




# Cancer time trend in a population following a socio-economic transition: results of age-period-cohort analysis

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## Abstract

**Objectives** To examine cancer trend using age-period-cohort analysis with a cohort of patients in Sardinia, Italy, where epidemiological transition occurred between 1950 and 1960.

**Methods** Poisson log-linear regression models were used to analyze time trend in patients undergoing upper endoscopy between 1995 and 2013.

**Results** A total of 10,546 clinical records (62.2% women) were retrieved. In 541 patients (5.1%), a diagnosis of cancer was reported, more often in men (5.5%) than in women (4.9%). Age and birth cohort were significantly associated with cancer rate according to age-period-cohort analysis ( $p < 0.0001$ ), whereas the effect of time period was

negligible ( $p = 0.875$ ). An upward trend for all cancers was observed in the younger generations (7.15% before 1950, 8.85% between 1950 and 1960, and 10.7% after 1960).

**Conclusions** Population aging and increased exposure to cancer risk factors after epidemiological transition were the major determinants associated with cancer in this Sardinian cohort, whereas time period had no effect, ruling out any variation in diagnostic accuracy. These results may facilitate the provision of preventive measures by the health care system, and improve population-tailored cancer screening strategies.

**Keywords** Cancer prevalence · Age-period-cohort analysis · Epidemiological transition · Sardinia

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## Introduction

Cancer prevalence is increasing worldwide and is becoming a serious concern both in economically developed and underdeveloped countries (Jemal et al. 2011). It was estimated that 14.1 million new cancer cases occurred throughout the world in 2012, and 24 million are predicted by 2035 (Ferlay et al. 2010). The number of deaths from cancer in all countries in 2012 was estimated at 8.2 million, equivalent to 5.2% of all deaths globally (Fitzmaurice et al. 2015). The increase in cancer incidence has been associated with various risk factors that may be categorized into modifiable, such as environmental and occupational factors, obesity and physical inactivity, smoking, and “western-like” diets, and non-modifiable, including genetic factors, gender and aging (Stein and Colditz 2004).

Considerable differences have been observed between countries in cancer incidence depending on different risk factors. In industrialized countries prostate, breast,

respiratory tract and colorectal cancer predominate, whereas in developing countries the overall cancer incidence and mortality rates are in general lower and involve mostly the stomach and liver (Lambert et al. 2012). However, in some developing countries the overall cancer rate is rapidly increasing as a result of the adoption of a “westernized” lifestyle by the middle class, as well as the massive use of pesticides in agriculture, such as chlorinated hydrocarbons acting as environmental contaminants, food additives and preservatives (Jaga and Dharmani 2005).

In populations that completed the socio-economic transition in the Mid-twentieth century, the scenario may be more complex, due to the coexistence of generations that have had different levels of exposure to environmental and nutritional risks for malignancies. In such populations unbiased estimates of the effect of modifiable and non-modifiable risk factors may prove to be more difficult. However, with a genetically homogeneous population it is easier, at least in part, to estimate the individual effect of aging and birth cohorts (Omran 1971). These conditions are substantially met in Sardinia, a Mediterranean island whose population underwent rapid economic development between the 1950s and 1960s, following the eradication of malaria (Tognotti 2009), the development of health services (Dodero 1999) and the adoption of a more nutritious diet (Pes et al. 2014). In Sardinia, individuals now aged 70 and older experienced childhood and early adulthood in the pre-transitional era characterized by uncontaminated environment and food, while individuals born after 1950 were exposed to environmental pollutants, an unhealthy diet and potential occupational risk factors for cancer (Cocco et al. 1997; Carta et al. 2004). Nevertheless, due to the improvement in hygienic and sociocultural conditions (Pes et al. 2015), the prevalence rate of some type of cancer (i.e. the infection-related ones) may have declined. Recently, the type-specific prevalence of cancer in the Sardinian population was reported as different from other developed countries (Budroni et al. 2013). While in industrialized countries lung cancer is the most commonly diagnosed type in both genders, among Sardinian males colorectal cancer is at the top of the list, followed by lung and prostate cancer, whereas among females, breast cancer is the most prevalent followed by colorectal and lung cancer (Budroni et al. 2013). Although several epidemiological cancer studies have been performed in Sardinia (Palomba et al. 2009; Budroni et al. 2013; Paliogiannis et al. 2013; Broccia et al. 2014; Cossu et al. 2014) to the best of our knowledge the effect of epidemiological transition on the distribution of cancer in different generations has never been addressed.

The purpose of this study was (1) to analyze the effect of age, year of birth and time period on the cancer rate in a large cohort of subjects in Sardinia, spanning several generations from 1920 to 1980 with attention paid to

analyzing time trends according to the probable aetiology of the cancer type, as described in previous studies (Wong et al. 2010; Chung et al. 2010, 2012); (2) to evaluate the concomitant role of other factors such as smoking habits, obesity, residence and occupation.

## Methods

### Study design and population

The clinical records of patients who underwent an upper endoscopy from January 1995 to December 2013 were collected. Patients were scheduled for esophago-gastro-duodenoscopy (EGD) for any reason, such as dyspeptic and/or reflux symptoms, surveillance programs, and follow-ups. Patients were referred to the Gastroenterology Unit of Sassari, by local (Sassari and hinterland) family physicians and/or specialists. Our endoscopy service is part of a university Department of Clinical and Experimental Medicine and functions in a completely integrated clinical environment. At the time of endoscopy each patient was evaluated by a gastroenterologist to obtain medical history comprising any current or past diagnosis of cancer. Demographic data including age, gender, body mass index (BMI), place of residence, smoking habits, adult occupation and endoscopy reports were also collected. To avoid bias, in the case of multiple EGDs for the same patient only the first endoscopy reporting a diagnosis of any cancer in his/her medical history was included in the analysis. For patients diagnosed with multiple cancers these were counted individually. Moreover, cancers were grouped into three different categories according to the presumed aetiology: (1) hormone-dependent cancers; (2) infection-related cancers, and (3) lifestyle-related cancers, as reported by Wong et al. (2010). Part of this database had previously been used for epidemiological and observational studies (Dore et al. 2015, 2016a, b).

### Ethical considerations

An Institutional Review Board approval was obtained from the local Ethics Committee: *Comitato di Bioetica, Azienda Ospedaliero-Universitaria di Sassari*, Italy (Prot No. 2099/CE, 2014).

### Statistical analysis

The effects of age, time period, and birth cohort on cancer prevalence were estimated by log-linear Poisson regression models with a maximum likelihood method (Holford 1991). Data for age and birth cohort were stratified in 10-year intervals, and for time periods in 5-year

intervals. The number  $n_{ijk}$  of patients cross-classified by  $i$  age groups ( $i \in 1, \dots, 8$ ),  $j$  time periods ( $j \in 1, \dots, 4$ ) and  $k$  birth cohorts ( $k \in 1, \dots, 8$ ) were reported in specific tables (see supplementary material). Log rates for cancer were assumed to result from an additive effect as follows:

$$\log(\lambda_{ijk}) = \log\left(\frac{t_{ijk}}{n_{ijk}}\right) = \mu + \alpha_i(\text{age}) + \beta_j(\text{period}) + \gamma_k(\text{cohort}) + \epsilon_{ijk}$$

The  $\lambda_{ijk}$  is the cancer rate in the  $i$ th age group in the  $j$ th year within the  $k$ th birth cohort. The  $t_{ijk}$  represents the expected number of cancers, assumed to be distributed as a Poisson variable;  $n_{ijk}$  indicates the exposed population in each cell;  $\mu$  the intercept;  $\alpha_i$  the effect of the  $i$ th age group;  $\beta_j$  indicates the effect of the  $j$ th time period;  $\gamma_k$  denotes the effect of  $k$ th birth cohort and  $\epsilon_{ijk}$  is the random error. To overcome the problem of multicollinearity in the regression models, potentially created by the linear relationship between age, birth cohort and period (birth cohort = period – age), only second-order changes were considered (inflection points detectable in the plots of regression estimates) as suggested by Wong et al. (2010). Several log-linear models were compared: a model with only age (A), two-factors models, namely age-period (AP) and age-cohort (AC) effect models, and the full APC model including all three factors. Model fitting was assessed using the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC). To compare the prevalence rate of cancer across the epidemiological transition time (1950–1960), patients aged 50–69 years were selected and the cancer rate was calculated separately in the subgroups of patients born before 1950, between 1950 and 1960 and after 1960. In addition, the effects of gender, smoking, body mass index, residence and occupation were also tested. Patients were stratified according to gender and smoking (non-smokers; current or former smoker). BMI had been calculated using the formula weight (kg)/height (m)<sup>2</sup>. Obesity was defined as BMI  $\geq$  30 kg/m<sup>2</sup>. Patients were also stratified by residence (urban or rural) and by their adult occupation in four groups: (1) graduate professionals; (2), undergraduate technicians and administrators; (3) clerks and salesmen; (4), semi-skilled and unskilled workers, and uneducated shepherds and peasants. The following Poisson regression model was used:

$$\log(\lambda) = \beta_0 + \beta_1(\text{gender}) + \beta_2(\text{smoking}) + \beta_3(\text{BMI}) + \beta_4(\text{residence}) + \beta_5(\text{occupation})$$

All statistical analyses were carried out using SPSS statistical software (version 16.0, Chicago, IL, USA).

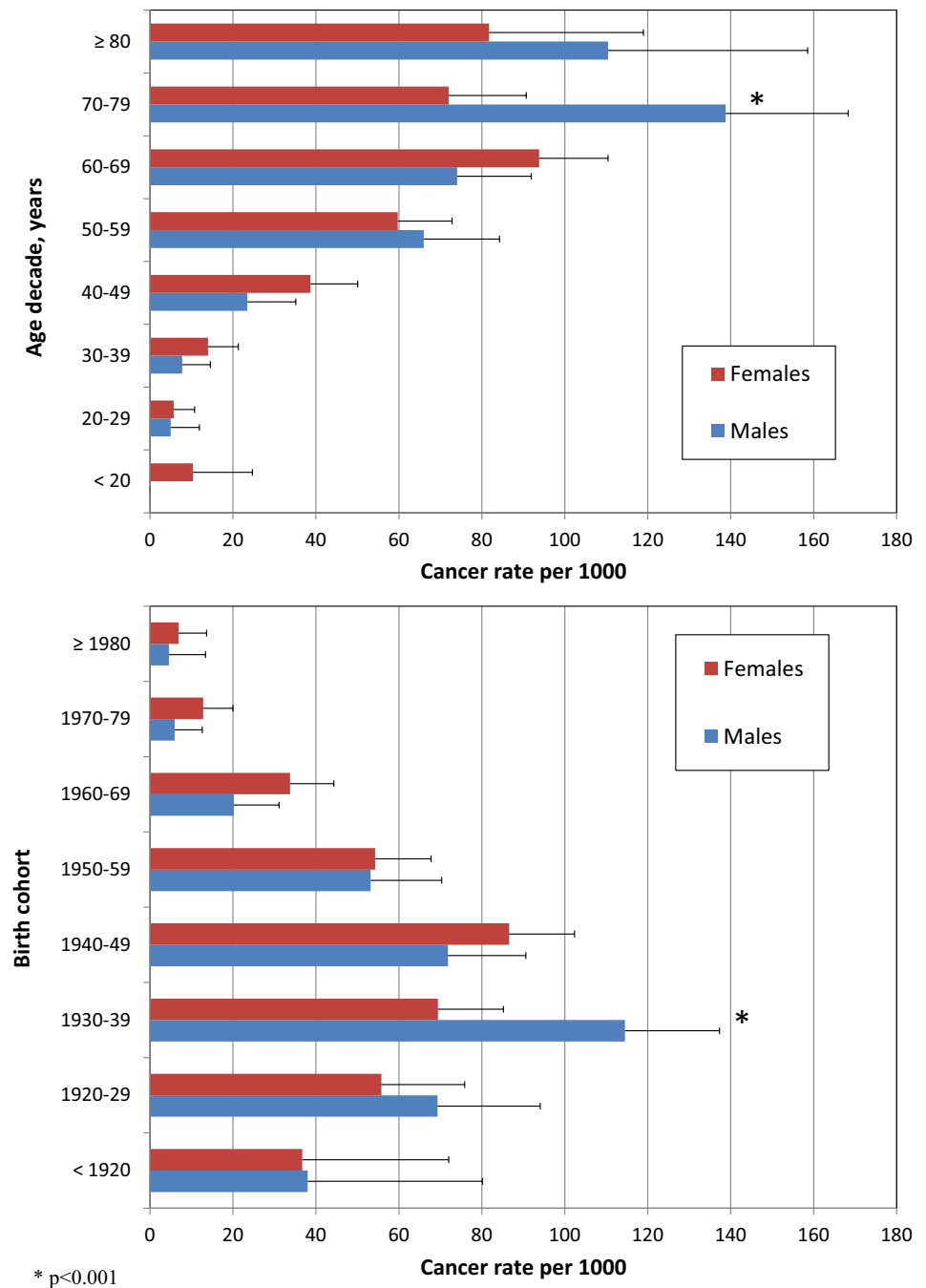
## Results

All patients were white Caucasians from Northern Sardinia. A total of 10,546 clinical records were available for the analysis, 6559 of which (62.2%) for female patients. Five-hundred and forty-one patients reported a diagnosis of at least one site-specific cancer (prevalence rate 5.1%). The distribution of all types of cancer by age decade and birth cohort is illustrated in Fig. 1. Cancer was more frequent in men (5.5%; 221/3987) than in women (4.9%; 320/6559) though the difference was not statistically significant, with the exception of age groups 70–79 and birth cohort 1930–1939. The cancer rate peak occurred in birth cohorts 1930–1939 among men, and 1940–1949 among women. Interestingly, cancer prevalence with respect to the epidemiologic transition period, was 7.15% (210/2937) for birth cohorts prior to 1950; 8.85%, (78/781) for patients born between 1950 and 1960; and 10.7% (3/28) for patients born after 1960, indicating a trend toward higher cancer frequency within and after economic and nutrition transition. The most prevalent cancer types in the cohort studied were: lymphoma and leukemia followed by liver and biliary tract, prostate, nasopharynx and colorectal cancers among men, but breast cancer, lymphoma and leukemia, thyroid and colorectal cancer among women (Fig. 2). Cancer distribution according to the most likely aetiology is reported in Fig. 3. It is of note that for generations born before 1960 infection-related tumors predominated, followed by hormone- and lifestyle-related ones, whereas for generations born after 1950 the most prevalent were hormone-related cancers.

Figure 4a–c illustrates the regression parameters and their 95% confidence bars for age, birth cohort and period (calendar time), estimated by the Poisson log-linear models. Age was the strongest predictor of the all-cancer rate with an exponential increase observed up to age 80 and beyond, without inflection points. The birth cohort curve showed a more variable trend, with a rise for generations born after 1920, a sharp upward inflection for generations born around 1950 and a downward inflection around 1970. In contrast, the time period did not show turning points, indicating that the cancer rate remained basically unchanged throughout the interval 1995–2013. APC plots for separate aetiological categories are not shown because of the small cancer counts. The comparison of model fit is reported in Table 1. The full APC model fits the data best, although the fitting did not change significantly following the addition of the period ( $P$ ) factor.

Poisson regression model also provided the relative magnitude of the other variables included in the analysis (Table 2). As expected, BMI greater than 30 kg/m<sup>2</sup> was significantly associated with all-cancer risk, whereas no effect was observed for place of residence and smoking habits. The risk of cancer was similar for

**Fig. 1** Distribution of all malignancies found in 10,546 subjects by age decade (a) birth cohort (b) and gender (Sardinia, Italy, 1995–2013)



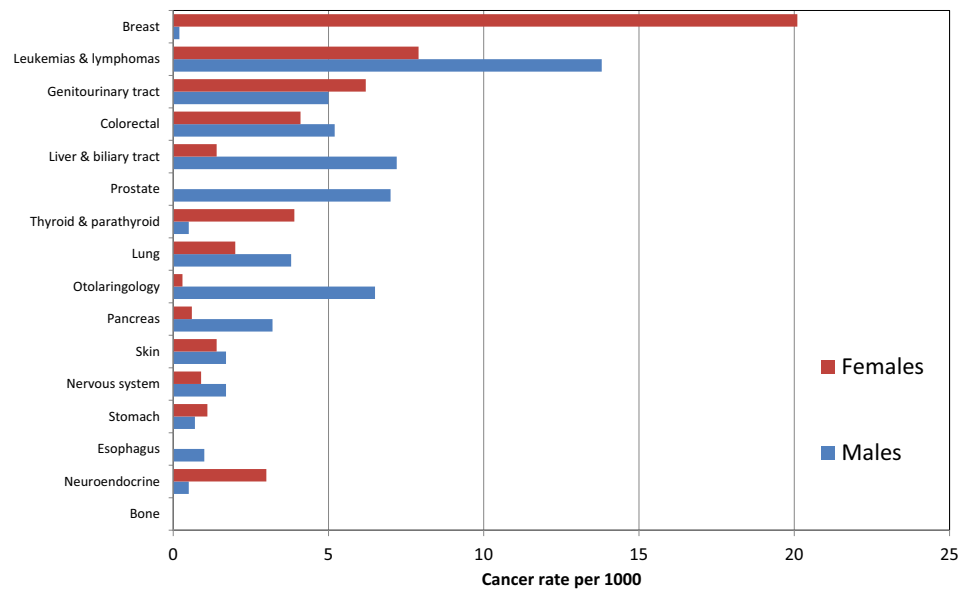
both genders except as regards gender-specific malignancies. In the cohort studied, cancer rate increased almost linearly from the lowest to the highest occupational categories (Table 2).

## Discussion

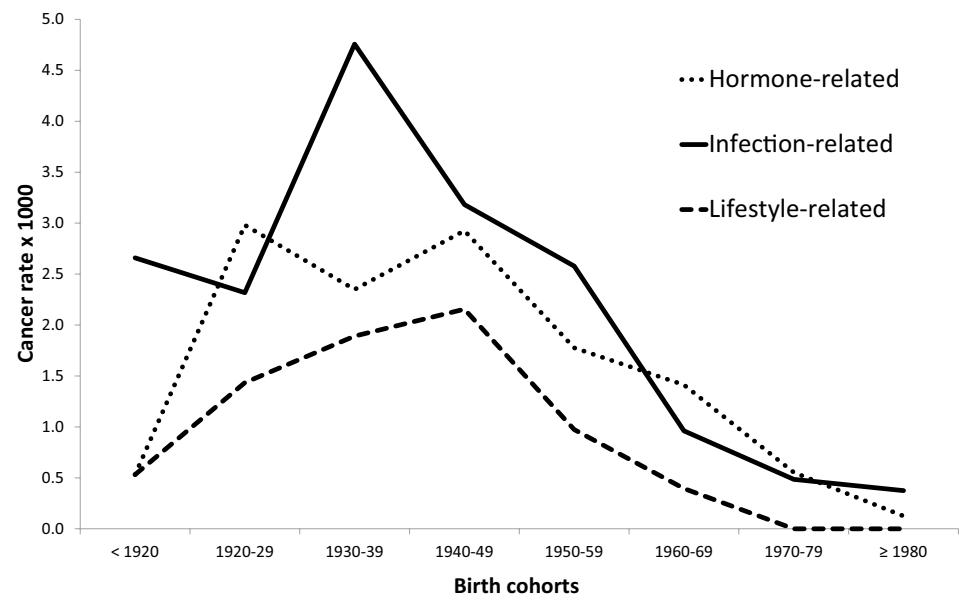
Cancer is a serious burden for society, both in terms of time lost in work productivity and increased health expenditure

(Hanly et al. 2015), including costs due to medical prevention and treatment, hospital admissions, long-term disability and premature mortality. In the population aged 65 years or over, cancer is the second leading cause of illness, preceded only by cardiovascular diseases, with obviously important socio-economic implications (Prince et al. 2015). Considerable differences have been observed between countries in cancer risk, as well as within the same geographic area depending on the influence of specific local

**Fig. 2** Distribution of cancer type in 10,546 subjects according to gender (Sardinia, Italy, 1995–2013)



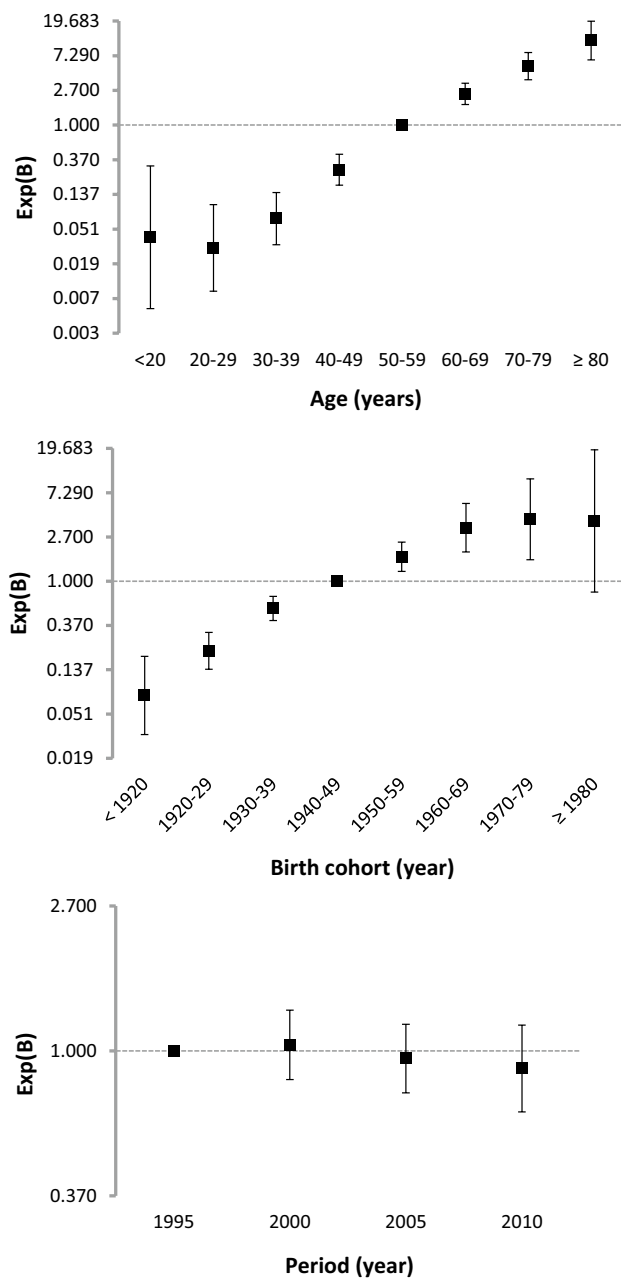
**Fig. 3** Distribution of cancer type in 10,546 subjects according to the most likely aetiology (Sardinia, Italy, 1995–2013)



conditions, including exposure to environmental and/or dietary carcinogens (Ferlay et al. 2010).

Up until World War II the Mediterranean island of Sardinia was considered a “low-resource” region compared with mainland Italy. Only in 1951 was endemic malaria definitively eradicated and the island underwent rapid economic development improving the standard of living of the population (Tognotti 2009). Adult mortality rate, which before World War II exceeded the national average, decreased progressively and in 1950 became one of the lowest of all Italian regions (979 compared with 1048/100,000 in mainland Italy) (Pes et al. 2014). Still in 1950 Sardinia ranked 17th among the 19 Italian regions

for cancer prevalence (63.2 versus 107 per 10<sup>5</sup>) (Pes et al. 2014). However, the crude prevalence of cancers rose sharply between 1970 and 2012 (Budroni et al. 2013). Moreover, site-related cancer distribution is quite distinct from that recorded in mainland Italy. For instance, colorectal cancer is the most frequently diagnosed malignancy in Sardinia—the estimated incidence of 106 per 100,000 persons/year among men is somewhat higher than the rest of Italy—followed by lung and prostate cancer. In women, breast cancer is the most frequent, followed by colorectal, lung, melanoma, stomach and cervical cancers. These data suggest that genetic, environmental and/or nutritional factors are major determinants of the differences in cancer



**Fig. 4** Poisson regression estimates of cancer for age, birth cohort and time period (calendar time) in 10,546 subjects (Sardinia, Italy, 1995–2013).  $Exp(B)$  exponentiated regression coefficient. The categories chosen as reference are, for age (a) age 50–59 years; for time period (b) the interval 1995–1999; for birth cohort (c) the generations born in 1940–1949

rate recorded in Sardinia compared with other countries. During the 1950–1960s the Sardinians experienced a dramatic improvement in their standard of living. As a result of increased wealth, Sardinians have been exposed to potential environmental, occupational and dietary factors (unprocessed and processed meat, animal fats) acting as pro-carcinogens (Pes et al. 2014). For instance, the diet of

the generations born in the first half of twentieth century, reportedly one of the determinants of delayed aging and increased longevity recorded for these generations at the end of last century (Poulain et al. 2004) has been replaced with an unhealthier, “Western-like” diet (Pes et al. 2015). Since epidemiological transition influenced several generations at roughly the same time, Sardinia represents an ideal setting to evaluate the temporal trend of cancer.

In this study, we investigated the single effect of age, birth cohort and time period on cancer rate in a large cohort of patients of Northern Sardinia undergoing upper endoscopy. As expected, our findings confirmed previous reports indicating that aging *per se* is an independent risk factor for cancer occurrence (Thakkar et al. 2014; Harding et al. 2012; Franceschi and La Vecchia 2001; Hansen 1998; Budroni et al. 2013). A steep upward trend was noticed up to the age of 80 and beyond. With regard to the cohort effect, the proportion of infection-related cancers was greater in generations born before 1960 than in those born after this period, as observed in other developing populations (Wong et al. 2010). However, no definite conclusions could be drawn in our study, given the small size of the aetiological subgroups. A stronger cohort effect was noticed in the generations born from 1950 onward compared with those born earlier, suggesting that the transitional generations were exposed to a significantly increased risk of cancer. However, in these generations the proportion of infection-related cancers was lower, whereas hormonally modulated cancers were responsible for the largest contribution to overall cancer risk. The downward inflection observed for generations since 1970 is too recent for us to rule out whether it is due to chance, and it is premature to interpret it as being due to a reduction in infection-related cancers. Unfortunately, in our study the APC analysis of cancers based on presumed aetiology was not possible because of the small subgroup size. However, the relative increase in hormone-related cancers was not only at the expense of infection-related cancers but also, to a lesser extent, to lifestyle-related cancer. The decline of the latter in the Sardinian population might result from the sharp change in smoking habits determined by successful anti-smoking campaigns. The percentage of male smokers in Sardinia was 48%, reported in a survey of 1984, whereas in 2009 it had decreased to almost 17.5% in males and 13.8% in females (Muntoni et al. 2009), a time trend also reported in Caucasian and Asian populations (Bray et al. 2004). In contrast, no change in cancer rate was observed in our cohort over the observation period, and it is, therefore, unlikely that the rise recorded in the most recent decades is due to an improvement in diagnostic techniques over the last 20 years. These results indicate that the recent increase in cancer prevalence in Sardinia is mostly due to aging, as reported by Budroni et al. (2013).

**Table 1** Comparison of age-period-cohort Poisson regression models for cancer trends in 10,546 patients undergoing upper endoscopy (Sardinia, Italy, 1995–2013)

Goodness-of-fit	Regression models			
	Age	Age-period	Age-cohort	Age-period-cohort
$Df^a$	10,538	10,535	10,531	10,528
Change in $df^a$	–	3	4	3
Deviance	2926.822	2925.919	2831.105	2829.486
Change in deviance	–	0.903	95.717	97.336
AIC <sup>b</sup>	4024.822	4029.919	3943.105	3947.486
BIC <sup>c</sup>	4082.930	4109.817	4052.058	4078.229
<i>P</i> value	–	0.875	<0.0001	<0.0001

The model comparison  $\chi^2$  test was performed with model 'Age' as reference. Decreasing residual deviance indicates a better fit

<sup>a</sup>*Df* degrees of freedom

<sup>b</sup>AIC Akaike's Information Criterion

<sup>c</sup>BIC Bayesian Information Criterion

**Table 2** Poisson regression estimates of the covariate effect on cancer rate in 10,546 patients undergoing upper endoscopy (Sardinia, Italy, 1995–2013)

Covariate	Exp( <i>B</i> ) <sup>a</sup>	95% Wald confidence interval for Exp( <i>B</i> )	<i>p</i> value
<b>Gender</b>			
Women	1.000	–	–
Men	1.045	(0.762–1.432)	0.785
<b>Smoking habits</b>			
Non-smokers	1.000	–	–
Smokers	1.117	(0.952–1.298)	0.199
<b>BMI<sup>b</sup></b>			
<30 kg/m <sup>2</sup>	1.000	–	–
≥30 kg/m <sup>2</sup>	1.635	(1.427–1.895)	<0.0001
<b>Residence</b>			
Urban	1.000	–	–
Rural	0.971	(0.754–1.25)	0.844
<b>Occupation<sup>c</sup></b>			
I	1.000	–	–
II	0.783	(0.50–1.20)	0.268
III	0.662	(0.42–1.03)	0.066
IV	0.586	(0.38–0.89)	0.012

<sup>a</sup>Exp(*B*), exponentiated regression coefficient

<sup>b</sup>Body Mass Index (kg/m<sup>2</sup>)

<sup>c</sup>I graduate professionals, II undergraduate technicians and administrators, III clerks and salesmen, IV semi-skilled and unskilled workers, and uneducated shepherds and peasants

As for the other variables entered in the regression model, only body mass index was a risk factor for malignant tumors, whereas belonging to the lowest social status, measured by current occupation, was a negatively associated (protective) factor.

Our study has strengths and limitations. Among the former are the genetic and ethnic homogeneity of the

population (Cavalli-Sforza et al. 1994), and the accuracy in retrieving information on patients cancer history. On the other hand, the cohort studied, came from Northern Sardinia and could not be considered as representative of the entire island population; the date of cancer diagnosis was not available but only the date of the EGD procedure. Moreover, the selection of patients who underwent EGD may have biased cancer frequency although it was minimized, since medical history was collected by trained clinicians throughout the period considered. Finally, the cohort size was rather limited, therefore, the APC analysis was performed considering all cancers together, and the analysis of individual aetiological categories was purely descriptive.

Nevertheless, we think that the findings of this study may be helpful to delineate better the influence of epidemiological transition on the recent cancer rate trend in Sardinia, and may provide clues for the adoption of preventive measures by the health care system, such as programs to reduce tobacco-smoking, pollution in contaminated areas, obesity and unhealthy food choices, as well as population-tailored cancer screening strategies.

**Author contributions** GMP and MPD designed the study and wrote the manuscript; MPD and SB collected the medical history and obtained the informed consents, FC and GM recorded the data; GMP and MPD analyzed the data and critically reviewed the manuscript.

**Compliance with ethical standards**

**Conflict of interest** None disclosed.

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