Letter to the editor

## Oral cancer prevention worldwide: Challenges and perspectives

Oral squamous cell carcinoma (OSCC) is the most common type of head neck SCC (HNSCC), and a major cause of cancer-associated morbidity and mortality affecting more than one million people worldwide in 2016 (https://ourworldindata.org/cancer [1]). OSCC is associated with the greatest risk of death among all HNSCC anatomical subsites [2], that is commonly due to advanced loco-regional disease at diagnosis. Since OSCC may develop from oral premalignant lesions (OPML), oral erythroplakia and leukoplakia being the most common ones [3–5], prevention of malignant transformation of OPML to OSCC may substantially improve the clinical outcome. Notably, oral leukoplakia (OL) is the most common OPML with an overall worldwide prevalence of 2% [6], varying between less than 1% and more than 5%. The potential for malignant transformation of OL was first described in 1890, in a publication showing that "the best plan was to destroy them entirely with Paquelin's cautery" [7]. Since this first publication, more than one hundred years have passed and it is now established that surgical resection, as well as alternative techniques of OL destruction (cryotherapy, laser…), have not been shown to reduce cancer development in the entire mucosa of the head and neck [8,9]. Pitfalls associated with OL excision/destruction remain the multifocal nature of "field cancerization" [10] and the notion that normal-appearing mucosa may also have the potential for malignant transformation. Therefore, the main challenges for the prevention of OL transformation to invasive SCC are: i-to identify patients suffering from OL at high risk of HNSCC, and ii-to treat them using chemopreventive agents in order to prevent malignant transformation of the entire head neck mucosa. Because clinical and pathological factors have inconsistent predictive values of oral cancer risk [9], there is a need for the development of biomarkers. Moreover, OL may transform into invasive cancers over periods of up to 30 years [11,12] and therefore, evaluation of chemopreventive strategies would require prospective inclusion of large cohorts of patients with long-term followup. Recently, The Erlotinib Prevention of Oral Cancer trial (EPOC; NCT00402779) [4] was the first molecularly-based precision medicine trial in cancer prevention that evaluated erlotinib in patients at high-risk of developing oral cancer based on loss of heterozygosity (LOH) at specific chromosomal sites, the most validated biomarker of risk so far [4,13–16]. Unfortunately, while the study prospectively validated the value of LOH for identifying patients at high-risk of malignant transformation, it did not reach its primary endpoint. Therefore, there is still no effective therapy for prevention of malignant transformation of high-risk OL [5].

As we recently reported [17], scientometric analysis of publications can provide an objective overview of knowledge base and network features in a field of research that may be informative for researchers. Therefore, we performed a similar approach in order to build scientific worldwide networks including all countries contributing to the research in oral erythroplakia and leukoplakia (OEL) for different successive decades (1970s, 1980s, 1990s, 2000s and 2010s). To do this, we used the bibliometric dataset of research in OEL, that we previously extracted from the SCOPUS database as part of our recently published bibliometric study showing the leading position of US, India and the UK as contributing countries to research in this field [18]. These data extracted from the SCOPUS database was imported to Table2Net (http://tools.medialab.sciences-po.fr/table2net/) [19], in order to build scientific networks. Using the Gephi software to visualize these networks [20], we observed an increasing number of collaborations over time expanding to Asia between 1990 and 2016 (video file; Fig. 1A), which underlies the emerging role of China in collaborative research. In addition, in order to identify important topics of published items, we performed a term co-occurrence network using the VOSviewer software [21]. From the 53,005 terms extracted from abstract and title fields of the SCOPUS bibliometric dataset [18], 585 relevant terms were selected (using default parameters). Five distinct clusters were identified (Fig. 1B): cluster 2, 3, 4 and 5 were defined by "clinical" terms related to treatment (surgery, chemoprevention, phototherapy dynamic…), epidemiology (prevalence, risk factors…), clinical diagnosis (sign, examination, examination, differential diagnosis…) and oral viral infection (HIV, infection, EBV…) respectively, whereas cluster 1 included terms referring to biology (biomarker, expression, immunohistochemistry, PCR, apoptosis,…). Of note, terms from cluster 2, 3, 4 and 5 were close enough in the clustering network with many connecting lines between them, while a gap between these four clusters and cluster 1 related to biology was observed. This observation could potentially explain the lack of consensual management of OL and suggests an urgent need for more translational research studies in the future.

A

B

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Fig. 1. Networks analysis of research in oral and erythroplakia (OEL). (A) Network of international scientific collaborations in OEL research. International scientific network was built using Table2Net [19] and then exported to the Gephi software [20] where the "Map of countries" and "geolayout" were used to visualize the network. The network includes nodes (countries) as well as edges (connection of two countries in a collaborative work). Node size and colors (from light yellow to dark red) are defined by degree (corresponding to the quantity of direct neighbors of a country in the network) and betweenness centrality (corresponding to the measure of how often a country lies on the shortest path between other countries in the network) respectively. Turquoise, blue and night blue colored lines connect two countries which collaborated once, twice to four times, and more five times respectively. (B) Co-occurrence network of the most relevant terms related to OEL research. The VOSviewer software (version 1.6.5) [21] was used in order to perform a term co-occurrence map based on text data extracted from title and abstract fields of SCOPUS, using the binary counting method. Mapping of co-occurring terms on clustering network visualization. The thickness of the line between two co-occurring terms is associated with closer links. Co-occurring terms were clustered, and five clusters were identified using different colors.

Collaborations:
- turquoise: 1
- blue: 2 to 4
- dark blue: ≥ 5

1980-1990
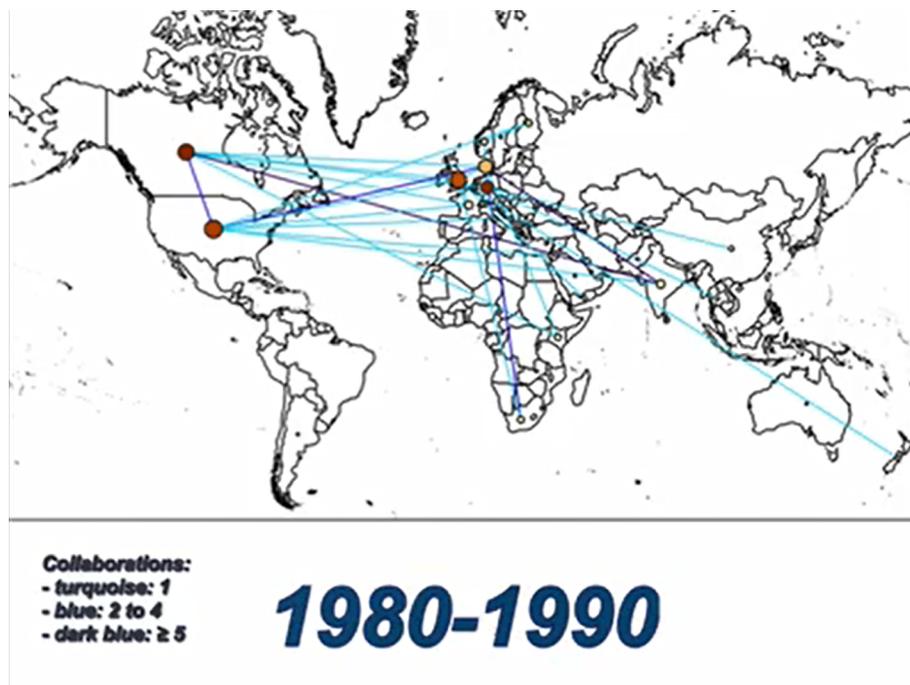
Video 1. Video File: Dynamics of international scientific network of countries contributing to OPML research over time. International scientific networks were built (using Table2net [19]) and visualized (using Gephi [20]) for different decades (1970s, 1980s, 1990s, 2000s and 2010s) and animated using videopad video editor free.

Clearly, large prospective studies including extensive collection of biospecimens and clinical information with long-term follow-up are urgently needed. With the development of omics technologies, they will allow to validate previously published biomarkers and to refine risk prediction models [22–24], to embed clinical trials that will evaluate pharmacological (including immunoprevention strategies) and non-pharmacological interventions including smoking/alcohol cessation programs as well as qualitative psychological/sociological human science studies to better understand frequent failure to quit in this frequently underserved population of patients. The development of international scientific networks including groups in North and South America, Europe and Asia is critical, as the biology of oral tumorigenesis may be different in different parts of the world. The recent increase of oral cancer in young women [25] remains poorly understood and studying OL in patients with no smoking or alcohol history may help understanding this epidemiological observation. Following the success of The Cancer Genome Atlas (TCGA) and the International Cancer Genomics Consortium (ICGC), a large effort needs to be engaged worldwide with the goal to characterize early molecular alterations both in tumor cells and the microenvironment of preneoplastic lesions. Such efforts are ongoing in the US [26–28]. Finally, the success of immunotherapies in the treatment of HNSCC [29,30] brings some hope that immunoprevention strategies, which have been also recently tested in the mouse 4NQO model of oral carcinogenesis [31], may work, especially in the immunological subtype of OPML as we recently published [32]. Engaging all stakeholders including pharma companies, in oral cancer prevention research should be set as a priority.

Conflict of interest statement

The authors declare no conflicts of interests.

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