

Frauds in science

- The „Jon Sudbø case” -

Jon Sudbø



Jon Sudbø

- born on May 3, 1961
- Norwegian dentist / physician / oral surgeon
- renowned researcher in the field of oncology
 - articles in NEJM, Journal of Clinical Oncology (IF=18.4), The Lancet, Journal of Pathology, etc.
- associate professor @ University of Oslo
 - until 2006
- consultant oncologist @ Radium Hospital
 - until 2006

The paper

THE LANCET

Volume 366, Issue 9494, 15–21 October 2005, Pages 1359–1366

Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study

J Sudbø, J J Lee, S M Lippman, J Mork, S Sagen, N Flatner, A Ristimäki, A Sudbø, L Mao, X Zhou, W Kildal, J F Evensen, A Reith, A J Dannenberg

Background

- Squamous cell carcinoma
 - Poor prognosis
 - Major cause: tobacco smoking (and alcohol)
 - High risk for patients with oral leucoplakia & aneuploidy
 - 5-years survival → 30%
 - Surgical resection → no reduction of high risk

(...), „NEED FOR NEW TREATMENT STRATEGIES“ (...)



<http://www.merckmanuals.com/professional/ear,-nose,-and-throat-disorders/tumors-of-the-head-and-neck/oral-squamous-cell-carcinoma>



http://www.drbcuspide.com/user/images/content_images/nws_rad/2009_05_19_12_22_42_314_2009_05_21_squamous_cell_carcinoma.jpg

Background

- Cyclooxygenase-2 and prostaglandin-E2
 - Biological role:
 - cell proliferation
 - Angiogenesis
 - Immune stimulation
 - **involved in various malignacities**
 - E.g. squamous cell carcinoma
- **NSAIDs** → inhibition of Cyclooxygenase-2 & prostaglandin-E2
 - Reducton of risk to develop cancer in animal models
 - Few epidemiological data

Materials and Methods - Overview -

- „Population-based case-control study“

- Data from: Cohort of Norway (**CONOR**)



- Longitudinal health surveys
 - Standardised questionnaires, detailed clinical information on participants, ...
- 123.234 „active“ participants

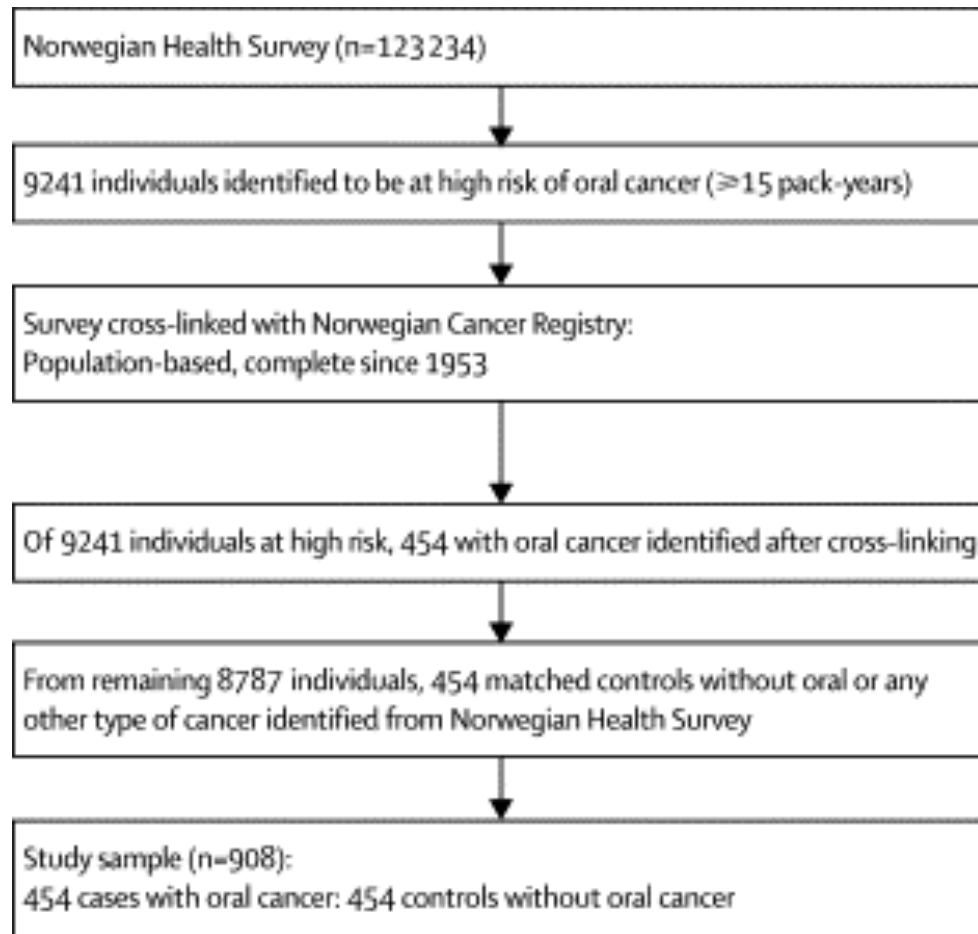
Crosslinked with

- Data from **disease registries**, e.g. Norwegian Cancer Registry

Materials and methods

- Detailed information on
 - age
 - sex
 - risk factors for head and neck cancer
 - **Treatment drug use**
 - Type and duration of NSAID use
 - Survival
 - etc.
- All data obtained from „central registers“
 - Participants from CONOR and Norwegian Cancer Registry
 - Survival data → „National death certificate registry“
 - Detailed information on prescriptions → „central registry“
 - etc.

Materials and Methods



Materials and methods

„(...)The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.(...)“

Results

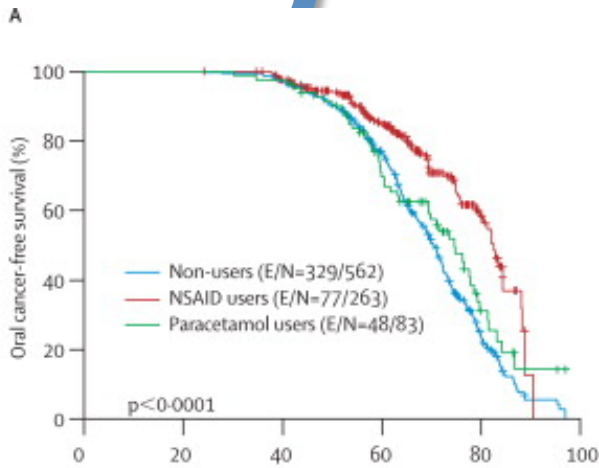
- total: n=908
 - oral cancer **cases**: n=454
 - tongue: n=157
 - floor or mouth: n=149
 - other: n=148
 - high risk **controls**: n=454
 - without oral SCC
- 29% NSAIDs and 9 % paracetamol intake (>6 months)

Results

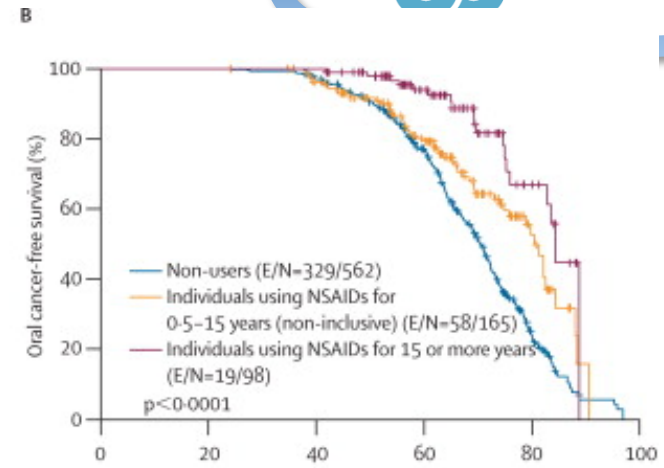
	Cases (n=454)	Controls (n=454)*	Total (n=908)
Age (years)†			
At time of oral cancer or last follow-up	63.3 (13.2)	63.3 (13.2), 73.6 (10.1)‡	63.3 (13.2), 68.4 (12.8)‡
At death or last follow-up	70.4 (10.7), 71.9 (10.9)‡	70.4 (10.7), 73.6 (10.1)‡	70.4 (10.7), 72.8 (10.5)‡
Sex			
Male	279 (61%)	279 (61%)	558 (61%)
Female	175 (39%)	175 (39%)	350 (39%)
Tobacco smoking			
Number of cigarettes			
15–20 cigarettes/day	186 (41%)	189 (42%)	375 (41%)
21–30 cigarettes/day	166 (37%)	153 (34%)	319 (35%)
31–40 cigarettes/day	76 (17%)	81 (18%)	157 (17%)
>40 cigarettes/day	26 (6%)	31 (7%)	57 (6%)
Pack-years	43.0 (14.6)	39.0 (14.7)	41.0 (14.8)
Alcohol			
Never	24 (5%)	30 (7%)	54 (6%)
1–5 units/week	164 (36%)	165 (36%)	329 (36%)
>5 units/week	194 (43%)	199 (44%)	393 (43%)
No information	72 (16%)	60 (13%)	132 (15%)
Drug type used			
NSAID			
Aspirin	77 (17%)	186 (41%)	263 (29%)
Ibuprofen	5	9	14
Ibuprofen	13	39	52
Naproxen	16	39	55
Indometacin	15	47	62
Piroxicam	17	35	52
Ketoprofen	11	17	28
Paracetamol	48 (11%)	35 (8%)	83 (9%)
Length of NSAID use (years)			
<5	10	21	31 (12%)
5–10	22	25	47 (18%)
10–15	26	61	87 (33%)
≥15–26	19	79	98 (37%)

Results

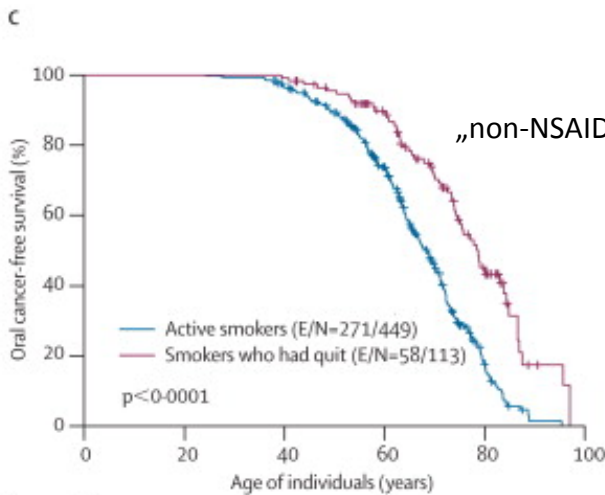
- Use of NSAIDs & paracetamol
 - reduced risk of oral cancer
 - NSAIDs → reduced risk even for heavy smokers (>40 pack years)
 - no association with overall survival
 - some NSAIDs → increased risk for cardiovascular-disease-related death



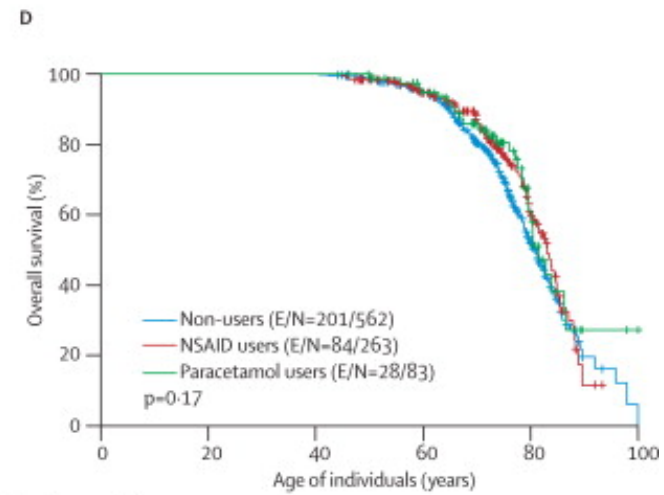
Numbers at risk	0	20	40	60	80	100
Non-users	562	531	351	50		
NSAID users	263	249	162	33		
Paracetamol users	83	80	49	11		



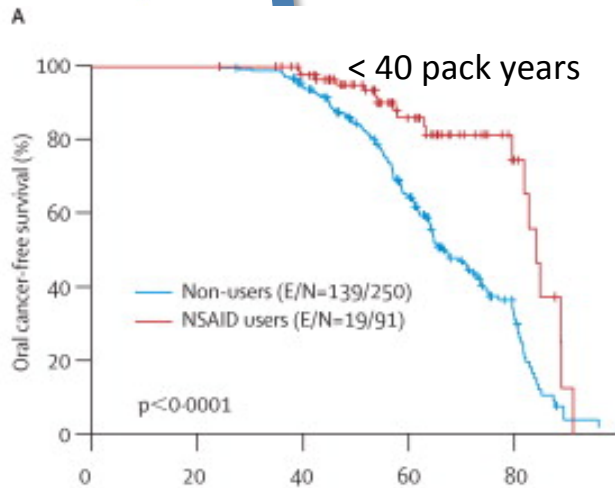
Numbers at risk	0	20	40	60	80	100
Non-users	562	531	351	50		
Individuals using NSAIDs for 0-15 years (non-inclusive)	165	151	98	18		
Individuals using NSAIDs for 15 or more years	98	98	64	15		



Numbers at risk	0	20	40	60	80	100
Active smokers	449	419	263	26		
Smokers who had quit	113	112	88	24		

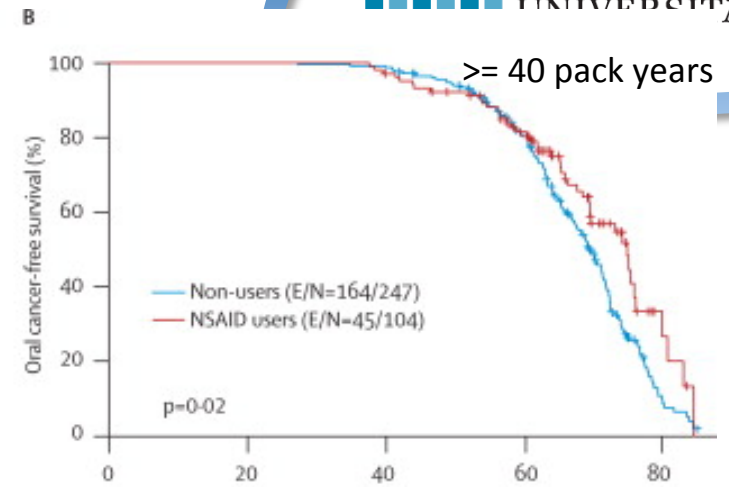


Numbers at risk	0	20	40	60	80	100
Non-users	562	562	460	98		
NSAID users	263	263	213	53		
Paracetamol users	83	83	71	19		



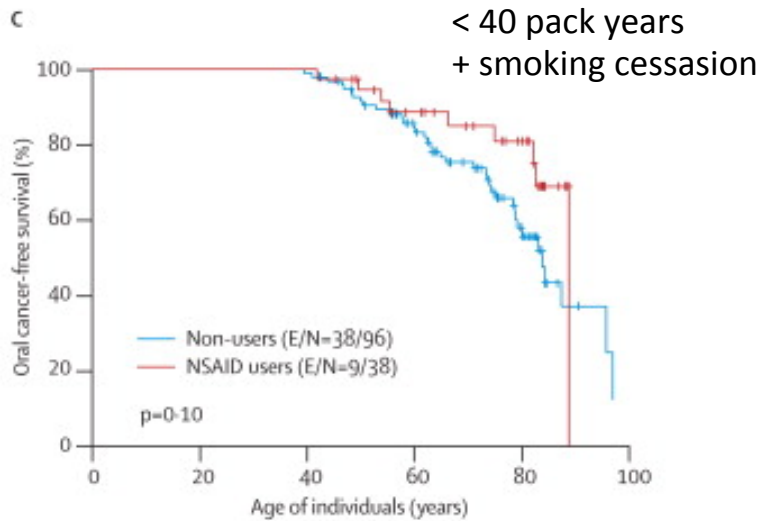
Numbers at risk

Non-users	250	220	114	24
NSAID users	91	82	40	9



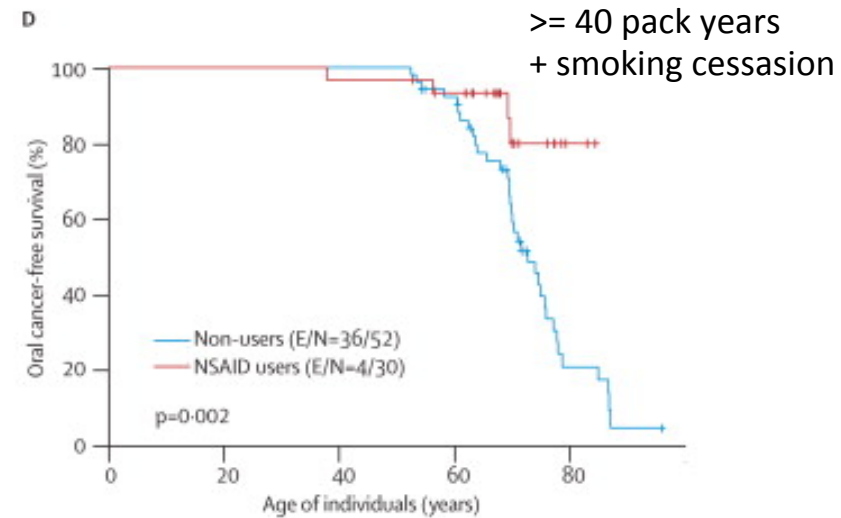
Numbers at risk

Non-users	247	244	174	8
NSAID users	104	100	69	4



Numbers at risk

Non-users	96	95	67	23
NSAID users	38	38	27	17



Numbers at risk

Non-users	52	52	45	6
NSAID users	30	29	26	3



Univariate analysis

Individuals who had not used NSAIDs	41 (7%)	562
Individuals who had used NSAIDs	42 (16%)	263	2.06 (1.34–3.18)	0.001
Aspirin	2 (14%)	14	1.16 (0.28–4.80)	0.84
Ibuprofen	12 (23%)	52	2.86 (1.50–5.45)	0.001
Naproxen	7 (13%)	55	1.70 (0.76–3.79)	0.20
Indometacin	10 (16%)	62	2.26 (1.13–4.52)	0.02
Piroxicam	7 (13%)	52	1.84 (0.82–4.11)	0.14
Ketoprofen	4 (14%)	28	1.90 (0.68–5.31)	0.22
Individuals who had used paracetamol	4 (5%)	83	0.51 (0.18–1.42)	0.20

Multivariate analysis

NSAID use	2.05 (1.33–3.16)	0.001
Paracetamol use	0.50 (0.18–1.40)	0.18
Smoking pack-years (<40 or ≥40)	1.02 (0.65–1.60)	0.93
Quit smoking (yes or no)	1.13 (0.72–1.77)	0.60



Discussion

- advantages vs. disadvantages by long-term NSAIDs and paracetamol intake
 - cancer risk vs. cardiovascular risk
 - promising results especially in high-risk groups
 - more acceptable than in low-risk groups?
 - tantamount to cancer therapy?

...

„Bad luck“

Christmas 2005

- *Camilla Stoltenberg* (head of Norwegian Institute of Public Health AND sister of Prime Minister of Norway)
 - found it suspicious that



the database - mentioned in the article - was supposed to open at the **beginning of 2006**

„Bad luck“

- C.S. started „digging“ and found out that



250 of the patients had birthday
on the same day



Report in “**Dagbladet**”

The fraud

Stein Vaaler, director of strategy @ Radium Hospital :

(...)“He faked everything: names, diagnosis, gender, weight, age, drug use. There is no real data whatsoever, just figures he made up himself. Every patient in this paper is a fake“ (...)

The fraud

- some days later, Sudbo has acknowledged that:

“he has faked at least two more papers“
(published in NEJM and Journal of Clinical Oncology)



an independent Commission of Inquiry
led by Prof. *Anders Ekbom*,
started further investigation

The fraud

30 June of 2006
report of the commission:



15 of his articles were **fraduelent**,
incl. his **doctoral dissertation**

Consequenses

Retraction of several fraudulent articles

Articles

Non-steroidal anti-inflammatory drugs and the risk of oral cancer: a nested case-control study

[Sudba, J, Lee, S M, Lippman, M, S, Sagen, N, Friese, A, Björnå, A, Sudba, L, Mao, X, Zhou, W, Wang, J, Forman, A, Roth, A] December

Summary
Background: Non-steroidal anti-inflammatory drugs (NSAIDs) seem to prevent several types of cancer, but could increase the risk of cardiovascular complications. We investigated whether use of NSAIDs was associated with a change in the incidence of oral cancer overall or cardiovascular mortality.

Methods: We undertook a nested case-control study to analyze data from a population-based, nationwide cohort of Norway (CONOR), which consisted of prospectively obtained health data from all registered Norwegian people. Oral cancer was identified from the 5243 individuals in CONOR who were at increased risk of oral cancer because of heavy smoking (>15 pack-years), and matched controls were selected from the remaining 100,000 individuals who did not have cancer.

Results: We identified and analyzed 434 (94%) people with oral cancer (217 men and 217 women; 303 age at diagnosis 65 [13-2] years) and 454 matched controls (460 men and 448 women; 303 age at diagnosis 65 [13-2] years) and 454 matched controls (460 men and 448 women; 303 age at diagnosis 65 [13-2] years) had used NSAIDs, 35 (8%) had used paracetamol (for a minimum of 6 months), and 562 (62%) had used neither NSAIDs nor paracetamol. Use of NSAIDs was associated with a reduced risk of oral cancer (including in heavy smokers) (odds ratio 0.47, 95% CI 0.25-0.86, p=0.0001). Smoking cessation also lowered the risk of oral cancer (0.32, 95% CI 0.18-0.57, p<0.0001). Additionally, long-term use of NSAIDs (but not paracetamol) was associated with a reduced risk of cardiovascular disease-related death (2.46, 1.34-3.18, p=0.001). NSAID use did not significantly reduce overall mortality (p=0.17).

Interpretation: Long-term use of NSAIDs is associated with a reduced incidence of oral cancer (including in active smokers), but also with an increased risk of death from cardiovascular disease. These findings highlight the need for a careful risk-benefit analysis when the use of NSAIDs is considered.

Introduction
Squamous cell carcinoma of the oral cavity is associated with severe disease-related morbidity and mortality and a poor prognosis. The incidence of oral cancer has increased markedly over the past three decades.^{1,2} Tobacco smoking is the major cause of this disease.^{3,4} Patients with oral leukoplakia with the potential for malignant transformation have an 8% risk of developing oral cancer with a high relative rate and a 70% risk of dying within 5 years.⁵ Complete surgical resection of oral cancer with a high risk of recurrence is difficult to achieve, and oral cancer often could offer some prognostic information. Therefore, there is an urgent medical need for new strategies, such as chemoprevention with non-steroidal anti-inflammatory drugs (NSAIDs), to reduce the risks of cancer in patients with atypical oral leukoplakia.^{6,7}

NSAIDs inhibit cyclooxygenase (COX) activity and thereby suppress the synthesis of prostaglandin E₂. Elevated concentrations of prostaglandin E₂ have been detected in both premalignant and malignant lesions, including squamous cell carcinoma of the oral cavity.^{8,9} This increase results from the overexpression of COX-2. Several lines of evidence, beyond the finding of raised amounts of prostaglandin E₂ in lesions, suggest that COX expression contributes to the development of oral cancer. COX can convert polyketic

This article has been retracted: N Engl J Med 2006;355(18):1927.

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

The Influence of Resection and Aneuploidy on Mortality in Oral Leukoplakia

Jon Sudba, M.D., D.D.S., Ph.D., Scott M. Lippman, M.D., J. Jack Lee, D.D.S., Ph.D., Li Mao, M.D., Wanja Kildal, M.Sc., Asle Sudba, Ph.D., Simone Sagen, M.P.H., Magne Bryne, D.D.S., Ph.D., Adel El-Naggar, M.D., Ph.D., Björn Risberg, M.D., Ph.D., Jan F. Evensen, M.D., Ph.D., and Albrecht Reith, M.D., Ph.D.

ABSTRACT

BACKGROUND

Although the standard treatment of oral leukoplakia ranges from watchful waiting to complete resection, the value of these approaches is unknown.

METHODS

We studied the relations among resection, ploidy status, and death from cancer in 103 patients with diploid dysplastic oral leukoplakia, 20 patients with tetraploid lesions, and 27 patients with aneuploid lesions. Data on cancer-specific mortality and treatment were obtained from the Cancer Registry of Norway, Statistics Norway, and chart reviews.

RESULTS

Primary oral carcinoma developed in 47 of the 150 patients with leukoplakia (31 percent) — 5 with diploid, 16 with tetraploid, and 26 with aneuploid leukoplakia — during a mean follow-up of 80 months (range, 4 to 237). The margin status of the initial leuko-

From the Departments of Medical Oncology and Radiotherapy, Division of Cytology, Department of Pathology, The Norwegian Radium Hospital, and Dental Faculty, University of Oslo, and Avoti Tannhelse AS, Oslo, Norway. Submitted March 27, 2004; accepted November 1, 2004. Supported in part by grants P01 CA106561 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; The Norwegian Cancer Society (E 02010202, E 03010203, and HF-01018); and the Research Foundation of the Norwegian Radium Hospital (02020213, SE 0207, and SE 0411), as well as grants from the Norwegian Cancer Society, Hovud Department of Physics (Norwegian University of Science and Technology, Trondheim, Norway) (A.E.-N.), University of Texas Anderson Cancer Center, Hovud Department of Physics (Norwegian University of Science and Technology, Trondheim, Norway) (A.S.), and the Department of Oral Biology, University of Oslo, Oslo, Norway (M.B.). Address reprint requests to Dr. J. Sudba at the Department of Med-

VOLUME 23 • NUMBER 9 • MARCH 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

This article was retracted in December 2006.

Risk Markers of Oral Cancer in Clinically Normal Mucosa As an Aid in Smoking Cessation Counseling

Jon Sudba, Roy Samuelsson, Björn Risberg, Stig Heistad, Christian Nyhus, Margaretha Samuelsson, Ruth Pantertvold, Eva Sigstad, Ben Davidson, Albrecht Reith, and Amund Berner

ABSTRACT

Purpose

Quitting smoking may prevent oral cancer. Behavioral intervention to quit smoking may be more efficient if persons are assigned an individual risk of cancer.

Patients and Methods

In this prospective study, we provided counseling and behavioral intervention toward smoking cessation, supplemented by genetic analyses in clinically normal oral mucosa of heavy smokers. Measurement of serum cotinine was used to assess changes in smoking habits.

Results

In cytologic scrapings from 275 heavy smokers with clinically normal mucosa, we found tetraploidy in four and aneuploidy in 19 persons (23 of 275; 8%). Twenty one (91% of 23 persons with aneuploidy had quit or reduced their smoking habits at the 3-month follow-up, 20 (87%) of 23 persons had done so at 12 months, and 21 (81%) of 23 persons had done so at 24 months. Eighteen (76%) of the 23 persons with tetraploidy had quit or reduced their smoking habits at the 3-month follow-up, 17 (74%) of 23 persons had done so at 12 months, and 16 (69%) of 23 persons had done so at 24 months.

Consequences

- Resigned from all university-based positions in 2006
- Revocation of the license to practice medicine and dentistry 2006
- Revocation of the doctoral thesis in 2006

Effects of fraud

- massive critics on University of Oslo & Radium hospital
 - lack of control → faked dissertation(!)
- Norway's scientific reputation
 - some projects granted by U.S. National Cancer Institute
- effects on co-authors
 - although not involved, massive effects on reputation

Today

- 2009 → grant of restricted authorizations to **practice dentistry**
 - Head of Seljord Dental Clinic
(Telemark fylkeskommune, Norway)



- prohibition of involvation in research

Interesting

- wife and brother → co-authors



- no knowledge of the fabrication!

Interesting

- key-role of sister of Norwegian Prime Minister



- two weeks after announcement



new law: medical fraud as criminal act,
„Norway as first country“

Questions?

References

- **Case Summary: Sudbo, Jon:** DEPARTMENT OF HEALTH AND HUMAN SERVICES, Office of the Secretary, Findings of Scientific Misconduct,
<http://ori.hhs.gov/content/case-summary-sudbo-jon>
- <http://www.the-scientist.com/?articles.view/articleNo/25540/title/Norwegian-dentist-falsified-grant/>
- <https://www.timeshighereducation.com/features/cleaning-up-the-act/403288.article>
- http://www.naturalnews.com/019353_medical_ethics_stem_cell_research.html
- **Research misconduct: lessons to be learned?** by *Magne Nylenna, Professor of community medicine*
Department of Public Health and General Practice Norwegian University of Science and Technology
<http://www.dnms.no/pdf/2007/1-7-9.pdf>
- http://www.hopkinsmedicine.org/research/synergy/offices/OPC/Research_Integrity/Deans_Lectures_2011_2012/DeansRILecture6_02152012_Hruban.pptx