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Preamble: IARC presentation

International Agency for Research on Cancer (IARC/CIRC) is the World Health Organization (WHO) branch dealing with cancer research. It was created in 1967 in Lyon. About 300 people work at IARC, representing over 50 countries. English and French are the working languages. Everyone understands English and most people, but not all, French. Staff includes many doctoral and postdoctoral students.

Figure 1 shows IARC general organisation. It changed this year, after the new director took office. As this restructuration occurred before my arrival, I could not see its effects on work atmosphere. I worked in the Early Detection and Prevention section, Prevention group. The goal of the Prevention group is to assess the importance of risk factors on cancer burden and to evaluate how prevention activities contribute to cancer control. It concentrates on effects of prevention methods on cancer incidence and mortality. It studies in details, among others, skin cancer prevention.

More generally, this agency aims at studying cancer causes (genetic and lifestyle) and prevention. Research at IARC is multidisciplinary as it comprises epidemiology, biostatistics, lab research and other fields. An important role of IARC is to publish results about cancer risks factors. Grading of risks factors, from 1 (“carcinogenic to humans”) to 4 (“probably not carcinogenic to humans”) is frequently done at IARC. Results are published in IARC Monographs. The most recent issue (Volume 100, D: Radiation) changed UV-exposure (solar radiation and sunbeds) group from 2A (“probably carcinogenic to humans”) to 1 (“carcinogenic to humans”). IARC also issues Cancer Incidence in Five Continents every five years. This book regroups incidence results of cancer registries in the world. It comprises data about all neoplasms. Eventually, like every research centre, staff members publish scientific articles. The number of publications is astonishing: 294 publications in 2008 (as first or collaborating author)!

International collaboration is omnipresent. IARC focuses on cancer in low and middle income countries. It also provides education and trainings for people from these countries, like the IARC summer school. A big part of doctoral and postdoctoral students are from less developed countries and conduct projects about cancer management in their home country.

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1 Dr Christopher P. Wild replaced Dr Peter Boyle on January 1st, 2009.
3 3-weeks intensive course about Cancer registration and epidemiology groundings. I helped a week as teaching assistant.
Figure 1: IARC Organisational structure

International Agency for Research on Cancer
World Health Organization
22 June 2009

<table>
<thead>
<tr>
<th>IARC Scientific Council</th>
<th>IARC Governing Council</th>
<th>Director-General, WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairperson</td>
<td>Chairperson</td>
<td>Director, IARC</td>
</tr>
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<td>Dr. H. Caner</td>
<td>Dr. E. Lübbert</td>
<td>Dr. C. P. Wild</td>
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<td>Dr. E. Lübbert</td>
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| Sector of Cancer        | Sector of Mechanisms  | Sector of Molecular |
| Information (CSIN)      | of Carcinogenesis     | Pathology (MCA)     |
|                         | (IMC)                 | (MFA)                |
| Dr. M. P. Caruso        | Dr. V. Cagnacci       | Dr. P. Halmat        |
| (Austria)               |                       |                       |

| Sector of Infections    | Sector of Environment | Sector of Early |
| (INF)                  | (ENV)                 | Detection and    |
| Dr. S. Francisci       | Dr. P. Boffetta       | Prevention       |
| (Argentina)            |                       | (EDP)             |

| Sector of Genetic       | Sector of Lifestyle   |
| Cancer Susceptibility   | and Cancer Biology   |
| (GCS)                  | (LCA)                |
| Dr. S. Tartiglia        | Dr. P. Boffetta      |

| Sector of Health        |
| Research (SMA)          |
| Dr. P. Brennan          |

| Sector of Education     |
| and Training (ETR)     |
| Mr. H. Nastock         |

| Sector of Scientific   |
| Coordination Office    |
| (SSO)                 |
| Mr. E. Kato            |

| Sector of Early        |
| Detection and Prevention (EDP) |
| Dr. B. Sangorski       |

| Sector of Baseline     |
| Screening (SSC)        |
| Dr. L. van Kerkhoven   |

| Sector of Support      |
| Human Resources Office (HRO) |
| Mr. D. D’Angelo        |

| Sector of Support      |
| IARC Grants Office (SSO) |
| (SSO)                  |
| Dr. G. Rekhotz         |

| Sector of Support      |
| Information Technology Services (ITP) |
| Mr. M. Simons          |

TBA: to be appointed
Summary

Cutaneous malignant melanoma, the deadliest skin neoplasm, is also the fastest incidence-growing cancer. Melanoma incidence has been increasing worldwide for decades. Increases were mainly observed for early-stage lesions, even if advanced lesions incidence rates are increasing too (but slower). Recent level-offs were observed in high-incidence countries, in specific subpopulations, suggesting future improvements. However, it is necessary to analyse accurate and recent melanoma mortality data to evaluate the real burden of the disease. Does mortality reflect incidence worrisome trends? Are these trends similar to other skin cancers? How can we explain melanoma epidemiology tendencies?

In order to answer to those questions, we widely reviewed literature on melanoma epidemiology. Then, we studied mortality trends using the WHO mortality database in 54 countries worldwide, for the longest available time period (up to 53 years). For each country, we computed World age-standardised and age-specific mortality rates. Then, we conducted Joinpoint analyses, Poisson regression models and cohort analyses. Finally, we made a simpler analysis with NMSC (38 countries) in order to compare CMM and NMSC mortality trends.

About incidence trends, it is still growing in most countries. Regardless, there are levels-offs in high incidence countries. This suggests incidence cannot increase further in those countries. Concerning mortality, we found a clear pattern worldwide. Mortality has been increasing until the 1970s to 1990s. Then, it either levelled-off or decreased. This pattern is likely to be linked with a period effect. To conclude, CMM incidence is increasing whereas mortality is levelling-off, so CMM incidence increases are likely artificial.

List of abbreviations used in this report:
- 95% CI: 95% confidence intervals
- AIC: Akaike’s information criterion
- AJCC: American joint committee on cancer
- ALM: acral lentiginous melanoma
- BCC: basal cell carcinoma
- CMM: cutaneous malignant melanoma (also CM, cutaneous melanoma and MM, malignant melanoma)
- EAPC: estimated annual percent change (also APC, annual percent change)
- IARC/CIRC: international agency for research on cancer/centre international de recherche sur le cancer
- ICD: international classification of diseases
- IP: inflection point
- LMM: lentigo maligna melanoma
- NM: nodular melanoma
- NMSC: non-melanoma skin cancer
- SCC: squamous cell carcinoma
- SEER: surveillance, epidemiology and end results
- SSM: superficial spreading melanoma
- TNM: tumour node metastasis
- UICC: union internationale contre le cancer
- UN/ONU: United Nations/Organisation des nations unies
- WASR/EASR/ASR: world age-standardised rate/European age-standardised rate/Age-Standardised rate
- WHO/OMS: world health organisation/organisation mondiale de la santé
- F/M: Female/Male

V
1 Introduction

1.1 Generalities

Cutaneous malignant melanoma is a particular skin cancer that mainly affects fair-skinned populations in developed countries. The malignant cell is melanocyte. These cells are found in the bottom layer of the epidermis (and several other locations such as eye) and produce a pigment called melanin. Because they have a nervous origin, tumourous melanocytes can easily make metastases. Once a melanoma has made metastases, it is extremely difficult to cure.

The malignant tumour has important characteristics that are widely used to determine its severity. Clark level (of invasion) represents tumour penetration in relation to anatomic layer. There are five levels, from I (in situ melanoma; located within the epidermis) to V (penetration in the fat layer below dermis). Breslow thickness (or rarely depth) is the vertical dimension of the tumour and can be easily measured (in mm). Figure 2 illustrates those important notions. Up to now, this is the best prognosis factor. But even if these characteristics are very useful to physicians, they do not wholly describe clinical stage. The exact tumour stage is defined by tumour-node-metastasis (TNM) classification. This classification is frequently issued by the AJCC. Melanoma TNM classification is used to characterise a melanoma in great details. It takes account of tumour thickness, metastatic nodes and distant metastases. Several levels and sublevels describe each characteristic and there are plenty of combinations, so the stage is very accurate. There is another TNM classification issued by the UICC, but it is less frequently used. Moreover, differences between these two classifications are rather slight.

There are also four melanoma subtypes with different characteristics. The most frequent among white-skinned populations is superficial spreading melanoma (SSM); then we have nodular melanoma (NM, the most dangerous because undetectable with standard criteria), lentigo maligna melanoma (LMM) and eventually acral lentiginous melanoma (ALM, very scarce in fair-skinned populations, but the most common in Asian populations). Melanoma subtype is determined microscopically and is often called histological (sub)type.
1.2 Study context

Risk factors for CMM are nowadays well-known. UV-exposure (mainly sun exposure, but also sunbeds and sunlamps use\textsuperscript{4,16}) habits play a very important role in melanoma, especially during childhood (but not only\textsuperscript{1,21}). Intermittent, intensive exposure without adequate protection is from afar the most dangerous behaviour. There are also genetic factors that increase the risk of developing a melanoma, for example light hair, eye and skin colour, childhood freckles, etc.

There is a marked difference in epidemiology according to sex. Melanoma incidence is higher for women, while mortality is higher by men. Moreover, body site distribution is not the same. Trunk is the most prevalent site by men, whereas it is lower limbs by women\textsuperscript{12,54}. Such gender divergences are common in other malignancies, but remain unexplained\textsuperscript{20}. CMM incidence differs with social status: the most exposed people are the richest\textsuperscript{32,79}. So, high social status is associated with a higher risk of melanoma.

Since the first population-based cancer registries were created (in the late 1950s/early 1960s), MM incidence has been dramatically increasing worldwide. CMM has become a major health care topic in Australia\textsuperscript{10,34}, New-Zealand\textsuperscript{60,63,73} then in the USA\textsuperscript{2,30} and Northern Europe\textsuperscript{54-60} these last 40 years. Therefore, education campaigns took place in those countries\textsuperscript{58,29}. The goal of such campaigns was to inform local population and health care practitioners about sun-exposure risks and melanoma detection. The underlying purpose was to improve early detection of malignant tumours and reduce the number of thick tumours (linked to poor prognosis). Those campaigns introduced simple detection methods like the “ABCD(E)” rule: A for Asymmetry, B for irregular Borders, C for varied Colour, D for Diameter greater than 6mm and E for Evolution.

Effects of those campaigns were observed in the following years and decades and were reported in many studies\textsuperscript{58,31,84,85}. Most of them reported a very rapid increase in incidence (and proportion) of thin tumours. Meanwhile, the proportion of thick tumours decreased mechanically, but their incidence was either stable or increasing. A lot of hypotheses can explain these trends. Increases in incidence could be either real, or owing to increased awareness of general population (and medical practitioners) or to better registration. In fact, many scientists are not convinced that CMM increase in incidence is real. They think the increase is artificial and caused by “over-diagnosis”, \textit{i.e.} reports of suspicious pigmented lesions as cutaneous malignant melanomas\textsuperscript{51,22}. Precautionary principle would also be applied to unusual skin lesions.

There was no significant breakthrough in melanoma treatment these last decades, so treatment does not influence mortality trends as it can be observed for other illnesses. Therefore, decreases in mortality are unlikely owing to better treatment. But on the other hand, recent improvements in melanoma survival were shown\textsuperscript{19}. 

2 Material and methods

2.1 Literature search

Before starting data extraction and analysis, I did some literature search in order to look for information about CMM incidence and mortality trends in the world. This was also a great opportunity to learn more about melanoma biology and background (this was actually an underlying goal of this search). My search directions were very specific. To sum up, I had to find peer-reviewed paper (without language restriction) on trends in melanoma incidence and mortality in any possible country, for the longest available time period. The final goal was to obtain trends in melanoma incidence by severity of the disease, in order to compare them with mortality trends. These data were to be essentially compiled by population-based cancer registries. Severity of the disease was ideally defined by Breslow thickness, but it could also be Clark level of invasion, clinical staging or even histological subtype.

To achieve this goal, I did several PubMed advanced searches with Sharon Grant’s help. We started with wide, general terms and progressively restricted the search field. We stopped searches when we had about 850 papers matching our query. We aimed at leaving no article behind. Used key words were: “skin cancer*”, “skin tumor*”, “skin tumour*”, “skin neoplasm*”, “epidemiology”, “incidence”, “mortality”, “melanoma”, “registry”, “Registries”, “histology*”, and “trend*”. I read all available abstracts and made a first selection, because even if the search was narrow, irrelevant articles remained. Then I picked up references of interesting articles, retrieved complete papers on the web or from IARC library, read and summarised them. Finally, I read and summarised 88 articles. This was a big part of my work (cf. Bibliography).

2.2 Data extraction

2.2.1 Basic files

Mortality data was provided by the WHO mortality database. I had actually to deal with four files containing hundred of thousands or even millions of lines. Each file matched a revision of the international classification of diseases (ICD7 to 10). Each revision has specific codes for all causes of death. There were sometimes several lists for a single revision, so several codes for the same cause. Codes for cutaneous malignant melanoma were: 190 (ICD7), 172 (ICD8), B111 (ICD9), C43, C430 to C439 and 1035 (ICD10). Non-melanoma skin cancer (NMSC) codes were: 191 (ICD7), 173 (ICD8), B112 (ICD9), C44 and C440 to C449 (ICD10).

These files covered up to 53 years according to the country, from 1955 to 2007. They contained the number of deaths by age, sex (1 for men, 2 for women), year and country (unique 4-digit WHO code) for each cause recorded in the corresponding ICD
version. Deaths by age were given either by 5-years or by 10-years age groups according to country and year. Deaths by 5-years groups were given from 0-4 years to either 95 or 85 or 75 or 70 or 65 years and more. Deaths by 10-years age groups were recorded as follows: 0-4 years, 5-14 years…. 75 or 65 years and more. This “age format” could change within a country with time (towards greater precision). There were in total 144 different countries in the database.

Population data was obtained from United Nations world population prospects (2008 revision). It contains population estimates (in thousands) by age for each state member of United Nations from 1950 to 2010. Estimates are given by 5-years age groups, from 0-4 years to 80 and more years until 1989, and until 100 years and more from 1990 onwards (no exception). 2009 and 2010 are projections and were not used in the study because there are no deaths projections for CMM; 2008 population was not used because there were no available death records. Each country is identified by a unique 3-digit code. UN code has nothing in common with WHO code. In this study, data from 1955 to 2007 was useful. There were two files, one for each sex. There were 188 available countries.

Data extraction for melanoma had previously been done by Mary Heanue for another study. Her programme was in SAS (version 9.2). The first thing to do was to check her code. We modified it because we found some mistakes (such as a missing age group) and a few missing countries. Meanwhile, I did the data extraction with R. Eventually data was complete (CMM mortality and population data) for 107 countries. So there were 37 “missing” countries, of which 27 had no population estimates. WHO does have population estimates of all countries, but quality is very poor, so we did not use it. Missing countries were either bigger countries subdivisions (e.g Scotland), or former countries (e.g former USSR) or non UN members (e.g Taiwan). The 10 remaining countries had either only partial mortality data (e.g China and several very populated countries) or special code lists without melanoma (e.g Belarus).

2.2.2 Data standardisation and selection

Mortality rates were computed and age-standardised (for 100000 person-years) by the direct method, using the world standard population as reference. This standardisation enables us to compare rates in diversified populations. Age standardised rates were calculated as follows:

\[
\text{StdRate} = \frac{\sum_{i=1}^{n} \frac{\text{mor}_i}{\text{pop}_i} \times \text{WorldPop}_i}{\sum_{i=1}^{n} \text{WorldPop}_i}
\]

(0)

The world standard population, a virtual 100000 population, is given in Table 1. In order to compute correct age-standardised mortality rates, we had to modify some data in population and/or mortality files. Actually, we only regrouped some age classes. We used as many age groups as possible.

\(^*\) IARC Technical Officer, Descriptive Epidemiology Production group.
Table 1: World Standard Population

<table>
<thead>
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<th>Age (years)</th>
<th>0-9</th>
<th>10-14</th>
<th>15-19</th>
<th>20-24</th>
<th>25-29</th>
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<td></td>
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</tr>
<tr>
<td>Population</td>
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<td>500</td>
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</table>

Rates were calculated for each sex and for the longest available time period. The time range was 1 to 53 years (median: 18 years; mean: 22.25 years). After that they were represented with R (version 2.6.2 for Windows). All presented graphs were done with R. As the goal of this internship was studying mortality time trends, countries with less than 10 years of recorded data were excluded from the study. Moreover, too small countries with less than 10 deaths per year on average were also removed because no trends could be deduced from those datasets. We used the same selection criteria when we computed non-melanoma skin cancer (NMSC) trends.

We used the same standardisation method when we computed rates by age. We calculated 4 age-specific rates: less than 50 years, 50 to 59 years, 60 to 69 years and more than 70 years. We modelled these data with JoinPoint, using the same parameters as for age-standardised rates (see 2.3 Joinpoint analyses).

Some data were arbitrarily excluded from the study. For example, we deleted 1968 data in France because the number of deaths was about the double of the 1967 and 1969 ones. This anomaly was spread over all age groups. Jean-François Doré explained to me it was the exact opposite for NMSC in France in 1968. I checked this when I computed NMSC age-standardised mortality rates. So, this outlier is very likely owing to skin cancer misclassification in 1968 and had to be removed. We also removed the first 7 years (1960 to 1967) from the USA dataset because there were no data between 1968 and 1978 inclusive. This raised a problem because our models found changes in trends (Joinpoints and inflection points; see 2.3 Joinpoint analyses, 2.4 Poisson regression and 3.2 CMM age-standardised mortality for details) right after the gap. But those changes may have occurred within the gap. As there is no way to know when the change occurred, we restricted our study to 1979-2005. Some other countries (e.g. Poland) had gaps, but we removed years only when it induced changes at the end of missing data. Finally, years (2004-2007) were omitted because of problems during transition between coding lists 09B to 101 in Kazakhstan.

Eventually, 54 countries met our requirements and were studied more precisely. Most were European (31) or American (15) countries, but each continent was represented (5 countries in Asia, 2 in Australasia and 1 in Africa). 38 (out of 79) countries were selected for NMSC analysis: 26 in Europe, 5 in Asia, 4 in America, 2 in Australasia and 1 in Africa. Joinpoint analyses were conducted on age-standardised rates.

vIARC Visiting Scientist, Prevention group.
2.3 Joinpoint analyses

Joinpoint analyses were done with the SEER Joinpoint software (version 3.3.1). I used a log-linear Poisson model to deal with heteroscedasticity (instead of constant variance). The dependent variable was the corrected number of deaths for each age group \((i.e. \text{WASR} \times \text{Population})\) and the independent variable was the year. Those analyses were done for each selected country and both sexes. Advanced parameters were taken as default.

Basically, this software models time trends. It inputs a file with observations and outputs a modelled piecewise linear or log-linear data with 0 to 3 Joinpoints. It actually computes all models (4 in total) and selects the best one by maximum likelihood methods. There are at least 4 observations between two Joinpoints (this parameter can be modified). The output contains each model characteristics \((e.g. \text{Joinpoint(s)} \text{ position(s)}, \text{APCs with } 95\% \text{ CI, comparisons between models, etc.})\). All outputs may be exported for further analyses. Because of poor graphical quality, we redid graphs with \(R\), using JoinPoint data.

2.4 Poisson regression

After Joinpoint analyses, we decided to model mortality rates differently. We built with \(R\) a Poisson model allowing a single infection point (IP), which had to be the same for both genders. We modelled the rounded theoretical number of deaths and plotted standard rates. The model was the following:

\[
\ln(\text{Deaths}) = \beta_0 + \beta_1 \cdot \text{Sex} + \beta_2 \cdot \text{Year}_m + \beta_3 \cdot (\text{Sex} \cdot \text{Year}_m) + \beta_4 \cdot \text{Year}^* + \beta_5 \cdot (\text{Year}^* \cdot \text{Sex})
\]

\[
\text{Year}_m = \text{Year} - \text{Year}[\text{IP}]
\]

\[
\text{Year}^* = \begin{cases} 0 & \text{if } \text{Year}_m < 0 \\ 1 & \text{if } \text{Year}_m \geq 0 \end{cases}
\]

We considered each year (from the second to the next-to-last recorded year) as a potential infection point. We made as many models as possible infection points and stocked AIC \((-2 \times \log(\text{likelihood}) - 2 \times \text{Parameters})\) of each model. For each simulation, we tested whether the interaction \(\text{Year}^* \cdot \text{Sex}\) improved the fit. To do this, we simply compared AICs of the two models. Once we tested each year, we kept the best model \((i.e. \text{the smallest AIC})\). We plotted the best fits for each country and grouped countries by regions and continents.

2.5 Cohort Analysis

In order to go further in the analysis, we conducted cohort analysis. The goal of this analysis was to determine whether the trends we observed in the first analyses were owing

\(\text{vi}^\text{th} \) There were countries selected for CMM, and not for NMSC, and vice-versa. 37 countries were selected for both CMM and NMSC.
to cohort or period effects (see 3.2 CMM age-standardised mortality and 3.3 CMM mortality trends by age). To do this, we used age-specific rates (no age standardisation) and plotted results using a semi-log scale. The final plot contained rates on the y-axis and birth cohorts (i.e. Year − Age\(^viii\)) on the x-axis. We computed rates for both sexes and people aged 45 or more. Rates for younger people were very low and no trend could be deduced. Adding those age groups would have made graphs unclear. That is why we omitted them for graphical representation (but rates were computed for all ages).

3 Results

3.1 Melanoma incidence trends

We read about 58 articles dealing with CMM incidence trends. The most studied areas were Northern Europe (especially Scotland and Scandinavia), Western Europe and Australasia (in particular Queensland, North of Australia). As expected, the highest incidence regions were the most studied. The highest incidence area we found was Auckland White population\(^ix\) (New-Zealand), with 58.0 cases per 100000 men and 55.2 cases per 100000 women. There is a marked incidence gradient in those regions. In North America and Australasia\(^{63}\), people living near the equator have a higher CMM incidence rate. This is the contrary in Europe, where the highest rates are found in areas close to the polar circle\(^{17,72}\). The European inverse gradient is explainable. Generally speaking, Northern Europeans have lighter hair, skin and eyes than Southern Europeans, which is associated with a greater risk of melanoma. In the USA and Australasia, most fair-skinned people are of British origin. So, Caucasian population in those regions is more homogenous than in Europe. Therefore, most exposed populations (i.e. living near the equator) have the highest incidence.

There were also studies in low incidence countries, like Asia. However, those studies comprised so few patients\(^{12,43,80}\) that trends were rarely analysed, even if for long studies, because variations were never significant. These studies remained useful to assess differences in melanoma incidence in the World. We found no study about Black African populations (the only African study was conducted on 100% European descent Cape Town population\(^75\)). It is known that melanoma cases by such people are exceptional (scarcer than in Asian populations!). The lack of data for such “no-risk” populations is therefore easily understandable. But oddly enough, we could retrieve no study conducted in Latin America. Incidence is likely to be relatively low, lower than in Europe but higher than in Asia. There are cancer registries and publications about melanoma in this region. But results are published in local and unrecognised journals. Articles are written in Spanish or Portuguese. We could find those articles (and/or English translation) neither online, nor at IARC library. Judging from English abstracts we read, incidence is relatively low, but is increasing.

\(^viii\) We took the youngest age of each age group, for example 50 for the 50-54 years age group.

\(^ix\) age-standardised rates; Auckland Caucasian Population as reference
About general incidence trends, all studies showed a general increasing trend, with a possible level-off or decrease in recent years for some subpopulations. The most impressive evolutions in Europe were found in Scandinavia (e.g. Norwegian men\textsuperscript{17}: from 3.0 in 1953 to 30.7 in 1997 cases per 100000 -a tenfold increase- EASR for people aged 25 and more). Important increases were also reported in the rest of Europe\textsuperscript{17,46}, Australasia\textsuperscript{2,63} and North America\textsuperscript{2,36}. In high incidence countries, the female/male (F/M) is close to 1\textsuperscript{65} whereas in medium or low incidence countries the F/M ratio is significantly higher than 1\textsuperscript{69}. This means incidence is higher by women in low/medium incidence countries, while there are no differences in high incidence countries.

These dramatic increases in incidence are mainly explained by the increase of early stage tumours. All papers studying melanoma incidence by severity of the disease show this particular increase\textsuperscript{54-59,23,15}. This phenomenon happened in all countries from the 1970s/1980s onwards. Earlier studies are rarer. Thicker tumours trends differ from a study to another. In general, the more the tumour is thick, the less its incidence increases. But incidence rarely decreases, even for the thickest lesions. Most of time, thick lesions have either a stable or a slightly increasing incidence\textsuperscript{17}. The only decreases we found were observed in Scotland\textsuperscript{55}. But these decreases were temporary and happened in the 1980s. The general trend is still upward. Intermediate lesions show an increase in incidence, but milder than thin lesions. In European descent populations, there is also a marked shift toward SSM subtype. It was already the most prevalent subtype, and its proportion increases with time. It also happens in Asian populations, at the expense of NM. However, ALM remains the most frequent subtype in Asia\textsuperscript{77}. Meanwhile, survival\textsuperscript{8} improved with time\textsuperscript{55} for all stages and thickness groups. Survival for thin melanomas is close to 100\%\textsuperscript{49,65}.

Incidence decreases were observed by young Australians\textsuperscript{50}. This suggests that CMM has reached a peak in Australia, and that incidence will probably decrease when those young Australians get older. To conclude with incidence trends, despite prevention campaigns, advanced melanomas incidence is not decreasing. Early melanomas increases in incidence seem directly linked to prevention campaigns\textsuperscript{31}.

The following parts deal with selected countries only. Presented graphs were carefully selected to illustrate typical general patterns and differences between methods. Graphs were made for each selected countries, but all results cannot be displayed in this report because of space restrictions.

3.2 CMM age-standardised mortality trends

Considering only current rates (leaving alone time trends for the moment), a mortality gradient can be observed in mortality rates. In Europe, Northern countries have the highest mortality rates\textsuperscript{17}, whereas is the rest of the world (actually North America and Australasia\textsuperscript{34}), populations living close to the equator have a bigger mortality rate. This was expected\textsuperscript{3,7,34}. Actually, the mortality gradient is the same as incidence gradient.

\textsuperscript{x} 5- or 10-years survival in most studies.
Concerning temporal trends, countries can be divided into two groups. The first group contains populated and/or developed countries. Data for those countries is very complete (often more than 40 recorded years). Mortality rates are increasing fast until the 1970s/1980s. After that, trends are clearly levelling-off. Those worldwide levels-offs or decreases were detected in a previous study. Mortality rates either keep rising, but slower (e.g. Spain), or stabilise (e.g. Hungary, Sweden) or slightly decrease (e.g. the USA, Australia). This change in trends can be observed in high (e.g. New-Zealand), medium (e.g. Italy) and low (e.g. Japan) mortality countries. Both sexes were affected by this evolution at the same time. For most countries, modelled curves are about parallel, with male’s rates higher than female’s. Women presented in general more favourable trends (milder increases, stronger decreases) than men. The phenomenon touched first Scandinavian countries in the 1970s (Poisson model: Finland: 1970; Norway: 1976; Sweden: 1978), then Western Europe and Australasia in the 1980s and finally the rest of Europe and America in the 1990s.

In the second group (data not shown), melanoma mortality steadily increases or is stable over the whole recorded period. These countries are in general medium- or small-sized, with a few exceptions like Korea and Germany. There are nearly always fewer recorded years than in the first group. 1970s and 1980s are rarely fully recorded. So, there may have been unrecorded level-offs in those countries. As they are relatively small, these countries are not widely studied and data is lacking. Therefore, we can only make guesses about unrecorded trends. Meanwhile, we have to keep in mind that there are countries with more than 40 recorded years and without infection or Joinpoint. The most relevant ones are Greece and Belgium (Figure 10), where mortality rates keep increasing since 1966 and 1955, respectively.

A result of Joinpoint model is given in Figure 3. Figure 4 shows the interest of the Poisson model, in comparison with the Joinpoint model. With the Poisson model, the male small drop of the Joinpoint model (1970-1973; not significant) is cleared. Results remain about the same with the two models. Joinpoints were always close between genders, here 1979 for men and 1981 for women. The Poisson model imposes a common inflection point, here 1981. There is a clear breakpoint in melanoma mortality in the early 1980s for both models. Also, both models fit data well. Differences between these models are further discussed in 4.2 Comparison of Joinpoint and Poisson models.

3.3 CMM mortality trends by age

We conducted only Joinpoint analysis on rates by age (less than 50, 50-59, 60-69 and more than 70 years). Results are less clear than for age-standardised mortality rates, but we can still underline some general patterns. First of all, and unsurprisingly, mortality rates are higher by older age groups. Age-standardised mortality rates are nearly equal to 0 for the youngest age group. We also represented data according to a semi-log scale (data not shown). Rates are rather stable for young age groups, and the bigger increases are found by the oldest people. There are not always joinpoints for each age group. In general there are as many joinpoints as for the age-standardised mortality rate. When there are Joinpoints, they occur first in the younger age groups, then in older ones, as shows Figure
In this particular case, levels-off occur first in the youngest age group (1981), then in the 50-59 group (1985), then in the 60-69 group (1988) and finally in the oldest one (1991). Those gradual breakpoints happen in a lot of countries. They suggest a cohort effect. The “kingpin-cohort” would be in the first group in 1981, in the second in 1985, etc. These results lead us to cohort analysis. We would have not necessarily done it with different age-specific results.

Figure 3: JOINPOINT Model
Melanoma mortality rate in France between 1955 and 2006

Figure 4: Poisson Model
Melanoma mortality rate in France between 1955 and 2006

3.4 CMM mortality trends by birth cohorts

The latter result suggested a cohort effect, but it could also be a period effect. If there was a cohort effect, there would be a slope change at a specific cohort. It it was a period effect, slope would change the same year for all cohorts. Figure 6 shows the result for Italian women (same data as Figure 5). There is no cohort effect, but a period effect. Indeed, all age-specific rates are stabilising, but not at the same birth cohort. For example, the 75-79 years rate is roughly stabilising for cohorts born after 1900, and the 65-69 since 1910, etc. Rates for younger people are stabilising at younger cohorts. If there was a cohort effect, all rates would stabilise at the same time. This is clearly not the case here, as in nearly all other countries (data not shown). Therefore, we can conclude that changes in mortality rates are mainly owing to a period effect occurring in the 1970s, 1980s or 1990s depending on the considered country. Actually, all age groups were touched at the same time.

However, there are exceptions. In the USA there is a slight cohort effect since the 1930s for men (Figure 7) and the late 1920s for women (Figure 8). We also found a cohort effect in Australia (stabilisation since the 1920s for both genders). These are the only...
countries where there is a cohort effect. We found no reason for this difference. We found cohorts effect in the literature, but they mainly concerned incidence rates\textsuperscript{15}.

**Figure 5**

Female melanoma mortality rate in Italy between 1958 and 2008 by age

3.5 Comparison with non-melanoma skin cancer mortality trends

As its name suggests, non-melanoma skin cancer regroups all skin neoplasms but CMM. Most of NMSC are either basal cell carcinomas (BCC; tumourous cell = basal cell) or squamous cell carcinomas (SCC; tumourous cell = keratinocyte). Other skin malignancies are scarcer. NMSC incidence is much higher than CMM\textsuperscript{78,42,33,37,38,72,45}, moreover it is about stable in most countries\textsuperscript{33,37,72}. The highest incidence rates are found in Australasia, like for melanoma. However, NMSC mortality is very low when compared with CMM\textsuperscript{25}. For those reasons, NMSC is less broadly studied than CMM. We wanted to compare CMM and NMSC data in order to determine whether CMM had the same trends as other skin cancers. While extracting data from the WHO mortality database, we noticed there were less data available for NMSC. There were fewer countries and less recorded years: several countries had no data for the 2000s. This confirms that NMSC is no major health concern. We modelled NMSC data with Joinpoint analyses and the same Poisson model as for CMM data. We did not find the same trends as CMM.
As expected, we found a lower mortality rate for NMSC. High mortality countries remained the same for CMM and NMSC. We found mostly decreasing trends, either continuous, or reaching a plateau in the 1970s or 1980s. When mortality rate levels off, it usually happens for both genders at the same period, as shows Figure 9. The result was the exact opposite in Australia and New-Zealand (highest skin cancer incidence and mortality countries), were the rate was stable and started increasing in the 1960s for New-Zealand, in the 1980s for Australia (Figure 11).

4 Discussion

4.1 Literature search

Finding articles about melanoma incidence by severity of the disease was not very difficult. Comparing results of numerous studies conducted all over the world at different time periods was harder.

First, all studies did not use the same tools to evaluate melanoma trends. Most used age-standardised rates, but other used raw number of cases, annual percentage changes, proportions or combinations of the latter. Actually, APCs and proportions are often deceptive. For example, the proportion of thick melanomas decreased in most countries, but this does not necessarily mean that there are fewer advanced cases. In fact there are more thin tumours, and the decrease in proportion of thick tumours does not reflect absolute incidence. When there are only percentages and no data about the number of cases studied, it is impossible to determine real incidence evolution. So we had to keep in mind that proportions are not equal to incidence. APCs are not as misleading as proportions, but it still may induce interpretation errors, because trends are given in percents. A small augmentation may be linked to a huge APC (e.g. from 0.1 to 0.2: +100%), whereas a big increase can be associated with a mild APC (e.g. from 4 to 5: +20%). Absolute variations are not assessable with percentages. Percentages are useful to evaluate relative variations, but this was not our purpose. So, we preferred absolute, age-standardised incidence and mortality rates.

As a consequence, age-standardised rates seem easier to interpret. But we ran into a second problem: age-standardisation is not always done with the same reference population. Most studies provided World or European age-standardised rates, but some used a local population census as reference. In those cases, rates are difficult to compare with other studies. Happily enough, such cases remained rare and we were able to compare many rates.

This leads us to a third issue. We had ideally age-standardised rates by Breslow thickness. But there are no conventional thickness groups, so each study chooses different groups. We found from 2 to 5 thickness groups. Classifications may follow AJCC or UICC recommendations, but these recommendations changed several times. The current classification mostly used today comprises four thickness groups: less than 1.00mm, 1.01-2.00mm, 2.01-4.00mm and more than 4.00mm. A former classification used in older (but
also present) articles is; less than 0.75mm, 0.76-1.50mm, 1.51-4.00mm and more than 4.00mm. There are many possible thickness groups, so results can be difficult to compare precisely. But this was not our main problem, because a lot of studies had the same groups. Moreover, even if groups were different, partial comparisons were always possible because there were very often common groups between studies. Some studies studied only median (or mean) Breslow thickness. Of course, it obviously decreased because there were more and more early tumours.6,64

A fourth difficulty was population coverage. Data were ideally provided by population-based cancer registries. However, we found some hospital-based studies7,70,61,81,12,37,38,41. At the contrary of population-based studies, clinical-based studies are prone to population variations. So for these studies, population coverage may evolve during the study. Therefore, variations in incidence are not always owing to real fluctuations. Moreover, hospitals cover a relatively small population, so variability is bigger in clinical-based registries. We kept those studies because they took place in countries without population-based cancer registries.81 In general, we preferred population-based studies because results are easier to interpret.

Eventually, as tumour thickness is not recorded in the WHO mortality database, we could not compare results about mortality by severity of the disease. But it is obvious that most deaths are owing to advanced tumours.

Figure 6
Female melanoma mortality rate in Italy by cohorts
Figure 7

Male melanoma mortality rate in United States of America by cohorts

Figure 8

Female melanoma mortality rate in United States of America by cohorts

Figure 9: Poisson Model

Nonmelanoma skin cancer mortality rate in Spain between 1955 and 1998
4.2 Comparison of Joinpoint and Poisson models

We used two distinct models to analyse melanoma mortality trends: Joinpoint and Poisson. Each model has its advantages and drawbacks. Let us try to evaluate differences between those models. We started with Joinpoint because it is a general model that has a wide application field. It can be used to assess any temporal trend, and especially cancer epidemiology trends. Joinpoint has a lot of adjustable parameters (linear or log-linear model, homo or heteroscedasticity, model selection methods, etc.) and is very simple to use (even a non-statistician could use it). As it treats men and women independently, close or common joinpoints between genders cannot be explained by modelling grounds. Actually, the software computes 4 different models (with 0, 1, 2 or 3 jointpoints) with their individual characteristics, and chooses the best one (and the most parsimonious), statistically speaking. But the best statistical model is not always the most relevant one, as shows Figure 3. Small artefacts may be taken for real variations and can induce unsuitable joinpoints. The first 2 joinpoints (1970 and 1973) do not provide essential pieces of information. But as the model with a single Joinpoint is not statistically better, we did not accept it because we wanted to remain objective. Joinpoint has other drawbacks such as slow execution (up to 4 minutes for one country, and there were 54 countries) and poor graphical outputs (we had to extract observed and modelled data and make graphs again with R). Joinpoint gave us a general idea of melanoma mortality trends in the world. But it was not fully adapted to our study.

As Joinpoint model results suggested a single inflection points for both sexes in a lot of countries, we decided to build our Poisson model. We made this model because we wanted to go further in the analysis. This model was precisely adapted to our particular situation. It could not be used for another purpose. This model imposes more technical constraints, but remains quite simple and parsimonious (4 or 5 parameters). The inflection point has to be the same for both sexes, so it is not the best possible model, but the best compromise between male and female individual situations. As joinpoints found in the latter analysis showed that they were close, we assumed the inflection point found with the Poisson model was very close to individual best inflection points. As this model was done “by hand”, we made exactly what we wanted. In fact we compared two Poisson models (with or without Year*Sex interaction), and selected the one having the smallest AIC. Then, we made the corresponding graphs. At all the process was automatically done, data treatment was very fast (less than 4 minutes for all countries). But this duration does not include coding…. In conclusion, Joinpoint analyses gave us a general view of the problem, and Poisson model enabled us to make a more precise simulation. These models are complementary: Joinpoint model suggested building the Poisson model, and Poisson model completed Joinpoint analysis.
4.3 Interpretation

4.3.1 Incidence trends

CMM incidence has been increasing worldwide since the first studies were conducted. The most dramatic increases affect early stage lesions. Those cancers are easily curable and survival is very good. This increase has been attributed to prevention campaigns. This would mean that education campaigns about melanoma are efficient, because CMM would be detected earlier. However, this is an optimistic point of view of the situation. Prevention campaigns induced an increase of the absolute number of melanomas diagnosed. This is a normal effect of education campaigns. When people are informed, they tend to examine their skin lesions and to go to dermatologists. Therefore, until recently, increased awareness were often considered as the main cause of general melanoma increase in incidence. Fact is, that increases in incidence are strongly linked to education campaigns. As melanoma became a major health topic in some regions like Australasia and Northern Europe, people are more disposed to change their UV-exposure habits. Long-term effects of prevention campaigns on CMM epidemiology cannot be assessed yet. Indeed, sun-exposure behaviour during childhood is an important risk factor for CMM. If kids had less sunburns after education campaigns took place, there will a a decrease in CMM incidence when those kids become middle-aged people. Therefore, scientists need to wait a few more years. Such outcomes will be evaluable in the next 20 to 30 years.

But the real goal of prevention campaigns was to reduce incidence, and especially for advanced tumours associated with poor survival prognosis. The final goal was to reduce CMM mortality. The latter goal was partly reached (see 3.2 CMM age-standardised mortality trends), but not the first (cf. 3.1 Melanoma incidence trends). Thick lesions incidence is not going down. Even if it evolves slower than thin tumours, its incidence rate is still increasing in most countries. If prevention campaigns had been really effective, the number of advanced melanomas would have been reduced in most countries. We noticed no study showing such an improvement for a long period. We detected no permanent drops in advanced CMM incidence.

To conclude, melanoma incidence is still increasing in the world and for all stages. Advanced melanomas situation remains a question of point of view. On the one hand, the proportion decreased largely. But on the other hand, its real incidence (i.e. using ASR and not percentages, see 4.1 Literature search) is slowly but steadily increasing. Incidence of thin melanomas has been greatly increasing for decades. More and more scientists are convinced that this increase is not entirely real. To them, benign melanocytic lesions are more and more often recorded as stage I melanoma. Our mortality results is one more argument in favour of this theory. If incidence was really increasing, whereas no improvement in treatment was done in the last 30 years, mortality would increase too.

4.3.2 Mortality trends

In countries having a suitable recorded period, there is a clear level-off in mortality since the 1970s to 1990s according to the country. Such trends had already been identified in some studies. Our study shows that this pattern is worldwide. It
happened about at the same time for both genders. The initial increase in incidence and mortality is well-explained by tanning fashions of the 20th century. But it is very difficult to find a suitable explanation for the mortality decline, as it touches American, European, Australasian and Asian populations at the same time. Those populations have different skin types and are more or less exposed to UV. We formulate several hypotheses to explain such trends, but none is fully satisfactory, because there are always countries that do not match the hypothesis.

We know from literature that melanoma treatment has not significantly evolved during the study period. The only changes in melanoma treatment were the reduction of resection margins, because it has no influence on recurrence and sentinel node biopsy (replaced elective lymph node biopsy; the goal is to evaluate clinical staging). Usefulness of sentinel node biopsy for CMM patients has been widely debated. In spite of this absence of change in treatment, CMM survival increased these last years. Improvement in survival were observed for all clinical staging. This advance in survival explains partly mortality trends, but leads us to a second question. What made survival improve?

The answer is certainly a combination of multiple causes. First, better access to health care and treatment has been progressing worldwide since the 1950s. There was no improvement in treatment, but treatment is always better than no treatment. That would be a good explanation for CMM survival improvement. Second, changes in sun-exposure habits or global UV irradiation may explain survival improvements, and therefore mortality levels-offs.

We found other explanations for levels-offs in mortality in the literature. An Australian study suggested that massive immigration from 1948 onwards in Australia played a role in the decreasing mortality. Indeed, immigrants came mainly from low-risk countries. So, the total population increased faster than the population at high risk. This explains the Australian situation quite well, but not the World trends. There was immigration in developed countries, but the Australian case is extreme. Therefore, large scale immigration is unlikely to explain mortality trends in Europe.

But this amelioration can be owing neither to changes in registration nor to prevention campaigns. The first point is not plausible because such changes are impossible at world scale on a short time period. Moreover, all studies conducted in given countries noticed no modification registration routines. Finally, there is no reason for such an adjustment. The second point is also very unlikely. First, the mortality level-off occurred before prevention campaigns took place is some countries (e.g. Finland). Furthermore, it happened in low-incidence countries where there was no campaign (e.g. Japan, Mexico....). Finally, if education attempts influenced CMM mortality, it would take years to evaluate them. Such campaigns cannot have immediate effects on mortality. To sum up, effects of prevention campaigns on CMM mortality are not assessable yet.
5 Conclusions

Our study shows that relationships between CMM incidence, mortality and survival are very complex. Great increases in incidence have nothing to do with levelling mortality trends. But survival improvement may be the cause of mortality recent trends.

CMM incidence is rapidly increasing in numerous countries, especially for early stage tumours. There is no sign of a future level-off in incidence, except for small population subgroups. We think that those dramatic increases in incidence are, at least partly, due to overdiagnosis. Benign lesions would be recorded as stage I melanoma and treated as such. Prevention and education campaigns that aimed at raise general population awareness about UV-exposure and other CMM risks factors have a great influence on CMM incidence. Notwithstanding, their leverage on mortality is much less pronounced.

Unlike incidence, melanoma mortality has been levelling-off worldwide since the 1970s-1990s. The phenomenon started in Northern Europe and spread all over the World in the next years. The mortality break is clear and affected both sexes at the same time. Reasons for this settling remain unclear, but improved survival and access to health care are the most likely explanations we found. Older studies found some other groundings for this pattern. Even if they explain local trends, those reasons are not satisfactory at a worldwide level.

Scientific progress those last 40 years were essentially discovery of better prognosis factors and building of new staging systems. Moreover, risks factors are nowadays better known and assessed. Sun-exposure was known to be a risk factor for CMM. Up to now, the role of UV-exposure is more precisely known. No new risk factor was identified. Despite these progresses, a lot of points remain unexplained.

For instance, the difference between men and women is not fully explained yet. Men have a lower incidence and higher mortality than women. Higher mortality is often explained by less favourable body sites and more advanced cases at diagnosis. Extremities, i.e. favourable sites, are the commonest anatomical site by women. They are rarer by men. Males have more frequently melanomas on the trunk. Trunk melanomas are harder to (self-)detect, in particular tumours on the back. That would explain why men tend to present more advanced cases. Furthermore, women are said to be more attentive to their skin lesions, and health in general. But a Dutch study showed that gender difference was independent of body site and histological subtype. So, the gender difference is still a mystery.

Cutaneous malignant melanoma is nowadays broadly studied. However, it is still an active research field. Many points about CMM epidemiology have to be further investigated. Aside from the gender difference, an international study showed an unexpected feature: there are significantly more melanomas on the left side of the body than of the right one (overall left/right ratio: 1.10; 95% CI: 1.08-1.11). Studies about melanoma (a)symmetry are scarce. Studies by body site usually do not take laterality into account. In this study, authors made two hypotheses to explain this fact: asymmetry in sun
exposure and/or asymmetry in melanocyte distribution (little is known about factors that determine the density of those cells).\

Future prospects are interesting. As mortality is reaching a peak in a lot of countries, we expect further stabilisations and decreases worldwide. Perspectives about incidence seem less favourable, but they also look artificial. A better evaluation of these increases would be needed. It is important to know to what extend increases in incidence are artificial. But distinguishing real and fake increases is hard. This would require an exhaustive, large scale case review by a panel of pathologists in several countries. A lot remains to be done!

Figure 10:

Melanoma mortality rate in Belgium between 1955 and 1999

![Melanoma mortality rate in Belgium between 1955 and 1999](image)
Figure 11:

Nonmelanoma skin cancer mortality rate in Australia between 1955 and 1997

Continuous line, crosses: females (modelled, observed); Dotted line, circles: males (modelled, observed)

Inflection point: 1985

ICD code: 5025


