Lifestyle habits and the risk of head and neck cancer in Zagreb region

Znaor, Ariana; Virag, Mišo; Znaor, Tin; Manojlović, Spomenka; Kušec, Rajko

Lifestyle Habits and the Risk of Head and Neck Cancer in Zagreb Region

Ariana Znaor[1,2], Mišo Virag[3], Tin Znaor[4], Spomenka Manojlović[3] and Rajko Kušec[3]

[1] Croatian National Institute of Public Health, Zagreb, Croatia
[2] »Andrija Štampar« School of Public Health, Zagreb, Croatia
[3] University of Zagreb, Dubrava University Hospital, Zagreb, Croatia
[4] University of Zagreb, »Merkur« University Hospital, Zagreb, Croatia

A B S T R A C T

In 2002, International Agency for Research on Cancer launched a multicentric case-control study of head and neck cancer in 15 centres in 11 European countries, Croatia included. The Alcohol-related Cancers and Genetic Susceptibility in Europe (ARCAGE) study database with approximately 2500 case-control pairs is currently the largest head and neck cancer patients database in Europe. The aim of the present study was to estimate the risk of smoking and alcohol consumption in head and neck cancer patients from Zagreb region recruited in scope of the ARCAGE study. The cases (45 males, 9 females) and the controls (37 males, 9 females) were recruited from University Hospital Dubrava and Merkur University Hospital. A blood sample and a lifestyle questionnaire were collected from all study subjects. Data were analysed by logistic regression analysis. The distribution of cases was: 43 oral, 9 pharyngeal and 2 laryngeal cancer cases. Ever-smokers had a 4-fold higher cancer risk (adjusted OR 4.3 (CI 1.20–15.4)) compared to never-smokers. The adjusted odds ratio for alcohol consumption more than once a week was 4.1 (CI 1.5–11.2). The results are in keeping with previously published data from other countries.

Key words: *head and neck cancer, alcohol consumption, smoking*

Introduction

Head and neck cancer includes cancers of oral cavity, pharynx, larynx and oesophagus. Worldwide, it is the most common cancer in men younger than 55 years, with the highest proportion of cases between the ages 45 and 64. The incidence is decreasing in men, while an increasing trend has been observed in women[1,2]. There are estimated 177,000 new cases of these cancers yearly in Europe, comprising 8.0% of male and 2.5% of female cancer incidence[3]. In Croatia, there are 1,179 new cases yearly, which is 8.7% of male and 1.8% of female cancer incidence[4]. No significant improvement of survival of European head and neck cancer patients has been observed over the last 20 years[5–8]. Alcohol and tobacco consumption are well established risk factors for head and neck cancers[9,10]. Different types of DNA damage have been shown to occur in human tissues from subjects who consume alcohol; however, the relationship between oxidative stress-induced DNA lesions and alcohol consumption has not been well established. Ehtanol metabolite acetaldehyde reacts with DNA to form different DNA adducts, and elevated levels of acetaldehyde-derived DNA adducts have been detected in white blood cells of individuals who are heavy drinkers. Some of these adducts are mutagenic in human cells[10]. Tobacco smoke is genotoxic in humans and in experimental animals. The smoking-related DNA adducts are derived from various compounds including aromatic amines (e.g. 4-aminobiphenyl), polycyclic aromatic hydrocarbons (e.g. benzo[a]pyrene), tobacco-specific nitrosamines (e.g. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), benzene, acrylamide and acrylonitrile[9]. Some polymorphisms of genes involved in alcohol metabolism (such as alcohol and aldehyde dehidrogenases), tobacco metabolism (such as cytochrome P450 N-acetyl-trasnsferase and glutathione-s-transferase family), as well as DNA repair and cell cycle control genes are associated with head and neck cancer risk and may contribute to interindividual variations in risk[11–19].

The role of HPV infection in pathogenesis of some of these cancers has also been established[20]. To address these factors, as well as their interactions, in 2002 IARC launched an international multicentre study »Alcohol--related Cancers and Genetic Susceptibility in Europe (ARCAGE)« including 15 centres in 11 countries. The duration of the study was between 2002 and 2005, throughout which period, data on 2347 cases and 2254 controls were collected, and the results on both genetic and environmental factors were published subsequently[21–23]. In scope of the Croatian part of the study, data on 100 subjects were collected. The aim of our study was to describe the study population and estimate the risk of smoking and alcohol consumption in head and neck cancer patients from Zagreb region.

Methods

Data collection

The 54 cases (45 men, 9 women) and 46 controls (37 men, 9 women) were recruited from two hospital centres, Dubrava University Hospital and »Merkur« University hospital in the period 2003–2005. The distribution of the cases was 43 oral, 9 pharyngeal and 2 laryngeal cancers. Mean ages of the cases were 54.91 (1.33) for men and 56.78 (3.07) for women. Mean ages of the controls were 59.16 (1.77) for males and 54.78 (3.70) for females. Cases were defined as patients with a cancer of the oral cavity (excluding parotid gland), pharynx (excluding nasopharynx) and larynx, and identified from the participating hospitals as soon as possible after diagnosis was established and no later than six months after diagnosis. No oesophageal cancer cases were recruited into the study. Only patients with histologically confirmed diagnosis were considered eligible for the study. Controls were also recruited from the participating hospitals and frequency matched by age and sex. All study subjects were from Zagreb and the surrounding county. The definition of the controls was based on admission diagnoses not related to alcohol or tobacco consumption and dietary habits. Participation rates were 95% for cases and 100% for controls. A lifestyle questionnaire developed for the ARCAGE study was collected from all subjects. The questionnaire was administered by a trained interviewer and comprised sections on smoking, alcohol and dietary habits, oral health and occupational history. Blood samples of 10ml were collected from all study subjects, and processed at the laboratory Merkur according to the ARCAGE study protocol[21]. All study subjects have signed the informed consent form for both lifestyle interview and blood sample collection. Ethical approval for the study has been obtained from both hospital centres, as well as from the Croatian National Institute of Public Health.

Statistical analysis

The data describing study population are presented for men and women separately, while they were collapsed for the purpose of analysis. Since the category of ever al-cohol consumption was very broadly defined as »at least once a month«, for the purpose of the analysis we created a new variable for »at least once a week« alcohol consumption. Therefore some missing values were generated.

Odds ratios (OR) and 95% confidence intervals (CI) for head and neck cancer were estimated according to smoking and alcohol habits using unconditional multiple logistic regression models. All ORs were adjusted for age, center and level of education. OR corresponding to one habit was obtained after adjusting for the other habits[24].

Results

Altogether 100 subjects were recruited into the study, 54 cases and 46 controls. The distribution of cases and controls by sex, educational level and smoking and alcohol habits is presented in Table 1. The distribution of education levels were similar in male cases and controls, while for females, the proportion of cases with more than 8 years of education was higher than in controls. The proportions of ever smokers were higher in cases, but still very high in control populations. The proportion of subjects consuming alcohol more than once a week was higher in cases.

Table 2 presents the odds for ever smoking and drinking and the risk for UADT cancer. Adjusted OR for ever smoking was OR 4.3 (CI 1.20–15.4), while the adjusted odds ratio for alcohol consumption more than once a week was 4.1 (1.5–11.2). Education level was not a significant risk factor in the analysis.

Discussion

In spite of the recently established role of HPV infection in the causation of a subset of head and neck cancers, smoking and alcohol consumption still remain the most important risk factors, which is of a particular im-

TABLE 1
DISTRIBUTION OF THE CROATIAN ARCAGE STUDY SUBJECTS BY EDUCATION, SMOKING AND DRINKING HABITS, GENDER AND CASE/CONTROL STATUS

	Cases				Controls			
	M		F		M		F	
	N	%	N	%	N	%	N	%
Education								
<8 years	15	33.3	2	22.2	13	35.4	3	33.3
>8 years	30	66.7	7	77.8	24	64.9	6	66.7
Smoking								
Never	3	6.7	2	22.2	9	24.3	4	44.4
Ever	42	93.3	7	77.8	28	75.8	5	55.6
Alcohol*								
<1 × weekly	10	23.3	1	11.1	14	50.0	4	66.7
>1 × weekly	33	76.7	8	88.9	14	50.0	2	33.3

*Lower number of cases and controls due to missing values

TABLE 2
ODDS RATIOS FOR EVER SMOKING AND DRINKING HABITS IN
THE CROATIAN ARCAGE STUDY SUBJECTS

	Controls	Cases	OR	95%CI	OR*	95%CI
Smoking						
Never	13	33	1.0	–	–	–
Ever	5	49	3.9	1.3–11.9	4.3	1.2–15.4
Alcohol						
<1 × weekly	18	11	1.0	–	–	–
>1 × weekly	16	41	4.2	1.6–10.8	4.1	1.5–11.2

* OR adjusted for age, education level, sex, smoking or alcohol consumption

portance in areas with high prevalence of these lifestyle habits, such as Eastern and South-East Europe[9,10,20,25]. In our study population, there was a high prevalence of smoking even among the controls, reflecting the high prevalence of this habit in Croatia. The results of the 2003 Croatian Health Survey report the prevalence of smoking of 33.8% in males, and 21.7% in females older than 18 years[26]. In spite of the fact that the Croatian age-standardised mortality rates of both cancer and cardiovascular diseases are among the highest in Europe, the smoking ban was introduced in May 2009, but was subsequently withdrawn[25,27]. The 2003 Croatian Health Survey also demonstrated high prevalence of alcohol consumption[28]. According to our results, smoking and regular alcohol consumption increased the risk of UADT cancer more than 4-fold each, which is in keeping with the previously published evidence[9,10]. Due to small number of subjects, we have not analysed the interaction between the two habits, but their synergistic effect has been documented elswhere[10].

The evidence on the association between fruit and vegetable consumption and the reduction of UADT cancer risk was evaluated as »probable, but not convincing«[29]. The results of the ARCAGE study have shown that the consumption of red meat, but not poultry, was significantly associated with increased UADT cancer risk, while the consumption of fresh non-starchy vegetables, fruits, olive oil and tea was associated with reduced UADT cancer risk[22]. Another study from central and Eastern Europe has shown the inverse association between consumption of yellow/orange vegetables and oral, pharyngeal and laryngeal cancer[30]. The Croatian part of the ARCAGE study results showed no statistically significant differences between cases and controls in frequency of different food items consumption. Of the seven items analysed, the one most frequently consumed was coffee (14 times a week for all strata), while the one most infrequently consumed was olive oil (ranging between 0 and 0.3 times a week). Consumption of all meat was very frequent (median 5.2–6.6 times a week), while fish consumption was very low (median 0.5–1 times a week). All vegetables consumption was low, 4 times a week for all strata except for female controls, while fruit consumption was even lower, ranging between 2 and 4 times a week[22]. The 2003 Croatian Health Survey has shown that the there are large differences in dietary habits at county and regional level. The catchment area of our study was within Northern Croatian region, which had significantly higher consumption of animal fats and lower consumption of fruits and vegetables than partly Mediterranean Southern and Western regions[31]. The findings on frequency of different food items consumption from our study confirm this unsatisfactory state of dietary habits.

In spite of the growing evidence on the role of different metabolic polymorphisms in the carcinogenesis of head and neck cancers[17–20,24,32], the scope for prevention still remains with modifiable risk factors. The age-standardised rates (W) of head and neck cancer incidence (32.5/100,000 for males and 3.9/100,000 for females in 2009) in Croatia are high, and the burden of these cancers is still increasing[4]. The major part of this burden in Croatia, as well as in the other areas could be reduced by applying effective prevention measures.

The ARCAGE study was one of the first epidemiological European Comission Framework 5 Programme studies with Croatian participation. Even though the number of subjects recruited was modest due to non-applicability of Croatia for EC funding at that time, consequently not yielding possibilities for detailed analysis, it contributed to the important new evidence on both environmental and genetic risk factors for head and neck cancers obtained in scope of the ARCAGE study[22,23,32]. In light of newly available molecular methods such as genome-wide association studies, multicentric case-control studies or study consortia with a large number of subjects provide novel opportunities for clarifying disease etiology. Consequently, there is a continuing development of statistical methodology. In Croatia, such methodologies, as well as education for their application are only partially available. Therefore, the participation of Croatia in international multicentre studies is very important, both in terms of contribution to the body of scientific evidence, and to the Croatian science.

REFERENCES

1. FERLAY J, SHIN HR, BRAY F, FORMAN D, MATHERS C, PARKIN DM, GLOBOCAN 2008 cancer incidence, mortality and prevalence worldwide IARC CancerBase No. 10, version 1.2 (International Agency for Research on Cancer, Lyon, 2010.). — 2. CURADO MP, HASHIBE M, Curr Opin Oncol, 21 (2009) 194. — 3. FERLAY J, PARKIN DM, STELIAROVA-FOUCHER E, Eur J Cancer, 46 (2010), 765. — 4. CROATIAN NATIONAL INSTITUTE OF PUBLIC HEALTH: Cancer incidence in Croatia. Bulletin No. 34 (Croatian National Institute of Public Health, Zagreb, 2011). — 5. BERRINO F, SANT M, VERDECCHIA A, CAPOCACCIA R, HAKULINEN T, ESTEVE J, Survival of cancer patients in Europe. The EUROCARE study. IARC Scientific publications No. 132. (International Agency for Research on Cancer, Lyon, 1995). — 6. BERRINO F, CAPOCACCIA R, ESTEVE J, GATTA G, HAKULINEN T, MICHELI A, SANT M, VERDECCHIA A, Survival of cancer patients in Europe: the

EUROCARE-2 study. IARC Scientific Publications No. 151. (International Agency for Research on Cancer, Lyon, 1999). — 7. SANT M, AARE-LEID T, BERRINO F, BIELSKA LASOTA M, CARLI PM, FAIVRE J, GROSCLAUDE P, HÉDELIN G, MATSUDA T, MØLLER H, MØLLER T, VERDECCHIA A, CAPOCACCIA R, GATTA G, MICHELI A, SAN-TAQUILANI M, ROAZZI P, LISI D, EUROCARE WORKING GROUP, Ann Oncol, 14 Suppl 5 (2003) v61. — 8. SANT M, ALLEMANI C, SAN-TAQUILANI M, KNIJN A, MARCHESI F, CAPOCACCIA R; EUROCA-RE WORKING GROUP, Eur J Cancer, 45 (2009) 931. — 9. INTERNA-TIONAL AGENCY FOR RESEARCH ON CANCER, Tobacco smoke and involuntary smoking, IARC Monographs on the Evaluation of Car-cinogenic Risk of Chemicals to Humans, Vol. 83. (International Agency for Research on Cancer, Lyon, 2004). — 10. INTERNATIONAL AGE-NCY FOR RESEARCH ON CANCER. Alcoholic Beverage Consumption and Ethyl Carbamate (Urethane), Vol. 96, 6–13 February 2007, accessed 01.07.2009. Available from: URL: http://monographs.iarc.fr/ENG/Meet-ings/vol96-summary.pdf. — 11. SANDERSON S, SALANTI G, HIG-GINS J, Am J Epidemiol, 166 (2007) 741. — 12. MORITA S, YANO M, TSUJINAKA T, OGAWA A, TANIGUCHI M, KANEKO K, SHIOZAKI H, DOKI Y, INOUE M, MONDEN M, Int J Cancer, 79 (1998) 517. — 13. OLSHAN AF, WEISSER MC, WATSON MA, BELL DA, Cancer Epide-miol Biomarkers Prev, 9 (2000) 185. — 14. STACY A, GEISLER A, OL-SHAN A, Am J Epidemiol, 154 (2001) 95. — 15. HASHIBE M, BREN-NAN P, STRANGE RC, BHISEY R, CASCORBI I, LAZARUS P, OPHIU M, BENHAMOU S, FOULKES W, KATOH T, COUTELLE C, ROMKES M, GASPARI L, TAIOLI E, BOFFETTA P, Cancer Epidemiol Biomar-kers Prev, 12 (2003) 1509. — 16. SUGIMURA T, KUMIMOTO H, TOH-NAI I, FUKUI T, MATSUO K, TSURUSAKO S, MITSUDO K, UEDA M, TAJIMA K, ISHIZAKI K, J Oral Pathol Med, 35 (2006) 11. — 17. HA-SHIBE M, BOFFETTA P, ZARIDZE D, SHANGINA O, SZESZENIA--DABROWSKA N, MATES D, JANOUT V, FABIANOVA E, BENCKO V, MOULLAN N, CHABRIER A, HUNG R, HALL J, CANZIAN F, BRE-NNAN P, Cancer Epidemiol Biomarkers Prev, 15 (2006) 696. — 18. BRE-NNAN P, LEWIS S, HASHIBE M, BELL DA, BOFFETTA P, BOUCHA-RDY C, CAPORASO N, CHEN C, COUTELLE C, DIEHL SR, HAYSE RB, OLSHAN AF, SCHWARTZ SM, STURGIS EM, WEI Q, ZAVRAS AI, BENHAMOU S, Am J Epidemiol, 159 (2004) 1. — 19. PETERS ES, MC-CCLEAN MD, LIU M, EISEN EA, MUELLER N, KELSEY KT, Cancer Epidemiol Biomarkers Prev, 14 (2005) 476. — 20. INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, Human Papillomaviruses. IARC Monographs on the Carcinogenic Risk of Chemicals to Humans (International Agency for Research on Cancer, Lyon, 1995). — 21. LA-GIOU P, GEORGILA C, MINAKI P, AHRENS W, POHLABELN H, BEN-HAMOU S, BOUCHARDY C, SLAMOVA A, SCHEJBALOVA M, MER-LETTI F, RICHIARDI L, KJAERHEIM K, AGUDO A, CASTELLSAGUE X, MACFARLANE TV, MACFARLANE GJ, TALAMINI R, BARZAN L, CANOVA C, SIMONATO L, LOWRY R, CONWAY DI, MCKINNEY PA, ZNAOR A, MCCARTAN BE, HEALY C, NELIS M, METSPALU A, MAR-RON M, HASHIBE M, BRENNAN PJ, Eur J Cancer Prev, 18 (2009) 76. — 22. LAGIOU P, TALAMINI R, SAMOLI E, LAGIOU A, AHRENS W, PO-HLABELN H, BENHAMOU S, BOUCHARDY C, SLAMOVA A, SCHEJ-BALOVA M, MERLETTI F, RICHIARDI L, KJAERHEIM K, AGUDO A, CASTELLSAGUE X, MACFARLANE TV, MACFARLANE GJ, BIGGS AM, BARZAN L, CANOVA C, SIMONATO L, LOWRY R, CONWAY DI, MC-KINNEY PA, ZNAOR A, MCCARTAN BE, HEALY CM, MARRON M, HA-SHIBE M, BRENNAN P, Int J Cancer, 124 (2009) 2671. — 23. CANOVA C, HASHIBE M, SIMONATO L, NELIS M, METSPALU A, LAGIOU P, TRI-CHOPOULOS D, AHRENS W, PIGEOT I, MERLETTI F, RICHIARDI L, TALAMINI R, BARZAN L, MACFARLANE TV, MACFARLANE GJ, HOL-CATOVA I, BENCKO V, BENHAMOU S, BOUCHARDY C, KJAERHEIM K, LOWRY R, AGUDO A, CASTELLSAGUE X, CONWAY DI, MCKIN-NEY PA, ZNAOR A, MCCARTAN BE, HEALY CM, MARRON, BRENNAN P, Cancer Res, 69 (2009) 2956. — 24. BRESLOW NE, DAY NE, Statistical Methods in Cancer Research. Vol. II. The analysis of case-control studies. IARC Scientific Publications No. 32. (International Agency for Research on Cancer, Lyon, 1980). — 25. WHO REGIONAL OFFICE FOR EUROPE. European Health for All database (HFA-DB), ACCESSED 01.07.2009. Available from: URL: http://www.euro.who.int/hfadb. — 26. KOVAČIĆ L, GAZDEK D, SAMARDŽIĆ S, Acta Med Croatica, 61 (2007) 281. — 27. To-bacco product use restriction act [In Croatian], Narodne novine 125 (2008). — 28. MILOŠEVIĆ M, MUSTAJBEGOVIĆ J, ABDOVIĆ S, ŠULENTIĆ P, PUCARIN-CVETKOVIĆ J, Acta Med Croatica, 61 (2007) 275. — 29. IN-TERNATIONAL AGENCY FOR RESEARCH ON CANCER, Fruit and Ve-getables. IARC Handbooks of Cancer Prevention Vol. 8 (International Agency for Research on Cancer, Lyon, 2003). — 30. SAPKOTA A, HSU CC, ZARIDZE D, SHANGINA O, SZESZENIA-DABROWSKA N, MATES D, FA-BIANOV E, RUDNAI P, JANOUT V, HOLCATOVA I, BRENNAN P, BOF-FETTA P, HASHIBE M, Cancer Causes Control, 19 (2008) 1161. — 31. KAIĆ-RAK A, PUCARIN-CVETKOVIĆ J, KULIER I, Acta Med Croatica, 61 (2007) 259. — 32. HASHIBE M, MCKAY JD, CURADO MP, OLIVIERA JC, KOIFMAN S, KOIFMAN R, ZARIDZE D, SHANGINA O, WÜNSCH--FILHO V, ELUF-NETO J, LEVI JE, MATOS E, LAGIOU P, LAGIOU A, BENHAMOU S, BOUCHARDY C, SZESZENIA-DABROWSKA N, MENE-ZES A, DALL'AGNOL MM, MERLETTI F, RICHIARDI L, FERNANDEZ L, LENCE J, TALAMINI R, BARZAN L, MATES D, MATES IN, KJAE-RHEIM K, MACFARLANE GJ, MACFARLANE TV, SIMONATO L, CA-NOVA C, HOLCATOVA I, AGUDO A, CASTELLSAGUE X, LOWRY R, JA-NOUT V, KOLLAROVA H, CONWAY DI, MCKINNEY PA, ZNAOR A, FABIANOVA E, BENCKO V, LISSOWSKA J, CHABRIER A, HUNG RJ, GABORIEAU V, BOFFETTA P, BRENNAN P, Nat Genet, 40 (2008) 707.

A. Znaor

Croatian National Institute of Public Health, Croatian National Cancer Registry, Rockefellerova 7, 10000 Zagreb, Croatia
e-mail: ariana.znaor@hzjz.hr

ŽIVOTNE NAVIKE I RIZIK ZA RAK GLAVE I VRATA U ZAGREBAČKOJ REGIJI

SAŽETAK

Međunarodna agencija za istraživanje raka 2002. godine započela je multicentrično slučaj-kontrola istraživanje raka glave i vrata u 15 cenara u 11 europskih država uključujući Hrvatsku. Baza podataka istraživanja ARCAGE s oko 2500 parova slučaj-kontrola trenutno je najveća baza podataka o bolesnicima od raka glave i vrata u Europi. Cilj ovog istra-živanja bio je procijeniti rizik pušenja i konzumacije alkohola u bolesnika od raka glave i vrata iz zagrebačke regije regrutiranih u okviru istraživanja ARCAGE. Slučajevi (45 muškaraca i 9 žena) i kontrole (37 muškaraca, 9 žena) regru-tirani su iz Klinčke bolnice Dubrava i Kliničke bolnice Merkur. Od svih ispitanika prikupljen je uzorak krvi i anketni upitnik. Podaci su analizirani logističkom regresijom. Raspodjela slučajeva bila je: 43 slučaja raka usne šupljine, 9 ždrijela i 2 grkljana. Pušači su imali četverostruko veći rizik za rak glave i vrata od nepušača (OR 4,3 (CI 1,20–15,4)). Prilagođeni odnos šansi za konzumaciju alkohola više od jednom tjedno bio je 4,1 (CI 1,5–11,2). Rezultati su u skladu s prethodno objavljenim podacima iz drugih zemalja.