Volatile organic compounds in the breath of patients with schizophrenia

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Abstract

***Aims*—To analyse the breath of patients with schizophrenia for the presence of abnormal volatile organic compounds.**

***Methods*—A case comparison study was performed in two community hospitals in Staten Island, New York. Twenty five patients with schizophrenia, 26 patients with other psychiatric disorders, and 38 normal controls were studied. Alveolar breath samples were collected from all participants, and volatile organic compounds in the breath were assayed by gas chromatography with mass spectroscopy. Differences in the distribution of volatile organic compounds between the three groups were compared by computerised pattern recognition analysis.**

***Results*—Forty eight different volatile organic compounds were observed in the breath samples. Three separate pattern recognition methods indicated an increased differentiation capability between the patients with schizophrenia and the other subjects. Pattern recognition category classification models using 11 of these volatile organic compounds identified the patients with schizophrenia with a sensitivity of 80·0% and a specificity of 61·9%. Volatile organic compounds in breath were not significantly affected by drug therapy, age, sex, smoking, diet, or race.**

***Conclusions*—Microanalysis of volatile organic compounds in breath combined with pattern recognition analysis of data may provide a new approach to the diagnosis and understanding of schizophrenia. The physiological basis of these findings is still speculative.**

(*J Clin Pathol* 1995;48:466–469)

Keywords: Breath tests, schizophrenia, pattern recognition

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Accepted for publication
26 September 1994

Patients with schizophrenia have been reported to give off a persistent unpleasant smell which is not related to uncleanliness.[1 2] Several other diseases have also been associated with a distinctive aroma, such as the fetor hepaticus of liver failure, the smell of decomposing apples in diabetic acidosis, and the odour of fresh baked brown bread in typhoid fever.[1] The common feature of these disorders might be an abnormal metabolic pathway which manufactures a volatile organic compound with a pungent smell.

Attempts to identify the responsible compound in the sweat of patients with schizophrenia have not met with success[3]; however, abnormal body odours can now be studied by analysis of the volatile organic compounds in the breath. Microanalysis of alveolar breath opens a unique and non-invasive window onto the pool of volatile compounds which circulate in the blood and rapidly diffuse across the pulmonary alveolar membrane.[4 5] Gas chromatography combined with mass spectroscopy (GC–MS) has revealed more than 100 volatile organic compounds in normal human breath, many of them in picomolar (10^{-12} M) concentrations.[6 7] Breath tests have shown that patients with schizophrenia expire increased amounts of pentane and carbon disulphide.[8 10]

Since GC–MS analysis reveals so many different compounds in a single sample of alveolar breath, the search for a disease marker is a difficult undertaking. Using techniques for statistical comparison volatile organic compounds can be tested one at a time for distribution differences between different populations. However, in the absence of an obvious major concentration difference in one or more of these compounds, computerised pattern recognition analysis can provide a powerful technique for identifying small yet significant changes in several volatile compounds simultaneously.[11 12]

We report here a study in which microanalysis of volatile organic compounds in the breath was combined with pattern recognition analysis in an attempt to detect abnormalities in multiple volatile compounds in patients with schizophrenia.

Methods

COLLECTION AND ASSAY OF VOLATILE ORGANIC COMPOUNDS

The method has been described.[13] Using a mobile apparatus, alveolar breath was collected from a donor inspiring chemically purified air. The volatile organic compounds in 10 litres of breath were trapped by adsorption to activated carbon and molecular sieve. The volatile organic compounds were thermally eluted from the trap in a microprocessor controlled automatic desorber, concentrated by two stage cryofocusing, then assayed by GC–MS with an ion trap detector. Each compound was identified by its mass spectrum and quantified by the area under the curve of its chromatograph peak.

HUMAN SUBJECTS

The subjects and recruitment procedures employed in this study have been reported pre-

viously.[10] In summary, 88 volunteers were studied at St Vincent's Medical Center of Richmond and Bayley Seton Hospital in Staten Island, New York. All gave their informed consent to participate in this research, which was approved by the institutional review boards of both institutions. They comprised:

(1) *Normal controls*—A group of 37 normal volunteers was drawn from the medical and nursing staff of both institutions. None gave any history of psychiatric illness.

(2) *Psychiatric controls*—Twenty six subjects were recruited from the psychiatric inpatient units of both hospitals. This was an intentionally heterogeneous group, selected in order to provide a diverse spectrum of non-schizophrenic psychiatric disorders. All had been diagnosed as suffering from a psychiatric illness other than schizophrenia by DSM-III-R criteria.[14]

(3) *Patients with schizophrenia*—Twenty five subjects were studied who had been previously diagnosed as suffering from schizophrenia. All had fulfilled DSM-III-R criteria for the diagnosis of schizophrenia before the hospital admission when the study was performed. All had experienced a recent exacerbation requiring admission to a psychiatric inpatient unit, where they shared the same environment and diet as the non-schizophrenic psychiatric controls.

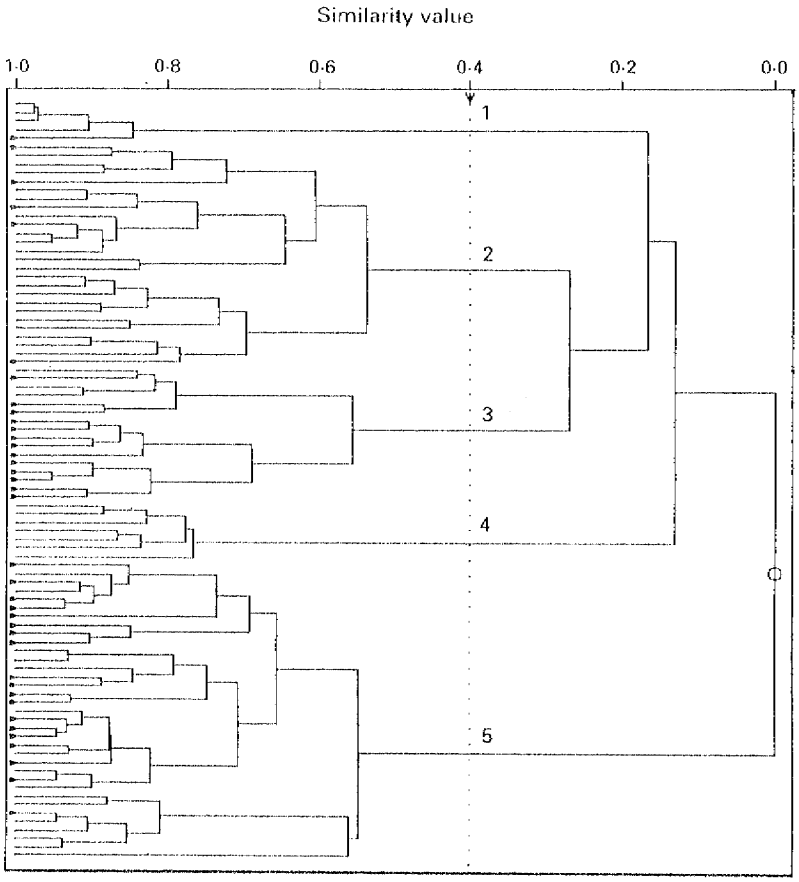

Figure 1 Hierarchical cluster analysis dendrogram of normalised alveolar breath data using the incremental link method. Five branches are defined at a similarity value of 0·40 and are numbered on the dendrogram starting at the top. Normal cases are highlighted by black squares attached to the branch end at similarity 1·0. Normals are more heavily distributed on branch 3 and portions of branch 5.

PATTERN RECOGNITION ANALYSIS OF DATA

Multivariate pattern recognition data analysis was performed using the Pirouette software system (Infometrix). Volatile organic compound concentrations in alveolar breath and background air were analysed separately. Hierarchical clustering associations were investigated among subjects in the same group, using complete link, single link, and incremental link methods. Scatter plots of the case scores for several principal components were examined for indications of structure (group associations) and outliers (highly distinct cases). Classification accuracies and diagnostics for predicting each case against its known health/disease status were assessed using K-Nearest Neighbor (KNN) and Soft Independent Modeling of Class Analogy (SIMCA) methods.[11 12]

VALIDATION OF PATTERN RECOGNITION ANALYSIS

The validity of the multivariate model was tested by evaluating its predictive capability for cases not included in the development of the model. The KNN results, listed above, were calculated in a "leave one out" method, where each sample was classified according to the neighbour votes of all the remaining samples. The SIMCA models were tested with a one third:two thirds cross validation method, where the models were retrained three times, each time leaving out one third of the cases and using the remaining two thirds for model development. The models were then applied to the excluded one third to judge prospective classification capability.

Results

HUMAN SUBJECTS

Breath samples were obtained from all subjects without any adverse effects. Multiple correlation tests did not show any statistically significant differences between the three groups in the distribution of age, sex, tobacco use, or race, nor was there any significant difference in the use of neuroleptic drugs between the patients with schizophrenia and the psychiatric controls.[10]

PATTERN RECOGNITION ANALYSIS OF VOLATILE ORGANIC COMPOUNDS

Multivariate data analysis provided three separate indications that the patterns of breath volatiles were distinctly different in patients with schizophrenia. Cluster analysis showed an imbalanced distribution on the dendrogram branches, while both a 2-D principal component scatter plot and a SIMCA category classification model separated most of the patients with schizophrenia from the other subjects. In contrast, results from the analysis of inspired air did not show an imbalance or differentiation between the three groups, indicating that the experimental design did not introduce artefacts arising from differences in environmental air exposure.

Table 1 Hierarchical cluster analysis branch case distribution. Group percentages in parentheses

	Normals	*Psychiatric controls*	*Schizophrenia patients*
Branch 1 (n=5)	1 (20%)	1 (20%)	3 (60%)
Branch 2 (n=28)	9 (32%)	11 (39%)	8 (29%)
Branch 3 (n=11)	8 (73%)	1 (9%)	2 (18%)
Branch 4 (n=7)	0 (0%)	4 (57%)	3 (43%)
Branch 5 (n=37)	19 (51%)	9 (24%)	9 (24%)
Total cases	38	26	25

Hierarchical cluster analysis—The dendrogram (fig 1) is cut into five branches by a dotted vertical line at similarity value 0.40. Normal subjects are highlighted by a square attached to the end of the subject's individual branch below the similarity value of 1.0. The distribution of normals and patients with schizophrenia was highly imbalanced: normals were more heavily distributed on branch 3 and portions of branches 2 and 5 (branches numbered at the cut from the top) while the patients with schizophrenia were more heavily distributed on branches 1, 2, and 4. The distribution of cases is detailed in table 1.

2-D principal component (pc) scatter plot—A scatter plot of the case scores for pc4 *v* pc2 is shown in fig 2. A hand drawn discriminant line in the plot separated 39/63 of non-schizophrenic patients from 20/25 of patients with schizophrenia (that is, sensitivity = 80·0%; specificity = 61·9%). The variables which contributed most influentially to the two principal components are shown in table 2, with their loading coefficients.

Category classification—The discriminating separation between subjects with and without schizophrenia (fig 2) was substantiated by the complementary approach of group differentiation using the two methods in Pirouette, KNN, and SIMCA. SIMCA results yielded

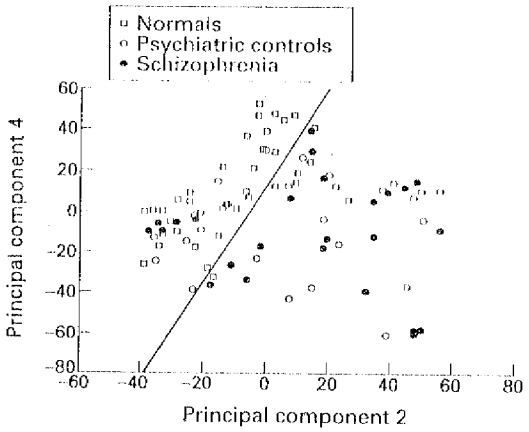

Figure 2 Alveolar breath data: principal component analysis. The scores for PC axis 4 are shown plotted versus PC axis 2. A discriminant function corresponding to the diagonal line would distinguish patients with schizophrenia with a sensitivity of 80·0% and a specificity of 61·9%.

the best separation. Using all of the 46 volatile organic compounds, SIMCA yielded a sensitivity of 40% and a specificity of 97%. When 11 compounds were used, chosen from the highest contributors to principal components in fig 2 and SIMCA models, sensitivity increased to 68·0% (17/25), while specificity decreased to 84·1% (53/63). These 11 compounds are shown in table 2 with their SIMCA modelling power coefficients and principal components loading.

Discussion

Microanalysis of the volatile organic compounds in alveolar breath combined with pattern recognition analysis identified patients with schizophrenia with a sensitivity of 80·0% and a specificity of 61·9%. Since, as Leff has observed, "The history of research into schizophrenia is replete with 'breakthroughs' which have later turned out to be illusory",[15] these findings merit sceptical scrutiny for possible sources of error.

Did all of the subjects designated as patients with schizophrenia really suffer from the dis-

Table 2 SIMCA modelling power and loadings for volatile organic compounds in alveolar breath and inspired air

Volatile organic compound		*SIMCA modelling power*			*Loading*			
		Class 1	*Class 2*	*Class 3*	*PC1*	*PC2*	*PC3*	*PC4*
2-Methylbutane	B				0·1979	0·1913	0·4152	−0·1037
	A				0·2380	0·2529	0·4082	−0·1507
Trichlorofluoromethane	B		0·834					
	A							
2-Pentanol	B	0·775	0·891	0·955	0·2637	0·5044	−0·4552	−0·6478
	A				0·2707	−0·9106	0·2356	
Pentane	B		0·754	0·761	0·1704	0·4997	0·4400	0·1378
	A						0·2154	0·2236
Dichloromethane	B				0·1294		0·2000	
	A				0·2218		−0·2011	0·4422
Trichloroethene	B	0·928		0·804	0·2028		0·1904	0·4729
	A				0·3930		−0·3851	0·2753
Benzene	B	0·819	0·782	0·708	0·4049		−0·5607	
	A				0·2800			0·1411
1-Chloro-2-methylbutane	B	0·743			0·2855	0·1651		0·2363
	A				0·5636	0·5073	0·2554	0·3911
2,3,3-Trimethylpentane	B	0·919	0·910	0·934	0·5874	0·1369	0·2084	0·6185
	A				0·1793			
2,2-Dimethylbutane	B		0·724		0·2283		−0·3617	
	A				0·3424		−0·1937	0·2898
Tetrachloroethene	B	0·710			0·3217		−0·2739	0·2274
	A							

Class 1 = normal; class 2 = psychiatric controls; class 3 = schizophrenic.

case? All had been admitted to the hospital with an episode consistent with an acute exacerbation of schizophrenia, and had previously been diagnosed as suffering from schizophrenia according to DSM-III-R criteria. These stringent criteria include continuous signs of the disturbance for at least six months. It is unlikely that any patients not suffering from schizophrenia could have been included in this group in error. It is equally unlikely that any of the normals or the psychiatric controls were suffering from schizophrenia.

Could the findings have been skewed by other factors, such as treatment with neuroleptic drugs? All of the patients with schizophrenia had been treated with neuroleptic drugs, unlike approximately half of the psychiatric controls and none of the normals. However, drug therapy did not appear to have skewed the composition of breath volatile organic compounds since pattern recognition analysis did not separate the psychiatric controls who had received neuroleptics from either the untreated psychiatric controls or the normal subjects. Other possible confounding variables such as age, sex, race, and cigarette smoking showed no statistically significant differences between the three groups.[10]

Could the separation observed with pattern recognition analysis have arisen from overfitting the data, some of which may have arisen from instrumental measurement error and random noise? A potential hazard of multivariate modelling is the tendency to overfit the category classifications by using too many variables or principal components in the models. This may introduce apparent differences between the classes, which are in fact due to random noise. However, the results of validation testing suggest that this did not occur: the principal component models using two to three components retained predictive capability, and their predictive performance only began to be degraded when more than five principal components were used. In addition, three philosophically different mathematical methods separated the patients with schizophrenia from the other subjects, supporting the conclusion that these differences were real rather than artefactual.

What physiological abnormalities might have accounted for the distinctive pattern of volatile organic compounds in the breath of the patients with schizophrenia? Among the most influential compounds listed in table 2, pentane has previously been observed in increased amounts in the breath of patients with schizophrenia,[8 10] possibly because of an accumulation of oxygen free radicals causing accelerated peroxidation of membrane lipids.[16] The compounds listed in table 2 may indicate derangements in other biochemical pathways, but their source is still unknown.

Could these findings account for the unusual smell of patients with schizophrenia, which prompted these studies in the first place? Again, the answer is not yet known, though the question suggests a future research study designed to compare the odour of patients with schizophrenia to the odour of a synthetic mixture of the compounds listed in table 2.

Was the full range of biochemical variation in all three groups adequately represented in this study? Only 25 patients with schizophrenia were studied, so it is possible that we failed to observe subcategories of schizophrenia with different biochemical profiles. This has important inferences for pattern recognition analysis, since SIMCA classification accuracy would most probably improve if schizophrenia were modelled by more than one class of biochemical variant.

We conclude that microanalysis of volatile organic compounds in alveolar breath, combined with pattern recognition analysis, appeared to distinguish patients with schizophrenia from non-schizophrenic controls. Further studies are required to validate these findings and to optimise breath testing methodology. With improved sensitivity and specificity, microanalysis of volatile organic compounds in the breath might offer a new approach to the detection of schizophrenia and better understanding of the metabolic basis of the disease.

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HBV is developing new strategies to counter the effects of vaccination and of antiviral therapy, with mutations in the genome, usually in the precore or pre-S regions. The precore-defective HBV can be spread in a family. Multiple deletions in the pre-S1 region may contribute to viral persistence. About 50% of patients with chronic HBV infection treated with interferon will lose the "e" antigen (HBeAg), a marker of infection. In 16%, 4–7 months after cessation of treatment, the surface antigen will also be lost. These results are similar to those recorded for spontaneous loss of HBseAg and HBsAg—ie, without the benefit of antiviral therapy. Reactivation of infection is similar in the two groups. Hepatic histological improvement is also usual irrespective of whether the infection is treated with interferon or allowed to run a natural course. An analysis of 372 liver transplants carried out for end-stage HBV infection between 1977 and 1990 in nineteen European centres showed 1-year survival of 75% and the 3-year survival of 63%. The 3-year HBV recurrence rate was 50%, increasing to 83% in those who were HBV DNA positive. Recurrence was less in those coinfected with hepatitis delta virus, probably because delta suppresses HBV. Long-term anti-HBs immunoprophylaxis reduced the HBV recurrence from 75% to 36%, but this therapy would bankrupt many hospital pharmacies. 20% of patients with acute viral hepatitis in Barcelona gave negative serological tests for viruses A, B, C, D, and E. Another virus is believed responsible. The disease tended to be benign and resolve uneventfully.

The slow granulomatous destruction of intrahepatic bile-ducts in primary biliary cirrhosis (PBC) is believed to be related to environmental factors operating in an immunogenetically susceptible host. The fact that mycobacteria can cause granulomas and initiate autoimmunity encouraged the Barcelona group to screen PBC sera for the presence of antibodies to ten atypical mycobacteria. All the PBC sera, but none of the controls, reacted with a protein extract from *Mycobacterium gordonae*, a saprophytic organism. Furthermore, the eluted immunoglobulins from *M gordonae* recognised the mitochondrial (M2) complex characteristic of PBC sera. Preliminary results with polymerase chain reaction have shown that *M gordonae* is present in the liver of PBC patients. Time will tell whether this organism has an aetiological role in PBC or whether this is simply another example of molecular mimicry.

About a quarter of patients with cirrhosis will bleed from oesophageal varices as the result of portal hypertension, 70% during the first 2 years of observation and 25% during the first 6 months. Prediction of the likelihood of bleeding would allow more intensive preventive measures. Doppler ultrasound can be used to measure portal vein calibre, portal flow velocity, and portal flow volume, and these measurements allow the calculation of a congestive index of the portal vein (ratio between vessel section area and flow velocity). Inclusion of this index with variceal size, the appearance of cherry red spots on varices seen with the endoscope, and the serum bilirubin concentration, leads to formulation of a prognostic index which identifies a high proportion of cirrhotic patients who will bleed within 6 months. Serial evaluations may allow the identification of cirrhotic patients who go on to have late variceal bleeding. Transjugular intrahepatic portosystemic stent shunting (TIPPS) is being increasingly used to control intractable bleeding from oesophageal varices, and is especially useful as a preliminary to transplantation. However, TIPPS may worsen the hyperkinetic circulatory state of cirrhosis, and even cause death from cardiac failure. TIPPS controls intractable ascites: urinary sodium excretion increases; plasma renin and aldosterone and catecholamine concentrations fall; but glomerular filtration is unchanged. These results are similar to those reported for a surgical side-to-side portacaval shunt or for a Le Veen peritoncovenous shunt. Post-TIPPS encephalopathy is seen in 20% of patients, more often in the elderly, in those with previous significant encephalopathy, and in those with severe liver disease. These figures resemble those reported after surgical side-to-side portacaval anastomosis. The advantage of TIPPS over surgical shunts is the possibility of controlling the size of the shunt in patients thought to be at high risk of encephalopathy.

European hepatologists will surely be kept busy for a few decades yet—until education controls alcoholism, hepatitis B vaccination eliminates hepatitis B, and clean syringes and blood donor screening reduce, if not eliminate, hepatitis C infection.

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Schizophrenia and the gut, again

In schizophrenia, a disorder with both mental and motor symptoms, no consistent physical abnormality has been found that can distinguish patients from normal individuals. This failure is not due to lack of effort or imagination—there have been so many false dawns that psychiatrists now greet every newly reported metabolic quirk or anatomical anomaly with seasoned scepticism. Ranging from the anthropometric claim that patients with schizophrenia can be distinguished by a leptosomatic habitus[1] to the pink spots seen on urine chromatography (and the spiders who abandoned their normally ordered web spinning when given such urine),[2] every abnormality has proved either to be unrepeatable or to be a consequence of differences in diet, life style, or medication. A report of increased pentane and carbon disulphide (CS_2) concentrations in the breath of patients with schizophrenia[3] will thus be received with only cautious enthusiasm.

Alkanes, such as ethane and pentane, in the breath may originate from sites of cellular injury when oxygen free radicals peroxidate membrane lipids,[4] and are raised in inflammatory conditions such as rheumatoid arthritis[5] and acute myocardial infarction.[6] Acute exposure to high concentrations of CS_2 can cause psychosis,[7] possibly through interference with dopamine β-hydroxylase.[3] Phillips et al[3] sampled alveolar breath from 37 volunteer doctors and nurses, 26 psychiatric inpatients with diagnoses other than schizophrenia, and 25 schizophrenic inpatients with recent psychotic exacerbations . Sampling took place over 5 min while the subjects inhaled chemically purified air. Concentrations of volatile organic compounds were assayed by gas chromatography/mass spectroscopy. Alveolar gradients (concentration in alveolar air minus concentration in inspired air) for pentane, CS_2, benzene, 2-methylbutane, and tetrachloroethene were significantly greater in schizophrenics than in non-psychiatric controls, an apparent replication of earlier findings by a different research group.[8] This time, however, only CS_2 was higher in schizophrenics than in psychiatric controls.[3]

Surprisingly, neither smoking nor neuroleptic medication affected CS_2 concentrations, and the most likely source of raised concentrations in the breath of schizophrenics is thought to be the metabolic activity of large-bowel flora. This is not the first time that the attention of schizophrenia researchers has been directed towards the gut. Intriguing reports of abnormalities in small-intestinal permeability,[9] which, it has been claimed, might facilitate the passage of postulated behaviour-changing exorphins, have not proved to be generally repeatable.[10]

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Oral cancer: necessity for prevention strategies

Oral cancer is one of the ten most frequent cancers world wide, with an estimated 378 500 new cases diagnosed in 1980.[1] Three-quarters of these cases arose in developing countries, where it is the third most common form of cancer after stomach and cervix. In Sri Lanka, India, Pakistan, and Bangladesh oral cancer outnumbers other cancers; in parts of India oral cancer represents over 50% of all cancers.[2] In the developed world, oral cancer ranks eighth, although the ranking varies between countries—eg, in France, oral cancer is the third most frequent form of cancer in men (after lung and prostate) and the second commonest form of cancer death (after lung).[3] Among member states of the European Community there are an estimated 32 000 new cases diagnosed annually,[3] and the proportion of deaths attributable to oral cancer in males varies from 1% in the Netherlands to 9% in France. In women the rates are about one-fifth of those in men. Mortality rates declined substantially during the earlier part of this century—eg, a ten-fold decline from mouth cancer and tongue cancer this century in England and Wales.[4]

However, there is now worrying information about recent trends. Tongue cancer incidence seems to be increasing in the USA[5] and in Scotland,[6] where cancer in the rest of the mouth is likewise increasing.[7] Pronounced upward trends in mouth cancer in younger birth cohorts of men are emerging in many European countries.[8] In the age range 35–64, mortality rates increased in Austria (from 4·1 per 100 000 in 1955–59 to 13·4 per 100 000 in 1985–89), Belgium (3·8 to 6·6), France (13·4 to 32·3), (the former Federal republic of) Germany (2·2 to 14·0), Italy (7·0 to 12·2), Poland (3·4 to 11·8), Spain (3·4 to 11·5), and Hungary (4·9 to 28·2). Only in Scandinavian countries have mortality rates not increased.[8]

What are the risk factors for oral cancer? Tobacco and alcohol are well known. Consumption of fruits and vegetables seems to be protective and experimental studies indicate that vitamins A and E may protect.[9]

It should be possible to prevent up to 75% of all cases of oral cancer in western countries (smoking cessation, moderation of alcohol consumption, and increased consumption of fruit and vegetables) and in developing countries (cessation of tobacco smoking and betel quid chewing and more fruits and vegetables), although it is increasingly likely that alcohol is a risk factor in developing countries too. However, the upward trends in young men in Europe run counter to our understanding of risk factors and clearly indicate the need for further research.

Doctors, dentists, and pharmacists should be targeted with information about early oral lesions and the importance of seeking a specialist opinion. Chemoprevention may be possible in patients with leukoplakia or other lesions that indicate that the individual is at high risk. Retinoids such as 13-*cis*-retinoic acid (isotretinoin) and fenretinide, and carotenoids such as beta-carotene can suppress oral leukoplakias.[9] Isotretinoin can also inhibit the development of oral carcinoma[10] and second primary tumours.[11] However, most retinoids have adverse effects, especially on liver and teratogenicity. Education remains an important way to help in primary prevention: when a person stops smoking, the risk of oral cancer drops to that of a lifelong non-smoker after 5–10 years.

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