OXFORD

JNCI J Natl Cancer Inst (2020) 112(9): djaa074

doi: 10.1093/jnci/djaa074
First published online June 1, 2020
Correspondence

RE: Oral Leukoplakia and Risk of Progression to Oral Cancer: A Population-Based Cohort Study

Burkhard H. Brandt, PhD,[1,*] Natalia Bednarz-Knoll, PhD,[2] Johannes Kleinheinz, MD,[3] Andre Franke, PhD,[4] Thomas Fillies, MD[5]

[1]Institute of Clinical Chemistry, University Hospital Schleswig-Holstein, Kiel, Germany; [2]Laboratory of Translational Oncology, Medical University of Gdańsk (formerly), Department of Medical Biotechnology, Intercollegiate Faculty of Biotechnology, Laboratory of Cell Biology, University of Gdańsk and Medical University of Gdańsk, Gdańsk, Poland; [3]Klinik für Mund, -Kiefer und Gesichtschirurgie, University Hospital Münster, Münster, Germany; [4]Institute of Clinical Molecular Biology, Christian-Albrechts-University of Kiel and University Hospital Schleswig Holstein, Kiel, Germany and [5]Klinik für Mund, -Kiefer- und Gesichtschirurgie, Marienhospital Stuttgart, Stuttgart, Germany

*Correspondence to: Burkhard H. Brandt, PhD, Institute of Clinical Chemistry, University Hospital Schleswig-Holstein, Arnold-Heller-Str. 3, 24105 Kiel, Germany (e-mail: Burkhard.Brandt@uksh.de).

We read with great interest the recent article from Chaturvedi et al. (1) investigating the risk of cancer in the oral cavity among patients with oral leukoplakia. Conducting this retrospective study of approximately 5000 patients, they calculated an incidence rate 40 times higher than in the general population. Approximately 40% of lesions that had transformed to cancer revealed no dysplasia. The authors therefore concluded a reinforced need for adjunctive tools to improve triage and reduce biopsy sampling errors. In our opinion, molecular analysis of epidermal growth factor receptor (*EGFR*), whose expression is a dominant event in HNSCC carcinogenesis, might still satisfy these demands (2). Detecting frequent *EGFR* gene alterations in leukoplakia (3), we supported its use as a marker for early transformation in leukoplakias. Chemoprevention studies of oral cancer applying EGFR-specific TKI have been conducted already. Unfortunately, no benefit for the patients has been achieved until now (4). Therefore, we performed a fine-mapping molecular analysis focused on *EGFR* in biopsies from 403 outpatients of the Cranio-Maxillofacial Surgery (CMS) Department, University Medical Center Muenster, prospectively collected from 1988 to 2001. Twelve patients developed oral cancer, corresponding to an incidence 30 times higher than the average in the North-Rhine-Westphalian Cancer Registry and comparable with the KPNC cohort of Chaturvedi et al. Even in nondysplastic leukoplasia, such *EGFR* alterations occurred in the 5'-regulatory sequence of the gene centered by a length polymorphism of 14-23 CA repeats, namely, CA SSR I. Baseline EGFR mRNA expression increases as CA repeat numbers in the DNA stretch decrease (5). Hence, conceivable genetic inheritance of leukoplakia progression toward oral cancer may be linked to the CA SSR I stretch length, because in our cohort we found an elevated risk for oral cancer in leukoplakia patients carrying a short CA repeat in both alleles (≤18 CA repeats) (n = 12, relative risk [RR] = 1.37, 95% confidence interval [CI] = 1.15 to 1.63, $P < .001$). The relative risk and 95% confidence interval are calculated according to Altman by MedCalc Software bvba, 2016. *P* values are 2-sided ($P = .001$). The poorly prognostic and most frequent tongue cancer (Chaturvedi et al.: 69%; CMS Muenster: 7 of 12 [58%], RR = 1.61, 95% CI = 1.38 to 1.88, $P \leq .001$) presented exclusively with alleles of 18 CA or less (Figure 1) and odds ratios of up to 123.81 (95% CI = 7.47 to 2051.66, $P < .001$). Moreover, every leukoplakia that progressed to oral cancer harbored at least 1 genetic aberration in that sequence (6 of 12 allelic imbalance, 5 of 12 copy number variation, 2 of 12 amplification), clarifying earlier results from Benchekroun et al. (6). This might be due to

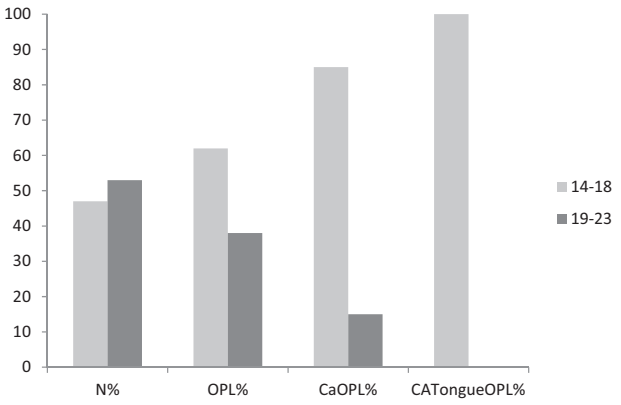

Figure 1. Epidermal growth factor receptor (*EGFR*) genotypes in normal population, oral premalignancy, and oral cancer. Frequency of *EGFR* CA SSR I allele length dichotomized for 18 or less and for greater than 18 CA repeats in a healthy German reference cohort (N%, n = 1333), CMS Muenster leukoplakia without cancer (OPL%, n = 391), CMS Muenster leukoplakia with cancer (CaOPL%, n = 12), and CMS Muenster leukoplakia with tongue cancer (CaTongueOPL%, n = 7).

Received: 19 March 2020; **Accepted:** 18 May 2020

enhanced mucosal proliferation pursuant to higher EGFR expression as concluded from the clinically significant association between 18 or less CA SSR I and severe skin rash under TKI therapy (7). Concurrent overexpression of EGFR protein in the presence of 18 or less CA repeats predicting poor disease-free survival for TKI nontreated oral cancer has also been demonstrated.

Finally, the request from Chaturvedi et al. for the routine biopsy of leukoplakia might be nourished with molecular lesion testing, especially in the absence of dysplastic signs (eg, using an easy-to-perform, low-cost CA SSR I microsatellite assay).

Funding

The author B.H.B. thanks Deutsche Krebshilfe (Project 102356), Bonn, and Fritz-Bender Foundation, München, for financial support.

Notes

Role of the funder: The funder had no role in the writing of this correspondence, the data collection and analysis, or decision to submit it for publication.

Conflicts of interest: The authors have no conflicts of interest to disclose.

References

1. Chaturvedi AK, Udaltsova N, Engels EA, et al. Oral leukoplakia and risk of progression to oral cancer: a population-based cohort study. *J Natl Cancer Inst*. 2020;112(10):djz238.https://doi.org/10.1093/jnci/djz238.
2. Grandis JR, Melhem MF, Barnes EL, Tweardy DJ, Elevated levels of transforming growth factor a and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. *Cancer Res*. 1996; 78(6):1284–3584.
3. Werkmeister R, Brandt B, Joos U. Aberrations of erbB-1 and erbB-2 oncogenes in non-dysplastic leukoplakias of the oral cavity. *Br J Oral Maxillofac Surg*. 1999; 37(6):477–480.
4. William WN Jr, Papadimitrakopoulou V, Lee JJ, et al. Erlotinib and the risk of oral cancer: The Erlotinib Prevention of Oral Cancer (EPOC) randomized clinical trial. *JAMA Oncol*. 2016;2(2):209–216.
5. Brandt B, Meyer-Staeckling S, Schmidt H, Agelopoulos K, Buerger H, Mechanisms of EGFR gene transcription modulation: relationship to cancer risk and therapy response. *Clin Cancer Res*. 2006;12(24): 7252–7260.
6. Taoudi Benchekroun M, Saintigny P, Thomas SM, et al. Epidermal growth factor receptor expression and gene copy number in the risk of oral cancer. *Cancer Prev Res*. 2010;3(7):800–809. DOI: 10.1158/1940-6207.CAPR-09-0163
7. Rudin CM, Liu W, Desai A, et al. Pharmacogenomic and pharmacokinetic determinants of erlotinib toxicity. *J Clin Oncol*. 2008;26(7): 1119–1127.