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Patients Compliance in an Early Detection Program for Upper Aero-Digestive Tract Tumours in North-Eastern Italy

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In Italy, the only epidemiologic data available for tumours of the upper aero-digestive tract (i e lip, oral cavity, pharynx and larynx) are mortality rates [1,2,3]. These mortality rates show that such tumours have been steadily increasing in recent years [1,3], especially in the younger age groups (< 65 years). Tumours of the upper aero-digestive tract have as primary risk factors, cigarette, pipe and cigar smoking, and heavy consumption of alcohol [4,5,6,7,8]. The effects of these risk factors combine in a multiplicative way, with a high relative risk (RR=35) [4,5] seen in those who smoke more than two packs of cigarettes per day and drink more than four glasses of alcoholic beverages per day.

In Northeastern Italy, the Friuli-Venezia Giulia Region shows mortality rates for upper aero-digestive tract tumours that are consistently higher than the rest of Italy for both males and females [2]. During the period from 1980 to 1983, tumours of the oral cavity in this region resulted in a number of deaths 2.3 times greater than the expected number for the country as a whole. In particular, laryngeal tumours were responsible for a number of deaths 36% greater than expected. Moreover, tumours of the oral cavity, while ranking fifth in the percentage of deaths attributable to individual tumours, are second only to lung cancer in terms of years of productive life lost (> 65 years), an important indicator of premature death [2]. These descriptive epidemiologic data correlate with population data on alcohol and cigarette consumption, for which the Friuli-Venezia Giulia ranks highest among all the Italian regions [9].

To date, only a few studies [5,7,10,11,12] have been conducted to evaluate the efficacy of screening programs for tumours of the aero-digestive tract, thus making it difficult to quantify with certainty their role in reducing associated mortality rates. As has also been evidenced in cytologic screening for tumours of the uterine cervix, screening for tumours of the upper aero-digestive tract has been rendered difficult by the socioeconomic gradient of these tumours. That is, the occurrence of these tumours is concentrated in the lower social classes and in older age groups, among whom the compliance with programs for screening or early diagnosis is usually low. The public health impact in terms of mortality and years of productive life lost, that upper aero-digestive tract tumours,and above all, tumours of the oral cavity, have had in the Friuli-Venezia Giulia region has led to this study for secondary prevention. This program was based on individual invitation to asymptomatic patients, but used a "targeted" approach for a group of subjects at elevated risk for upper aero-digestive tract tumours who were identified a priori by means of eliciting their histories of tobacco and alcohol consumption.

Materials and Methods

From December 1, 1988 to May 31, 1989, patients seen consecutively by 16 General Practitioners (GPs) in Aviano and surrounding villages located in the Friuli-Venezia Giulia region were considered for inclusion in the study. Smoking and drinking habits of each patient were investigated and an educational message was delivered aiming to make the patient aware of:

- the wide range of diseases caused by any level of tobacco smoking, including Ear, Nose and Throat (ENT) disorders and
- the health hazards of chronic levels of alcohol consumption which, however heavy, tend to be considered acceptable in the context of North-East Italy.

Only those who reported risk factors for tumours of the upper aero-digestive tract, i e any consumption of tobacco and/or consumption of more than four glasses of wine per day, were invited for a free check-up by an ENT specialist at the Cancer Referral Center (CRO) in Aviano. The CRO was utilized not only because it is a well-known center specializing in diagnosis and treatment of neoplasms, but also because of its location in the middle of the study area. This allowed us to minimize selection problems due to the distance and inaccessibility of a center for secondary referral, an important consideration especially for older or less motivated patients. The ENT visits were performed by the same two specialists (L B and G C) from

December 1, 1988 to June 30, 1989, with cross-validated diagnoses, i e half of the patients seen by one ENT specialist were randomly re-seen by the other and viceversa. The ENT examination consisted of a classical routine visit, i e rhinoscopy, indirect laryngoscopy and in many cases direct laryngoscopy with flexible endoscopes. A cytological smear was collected only for those patients with chronic inflammatory lesions while a multiple biopsy was performed in all precancerous and cancerous lesions. All pathological specimens were analysed by the same pathologist (A C) for the entire study period. The specialists' diagnoses were subsequently recoded into five categories:

- negative findings;
- chronic inflammatory processes;
- benign neoplasms (nodules, polyps, papillomas, angiomas, and cysts);
- precancerous lesions (leucoplakia, eritroplakia, eritroleucoplakia); and
- malignant neoplasms.

Although some data had been gathered initially by the GPs, in order to be complete and uniform, the demographic data for each patient and the presence of ENT symptoms were collected again during the visit with the specialist, who further elicited the amount of cigarettes smoked and alcohol consumed by the patient. Only the data from the ENT visits were used in the analyses. Ex-smokers and ex-drinkers were defined as individuals who had quit smoking or drinking for at least one year before the ENT visit. The consumption of alcoholic beverages (wine, beer and spirits) was translated into a number of glasses of wine per day by calculating the equivalent grams of alcohol [13].

Tab. 1. Distribution of 671 patients according to sex and response to the invitation from the GP for a free ENT visit

	Ear, nose and throat visit				total	(%)
	completed	(%)	not completed	(%)		
Males	290	(63.7)	165	(36.3)	455	(67.8)
Females	146	(67.6)	70	(32.4)	216	(32.2)

Results

During the study period, 671 high risk patients were consecutively seen by the 16 GPs and were invited for the free ENT check-up. Among these, 436 patients responded to the invitation (65%) (Table 1). The number of males responding was 290 out of 455, which constituted a response rate of 64% among males, whereas 146 out of 216 females responded at a rate of 68%.

The analysis of the 436 patients who completed the ENT visit (Table 2) showed a mean age of 53 years for males, and of 49 years for females. The percentage of respondents was highest in the 56–65 year age group for males (26%), and in the 36–45 year age group for females (23%).

Tab. 2. Response to the invitation for a free ENT visit according to sex and age

Age	Males	(%)	Females	(%)
≤ 35 years	46/79	(58.2)	30/53	(56.6)
36–45	47/87	(54.0)	34/51	(66.7)
46–55	65/109	(59.6)	33/47	(70.2)
56–65	76/101	(75.2)	26/34	(76.5)
> 65	56/79	(70.9)	23/31	(74.2)
Total	290/455	(63.7)	146/216	(67.6)

The analysis by age and sex of the 235 patients who did not make the ENT visit showed that the highest percentage of non-respondents came from the 46–55 year age group (27%) for males, and from the ≤ 35 year age group (33%) for females. The mean age for the non-respondents was 47 years for males and 42 years for females.

Analyzing the respondent sample with respect to cigarette smoking and alcohol consumption (Table 3), only 0.7% of males reported being neither habitual smokers nor drinkers; on the other hand, the percentage of those who drink six or more glasses of wine per day and smoke more than 20 cigarettes per day was substantial (13%). Among females, 16% reported a history of no cigarette or alcohol consumption, and only 5.5% reported smoking more than 20 cigarettes per day and drinking six or more glasses of wine per day. It is worth noting that only two males who were not at risk according to our criteria, were nevertheless seen by the ENT specialist, probably because of presence of symptoms. Among 24 females who were not at risk according to our criteria, two showed evidence of clinical symptoms and 22 were asymptomatic (results not shown). This may have occurred because of different information being provided to the GPs and ENT specialists by these patients. Diagnostic ENT outcomes for the 436 visits showed (Table 4) that chronic inflammatory processes were a very frequent finding (54% of the total), in both sexes and in all age groups. Among non-smokers, the ENT visit resulted most often in a negative finding (29%), while in smokers of more than 20 cigarettes per day a negative finding was seen in only 14%. A diagnosis of a precancerous lesion was made in about 17% of current smokers, but only in about 5% of non-smokers or ex-smokers.

Regarding alcohol habits, non-drinkers showed a negative finding most frequently (27%), compared to 16% for drinkers of six or more glasses of wine per day. It is interesting to note that while there are no notable differences between smokers and non-smokers and between drinkers and non-drinkers as regards the frequency of chronic inflammatory processes, there was an evident excess of precancerous lesions in current smokers and habitual drinkers compared to non-

smokers and non-drinkers, respectively. This difference was also seen in the comparison between sexes: males, who constituted the vast majority of current smokers and/or habitual drinkers in this sample, showed an elevated frequency of precancerous lesions (16%) compared to females (6%), while there was no appreciable difference in the frequency of chronic inflammatory processes between males and females.

Examining the presence of clinical symptoms reported at the ENT visit, it should be noted that chronic inflammatory processes were more frequently reported as symptomatic (57%), while precancerous lesions were much less frequently symptomatic (20%). The 55 precancerous lesions arose in about 75% of the cases in the oral cavity (cheek, trigone, tonsil, tongue) and in about 25% of the cases in the larynx (supraglot-

Tab. 3. Distribution of 436 patients who completed the ENT visit according to tobacco and alcohol consumption

Consumption of alcohol	No	(%)[a]	Tobacco consumption					
			Ex smokers	(%)[a]	Smokers			
					< 20 Cig	(%)[a]	≥ 20 Cig	(%)[a]
Males								
No	2	(0.7)	10	(3.4)	11	(3.8)	8	(2.8)
< 6 glasses	22	(7.6)	37	(12.8)	45	(15.5)	41	(14.1)
≥ 6 glasses	13	(4.5)	35	(12.1)	28	(9.7)	38	(13.1)
Females								
No	24	(16.4)	4	(2.7)	21	(14.4)	12	(8.2)
< 6 glasses	14	(9.5)	8	(5.5)	28	(19.2)	17	(11.6)
≥ 6 glasses	4	(2.7)	2	(1.4)	4	(2.7)	8	(5.5)

[a] Percentage of the total (M = 290; F = 146).

Tab. 4. Distribution of 436 patients who completed the ENT visit according to diagnostic outcome and various other characteristics

	ENT visit diagnostic outcome									
	Negative findings	(%)	Inflammatory lesions	(%)	Benign neoplasms	(%)	Precancerous lesions	(%)	Malignant neoplasms	(%)
Sex[a]										
Males	62	(21.4)	157	(54.1)	16	(5.5)	46	(15.9)	9	(3.1)
Females	41	(28.1)	79	(54.1)	16	(11.0)	9	(6.2)	1	(0.7)
Age										
≤ 35	19	(25.0)	44	(57.9)	6	(7.9)	7	(9.2)	–	
36–45	14	(17.3)	49	(60.5)	9	(11.1)	8	(9.9)	1	(1.2)
46–55	22	(22.4)	54	(55.1)	6	(6.1)	14	(14.3)	2	(2.0)
56–65	28	(27.5)	49	(48.0)	5	(4.9)	15	(14.7)	5	(4.9)
> 65	20	(25.3)	40	(50.6)	6	(7.6)	11	(13.9)	2	(2.5)
Smoking status										
Non smokers	23	(29.1)	43	(54.4)	7	(8.9)	4	(5.1)	2	(2.5)
Ex smokers	25	(26.0)	54	(56.3)	8	(8.3)	6	(6.3)	3	(3.1)
Smokers:										
< 20 cig	37	(27.0)	64	(46.7)	11	(8.0)	22	(16.1)	3	(2.2)
≥ 20 cig	18	(14.5)	75	(60.5)	6	(4.8)	23	(18.5)	2	(1.6)
Alcohol consumption[b]										
Non drinkers	25	(27.2)	52	(56.5)	9	(9.8)	6	(6.5)	–	
Drinkers:										
< 6 glass	55	(26.3)	105	(50.2)	18	(8.6)	27	(12.9)	4	(1.9)
≥ 6 glass	18	(16.2)	66	(59.5)	4	(3.4)	17	(15.3)	6	(5.4)
Symptoms at the ENT visit[a]										
No	85	(35.1)	102	(42.1)	7	(2.9)	44	(18.2)	4	(1.7)
Yes	18	(9.3)	134	(69.1)	25	(12.9)	11	(5.7)	6	(3.1)
Total	103	(23.6)	236	(54.1)	32	(7.3)	55	(12.6)	10	(2.3)

All percentages are of row total.
[a] Significant χ^2 for heterogeneity, $p < 0.01$
[b] Significant χ^2 for heterogeneity, $p < 0.05$

Tab. 5. Characteristics of the ten patients for whom a malignant neoplasm was nosed because of the ENT visit

Initials of the pts.	Diagnosis	Sex	Age	No smoke	Cig/day	No alcohol	Glass/day	Clinical symptoms	Stage
Z.P.	Lymphoma	M	61	Ex	30	Yes	2	Yes	
R.M.	Ca. ventricular fold	M	44	Yes	10	Yes	8	Yes	I
D.S.E.	Ca. vocal cord	M	66	Yes	25	Yes	6	Yes	I
R.L.	Ca. upper lip	M	75	Yes	6	Yes	2	No	I
M.L.	Ca. ari-epigl. fold	M	54	Ex	20	Yes	8	Yes	II
D.L.A.	Ca. vocal cord	M	64	Yes	10	Yes	4	No	I
P.F.A.	Ca. vocal cord	M	56	No	-	Yes	8	No	I
P.A.	Ca. vocal cord	M	59	Ex	20	Yes	8	Yes	II
C.G.	Plasmacytoma	F	56	No	-	Yes	7	Yes	
T.F.	Ca. tongue	M	49	Yes	25	Yes	4	No	I

tis, but more frequently glottis). The number of malignant neoplasms diagnosed were too few to be analysed in detail. In Table 5 the characteristics of the ten patients who were diagnosed with a malignant neoplasm are reported. Vocal cord carcinoma constitutes half of the epithelial tumours diagnosed (4/8), and, surprisingly, two of them were ENT manifestations of haematological tumours. Of the eight ENT tumours, six were diagnosed in clinical stage I and two in stage II.

Discussion

This study has been prompted by the high mortality rates and by the great social impact of premature mortality that tumours of the upper aero-digestive tract demonstrate in the Friuli-Venezia Giulia region, where consumption of tobacco and alcohol is elevated and widespread. Although this study can not obviously prove the efficacy of a screening program for tumours of the upper aero-digestive tract, for which a randomized controlled study would be necessary, it offers many indications of the possibility for conducting joint initiatives for secondary prevention between GPs and ENT specialists, at least in high risk areas and populations. The study also provides information about the compliance obtainable within a population for such initiatives. Regarding the first point, the study has been conducted with the full collaboration between the 16 GPs and the ENT Division of the Pordenone General Hospital at greatly reduced costs, thus providing encouragement for a subsequent study of greater scope involving about 40 GPs. As regards the second point, that is, the efficacy of the program, it is advantageous that compliance was higher in older subjects (> 55 years) than in younger subjects, even if this could be due to non-medical reasons (e g fewer work demands). In this study, only few resources were used for younger and low risk patients, this contrasting with other programs, such as those for tumours of the uterine cervix in which young women at relatively low risk presented voluntarily, thus absorbing a great part of the available resources.

While the "contamination" by younger subjects has not been serious, there has instead been a larger proportion of females, traditionally more attentive to health related problems, who participated in the study even without evidence of any risk factors. This problem reduced slightly the estimated efficacy of the study among females (10 precancerous lesions and malignant tumours diagnosed among 146 ENT visits in all females (6.8%) versus 10 among 124 high risk females (8.1%)). Possible solutions are to improve, above all, the referral mechanisms for subjects at risk from the GPs to the ENT specialist and to increase the threshold criteria used for inclusion in the screening program, i e cigarette and alcohol consumption, and age.

Besides the importance of this study in clinical terms, i e the reduction in serious diagnostic delays that are still often seen for this pathology, with respect to the efficacy of ENT screening in early diagnosis this study is limited by its relatively small sample size as a preventive intervention. However, in terms of prevention, this study has detected early lesions, not necessarily malignant but also inflammatory, which could serve as a warning signal for the patient and, thereby, provide an educational message about reducing or eliminating high risk behaviours such as tobacco and heavy alcohol consumption.

In conclusion, the feasibility of a program for early detection of oro/pharyngeal and laryngeal cancers was demonstrated in our study by the excellent cooperation which occurred between GPs and ENT specialists and, secondly, by the high response rate which was observed in the targeted population. Furthermore, this study resulted in the diagnosis of epithelial tumours at an early stage before their detection by the patient, and therefore amenable to less invasive surgical excision with minimal post-treatment morbidity. This, along with the high percentage of precancerous lesions identified, suggests that this study has been efficacious. A replication of this program on a larger scale would test its effectiveness, at least in a high risk area such as the Friuli-Venezia Giulia region which shows high mortality rates for these cancer sites.

Summary
An early detection program for tumours of the upper respiratory and digestive tract has been conducted from December, 1988 to May, 1989 in the Friuli Venezia-Giulia region, Northeastern Italy. This region shows very high mortality rates for cancers in these sites. Six hundred seventy-one high risk patients (i e habitual smokers and/or drinkers) were referred to Ear, Nose and Throat (ENT) specialists from 16 General Practitioners (GPs) for a free examination as part of the screening program. Four hundred thirty-six patients underwent the visit (65%) with fifty-five precancerous lesions and eight epithelial tumours detected among them. This program appears to have accomplished its aims of establishing a closer relationship between GPs and ENT specialists, discovering early cancerous and precancerous lesions, and targeting high risk patients with an educational message against smoking and heavy drinking.

Résumé
Analyse de la participation dans un programme de détection précoce des cancers des voies aéro-digestives respiratoires en Italie du Nord
Une étude pilote de dépistage a été conduite dans la région Friuli-Venezia Giulia, dans le Nord-Est d'Italie, depuis décembre 1988 jusqu'en mars 1989 concernant les cancers de l'appareil respiratoire et digestif supérieur. Ces régions montrent un taux très élevé de mortalité par les cancers. 671 patients à haut risque (fumeurs et/ou buveurs) ont été adressés aux spécialistes ORL pour une consultation gratuite de dépistage.

Zusammenfassung
Analyse der Beteiligung an einem Früherkennungsprogramm von Karzinomen der oberen Atem- und Verdauungswege in Nordost-Italien
Von Dezember 1988 bis Mai 1989 wurde in der Region Friaul-Venedig-Giulia in Nordost-Italien eine Pilotstudie zur Früherkennung von Tumoren des oberen Respirations- und Verdauungstraktes durchgeführt. Die Region ist gekennzeichnet durch sehr hohe Karzinom-Mortalitätsziffern dieser Lokalisationen. 671 Hochrisikopatienten (d h regelmässige Raucher und/oder Trinker) wurden von 16 Allgemeinpraktikern an Hals-Nasen-Ohren-Spezialisten zur kostenlosen Vorsorgeuntersuchung überwiesen. Bei den 436 Patienten, welche an der Untersuchung teilnahmen, wurden 55 präkanzeröse Läsionen und acht Epitheltumoren entdeckt.
Die Pilotstudie scheint das Ziel erreicht zu haben, die Beziehung zwischen Allgemeinpraktikern und Hals-Nasen-Ohren-Spezialisten zu verbessern, frühe kanzeröse und präkanzeröse Veränderungen zu entdecken und die Hochrisikopatienten über die gesundheitlichen Risiken von Rauchen und Trinken aufzuklären.

References

[1] *De Carli A, La Vecchia C.* Cancer mortality in Italy, 1981. Tumori 1987; *73:* 321–330.
[2] *Franceschi S, Bidoli E, Barra S, Gerdol D, Serraino D, Talamini R.* Atlante della mortalità per tumori nella Regione Friuli Venezia-Giulia, 1980–83. Aviano: Centro di Riferimento Oncologico, 1989.
[3] *La Vecchia C, De Carli A.* Trends in cancer mortality in Italy, 1955–1978. Tumori 1985; *71:* 201–218.
[4] *Blot W J, McLaughlin J K, Winn D M* et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res 1988; *48:* 3282–7.
[5] *McLaughlin J K, Gridley G, Block G* et al. Dietary factors in oral and pharyngeal cancer. JNCI 1988; *80:* 1237–43.
[6] *Ono I.* Mass screening for laryngeal cancer. Second report: incidence of laryngeal cancer in high risk groups. Nippon J Gakkai K 1982; *85:* 1494–1497.
[7] *Pindborg J J.* Oral cancer and precancer. Bristol: Wright J, 1980.
[8] *Steiner W.* Mass screening and early diagnosis of cancer of the upper aero-digestive tract. Acta Otorhinolaryngol Ital 1985; *5:* 35–39.
[9] ISTAT: Indagine statistica sulle condizioni di salute della popolazione e sul ricorso ai servizi sanitari, Novembre 1980. Bollettino Mensile Stat Statistica 1982; 12 (Suppl).
[10] *Axel L T.* A prevalence study of oral mucosal lesions in an adult Swedish population. Odontol Rev 1976; *27:* 31–36.
[11] *Prorock P C, Chamberlain J, Day N E, Hakama M, Miller A B.* UICC Workshop on the Evaluation of Screening Programmes for Cancer. Int J Cancer 1984; *34:* 1–4.
[12] *Ross N M, Gross E.* Oral findings based on an automated multiphasic health screening program. J Oral Med 1971; *26:* 21–26.
[13] *Fidanza F, Ligori G.* Nutrizione umana. Napoli: Idelson, 1984.

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