Epidemiology of Lentigo Maligna and Lentigo Maligna Melanoma in the Netherlands, 1989–2013

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Lentigo maligna (LM) is considered a precursor to LM melanoma (LMM). We assessed trends in LM and LMM incidence rates between 1989 and 2013 in the Netherlands, and estimated the risk of an LMM after LM. Data on newly diagnosed LM and LMM were obtained from the Netherlands Cancer Registry and PALGA: Dutch Pathology Registry. Age-standardized incidence rates (European standardized rate), estimated annual percentage changes, and the cumulative incidence of LMM after LM were calculated. Between 1989 and 2013, 10,545 patients were diagnosed with a primary LM and 2,898 with a primary LMM in the Netherlands. The age-standardized incidence rate for LM increased from 0.72 to 3.84 per 100,000 person-years, and for LMM from 0.24 to 1.19 between 1989 and 2013. LM incidence increased from 2002 to 2013 with 6.8% annually, before an even steeper rise in LMM incidence from 2007 to 2013 (estimated annual percentage change: 12.4%). The cumulative incidence of LMM after a primary LM after 25-year follow-up was 2.0% for males and 2.6% for females. The increased incidence of LM and LMM in the Netherlands seems, besides increased awareness and increased histological confirmation of LM, to reflect a true increase. The absolute risk of an LMM (at any location) after a histologically confirmed LM was low (2.0–2.6%).

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INTRODUCTION

Lentigo maligna (LM) is the most common subtype of melanoma in situ, accounting for three quarters of all cases (Hemminki et al., 2003; Swetter et al., 2005). It is considered a precursor of lentigo maligna melanoma (LMM), which represents 4–15% of all invasive melanomas (McKenna et al., 2006). Both LM and LMM are related to cumulative sun exposure and occur mostly in the head and neck region of elderly individuals (Smalberger et al., 2008).

Incidence rates of LM and LMM have increased in the recent decades (Swetter et al., 2005; Toender et al., 2014). There is controversy about whether this represents a truly increased incidence (caused by increased ultraviolet exposure), or that it is caused by a growing awareness of skin cancer among both patients and physicians (i.e., increased detection) (Higgins et al., 2015a). The stronger increase of melanoma in situ incidence than invasive melanoma incidence suggests at least a role for earlier detection (Buettner et al., 2005; Coory et al., 2006).

Surgical excision is considered the gold standard treatment for LM (Bichakjian et al., 2011). However, nonsurgical treatment options gain more interest, especially for large facial lesions or elderly patients, and even a wait-and-see policy may be considered (Bichakjian et al., 2011). Choosing less invasive, nonsurgical treatments is supported by data showing that the estimated lifetime risk of LMM in patients with a (clinically defined) LM appears to be low (2.2–4.7%) (Weinstock and Sober, 1987). However, this risk is based on a single epidemiological study from 1987 (Weinstock and Sober, 1987), and has not been investigated since.

The aims of this study were to investigate and compare the incidence trends of LM and LMM in the Netherlands over a period of 25 years (1989–2013), and to estimate the risk of a LMM after a histologically confirmed LM. In addition, the 5-year relative survival of both LM and LMM is presented.

RESULTS

Between 1989 and 2013, 10,545 patients were diagnosed with a primary histologically confirmed LM in the Netherlands and 2,898 with a primary LMM. Of all patients with LM, 58% were females (n = 6,114), which was comparable to the 57% (n = 1,649) females among patients with LMM. Most LM (74%, n = 7,845) and LMM (69%, n = 2,002) were located in the head and neck region.

The absolute annual number of patients with a histologically confirmed first primary LM increased from 110 in 1989 to 903 in 2013 and for LMM from 38 in 1989 to 292 in 2013. During the same period, the median age at diagnosis of LM increased for men (from 68 to 71 years) and women (from 67 to 71 years). For LMM, the median age at diagnosis increased

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Abbreviations: CI, confidence interval; EAPC, estimated annual percentage changes; LM, lentigo maligna; LMM, lentigo maligna melanoma; PALGA, Dutch Pathology Registry

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as well for both men (from 68 to 73 years) and women (from 71 to 72 years).

Time trends for LM

The age-adjusted incidence rates (European standardized rate) of LM increased between 1989 and 2013 from 0.68 to 3.57 per 100,000 person-years for males and from 0.76 to 4.16 per 100,000 person-years for females (Figure 1). For both sexes combined, the incidence rates increased from 0.72 to 3.84 per 100,000 person-years. Incidence rates of LM age-standardized to other standard populations can be found in Supplementary Table S1 online.

Incidence rates of LM increased for males between 1989 and 1994 (estimated annual percentage change [EAPC]: 23.8%; 95% confidence interval [CI], 11.9−37.1) and between 2002 and 2013 (EAPC: 7.4%; 95% CI, 5.8−9.0), but remained stable between 1994 and 2002 (EAPC: 0.8%; 95% CI, −3.3 to 4.9) (Figure 1). The same pattern with the largest annual increases in incidence rates at the beginning and the end of the study period was observed for females (EAPC 1989−1994: 19.0% [95% CI, 12.6−25.8]; EAPC 2007−2013: 8.7% [95% CI, 6.5−10.9]). The increase in incidence rates among females was also statistically significant between 1994 and 2007 (EAPC: 2.4% [95% CI, 1.4−3.4]) (Figure 1). For both sexes combined, the incidence rates increased each year with 22.1% (95% CI, 15.2−29.4) between 1989 and 1994, 0.5% (95% CI, −1.8 to 2.9) between 1994 and 2002, and 6.8% (95% CI, 5.9−7.7) between 2002 and 2013.

Time trends for LMM

The age-adjusted incidence rates (European standardized rate) of LMM increased between 1989 and 2013 from 0.26 to 1.25 per 100,000 person-years for males and from 0.22 to 1.18 per 100,000 person-years for females (Figure 2). For both sexes combined, the incidence rates increased from 0.24 to 1.19 per 100,000 person-years. Incidence rates of LMM age-standardized to other standard populations can be found in Supplementary Table S2 online.

Joinpoint regression analyses showed statistically significant increased incidence rates among males between 1989 and 2007 (EAPC: 4.6% [95% CI, 2.7−6.5]) and between 2007 and 2013 (EAPC: 14.1% [95% CI, 8.2−20.2]) (Figure 2). Among females, the incidence rates increased in a similar pattern, with 5.2% (95% CI, 3.9−6.5) between 1989 and 2009 and 14.4% (95% CI, 5.4−24.2) between 2009 and 2013 (Figure 2). For both sexes combined, the incidence rates increased between 1989 and 2007 with 4.8% (95% CI, 3.4−6.2) annually, and between 2007 and 2013 with 12.4% (8.0−16.9%).

The age-specific incidence rates of both LM and LMM increased with each study period, with the largest increase, for both sexes, during the most recent period (2009−2013), and among elderly (data not shown).

Risk of LMM after LM

Of the 10,545 patients diagnosed with LM, 124 were subsequently diagnosed with an LMM (at any anatomic location). The 5-year cumulative risk of getting an LMM after a histologically confirmed primary LM was 0.7% (95% CI, 0.5−1.0) for males and 0.8% (95% CI, 0.6−1.1) for females. The 10-year cumulative risk was 1.0% (95% CI, 0.6−1.3) and 1.6% (95% CI, 1.2−2.0), the 15-year cumulative risk was 1.4% (95% CI, 0.9−1.9) and 1.9% (95% CI, 1.4−2.3), the 20-year cumulative risk was 2.0% (95% CI, 1.2−2.8) and 2.2% (95% CI, 1.7−2.8), and the 25-year cumulative risk 2.0% (95% CI, 1.2−2.8) and 2.6% (95% CI, 1.9−3.3), for males and females, respectively (Figure 3).

Of the 124 patients with an LMM after LM, 101 LMMs had the same International Classification of Diseases for

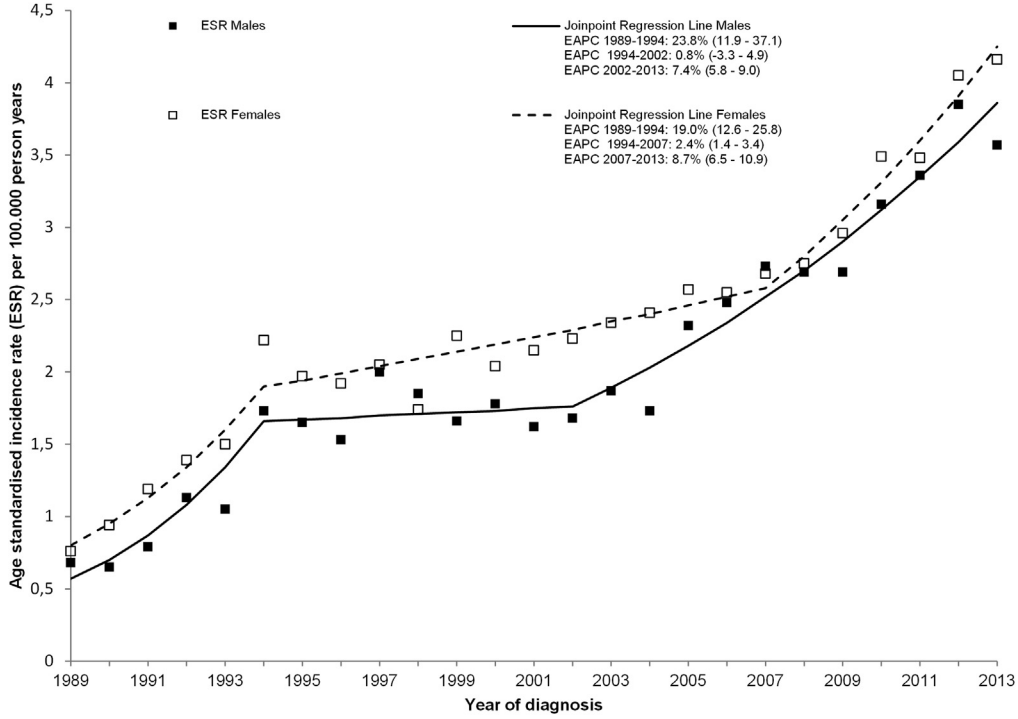

Figure 1. Lentigo maligna. Age-standardized incidence rates and trends. Age-standardized incidence rates per 100,000 person-years (ESR) and Joinpoint analyses with estimated annual percentage change (EAPC) of lentigo maligna in the Netherlands from 1989 to 2013 in males and females. ESR, European standardized rate.

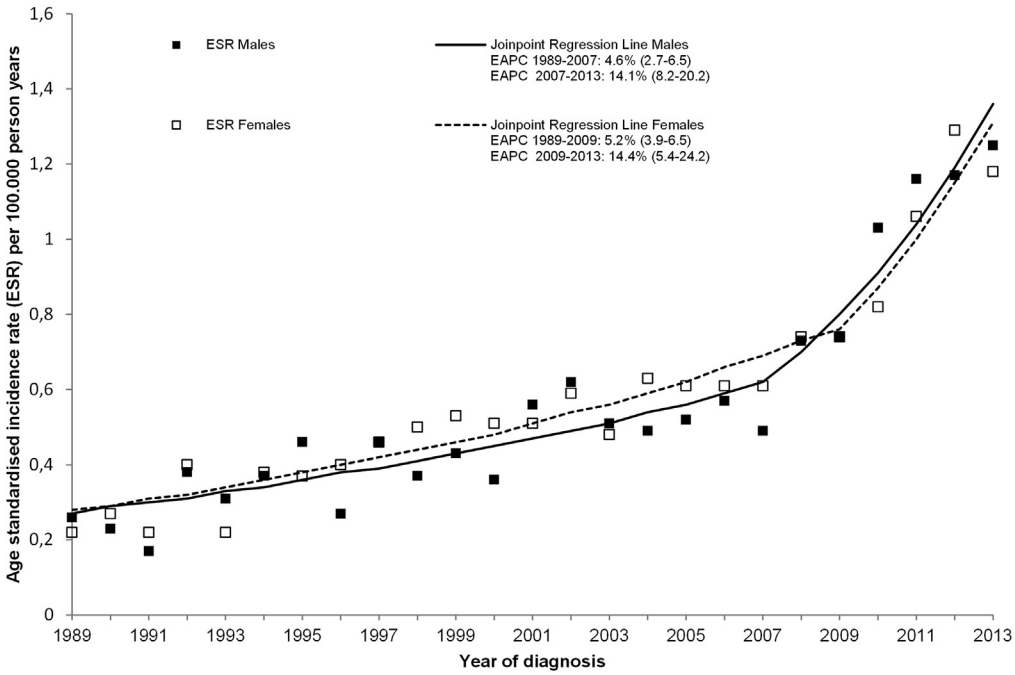

Figure 2. Lentigo maligna melanoma. Age-standardized incidence rates and trends. Age-standardized incidence rates per 100,000 person-years (ESR) and Joinpoint analyses with estimated annual percentage change (EAPC) of lentigo maligna melanoma in the Netherlands from 1989 to 2013 in males and females. ESR, European standardized rate.

Oncology topography and laterality codes as the LM: skin of the lip (n = 1), skin of the external ear (n = 3), skin of the other and unspecified parts of the face (n = 88), skin of the scalp and neck (n = 4), skin of the trunk (n = 3), skin of the upper limb and shoulder (n = 1), and skin of the lower limb and hip (n = 1).

To determine if the LMM occurred at exactly the same anatomical location as the LM, these 101 cases were linked to the Dutch Pathology Registry (PALGA). The exact locations could be determined in 71 cases. Of these 71 cases, the LM and subsequent LMM occurred at the same location in 64 cases. In 7 cases, this location was different. In the remaining 30 cases, the localizations remained unclear.

Of these 64 cases with similar anatomic locations, the LM and subsequent LMM occurred on the cheek (n = 39), nose (n = 5), forehead (n = 5), temporal area (n = 5), scalp (n = 3), ear (n = 3), eyelid (n = 1), upper limb (n = 1), neck (n = 1), and upper lip (n = 1).

Of the 64 LMs, 62 were treated, 51 (80%) with surgery, 7 (11%) with cryosurgery, and 4 (7%) with other or unknown therapies. The distribution of treatments was different compared with LM without LMM at the same location (n = 10,481), of which 10,265 LMs were treated, 9,369 (90%) with surgery, 262 (2%) with cryosurgery, and 634 (6%) with other or unknown therapies ($P = 0.004$).

Of all LMMs (n = 2,898), 662 (23%) were >1 mm deep. There was no significant difference between cases with prior LM (28%, 18 of 64) and cases without prior LM (23%, 644 of 2,834) ($P = 0.309$).

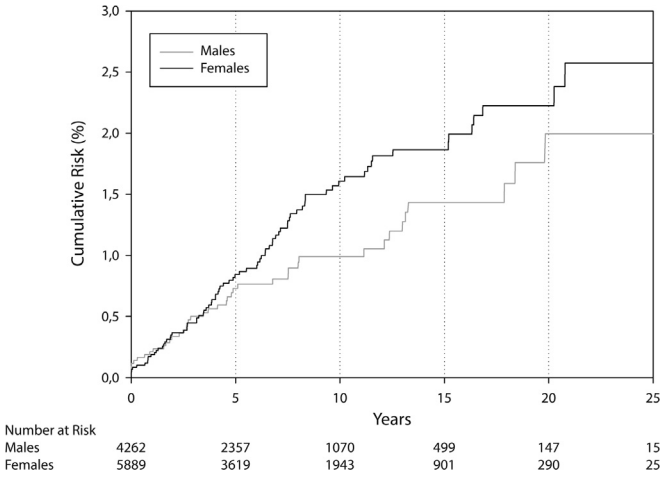

Figure 3. Cumulative incidence curve. Cumulative risk of a lentigo maligna melanoma (at any anatomical location) after a first histologically confirmed lentigo maligna.

Relative survival

The 5-year relative survival for LM was 104% (95% CI, 104−104), and for LMM 99% (95% CI, 97−101).

Of the 64 LMs with subsequent LMMs, 3 patients died in the first 5-year follow-up. The group was too small to calculate a 5-year relative survival.

DISCUSSION

The results of this large population-based study showed that the age-standardized incidence rates for both LM and LMM in the Netherlands increased between 1989 and 2013. During the most recent period, incidence rates increased with 7% for LM and 12% for LMM. The absolute risk of an LMM (at any anatomical location) after a histologically confirmed LM was low (2−3% after 25 years). The 5-year relative survival was high for both LM (104%) and LMM (99%).

When examining the rise in LM and LMM incidence over time, there are two interesting periods. The first is the steep increase of LM incidence between 1989 and 1994. Most likely, this steep increase could be explained by underreporting, because completeness of the database in the first

years is unknown. Also, the inception of higher awareness for skin cancer among the population and improved screening (de Rooij et al., 1995; Krol et al., 1990), leading to an increased histological confirmation of LM, may have contributed to this steep rise as well. The second interesting period is between 2002 and 2013, where the second increase of LM incidence is seen. This most recent acceleration of LM incidence coincided with an even steeper increase in LMM incidence rates; therefore, we think that this reflects, at least in part, a true increase. Another explanation could be the changed market forces in the Netherlands in 2006, which stimulated clinicians to treat skin cancer more rigorously than before (Flohil et al., 2013). Diagnostic drift has also been suggested as an explanation for more recent increases in melanoma incidence rates (van der Leest et al., 2015), as dermatopathologists are now more likely to diagnose melanoma in biopsies than they were 20 years ago (Frangos et al., 2012). Also, because immunohistochemistry is nowadays more commonly used in the histopathological diagnosis of LM and LMM than before, this has improved identification, and may have contributed to an increased detection as well.

Studies on incidence rates of in situ melanoma often do not report on histological subtypes specifically (Lee, 2001; Mocellin and Nitti, 2011; Vilar-Coromina et al., 2010), or the LM subtype is excluded because of concerns about consistency of identification over time (Coory et al., 2006; Ruiter et al., 2003; Thorn et al., 1998). Two population-based studies that did report on LM subtype both observed an average annual increase in incidence: 3.9% (95% CI, 1.7−6.2) in age group 45−64 years and 6.8% (95% CI, 5−8.7) in age group $\geq$ 65 years for both sexes in Northern California 1990−2000 (Swetter et al., 2005), and 1.7% (95% CI, 0.5−3.0) for men and 2.7% (95% CI, 1.7−3.8) for woman in Denmark 1997−2011 (Toender et al., 2014). For LMM, other population-based studies reported increased incidence rates in the order of 4−6% (Helvind et al., 2015; Hollestein et al., 2012; Mansson-Brahme et al., 2002; Swetter et al., 2005), similar to our earlier study period. However, as steep as the 12% increase that we found in our most recent study period has not been reported previously.

Age-adjusted incidence rates of LM and LMM were almost similar among men and women during the study period. This is different compared with cutaneous melanoma, in which there is a predominance found in women in European countries, and the opposite is found in Australia and North America (Arnold et al., 2014; Coory et al., 2006; Garbe and Leiter, 2009; MacKie et al., 2009). Cutaneous melanoma predominates over the lower limb in women and the trunk in men, whereas the upper limb and head and neck were similar for both sexes (Chevalier et al., 2014; Garbe and Leiter, 2009). LM and LMM occur mostly in the head and neck region, which may explain why we found no differences between sexes.

The risk of progression of LM to LMM is an important criterion that clinicians consider when deciding on a treatment strategy (e.g., surgical or local treatment). It is, however, very difficult to study the risk of progression, because the ideal study would comprise a prospective cohort in which LM lesions would be subjected to an intensive wait-and-see policy with a very long follow-up. In our study, we could not assess the progression of an individual lesion, and also the anatomic locations of LM and their subsequent LMM were different in 30 (of 124) cases and remained unknown in another 30 (of 124) cases. Therefore, we estimated the risk of a subsequent LMM at any anatomical location after a histologically confirmed LM. The cumulative risk of developing an LMM after a primary LM was estimated to be between 2% and 3% after 25 years. Whether this is a true risk or an overestimation or underestimation is debatable. The number of LM included only histologically confirmed LM and is therefore most likely an underestimation of the true number of LM in the Netherlands, caused by elderly patients left undiagnosed, or treated (with nonsurgical treatments or conservatively) without histopathological confirmation of the diagnosis. On the contrary, the registration of LMM is assumed to be virtually complete. The underregistration of LM combined with a complete registration of LMM may have resulted in an overestimation of the cumulative risk of LMM after LM.

On the other hand, it is also possible that there may be an underestimation of the cumulative risk of LMM after LM, because LM is normally treated in the Netherlands, which would decrease the risk of progression. Also, some of the LM diagnosed as an in situ lesion by initial biopsy or conventional excision may have already had an unrecognized component of dermal invasive melanoma and were actually representing LMM (Abdelmalek et al., 2012; Hazan et al., 2008; Iorizzo et al., 2013). Finally, LMM registered without a previous diagnosis of LM would not have been included in our analysis and may also have resulted in an underestimation.

Strengths of this study are the use of the national population-based cancer registry in the Netherlands that covers the whole Dutch population with high quality of the data over a long follow-up time (Schouten et al., 1994). Also, the link with the pathology database to retrieve if LMM occurred at exactly the same anatomical location as LM provided important additional information. A limitation is the lack of information on non-histologically confirmed LM, and on LMM without a previous diagnosis of LM, which could have led to an overestimation or underestimation of the risk of a subsequent LMM. Finally, the histopathological diagnosis of LM and LMM can be difficult because of sun-damaged skin, making these diagnoses challenging (Higgins et al., 2015b).

In summary, our results demonstrate an increasing incidence of LM and LMM in the Netherlands between 1989 and 2013. Besides factors such as increased awareness, increased histological examination, diagnostic drift, and changed market forces, this increased incidence also seems to reflect a true increase as the most recent accelerated increase of LM was followed by an even steeper accelerated increase of LMM. The absolute risk of an LMM (at any anatomical location) after a histologically confirmed LM was 2−3% after 25 years. The relative survival of both patient with LM and those with LMM was excellent 5 years after diagnosis. Our data may help physicians and patients to weigh the advantages and disadvantages of the different treatments for LM.

METHODS

Data were obtained from the Netherlands Cancer Registry on all cases of LM and LMM recorded between 1989 and 2013 in the Netherlands. The Netherlands Cancer Registry is based on all histologically confirmed malignancies in the Netherlands since 1989 by PALGA, a nationwide network and registry of histopathology and cytopathology (Casparie et al., 2007). The completeness on skin cancers (excluding basal cell carcinoma) was estimated to be 93% in 1994 (Schouten et al., 1994).

All patients with a first primary diagnosed LM or LMM (International Classification of Diseases for Oncology morphology codes 8742/2 and 8742/3) between 1989 and 2013 were included. International Classification of Diseases for Oncology topography codes were used to categorize anatomical sites: skin of the lip (C44.0), eyelid (C44.1), external ear (C44.2), skin of other and unspecified parts of the face (C44.3), skin of the scalp and neck (C44.4), skin of the trunk (C44.5), skin of the upper limb and shoulder (C44.6), skin of the lower limb and hip (C44.7), and other sites (C44.8–C44.9). The study period was divided into five time periods to study trends: 1989–1993, 1994–1998, 1999–2003, 2004–2008, and 2009–2013. Age-specific incidence rates were computed for 5-year age groups (0–4, …, 80–84, and 85+). Data were stratified by gender.

If a patient with a primary LM had a subsequent diagnosis of a primary LMM, the LM and LMM International Classification of Diseases for Oncology topography codes were compared. The Netherlands Cancer Registry data were additionally linked to PALGA to obtain more specific information on the exact anatomic location and determine if both locations were identical.

Statistical analysis

Incidence rates were calculated per 100,000 person-years, using population size (determined on 1 January each year) derived from Statistics Netherlands, and age-standardized to the European standard population (European standardized rate), world standard population 1968 (world standardized rate), world (WHO 2000–2025) standard population (world standardized rate 2000–2025), and US 2000 standard population (United States standardized rate).

EAPC with corresponding 95% CIs was calculated to evaluate incidence trends for LM and LMM over time. Joinpoint regression analyses were used to identify the years in which a significant change in trends occurred.

To estimate the risk of an LMM after a histologically confirmed LM, the cumulative risk up to 25 years after diagnosis of the first LM was calculated using a cumulative incidence curve taking the competing risk of death into account (Kim, 2007).

Five-year relative survival using traditional cohort analysis was calculated for LM and LMM as a proxy for disease-specific survival.

All analyses were carried out using SPSS statistics 21, SAS software (version 4.3, SAS Institute, Cary, NC) and Joinpoint regression program version 4.2.0.1 (Kim et al., 2000). *P*-values were two-sided and considered significant if $P < 0.05$.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.06.014.

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