

Does the morphology of cutaneous melanoma help explain the international differences in survival? Results from 1,578,482 adults diagnosed during 2000-2014 in 59 countries (CONCORD-3)

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1

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Data availability: These data are provided to us by more than 300 cancer registries worldwide. We hold the data in trust from each of the participating registries to perform the analyses agreed in the protocol. The protocol prohibits us from other analyses and from sharing the raw data with other parties without express approval from the participating cancer registries.

Ethics approval: This study contains the results of secondary analysis of sensitive personal data, carried out with statutory approval from the Health Research Authority and ethical approval from the NHS Research Ethics Service

What's already known about this topic?

The histopathologic features of cutaneous melanoma vary markedly world-wide. The proportion of melanomas with the more aggressive acral lentiginous or nodular histologic sub-types is higher in populations with predominantly dark skin than in those with predominantly fair skin. We set out to assess the extent to which these differences in morphology may explain international variation in survival from melanoma of the skin when all histologic sub-types are combined, as is usually the case.

What does this study add?

The study provides, for the first time, international comparisons of population-based survival at five years for the main histologic sub-types of melanoma for over 1.5 million adults diagnosed during 2000-2014. It highlights the less favourable distribution of histologic sub-types in Asia and Central and South America, and the poorer prognosis for nodular and acral lentiginous melanomas. We found that later stage at diagnosis does not fully explain the higher excess risk of death for nodular and acral lentiginous melanoma than for superficial spreading melanoma.

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Summary

Background

CONCORD-3 highlighted wide disparities in population-based 5-year net survival during 2000-2014. Clinical evidence suggests marked international differences in the proportion of lethal acral and nodular subtypes.

Objectives

We aim to assess whether the differences in morphology may explain global variation in survival.

Methods

We grouped melanoma into seven morphology categories: malignant melanoma, not otherwise specified (ICD-O-3 morphology code 8720), superficial spreading melanoma (8743), lentigo maligna melanoma (8742), nodular melanoma (8721), acral lentiginous melanoma (8744), desmoplastic melanoma (8745) and other morphologies (8722-8723, 8726-8727, 8730, 8740-8741, 8746, 8761, 8770-8774, 8780).

We estimated net survival with the non-parametric Pohar-Perme estimator, correcting for background mortality by single year of age, sex and calendar year in each country or region. All-ages survival estimates were standardised with the International Cancer Survival Standard weights. We fitted a flexible parametric model to estimate the effect of morphology on the hazard of death.

Results

Worldwide, the proportion of nodular melanoma ranged between 7%-13%. Acral lentiginous melanoma accounted for less than 2% of all registrations but was more common in Asia (6%) and Central and South America (7%). 36% of tumours were classified as superficial spreading melanoma.

During 2010-2014, age-standardised 5-year net survival for superficial spreading melanoma was 95% or higher in Oceania, North America and most European countries, but only 71% in Taiwan. Survival for acral lentiginous melanoma ranged between 66%-95%. Nodular melanoma had the poorest prognosis everywhere.

The multivariable analysis of data from registries with complete information on stage and morphology found that sex, age and stage at diagnosis only partially explain the higher risk of death for nodular and acral lentiginous subtypes.

Conclusions

This study provides the broadest picture of distribution and population-based survival trends for the main morphological sub-types of cutaneous melanoma in 59 countries. The poorer prognosis for nodular and acral lentiginous melanomas, more frequent in Asia and Latin America, suggests the need for health policies aimed at specific populations to improve awareness, early diagnosis and access to treatment.

Introduction

The incidence of cutaneous melanoma has been rising steadily in most populations of Caucasian origin over the past 50 years.^{1,2} It is now one of the 10 most common malignancies in Oceania, North America and Europe, with age-standardised incidence rates in the range 7.0 to 36.6 per 100,000 person-years. By contrast, melanoma is rare in populations of Asian and African origin, where incidence rates are in the range 0.4–3.0.³

The histopathologic features of cutaneous melanoma vary markedly world-wide. The proportion of melanomas with the more aggressive acral lentiginous or nodular histologic types is higher in populations with predominantly dark skin than in those with predominantly fair skin.^{4,5}

The third cycle of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3)⁶ highlighted wide disparities in 5-year net survival from cutaneous melanoma, which was lower in Asian populations than in the rest of the world. Age-standardised 5-year net survival for adults (15-99 years) diagnosed during 2010-2014 was 90% or higher in the US, Australia, New Zealand and most Nordic countries, but 60% or lower in Ecuador, China, Korea, Singapore and Taiwan.

Stage at diagnosis is recognised as the most important predictor of survival.⁷⁻¹⁰ Age at diagnosis is also a prognostic factor, and several studies have shown much higher survival for younger patients.¹¹⁻¹⁵

The prognostic role of morphology in cutaneous melanoma is controversial, however. Traditionally, melanomas of the skin have been classified into three fairly well-defined sub-groups, characterised by different patterns of growth: superficial spreading and lentigo maligna melanoma, which is characterised by a long period of superficial growth; nodular melanoma, which is more likely to penetrate into the deeper layers of the skin if not removed, and acral lentiginous melanoma, which mostly develops on the extremities but displays similar biological behaviour to that of nodular melanoma.¹⁶ Despite the advent of high-resolution genomics and other proposed approaches for the classification of melanocytic tumours, the diagnosis of the different subtypes should continue to be based on the pathologist's interpretation of the histology and how it fits into the WHO Classification of Tumours, commonly known as the WHO 'Blue Books'.¹⁷

However, the morphology classification has not been considered useful for prognostic purposes, because of the idea that the clinical development of all melanomas is similar, whatever the histologic subtype, spreading horizontally within the epidermis and then extending vertically into the dermis, and that they converge in their biologic behaviour once they metastasise.¹⁶

In this study, we aimed to describe the histologic distribution of cutaneous melanoma in 59 countries that contributed data to CONCORD-3, for adults diagnosed during 2000-2014, and to produce the first international comparison of trends in population-based age-standardised 5-year net survival by morphology sub-type. We also aimed to examine the role of morphology sub-type on the prognosis of cutaneous melanoma.

Materials and Methods

Anonymised individual tumour registrations for patients diagnosed during 2000-2014 with one of 18 cancers or groups of malignancies, including melanoma, were provided for CONCORD-3 by 322 population-based cancer registries in 71 countries worldwide. Patients were followed

up for their vital status to 31 December 2014. Data acquisition, ethical approval and data quality control have been described elsewhere.⁶

We asked participating registries to submit all registrations for malignant melanoma, regardless of anatomic site. Melanoma was defined by morphology codes in the range 8720-8790 in the International Classification of Diseases for Oncology, third revision [ICD-O-3].¹⁹ We focused this analysis of survival on melanomas arising in the skin (ICD-O-3 topography C44.0-C44.9), including the skin of the labia majora (C51.0), vulva (C51.9), penis (C60.9) and scrotum (C63.2). Survival from melanomas arising in internal organs and in the eye will be examined in a subsequent analysis. To facilitate quality control and comparison of the intensity of early diagnostic and screening activity, we requested all melanoma registrations, regardless of behaviour, whether benign (behaviour code 0), uncertain (1), *in situ* (2) or invasive (3). However, survival analyses included only primary, invasive melanomas.

Records with incomplete data, or of tumours that were benign, *in situ*, of uncertain behaviour, metastatic from another organ, or unknown if primary or metastatic, or for patients with age outside the range 15-99 years, were not included in survival analyses. We excluded tumours registered only from a death certificate or discovered at autopsy, since their survival is unknown, as well as records for which the sex or vital status was unknown, and those with an invalid date or sequence of dates.

Patients were grouped into seven morphology categories with the ICD-O-3 classification: malignant melanoma, not otherwise specified (NOS; morphology code 8720), superficial spreading melanoma (8743), lentigo maligna melanoma (8742), nodular melanoma (8721), acral lentiginous melanoma (8744), desmoplastic melanoma (8745) and other morphologies (8722-8723, 8726-8727, 8730, 8740-8741, 8746, 8761, 8770-8774, 8780).

Patients were grouped by calendar period of diagnosis: 2000-2004, 2005-2009, 2010-2014. We examined time trends in the morphology distribution in each country. We also estimated trends in age-standardised 5-year net survival by country and morphology with the non-parametric Pohar Perme estimator,²⁰ using the STATA²¹ command *stns*.²² The cohort approach was used for patients diagnosed during 2000-2004 and 2005-2009, because they had all been followed up for at least five years. We used the period approach²³ to estimate survival for patients diagnosed during 2010-2014, because 5 years of follow-up for vital status were not available for all patients by 31 December 2014.

To control for wide differences in background mortality between geographical areas, men and women, and over time, we constructed life tables of all-cause mortality in the general population for each country or registry by single year of age, sex, calendar year and, where possible, by race/ethnicity (Israel, Singapore, United States, Australian Northern Territory, and New Zealand).

We estimated five-year net survival by morphology in each of five age groups (15-44, 45-54, 55-64, 65-74 and 75-99 years). We obtained age-standardised estimates for all age-groups combined using the International Cancer Survival Standard type 2 weights for the five age groups (0.28, 0.17, 0.21, 0.20 and 0.14).²⁴ We did not estimate survival if fewer than ten patients were available for analysis in a given combination of morphology group and calendar period. If 10-49 patients were available in a given calendar period, we only estimated survival for all ages combined. If 50 or more patients were diagnosed in 2000-2004 and in 2005-2009, we attempted survival estimation for each age group in each calendar period. For 2010-2014, we estimated net survival using the period approach, including in the analyses all patients diagnosed during the 5 years 2010-2014, plus those diagnosed before 2010 who were still alive at the beginning of 2010. Therefore, for 2010-2014 the threshold of 50 or more patients for attempting age-standardisation applies to the combined cohort of patients. If a single age-

specific estimate could not be obtained, we merged the data for adjacent age groups and assigned the combined estimate to both age groups before standardisation for age. If two or more age-specific estimates could not be obtained, we present only the unstandardised estimate for all ages combined. The pooled estimates for countries with more than one registry do not include data from registries for which the estimates were less reliable. Less reliable estimates are shown with a flag (\$) in Table 2 when they are the only available information from a given country or territory (see footnote in Table 2 for the definition of less reliable estimates). We comment in the text only on reliable, age-standardised survival estimates. Continental regions were defined using the United Nations Geoscheme.²⁵

To estimate the effect of morphology on the hazard of death due to melanoma, we fitted a flexible parametric model on the log cumulative hazard scale, using *stpm2*²⁶ in STATA. We restricted this analysis to registries where at least 65% of registrations had a specific morphology code, i.e. not malignant melanoma, NOS. Among these registries, we further selected those for which data on stage were available for at least 75% of registrations in one of the following classifications: UICC Tumour-Node-Metastasis staging system, 7th edition,²⁷ Condensed TNM,²⁸ or SEER Summary Stage 2000.²⁹ With this constraint, we were able to include data from one regional cancer registry in Germany (Lower Saxony), two registries in Spain (Basque Country and Granada) and the Norwegian national cancer registry.

For each country, we first fitted a model with only morphology as a covariable (model 1). We then included, as additional covariables, sex, a restricted cubic spline for the effect of age at diagnosis (4 degrees of freedom) and stage at diagnosis (metastatic vs. non metastatic) (model 2). We excluded patients for which stage at diagnosis was unknown (complete case analysis).

Results

We obtained data from 284 registries in 59 countries on 2,303,095 adults who were diagnosed with melanoma during 2000-2014 (Table 1). Among these, 49% were diagnosed in North America, 37% in Europe, 12% in Oceania, and only 2% in Asia and less than 1% in both Africa and in Central and South America.

We excluded from survival analysis 637,957 patients (28%) who were diagnosed with an *in situ* tumour, ranging from 11% in Central and South America to 35% in North America. The proportion of *in situ* melanoma was 20% or higher in 10 countries (Table 1), suggesting a highly effective approach to early diagnosis. We additionally excluded 78,587 patients for other reasons (see footnote in Table 1). The proportion of melanomas of benign or uncertain behaviour was particularly high in Norway (22%), highlighting intensive activity of monitoring atypical naevi and pre-malignant lesions.

Of the 1,586,551 eligible patients, we further excluded 7,139 patients (0.5%) who were diagnosed only from a death certificate or discovered at autopsy and 930 patients (less than 0.1%) for other reasons. Finally, 1,578,482 patients diagnosed with a primary, invasive melanoma of the skin were available for survival analysis (99.5% of those eligible). More than 99% of these tumours were microscopically confirmed, either cytologically or histologically.

About 42% of the tumours were registered as malignant melanoma, NOS. The proportion was generally high in countries in Asia (76%), Central and South America (63%), North America (51%) and Africa (46%) and much lower in Oceania (33%). In Europe, the proportion of melanomas with a non-specific morphology was higher in Eastern European countries (57%) than in Southern (37%), Northern (32%) and Western European countries (27%). The proportion of melanomas diagnosed with a non-specific morphology fell substantially in Australia (from 40% in 2000-2004 to 26% in 2010-2014), Denmark (from 42% to 11%), Iceland

(from 36% to 18%), Italy (from 32% to 19%), Lithuania (from 85% to 35%), Portugal (from 70% to 35%) and the United Kingdom (from 39% to 23%) (Table A1).

Overall, superficial spreading melanoma was the second most common histology (36% of all cases). It accounted for more than half the patients in Denmark, France, Iceland, the Netherlands, Norway, Sweden and Switzerland (Figure 1). Nodular melanoma accounted for 7% of all cases in North America and Asia, 9% in Oceania and 13% in Central and South America. In Europe, 12% of the cases were registered as nodular melanoma, with higher proportions in Czech Republic, Ireland, Norway, Romania, Slovakia and Sweden. About 6% of adults were diagnosed with lentigo maligna melanoma, ranging from 2% in Asia to 8% in Oceania. Acral lentiginous melanoma was very rare in North America, Europe and Oceania (less than 2% of all cases) but the proportion was higher in Central and South America (more than 10% in Colombia, Costa Rica, Guadeloupe and Martinique) and Asia (more than 10% in Korea, Singapore and Taiwan). Desmoplastic melanoma represented less than 1% of the patients. The proportion of patients diagnosed with other morphologies was higher than 20% in Estonia, Italy and Latvia.

Malignant melanoma, not otherwise specified

Age-standardised 5-year net survival varied widely between world regions (Table 2). It was in the range 85-89% in Oceania and North America during 2010-2014. It was higher than 80% in all Western European countries and ranged from 54% to 79% in Eastern Europe. In Central and South America, age-standardised 5-year net survival ranged from 57% in Ecuador to 76% in Costa Rica and Puerto Rico. Five-year survival was lower than 70% in all Asian countries except Israel (88%), and as low as 47% in Taiwan.

Five-year survival increased between 2000-04 and 2010-14 by 10% or more in China (from 36 to 48%), Bulgaria (from 52 to 62%), Croatia (from 66 to 77%) and Estonia (from 71 to 83%).

Superficial spreading melanoma

Age-standardised 5-year net survival for patients diagnosed during 2010-2014 was 90% or higher in North America, Oceania and almost all European countries; survival was lower than 90% only in Slovakia, Poland, Lithuania, Portugal and Bulgaria. In Asia, survival ranged from 71% in Taiwan to 98% in Israel (Figure 2).

Lentigo maligna melanoma

This sub-type of melanoma had the most favourable prognosis: age-standardised 5-year net survival was close to 100% in North America, Australia and most European countries. Estimates were not available for most countries in Central and South America and Asia because of the small numbers of patients diagnosed with this specific sub-type.

Nodular melanoma

The prognosis for nodular melanoma was the poorest in all continents. Age-standardised 5-year net survival for patients diagnosed during 2010-2014 reached 72% in Canada and United States, 77% in New Zealand and 80% in Australia. In Central and South America, it ranged from 58% in Costa Rica to 72% in Argentina, and in Europe, from 58% in Poland to 80% in Ireland. Survival improved dramatically in Bulgaria (from 46% in 2000-2004 to 64% in 2010-2014) and in Portugal (from 59% to 76%).

Acral lentiginous melanoma

Five-year net survival for adults diagnosed during 2010-2014 was in the range 77-82% in North America and Oceania and 70-95% in Europe. Most of the estimates for countries in Asia and Central and South America were not age-standardised because of the small numbers of patients available for survival analysis.

Five-year net survival for adults diagnosed with desmoplastic melanoma during 2010-2014 ranged between 76% and 91%. Estimates were not available for Central and South America or for most countries in Asia because of the small numbers of patients available for analysis.

With the excess hazard of death for patients with superficial spreading melanoma taken as the reference category, the excess hazard ratio for patients diagnosed with nodular melanoma was 21.8 (95%CI 14.7-32.3) in Germany, 12.1 (8.1-18.1) in Spain and 6.7 (5.7-7.9) in Norway (Table 3). The excess hazard ratios were lower after controlling for sex, age and stage at diagnosis, but the excess hazard of death for patients with nodular melanoma was still 13.5 (9.6-18.9) times higher in Germany, 6.7 (4.8-9.3) times higher in Spain and 4.1 (3.6-4.8) times higher in Norway, than for patients in the same country diagnosed with superficial spreading melanoma.

The excess hazard ratio for patients diagnosed with acral lentiginous melanoma vs. superficial spreading melanoma was 15.2 (9.0-25.5), 9.0 (5.2-15.5) and 1.7 (0.5-5.1) in Germany, Spain, and Norway, respectively. After controlling for sex, age and stage at diagnosis, the excess hazard of death for patients with acral lentiginous melanoma was still 10.8-fold (6.8-17.1) in Germany, 5.0-fold (3.1-8.1) in Spain and 2.2-fold (1.0-4.9) higher in Norway, than in patients diagnosed with superficial spreading melanoma.

Discussion

This study of over 1.5 million adults diagnosed with cutaneous melanoma world-wide during 2000-2014 has highlighted wide international differences in the distribution of histologic sub-types as well as in survival by sub-type. The prognosis is poorest everywhere for nodular and acral lentiginous melanoma.

The prognostic role of the morphology of cutaneous melanomas is controversial. Clinical guidelines indicate that stage at diagnosis is the most important prognostic factor. The prevalent idea is that melanomas of different morphologies converge in their biologic behaviour once they metastasize,³⁰ so the recommended treatment options do not differ between morphological sub-types at a given stage at diagnosis. Clinical guidelines even indicate that the histologic sub-type is only an optional item for inclusion in pathology reports.³¹

Probably for this reason, the primary histologic sub-types of melanoma are often poorly specified, if at all, in pathology reports.^{11,14} In turn, this determines the high proportion of melanomas that are coded as "malignant melanoma, not otherwise specified (NOS)" in cancer registry data.¹³ In this global study, 43% of melanomas were registered as malignant melanoma NOS. The proportion varied widely, and was higher in Asia, Central and South America and Eastern Europe, as has been shown elsewhere.^{13,32} However, our study shows that the proportion of melanomas with poorly specified morphology has fallen in most countries over the last 15 years, suggesting improvements in pathological practice.³³

Overall, superficial spreading melanoma was the most frequent of the specific morphologies, and the proportion has been increasing over time. It is generally associated with an excellent prognosis in Europe, North America and Oceania, as has been shown in previous studies.^{13,14,30,34} Several international studies have shown an increasing incidence of thinner melanomas (1mm or less),^{15,35-41} as a result of raised public awareness and earlier detection, especially for superficial spreading melanomas. The result is an increasing number of people

with melanoma who are less likely to die because of their tumours. This phenomenon may help explain the improvement in the already high 5-year net survival from superficial spreading melanoma.

Acral lentiginous melanoma represented less 1% of the patients in Europe, North America and Oceania, but almost 6% of the patients in Asia and 7% in Central and South America. Very few studies have focused on survival from cutaneous melanoma in Asia and Central and South America, perhaps because the overall incidence is much lower than in fairer-skinned populations. In Singapore, acral lentiginous melanoma accounted for 16% of all cases diagnosed during 2008-2017.⁴² In a study of 915 patients diagnosed during 1997-2011 in Brazil, the acral sub-type accounted for 7% of all cases and that 5-year cause-specific survival was much lower (51%) than for superficial spreading melanoma (82%).⁴³ A study of 142 patients in China confirmed the poor prognosis for patients with acral lentiginous melanoma; 5-year cause-specific survival was 53%.⁴⁴ By contrast, an analysis of 252 patients diagnosed in a single institution in Japan during 2001-2014 showed no difference between 5-year survival for acral and non-acral lentiginous subtypes (59% vs. 62% in men and 71% vs. 85% in women),⁴⁵ although the numbers of patients were too small to derive definitive conclusions.

Our study found that age-standardised five-year net survival for acral lentiginous melanoma was generally lower than for other morphologies, with the only exception of nodular melanoma, and globally in the range 66-95%. The poorer prognosis for acral lentiginous melanoma, which usually develops on the palms, the sole of the foot or underneath the nails, is commonly ascribed to delayed diagnosis, because these areas are not routinely examined by patients or primary care physicians.⁴⁶ Moreover, the proportion of the acral sub-type is higher in Blacks than Caucasians;⁴⁷ but because the risk of melanoma in black populations is perceived to be low, the lack of secondary prevention is also considered a major cause of late diagnosis.^{48,49}

Nodular melanoma had the poorest prognosis in all countries, as has been reported elsewhere.⁵⁰⁻⁵² Forty years ago, a multivariable analysis of 339 patients diagnosed in a single institution in the US during 1960-1977 found that the increased risk associated with nodular histology was confounded by an increase in thickness and ulceration; in other words, the higher risk of death was due to more advanced stage at diagnosis, not intrinsic to the morphologic sub-type.⁵³ On the basis of this conclusion from a small study, the American Joint Committee on Cancer did not include histologic sub-type in the cutaneous melanoma staging system, because it was not considered to be a significant prognostic factor.⁵⁴ Thirty years later, however, a very large population-based study of 118,508 patients diagnosed in the US with superficial spreading or nodular melanoma during 1973-2012 showed that morphology is in fact an independent predictor of survival.³⁰ After controlling for thickness, ulceration, mitotic index and stage at diagnosis, nodular sub-type remained an independent risk factor for death from melanoma (HR 1.55, 95% CI 1.41 to 1.70). Another population-based study of 82,901 patients diagnosed in Germany during 1997-2013 showed that differences in 5-year survival by histologic subtype were partially explained by tumour size.⁵⁵

Our population-based study confirms these findings. The multivariable analysis of data from four population-based registries with complete information on stage and morphology highlights a much higher excess risk of death with nodular or acral lentiginous melanoma than for superficial spreading melanoma, after controlling for major confounders. Sex, age and stage at diagnosis only partially explain the higher risk of death for nodular and acral lentiginous subtypes. The different magnitude of the excess hazard ratios in Germany, Spain and Norway may be due to the low baseline hazard for superficial spreading melanoma in Germany, where national skin cancer screening for people aged 35 years or more with health insurance was introduced in 2008. This may have improved early detection of the generally slow-growing, less aggressive superficial spreading melanomas.⁵⁵

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Our study has also shown that while five-year survival from cutaneous melanoma in Eastern Europe has been increasing in recent years, survival continues to lag behind the rest of Europe for each morphologic sub-type of melanoma. A study of seven common malignancies diagnosed in Europe during 2000-2007 found that late stage at diagnosis alone did not explain the lower survival for melanoma of the skin in Eastern Europe.⁵⁶ In the current study, data on stage at diagnosis in Eastern European countries were only available for Russia and Slovakia, where the proportion of metastatic disease (6% and 7%) was higher than in Norway (2%) and Denmark (3%) (data not shown). More detailed information on morphology would have helped investigate the reasons for the persistent gap in survival.

The high proportion of melanomas registered with poorly specified morphology was the major limitation of our study, because it limited the interpretation of net survival estimates for melanomas with specific morphological sub-types in all countries. Information on stage at diagnosis was also limited; complete data could have contributed disentangling the prognostic role of morphology at international level. Additionally, we were not able to control for surgical margins, a relevant prognostic factor, because these data were not available.

Our study is the largest analysis to date of survival from cutaneous melanoma. It provides, for the first time, international comparisons of population-based survival for the main histologic sub-types of melanoma in more than 50 countries. The higher frequency and poorer survival of nodular acral lentiginous melanomas in Asia and in Central and South America suggest the need for health policies in these populations that are designed to improve public awareness, and especially to facilitate earlier diagnosis and prompt access to optimal treatment.

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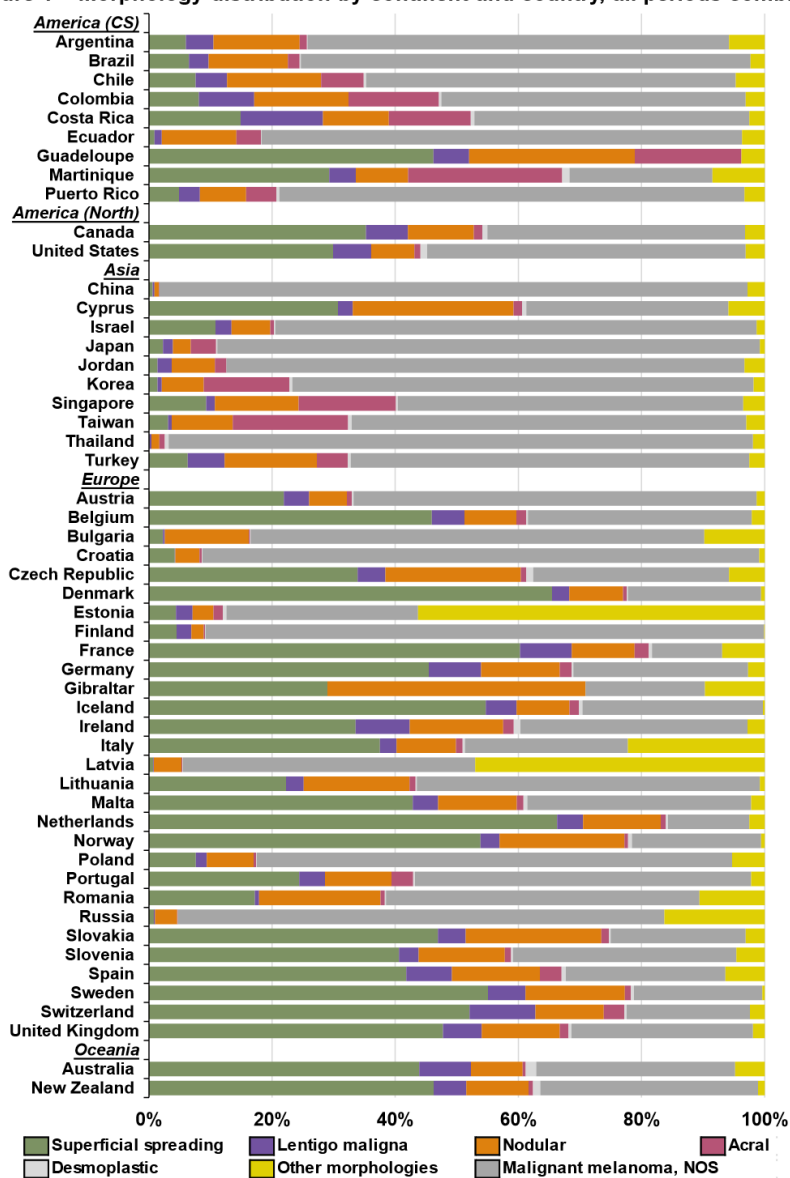
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Figure 1 – Morphology distribution by continent and country, all periods combined



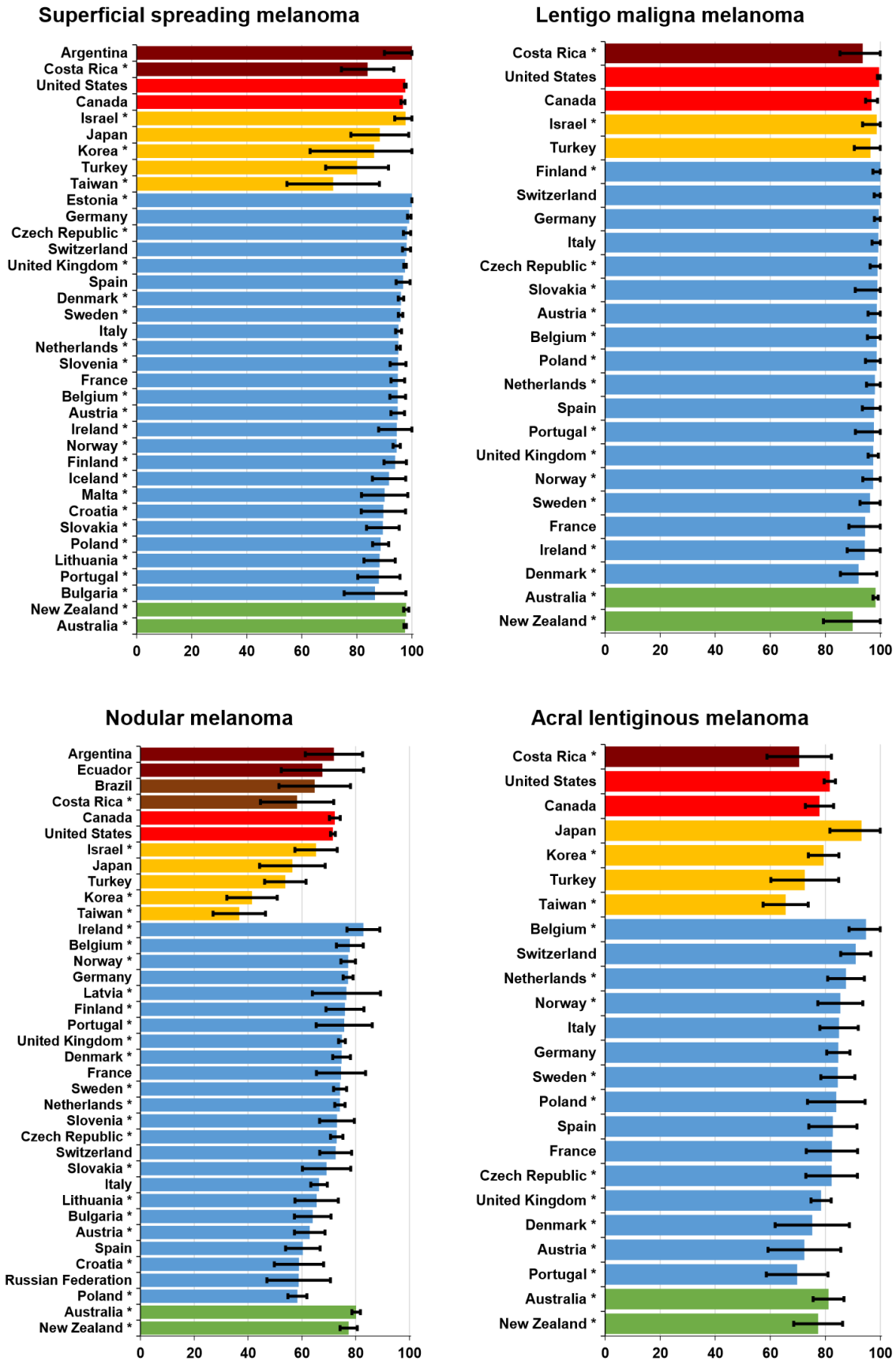
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Figure 2: Age-standardised 5-year net survival for patients diagnosed with cutaneous melanoma during 2010-2014 by continent, country and morphology group

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Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): adults (15-99 years) diagnosed with melanoma of the skin by continent, country, morphology and year of diagnosis (2000-2004, 2005-2009, 2010-2014)

	Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies			
	No. NS (%)	95% CI		No. NS (%)	95% CI		No. NS (%)	95% CI		No. NS (%)	95% CI		No. NS (%)	95% CI		No. NS (%)	95% CI		No. NS (%)	95% CI		
FRANCE AND SOUTH																						
2000-2004	31	98.5	92.3 - 100.0	24	100.0	85.9 - 100.0	76	58.1	45.8 - 70.4	30	71.2	50.7 - 91.7	18	64.1	38.2 - 89.9	131	66.7	57.8 - 75.5	10	44.8	14.6 - 75.0	
2005-2009	26	100.0	90.0 - 100.0	21	100.0	85.7 - 100.0	44	71.9	61.3 - 82.6	76	58.1	45.8 - 70.4	25	80.5	46.8 - 100.0	320	62.9	57.0 - 68.8	44	72.6	55.6 - 89.5	
2010-2014	41	84.4	65.0 - 100.0	19	100.0	100.0 - 100.0	75	71.7	61.8 - 81.7	13	65.8	36.0 - 95.6	377	65.2	58.5 - 71.9	259	76.0	70.1 - 81.9	11	52.0	26.6 - 77.5	
2000-2004	43	85.0	68.9 - 100.0	10	95.3	72.8 - 100.0	43	64.8	51.5 - 78.1	78	68.8	56.7 - 80.8	10	32.1	3.4 - 60.7	437	76.3	71.5 - 81.1	12	67.8	40.8 - 94.8	
2005-2009	11	100.0	100.0 - 100.0	10	95.2	61.5 - 100.0	28	50.8	30.2 - 71.4	78	68.8	56.7 - 80.8	59	57.0	42.6 - 71.4	251	69.7	64.4 - 75.1	13	33.7	5.6 - 61.8	
2010-2014	16	100.0	100.0 - 100.0	20	87.9	48.1 - 100.0	36	63.5	39.0 - 88.0	12	19.0	0.0 - 39.7	57	55.8	36.6 - 75.1	154	55.6	43.1 - 68.1				
2000-2004	29	85.0	70.0 - 100.0	16	100.0	85.1 - 100.0	53	41.8	24.8 - 58.8	45	81.6	62.1 - 100.0	45	81.6	62.1 - 100.0	196	54.9	46.9 - 62.9				
2005-2009	49	84.8	71.0 - 98.5	53	99.6	79.6 - 100.0	83	63.4	51.3 - 75.4	73	75.6	61.4 - 89.7	21	70.6	56.9 - 84.4	219	64.7	57.1 - 72.4	15	42.3	9.0 - 75.6	
2010-2014	47	100.0	95.8 - 100.0	33	100.0	100.0 - 100.0	34	72.6	55.2 - 90.1	46	75.3	59.0 - 91.5	43	55.8	46.6 - 65.0	43	55.8	46.6 - 65.0	10	35.0	7.2 - 62.8	
2000-2004	71	86.3	78.9 - 93.7	51	97.5	89.9 - 100.0	63	58.9	49.3 - 68.5	70	74.2	62.1 - 86.2	46	75.3	59.0 - 91.5	104	75.6	67.0 - 84.2				
2005-2009	90	83.9	74.4 - 93.4	103	93.6	85.3 - 100.0	49	58.2	44.6 - 71.9	65	70.5	58.8 - 82.2	70	74.2	62.1 - 86.2	183	69.9	62.5 - 77.4	23	88.2	59.1 - 100.0	
2010-2014	12	62.4	28.2 - 96.6	22	100.0	92.9 - 100.0	25	50.9	27.4 - 74.5	12	47.5	17.8 - 77.2	65	70.5	58.8 - 82.2	146	56.2	47.3 - 65.1				
2000-2004	19	71.9	50.4 - 93.3	17	82.0	66.4 - 91.5	45	61.0	44.3 - 77.7	12	27.6	2.9 - 52.3	12	27.6	2.9 - 52.3	319	60.1	53.5 - 66.6	13	54.7	23.2 - 86.3	
2005-2009	20	70.8	41.0 - 100.0	22	100.0	92.9 - 100.0	17	62.0	31.3 - 92.8	10	50.5	18.2 - 82.8	17	27.1	1.4 - 52.8	332	57.0	50.2 - 63.8				
2010-2014	16	0.1	0.0 - 0.2	11	38.5	0.0 - 90.8	11	38.5	0.0 - 90.8	14	78.0	42.3 - 100.0	14	78.0	42.3 - 100.0	28	92.1	76.0 - 100.0				
2000-2004	12	92.6	76.2 - 100.0	14	92.6	76.2 - 100.0	25	50.9	27.4 - 74.5	27	56.4	33.4 - 79.5	27	56.4	33.4 - 79.5	296	72.4	66.4 - 78.4	15	68.1	34.7 - 100.0	
2005-2009	18	100.0	89.5 - 100.0	14	92.6	76.2 - 100.0	36	38.9	20.8 - 56.9	14	35.3	7.7 - 62.8	14	35.3	7.7 - 62.8	340	79.9	74.9 - 85.0	11	57.8	26.7 - 88.9	
2010-2014	18	100.0	90.0 - 100.0	17	82.0	66.4 - 91.5	17	82.0	66.4 - 91.5	10	50.5	18.2 - 82.8	10	50.5	18.2 - 82.8	149	76.2	68.5 - 83.9				
2000-2004	6,720	95.1	94.1 - 96.1	1,219	97.6	95.9 - 99.4	2,076	72.1	69.8 - 74.4	297	86.1	81.6 - 90.5	131	79.6	69.4 - 89.8	8,737	83.9	82.9 - 84.9	661	75.6	71.7 - 79.4	
2005-2009	8,352	96.2	95.4 - 97.0	1,492	97.8	96.4 - 99.3	2,661	69.7	67.6 - 71.8	366	81.6	77.0 - 86.2	194	90.4	85.3 - 95.5	10,731	83.7	82.9 - 84.6	926	80.6	77.6 - 83.6	
2010-2014	10,737	96.8	96.0 - 97.5	2,301	96.8	94.6 - 99.0	3,119	72.3	70.3 - 74.3	391	77.9	72.8 - 83.0	266	91.8	87.3 - 96.4	11,139	84.8	84.0 - 85.6	762	80.9	77.7 - 84.2	
2000-2004	51,276	96.8	96.5 - 97.2	10,760	98.7	98.0 - 99.5	12,341	69.5	68.6 - 70.5	1,771	82.2	79.9 - 84.6	2,082	87.3	85.3 - 89.3	96,459	86.4	86.1 - 86.7	6,317	84.1	82.9 - 85.3	
2005-2009	66,456	97.5	97.1 - 97.8	13,531	99.3	98.7 - 99.9	15,772	71.2	70.3 - 72.0	2,229	82.6	80.6 - 84.6	2,442	89.1	87.3 - 91.0	111,496	88.2	87.9 - 88.4	6,469	85.3	84.1 - 86.4	
2010-2014	65,610	97.6	97.3 - 97.9	14,191	99.6	98.9 - 100.0	15,202	71.6	70.7 - 72.4	2,317	81.6	79.6 - 83.7	2,255	89.7	87.8 - 91.5	101,623	88.5	88.2 - 88.8	4,988	84.2	83.0 - 85.5	
2000-2004	72	96.2	88.9 - 100.0	59	73.8	62.8 - 84.7	59	73.8	62.8 - 84.7	59	73.8	62.8 - 84.7	15	84.7	59.6 - 100.0	110	36.0	26.0 - 46.0	13	83.6	34.4 - 100.0	
2005-2009	101	87.3	78.8 - 95.8	94	71.4	59.9 - 82.9	94	71.4	59.9 - 82.9	94	71.4	59.9 - 82.9	86	75.1	64.6 - 85.5	538	44.7	39.8 - 49.5	15	63.2	37.1 - 89.4	
2010-2014	585	93.3	90.1 - 96.5	141	97.6	92.2 - 100.0	251	69.6	63.0 - 76.2	22	66.6	41.0 - 92.2	22	66.6	41.0 - 92.2	623	48.4	43.2 - 53.6	17	69.9	41.1 - 98.7	
2000-2004	407	94.2	90.4 - 98.0	110	97.5	88.4 - 100.0	316	68.9	62.5 - 75.3	23	80.8	51.6 - 100.0	2,648	84.8	83.1 - 86.5	2,648	84.8	83.1 - 86.5	58	50.7	35.4 - 66.1	
2005-2009	335	97.7	93.8 - 100.0	74	98.7	93.6 - 100.0	208	65.3	57.4 - 73.2	26	79.3	56.6 - 100.0	11	51.0	20.7 - 81.2	3,614	89.3	87.9 - 90.6	42	51.1	34.3 - 67.9	
2010-2014	36	84.8	69.6 - 99.9	31	90.1	59.0 - 100.0	53	52.3	36.2 - 68.4	78	82.4	68.5 - 96.2	3,314	87.8	86.3 - 89.3	3,314	87.8	86.3 - 89.3	64	64.6	52.9 - 76.2	
2000-2004	42	88.4	77.8 - 98.9	25	89.0	57.8 - 100.0	57	56.5	44.3 - 68.7	71	93.2	81.7 - 100.0	703	68.7	64.7 - 72.7	703	68.7	64.7 - 72.7	14	35.8	7.9 - 63.6	
2005-2009																						
2010-2014																						

Number of patients and age-standardised 5-year net survival (NS, %) with 95% confidence interval (95% CI): adults (15-99 years) diagnosed with melanoma of the skin by continent, country, morphology and period of diagnosis (2000-2004, 2005-2009, 2010-2014)

m * 2000-2004 2005-2009 2010-2014	Superficial spreading melanoma			Lentigo maligna melanoma			Nodular melanoma			Acral lentiginous melanoma			Desmoplastic melanoma			Malignant melanoma, NOS			Other melanoma morphologies		
	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI	No.	NS (%)	95% CI
	15,962	97.5	95.5 - 99.5	2,142	98.0	94.7 - 100.0	5,109	73.1	68.6 - 77.6	519	81.7	73.8 - 89.5	155	36.5	1.9 - 71.1	15,485	79.2	76.1 - 82.2	951	70.3	61.1 - 79.5
	25,047	97.4	96.8 - 97.9	3,254	98.0	96.1 - 99.8	6,925	74.5	73.2 - 75.8	714	79.7	75.9 - 83.5	225	83.3	76.8 - 89.8	17,094	82.1	81.4 - 82.8	1,189	84.4	81.8 - 87.1
	37,002	97.5	97.1 - 98.0	4,940	97.4	95.6 - 99.3	8,735	74.9	73.7 - 76.2	1,033	78.5	74.8 - 82.1	373	82.3	75.3 - 89.3	15,586	84.3	83.6 - 85.1	895	85.0	82.1 - 87.9
2000-2004	18,244	97.4	96.8 - 97.9	3,523	98.6	97.5 - 99.7	3,930	79.3	77.8 - 80.8	230	78.1	71.5 - 84.6	805	84.6	81.3 - 87.8	19,244	88.5	87.9 - 89.1	2,574	93.2	91.8 - 94.7
2005-2009	24,151	97.5	97.0 - 97.9	5,186	97.9	96.9 - 98.9	4,574	79.5	78.0 - 81.0	274	82.3	76.6 - 88.0	918	84.9	81.8 - 88.1	17,740	87.9	87.3 - 88.5	2,384	93.2	91.7 - 94.7
2010-2014	26,279	97.5	97.1 - 98.0	4,376	98.3	97.3 - 99.2	4,643	80.2	78.6 - 81.8	288	81.2	75.6 - 86.8	894	84.8	81.4 - 88.2	13,506	87.2	86.4 - 87.9	2,539	94.1	92.6 - 95.6
2000-2004	3,633	96.9	95.6 - 98.2	563	94.8	91.9 - 97.7	889	75.3	71.7 - 78.8	68	90.4	82.5 - 98.4	105	79.7	70.4 - 89.1	3,617	86.3	84.8 - 87.8	146	84.9	77.9 - 91.8
2005-2009	4,998	97.2	96.3 - 98.2	488	95.4	92.1 - 98.8	1,034	78.0	74.7 - 81.2	65	80.7	71.2 - 90.3	122	88.5	82.3 - 94.8	3,891	86.6	85.2 - 88.0	70	81.2	67.7 - 94.8
2010-2014	5,786	97.9	97.0 - 98.9	617	90.0	79.3 - 100.0	1,232	77.4	74.2 - 80.6	100	77.4	68.5 - 86.3	134	89.9	83.9 - 95.8	3,523	87.0	85.6 - 88.5	129	81.6	73.9 - 89.3

coverage of the national population considered less reliable, because 15% or more of patients were (a) lost to follow-up or censored alive within five years of diagnosis (or if diagnosed in 2010 or later, before 31 December 2014), or (b) registered only from a death certificate or at autopsy, or (c) registered with e., unknown year of birth, unknown month and/or year of diagnosis or unknown year of last vital status
 val estimates that are not age-standardised due to a low number of cases (less than 50), or where two or more age-specific net survival estimates could not be produced..

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Table 3. Excess hazard ratio of death in patients with malignant melanoma of the skin, by morphologic type (reference category superficial spreading melanoma) in Germany, Spain and Norway

	Germany (Lower Saxony)			Spanish registries [‡]			Norway [¶]		
	No. (%)	Model 1	Model 2	No. (%)	Model 1	Model 2	No. (%)	Model 1	Model 2
Superficial spreading	9,326 (58.9)	1.0	1.0	1,642 (39.8)	1.0	1.0	8,624 (54.0)	1.0	1.0
Lentigo maligna	1,305 (8.2)	0.2 (0.0-35.1)	0.1 (0.0-26.9)	232 (5.6)	0.4 (0.0-17.2)	0.4 (0.1-2.1)	478 (3.0)	0.3 (0.1-6.4)	0.5 (0.2-1.4)
Nodular	1,514 (9.6)	21.8 (14.7-32.3)	13.5 (9.6-18.9)	627 (15.2)	12.1 (8.1-18.1)	6.7 (4.8-9.3)	3,234 (20.3)	6.7 (5.7-7.9)	4.1 (3.6-4.8)
Acral lentiginous	341 (2.2)	15.2 (9.0-25.5)	10.8 (6.8-17.1)	138 (3.4)	9.0 (5.2-15.5)	5.0 (3.1-8.1)	91 (0.6)	1.7 (0.5-5.1)	2.2 (1.0-4.9)
Malignant melanoma, NOS	2,953 (18.7)	6.5 (4.3-9.9)	5.4 (3.8-7.6)	1,178 (28.6)	4.2 (2.8-6.4)	2.9 (2.0-4.0)	3,338 (20.9)	3.9 (3.3-4.7)	2.8 (2.4-3.3)
Other morphologies	385 (2.4)	8.6 (4.7-15.6)	6.5 (3.8-11.0)	307 (7.4)	5.6 (3.4-9.2)	3.7 (2.4-5.6)	201 (1.2)	4.5 (2.9-6.9)	2.4 (1.6-3.7)

[‡] Granada and Basque Country

[¶] National coverage

Model 1: only including morphology. Model 2: including morphology, sex, age and stage at diagnosis

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