insufficient to establish the causality of an association. More well-designed prospective studies are required to replicate the association between sunscreen use and risk of melanoma. Moreover, sunscreen seems to remain as the most popular form of the sun in near future. Improvement in formulations and the sun protection properties of modern sunscreens and their effectiveness in reducing melanoma risk in real world condition need further investigation. Replication of the association between sunscreen use and risk of melanoma in other populations and among males is important for evaluating the generalizability of the findings. Prospective evidence of indoor tanning and risk of melanoma is also limited and not many prospective studies have had information on indoor tanning in different decades of life. Thus, there is still uncertainty about the importance of age at exposure and possible gene-environmental interactions.

It is important to determine genetic risk factors for melanoma. Few studies addressed the need to identify risk for melanoma among those without known risk factors. Future directions include determining the biological mechanisms underlying the non-pigmentary associations, evaluating the gene-gene and gene-environment interactions, and using this information to improve melanoma risk prediction models and testing their effect on motivating risk-reducing behaviours and cancer prevention strategies.

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