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Mutation Research 462 (2000) 355–363

Reviews in Mutation Research

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A population at high risk for esophageal cancer in the north-east of Italy

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Received 20 October 1999; received in revised form 3 December 1999; accepted 3 December 1999

Abstract

Esophageal cancer is generally characterised by relatively low incidence and mortality rates in Europe. However, a high-risk population for this tumour is resident in the north-east of Italy. Several studies have been conducted on this population of males confirming the major role of alcohol and tobacco consumption alone and in combination. The inhabitants of this area of Italy constitute an ideal target population for studies of molecular epidemiology aimed at elucidating the natural history of the disease which is still ill-defined, and the distribution of genetic alterations at a population level.

Keywords: Esophageal cancer; Tobacco; Alcohol; Genetic alterations

1. Background

In Western countries, cancer of the esophagus constitutes a relatively small proportion of all neoplasms. In Europe, most of the incidence rates are between five and eight cases per 100,000 per year, close to estimates in America, apart from black males who exhibit incidence rates of 15 per/100,000 per year for this neoplasia similarly to African black males, and to high-risk populations in China [1].

A comparative analysis between age-adjusted mortality rates for males in 27 countries has shown that many European countries including France, Switzerland, Luxembourg, and Italy are characterised by higher rates for this tumour.

In Italy, the rates for both mortality and incidence are less than 5/100,000 per year for males, but the rates are twice as high in the north-eastern area of the country [2]. For males in the Veneto Region, age-adjusted incidence rates exceed 10/100,000 per year and are the highest at a national level, as shown in Fig. 1 [3].

2. Study population

Thanks to the availability of incidence data from the Venetian Tumour Registry, which has been operating since 1987 [4,5], it has been possible to single out a subset of the Venetian population which appears at very high risk of esophageal cancer. Age-adjusted incidence rates for this neoplasia reach, for the

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PII: S1383-5742(00)00025-9

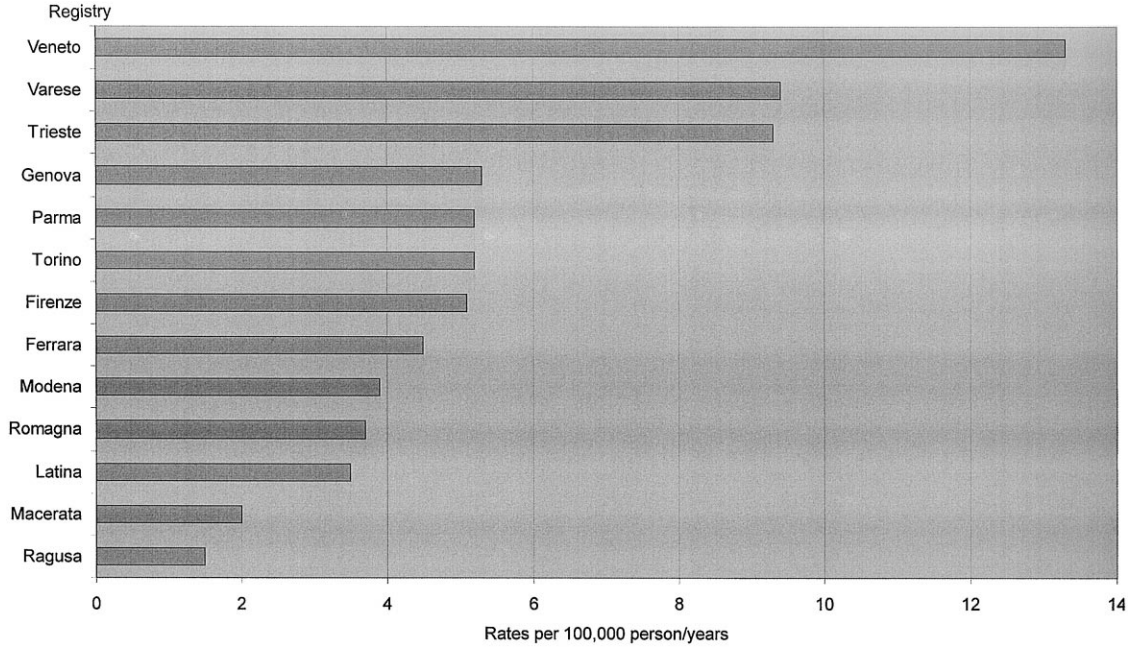

Fig. 1. Incidence rates of esophageal cancer in Italy in 1988–1992 (males).

male population (approximately 100,000) resident in the northern part of the region (Belluno Province), values of 15/100,000 per year, which is three times higher than in the rest of the country [3], and among the highest in Europe.

These findings are of particular concern when examining the temporal trend for this rapidly fatal neoplasia. The incidence in males of esophageal cancer has, in fact, been decreasing (Fig. 2) in the Veneto Region, as has been observed in the rest of the country. Yet, no decreasing trend is discernible among the male residents in the province of Belluno where, instead, slight increases in incidence rates have been observed.

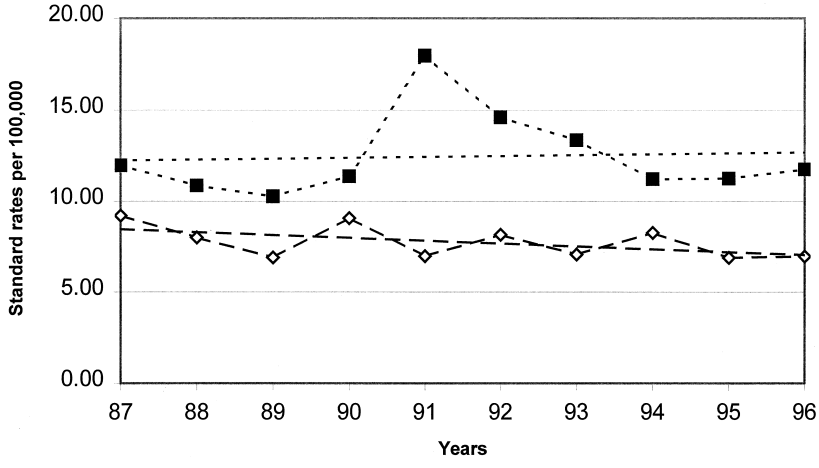

Fig. 2. Temporal trends of esophageal cancer in Veneto Region and Belluno Province (males). —◇—, Veneto; — — —, Linear trend (Veneto); - -■- -, Belluno; ------, Linear trend (Belluno).

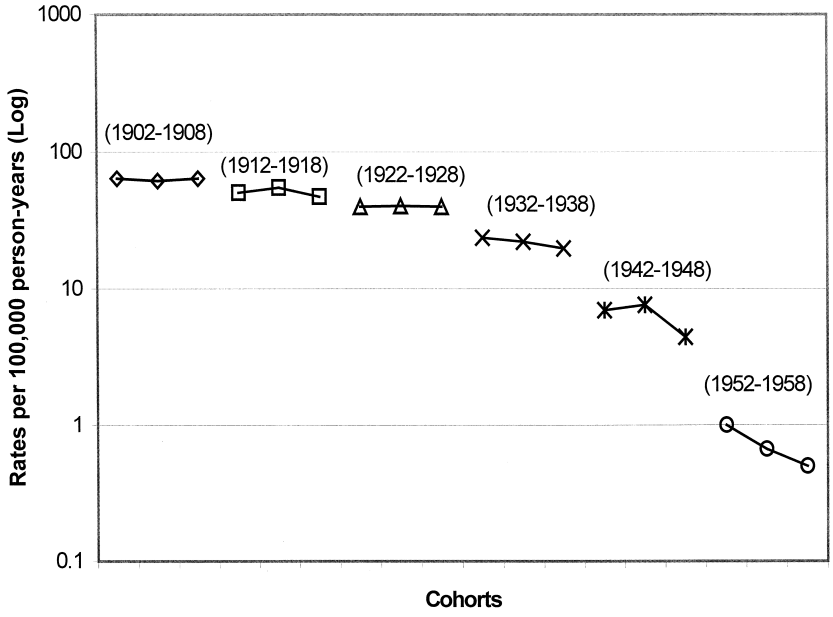

Fig. 3. Analysis by birth cohort of the temporal trends of esophageal cancer among males in the Veneto Region. Cohorts: —◇—, 85 + ; —□—, 70–79; —△—, 60–69; —×—, 50–59; —*—, 40–49; —○—, 30–39.

This pattern is confirmed by the analysis by birth cohorts (Figs. 3 and 4) which show a clear downward trend for cancer of the esophagus among males resident in the Veneto Region below age 59, while a similar analysis on males resident in the Belluno Province, although giving more unstable estimates due to smaller numbers, does not indicate any clear decreasing trend, particularly for younger cohorts, for which an increasing pattern is detectable.

3. Risk factors

Risk factors for esophageal cancer have been investigated in a large number of epidemiological

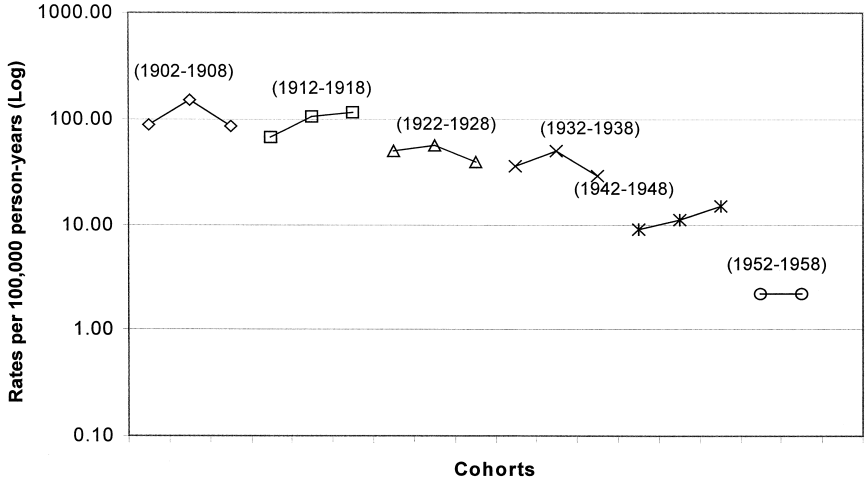

Fig. 4. Analysis by birth cohort of the temporal trends of esophageal cancer among males in the Belluno Province. —◇—, 85 + ; —□—, 70–79; —△—, 60–69; —×—, 50–59; —*—, 40–49; —○—, 30–39.

studies [6–8] and have indicated a potential role for several different exposures in various countries, but with alcohol and tobacco consumption always playing a major role. Several studies, in particular, have been carried out in northern France and northern Italy where heavy alcohol consumption is common, and provide good scientific evidence of the separate and interactive role of tobacco smoking and alcohol drinking in the etiopathogenesis of esophageal cancer at the population level [9–16].

In most of these studies, the risk of esophageal cancer was causally associated with alcohol and tobacco, the association being clearly dose-dependent. When both exposures were present, relative risks were in agreement with a multiplicative model.

High intake of fruit (particularly citrus fruit) and vegetables (particularly raw ones) can reduce the risk of esophageal cancer by two- to threefold [17]. The intake of various vitamins, most notably beta-carotene and vitamin C, is also inversely correlated with esophageal cancer risk, although generally less strongly than the consumption of fresh fruit and vegetables. Findings on other foods are less consistent [17], as illustrated by the example of maize intake.

North-eastern Italy offers one of the few examples of an area where maize (i.e., sweet corn or Indian corn) has traditionally been the cereal most widely grown and eaten in the form of polenta, a maize porridge [18]. Three independent studies, carried out in the Veneto Region in the 1970s [19], in Pordenone province in the 1980s [20], and in Veneto and Friuli Venezia Giulia Regions in the early 1990s (S. Franceschi, personal communication) showed a direct association between esophageal cancer risk and intake of polenta (Table 1). There was, however, a tendency of the strength of the association to diminish, along with the frequency of polenta intake, from the earliest to the most recent study.

Such findings are in agreement with several studies, mostly from Africa and China, where maize consumption consistently emerged as an important risk factor for esophageal cancer (Table 2). Van Rensburg et al. [21] found more than a fivefold elevated risk of developing esophageal cancer among Zulu men. In Linxian, People's Republic of China, Li et al. [22] showed a trend of increasing risk of cancer of the esophagus and gastric cardia with increasing consumption of maize and wheat, but not millet and sweet potatoes.

In addition, Warendorf et al. [23] found that in Henan, People's Republic of China, the frequent consumption of maize enhanced cancer risk, even after allowing for several other risk factors. Segal et al. [24] observed in South Africa a 25-fold enhanced risk of developing esophageal cancer among heavy

Table 1
Maize consumption and esophageal cancer risk in selected studies worldwide
Ca:Co = cases:controls.

Reference	Area	Ca:Co	Intake levels	OR	Adjustment
Rossi et al. [19]	Veneto, N-E Italy	150:150	≥ 106 vs. 0–35 g/day	6.2 (3.0–12.9)	Age, occupation, tobacco, alcohol
Van Rensburg et al. [21]	Durban, South Africa	211:211	Daily vs. less than weekly	5.7 (3.1–10.6)	Age, tobacco, occupation, margarine or butter
Li et al. [22]	Linxian, China	1244[a]:1314	> 367 vs. < 21 year	1.5 (1.2–1.9)	Age, sex, and tobacco
Franceschi et al. [20]	Pordenone, N-E Italy	68:505	≥ 3 week vs. never/occasional	2.1 (1.1–4.0)	Age, education, occupation, alcohol, tobacco, and vegetables and fruit
Franceschi et al. (personal communication)	Veneto and Pordenone, N-E Italy	229:491	≥ 1 week vs. never	1.4 (0.8–2.4)	Age, center, education, tobacco and alcohol

[a] They also include cancer of the gastric cardia.

Table 2
Distribution of 275 male esophageal cancer cases and 593 controls and OR[a] and corresponding 95% confidence interval (CI) of males esophageal cancer according to smoking and alcohol drinking habit from a recent study [34] carried out in North-eastern Italy, 1992–1998[b].

Alcohol intake (drinks/week)					
Smoking habit	0–20	21–34	35–59	≥ 60	Alcohol-adjusted
(Number of cigarettes/day)	Ca:Co OR (95% CI)				
Never	2:50	2:48	6:33	9:8	
	1[c]	2.05	8.9	56.08	1[c]
		(0.18–23.45)	(1.02–77.76)	(6.19–507.95)	
1–14	3:23	8:22	12:16	9:11	
		18.92	36.46	40.26	3.14
		(2.21–161.78)	(4.35–305.73)	(4.56–355.42)	(1.58–6.28)
15–24	1:27	14:19	21:19	43:19	
		35.25	57.21	117.62	5.32
		(4.30–288.87)	(7.16–456.89)	(14.99–923.11)	(2.82–10.03)
≥ 25	0:7	5:2	14:10	21:9	
	3.33	440.8	66.76	130.32	6.87
	(0.36–31.07)	(5.51–352.92)	(7.78–573.26)	(15.20–999.00)	(3.19–14.77)
Smoking adjusted	1[c]	7.25	13.04	28.48	
		(2.60–20.18)	(4.76–35.71)	(10.09–80.39)	
Ex-smokers	9:97	18:72	24:67	54:34	
Smoking adjusted	1[c]	2.63	4.58	23.96	
		(1.14–6.06)	(2.04–10.31)	(10.45–54.93)	
Total	15:204	47:163	77:145	136:81	

[a] Estimates from unconditional logistic regression equations, including terms for area of residence, age, education, and alcohol intake, and smoking habit as appropriate.
[b] Some strata do not add up to the total because of missing values. One drink corresponds to approximately 125 ml of wine, 330 ml of beer, and 30 ml of liquor (i.e., about 12 g of ethanol). Ca:Co = cases:controls.
[c] Reference category.

drinkers of traditional beer made from maize. Indeed by far the strongest evidence for a role of maize comes from surveys in Africa. Maize is an introduced crop in Africa, and its spread as a staple food and an ingredient in traditional beer seems to coincide, after allowing for latency, with the rise in the frequency of esophageal cancer [25–28].

Maize is easier to grow and more resistant to fungus and attacks by birds than other grains. However, particularly if it is refined, maize is less nutritious than other grains and can cause deficiencies of several micronutrients (chiefly riboflavin, folic acid, and niacin) [29]. Riboflavin deficiency has been suggested as one of the deficiencies that cause Plummer–Vinson syndrome, a long-recognized precancerous lesion of the upper digestive tract [30]. Maize not only is low in niacin and tryptophan (its precursor), but also contains large quantities of leucine, which is capable of interfering with oxidation–reduction reactions. Like the Plummer–Vinson syndrome, pellagra, a life-threatening disease caused by niacin deficiency, can result in widespread inflammation of the mucous surfaces, dysphagia, and esophageal lesions [31].

The elevation in risk resulting from frequent consumption of maize (Table 1) could not be easily explained in terms of the confounding effect of age, education, occupation, tobacco use, or alcohol intake since all examined studies made allowances for such factors. There are, in our opinion, three, not necessarily alternative, explanations for these findings. Firstly, a specific deficiency in certain nutrients predisposes maize-eating populations to pellagra and cancer of the esophagus [20], compared to populations whose staple foods are rice, cassava, peanuts, etc. [26]. The tendency of the maize-related excess risk to decline from the 1970s to the 1990s may thus be compatible with the steady decline of the impor-

tance of polenta in the habitual diet of the population of north-eastern Italy in the post-war period. Secondly, a relatively high intake of maize may be an indicator of a less affluent diet, potentially poor in various nutrients which can prevent esophageal cancer. It is not surprising that, in this respect, such indicators of diet can vary greatly from one country to another and tend to coincide with foods that represent major sources of energy in different populations (e.g., bacon and sausages in the black population of the United States, potatoes in northern France, certain types of meat in Argentina) [17]. Frequency of intake of such indicators is, thus, inversely correlated with a variety of food intake in the habitual diet. Obviously, the impact of such energy-dense, but nutritionally deficient, foods is aggravated, with respect to esophageal cancer etiology, by concurrent heavy consumption of alcoholic beverages [20].

Finally, it is also conceivable that the temperature at which polenta is eaten plays a role in the etiology of esophageal cancer. Hot, rather than cold, mate drinking has been shown to increase the risk of esophageal cancer in South America [32] and the habit of eating any soup or porridge ''burning hot''

Table 3
ORs and corresponding 95% CI[a] of male esophageal cancer according to type of alcoholic beverage from a recent study [34] carried out in 275 cases and 593 controls. Northern Italy, 1992–1998.

Type (drinks/week)[b]		Cases (*N*)	Controls (*N*)	OR	95% (CI)	OR[c]	95% (CI)
Wine							
	0–20[d]	25	246	1.00		1.00	
	21–34	71	190	3.97	(2.35–6.71)	4.23	(2.45–7.28)
	35–55	40	71	5.14	(2.80–9.43)	5.57	(2.96–10.47)
	56–83	85	62	12.47	(7.01–22.18)	12.90	(7.08–23.51)
	≥ 84	54	23	22.67	(11.27–45.60)	23.64	(11.34–49.27)
X_1^e for trend					104.16; $p < 0.001$		94.80; $p < 0.001$
Beer							
	0[d]	97	208	1.00		1.00	
	0.5–3	115	295	0.80	(0.56–1.14)	0.65	(0.43–0.98)
	≥ 4	63	87	1.19	(0.79–1.80)	0.58	(0.53–1.36)
X_1^e for trend					0.44; $p = 0.51$		0.58; $p = 0.45$
Grappa							
	0[d]	91	251	1.00		1.00	
	0.5–3	86	231	1.17	(0.80–1.72)	0.90	(0.58–1.40)
	≥ 4	97	109	2.01	(1.34–3.02)	1.12	(0.71–1.78)
X_1^e for trend					10.98; $p < 0.001$		0.23; $p = 0.63$
Amari							
	0[d]	152	362	1.00		1.00	
	0.5–1	70	139	1.25	(0.86–1.82)	1.43	(0.92–2.23)
	≥ 2	53	91	1.44	(0.94–2.19)	1.45	(0.89–2.36)
X_1^e for trend					3.24; $p = 0.07$		2.89; $p = 0.09$
Other hard liquor							
	0[d]	185	412	1.00		1.00	
	0.5–1	45	122	0.90	(0.59–1.36)	0.82	(0.51–1.31)
	≥ 2	45	58	1.58	(0.99–2.54)	1.08	(0.64–1.83)
X_1^e for trend					2.06; $p = 0.15$		0.00; $p = 0.97$

[a] Estimates from unconditional logistic regression equations, including terms for area of residence, age, education, and smoking habit.
[b] One drink corresponds to approximately 125 ml of wine, 30 ml of beer, and 30 ml of liquor (i.e., about 12 g of ethanol).
[c] As at footnote[a], plus all listed beverages.
[d] Reference category.
[e] Some strata do not add up to the total because of missing values.

has been associated with an increased risk in China [33]. In the study by Franceschi et al. [20], however, a direct association with polenta intake also emerged for cancers of the oral cavity and pharynx. This points to the possibility that high maize intake may affect, at least in populations heavily exposed to alcohol and tobacco, the whole upper digestive tract and not exclusively the esophagus.

4. Epidemiological evidence

Recently, a hospital-based case–control study of esophageal cancer was carried out in three areas of north Italy, characterised by some of the highest incidence rates for males in Europe.The results indicate extremely high Odds Ratios (ORs) for alcohol and tobacco consumption separately and combined [34].

In this study, the risk due to smoking, after adjusting for alcohol consumption, was 6.87, and the risk due to alcohol consumption after adjusting for smoking was 28.48 (Table 2).

Clearly, alcohol drinking is the major risk factor in this population at high risk for esophageal cancer.

We present from the same study in Table 3 the results of the analysis by the type of alcoholic beverage. No or only a moderate effect is discernible from the consumption of beer or strong alcoholic beverages while the only elevated ORs are associated with the consumption of wine for which there is a highly significant increasing trend with increasing dose reaching the value of 23.64 in the category with the heaviest consumption of wine. For none of the other alcoholic beverages are statistically increasing trends reported, and most of the values are close to one.

Dietary habits have been associated in several studies in France and Italy [35–39] with the risk of cancer of the esophagus. In the high-risk population considered here, a protective effect from antioxidants has been detected with values of ORs ranging from 0.6 to 0.3 depending on the antioxidant examined [40].

5. Perspective of prevention

All these information contribute to revealing an association between known risk factors and esophageal cancer in the north-east of Italy. Clearly, the avoidable and elevated consumption of wine by the male residents in this region must constitute the main target of any primary prevention strategy. However, there exists within this area sub-populations affected by higher rates of esophageal cancer which could not be totally explained by alcohol and tobacco consumption and are uniformly high in the whole resident population.

Also considering the poor survival for this cancer [41] for which early diagnosis is very difficult to achieve, and the limited knowledge of the natural history of this tumour [42], molecular epidemiology investigations of high-risk populations like those described in this paper are warranted for a better understanding of the etiopathology of this tumour, a sensible improvement of diagnosis, and, hopefully, a better prognosis.

Accordingly within the framework of a collaborative study between the International Agency for Research on Cancer and the Venetian Tumour Registry, it has been possible to obtain tissue samples from a subset of our cases in order to analyse the distribution of gene mutations and other genetic markers [43] of exposure to tobacco and alcohol. In particular, interest is focused on the two different histological types of esophageal cancer, namely squamous cell and adenocarcinomas, which appear to have different origins and patterns, with a substantial increase of adenocarcinomas being reported in western countries in recent years [44]. For both types of esophageal cancer, the role of genetic/familial aggregation as well as the mechanisms underlying the effect from various risk factors and the presence of a subset of multiple cancer cases are still unknown.

Acknowledgements

The study was partially funded by The Italian Association for Research on Cancer (AIRC).

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