Cancers attributable to infectious agents in Italy

Giulia Collatuzzo, Carlo La Vecchia, Fabio Parazzini, Gianfranco Alicandro, Federica Turati, Matteo Di Maso, Matteo Malvezzi, Claudio Pelucchi, Eva Negri, Paolo Boffetta

PII: S0959-8049(23)00018-7

DOI: https://doi.org/10.1016/j.ejca.2023.01.010

Reference: EJC 12787

To appear in: *European Journal of Cancer*

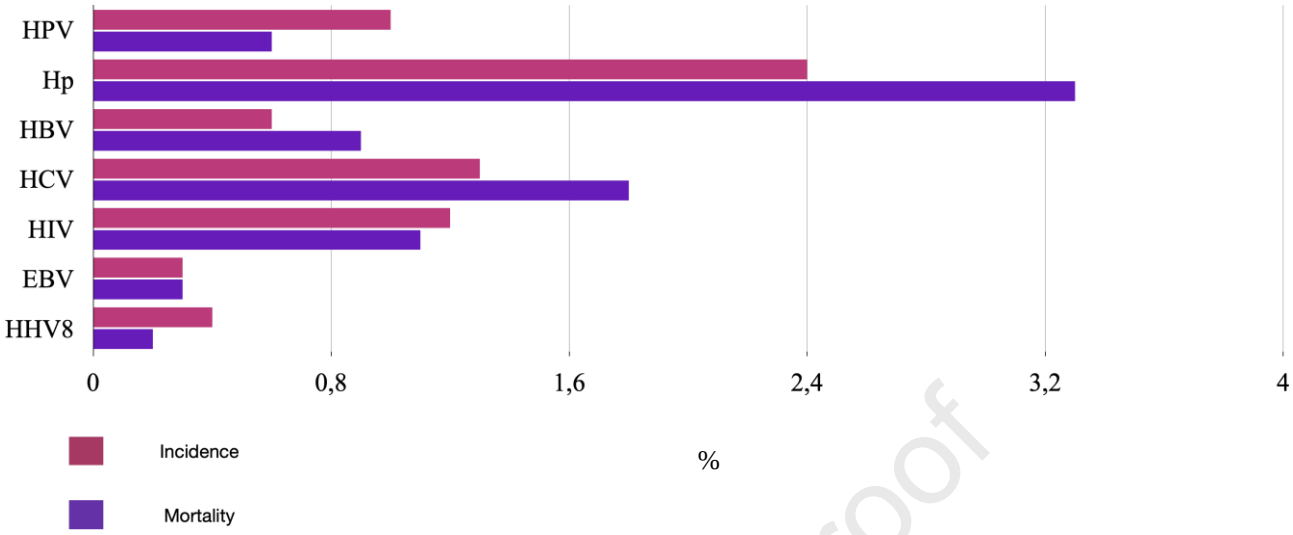
Received Date: 10 November 2022

Revised Date: 20 December 2022

Accepted Date: 10 January 2023

Please cite this article as: Collatuzzo G, La Vecchia C, Parazzini F, Alicandro G, Turati F, Di Maso M, Malvezzi M, Pelucchi C, Negri E, Boffetta P, Cancers attributable to infectious agents in Italy, *European Journal of Cancer*, https://doi.org/10.1016/j.ejca.2023.01.010.

Graphical abstract



Cancers attributable to infectious agents in Italy

Giulia Collatuzzo[1], Carlo La Vecchia[2], Fabio Parazzini[2,3], Gianfranco Alicandro[2], Federica Turati[2], Matteo Di Maso[2], Matteo Malvezzi[2], Claudio Pelucchi[2], Eva Negri[1,2], Paolo Boffetta[1,4]

1-Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

2-Department of Clinical Sciences and Community Health (DISCCO), University of Milan, 20122 Milan, Italy.

3-Department of Obstetrics, Gynecology, and Neonatology, University of Milan, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 12, 20122 Milan, Italy.

4-Stony Brook Cancer Center, Stony Brook University, Stony Brook, New York

Corresponding author

Paolo Boffetta, Stony Brook Cancer Center, Stony Brook University, Lauterbur Drive, Stony Brook, NY 11794.
Email: paolo.boffetta@ stonybrookmedicine.edu

Abstract

Objectives: To provide an evidence-based, comprehensive assessment of the current burden of infection-related cancer in Italy.

Methods: We calculated the proportion of cancers attributable to infectious agents (Helicobacter pylori [Hp]; hepatitis B and C viruses [HBV and HCV]; human papillomavirus [HPV]; human herpesvirus-8 [HHV8]; Epstein–Barr virus [EBV]; and human immunodeficiency virus [HIV]) to estimate the burden of infection-related cancer incidence (2020) and mortality (2017). Data on the prevalence of infections were derived from cross-sectional surveys of the Italian population, and relative risks from meta-analyses and large-scale studies. Attributable fractions were calculated based on the counterfactual scenario of a lack of infection.

Results: We estimated that 7.6% of total cancer deaths in 2017 were attributable to infections, with a higher proportion in men (8.1%) than in women (6.9%). The corresponding figures for incident cases were 6.5%, 6.9%, and 6.1%. Hp was the first cause of infection-related cancer deaths (3.3% of the total), followed by HCV (1.8%), HIV (1.1%), HBV (0.9%), HPV, EBV, and HHV8 (each ≤0.7%). Regarding incidence, 2.4% of the new cancer cases were due to Hp, 1.3% to HCV, 1.2% to HIV, 1.0% to HPV, 0.6% to HBV, and < 0.5% to EBV and HHV8.

Conclusions: Our estimate of 7.6% of cancer deaths and 6.9% of incident cases that were attributable to infections in Italy is higher than those estimated in other developed countries. Hp is the major cause of infection-related cancer in Italy. Prevention, screening, and treatment policies are needed to control these cancers, which are largely avoidable.

Keywords: infection; cancer; attributable fraction; estimates; Italy

Introduction

The discovery of infections as etiological factors of cancer dramatically changed cancer prevention and medical practice because of the avoidable nature of infectious causes. Several viruses may cause cancer in humans, including hepatitis B virus (HBV) and hepatitis C virus (HCV), which cause liver cancer, with HCV also causing non-Hodgkin lymphoma (NHL) [1]; human papillomavirus (HPV), primarily linked to cervical cancer, but also related to other anogenital cancers and cancer of the oropharynx [2]; Epstein–Barr virus (EBV), causing nasopharyngeal cancer and Hodgkin lymphoma [3]; HHV8, causing Kaposi sarcoma; and human immunodeficiency virus (HIV), which is associated with Kaposi sarcoma, anal cancer, and non-Hodgkin lymphoma (HL) [4]. Among bacteria, Helicobacter pylori (Hp) is the only established oncogenic agent, being the main risk factor for gastric cancer and gastric mucosa-associated-lymphoid tissue lymphoma (MALT) [5]. Parasites of the Schistosoma, Opisthorchis, and Clonorchis genera are established causes of bladder cancer and liver cholangiocarcinoma [6]. Other infectious agents are suspected causes of cancer, including the bacterium, Mycobacterium tuberculosis (Mt) [7], and the parasite, Plasmodium falciparum (Pf) [8]. Martel et al., based on the GLOBOCAN 2018 database, estimated a total of 2.2 million infection-attributable cancers worldwide in 2018, with Hp being the leading cause of cancer, followed by HPV, HBV, and HCV [9].

National estimates of attributable cancers due to infections have been calculated for several countries, including China [10], Vietnam [11], Korea [12], Japan [13], France [14], the UK [15], Brazil [16], the US [17], and Denmark [18].

Such estimates, however, are not available for Italy. This study aims at estimating the burden of cancer attributable to infections in the Italian population, based on mortality data from 2017 and cancer incidence data from 2020. Such estimates are important to set priorities and design interventions to reduce infection-related cancers, as well as to establish the cost-effectiveness of population-based preventive interventions in Italy.

Methods

Our study is part of a systematic analysis of attributable causes of cancer in Italy, based on evidence-based research with the purpose of estimating the numbers of cancer deaths in 2017 and cancer cases in 2020 in Italy that could be attributable to known carcinogens, including smoking, alcohol, occupational exposures, infections, and nutritional, reproductive, and anthropometric factors.

The proportion of disease in the total population that can be attributable to a risk factor is defined as the attributable fraction (AF) and commonly expressed as a percentage. We applied the classic formula originally described by Levin (1953) [19] to calculate the AF of cancer for specific infectious agents. It is a function of the relative risk (RR) of the disease (e.g., a specific cancer) associated with exposure to the risk factor (e.g., a particular infection) and the prevalence of the risk factor (P) in the population:

$$AF = \frac{P*(RR-1)}{[\ P*(RR-1)\ ]+1}$$

To estimate the AF, we used no infections as a counterfactual scenario. We considered all infectious agents classified into Group 1 (established human carcinogens) by the International Agency for Research on Cancer (IARC) [20].

The RR of the cancer incidence and mortality related to specific infectious agents and cancers were obtained from meta-analyses or large studies, as specified in Table 1. Data on the prevalence of infection around the year 2000 (i.e., we allowed a 15-to-20-year latency between infection and cancer) were obtained from several sources, as shown in Table 1 [21-31].

The sex-specific number of cancer deaths and incident cancer cases was obtained from the 2020 Report of the Italian Association of Cancer Registries (AIRTUM) [32]. We developed algorithms to estimate the number of deaths and cases of cancers not included in the AIRTUM Report, such as cardia and non-cardia gastric cancer (details are shown in Supplementary Table 1), and the number of cancer deaths and cases used in the analysis is listed in Table 2.

For cancers related to multiple infectious agents, like liver and anal cancer, we calculated partial AF based on the assumptions of independence of infection prevalence and RR (i.e., no interaction according to a multiplicative model) [33].

The data source and approach used to define exposure, RR, and prevalence are reported below.

Definition of exposure

We included the following cancers and their corresponding infectious agents in our study: liver cancer following infection with HBV and HCV; NHL following HCV; cervical, oral, pharyngeal, penis, anal, vaginal, and vulvar cancers following HPV infection; nasopharyngeal (NPC) and HL following EBV infection; gastric cancer, separately for cardia and non-cardia subsites, and gastric MALT following infection with Hp; Kaposi sarcoma following the infection with HHV8 and HIV; and anal cancer, and HL and NHL related to HIV infection.

Burkitt lymphoma was not included among the cancers associated with EBV because of the very low incidence of this disease in Italy. Clonorchis sinensis, Opisthorchis viverrini, and Schistosoma haematobium were not considered among the infectious agents because of the sporadic occurrence of these infections in Italy. Similarly, Merkel cell polyomavirus, associated with the homonymous skin carcinoma [34], was not accounted for because of the rarity of this cancer. Two infectious agents suspected to cause cancer in humans (Mt and Pf) were not included in the main analysis, but we provided separate estimates for them as well.

Data used for RR and prevalence

The RR used in the calculation of AFs was derived from meta-analyses or large-scale cohort studies (Table 2). We applied the same RR to men and women (i.e., we assumed no infection–sex interaction), and to mortality and incidence data (i.e., we assumed no effect of infection on cancer survival).

Results

AF and attributable cancer cases and deaths in Italy are provided in Tables 3 and 4. In 2017, 7.6% of all cancer deaths in Italy were attributable to infections (N=13,670), corresponding to 8,124 deaths among men (8.1%) and 5,546 (6.9%) among women. Gastric cancer (including non-cardia, cardia, and MALT-lymphoma) following Hp infection represented 3.3% of total cancer deaths, with a higher proportion in men (3.4%) than in women (3.0%).

Liver cancer following either HBV or HCV infection represented 2.7% of cancer deaths, with 0.9% being attributable to HBV and 1.8% to HCV, and a higher proportion in men than in women. HPV accounted for 0.6% of cancer deaths, with a higher proportion in women than in men (0.9% vs 0.3%). We estimated 1.1% of cancer deaths due to HIV, with similar proportions in men (1.2%) and women (1.0%).

The other infectious agents accounted for no more than 0.7% of cancer deaths each.

The number of cancer cases attributable to infections in Italy in 2020 was about 24,500. Hp was responsible for 2.4% of cancer cases, including 8976 gastric cancers (8512 non-cardia and 464 cardia cases in particular) and 167 gastric MALT cases. HBV and HCV resulted in 0.6% and 1.3% of cancer cases, equal to 2381 and 4519 liver cancer cases, respectively, with HCV also causing 203 non-Hodgkin lymphoma cases. HPV accounted for 1.0% of total cancer cases (n=3691), including 2365 cervical, 557 pharyngeal, 252 anal, 186 oral, 174 vulvar, 81 vaginal, and 76 penile cancer cases.

We calculated that 1.2% of cancer cases were attributable to HIV; of those, 899 were Kaposi sarcoma cases, 2884 NHL cases, 376 anal cancer cases, and 359 HL cases. Also, 0.3% of cancer cases were attributable to EBV, in particular 424 cases of nasopharyngeal cancer and 774 of HL. Finally, HHV8 accounted for all 927 cases of Kaposi sarcoma, corresponding to 0.2% of total incident cancers.

The AF calculated for Italy was higher than for many developed countries (Table 5).

Discussion

As the first study to assess the overall infection-related cancer burden in Italy using standardized methods, our research found that a total of 24,584 cancer cases in 2020 and 13,670 cancer deaths (8124 in men and 5546 in women) in 2017 in Italy were attributable to infections, corresponding to 6.5% and 7.6% of all cancer cases and deaths, respectively. In particular, 8.1% of cancer deaths in men and 6.9% of cancer deaths in women resulted to be attributable to infections. The main infectious cause of cancer in Italy is Hp, with 3.3% attributable cancer deaths from cancer in 2017, followed by HCV (1.8%), HBV (0.9%), and HPV (0.6%). Infection-related cancers accounted for a larger proportion of cancer deaths than that of cancer cases because of the high fatality of most infection-related cancers, notably liver cancer.

Based on our estimates, a higher proportion of cancers were attributable to infections in Italy than other European countries, such as France [14], Denmark [18] the UK [15], and the US [17]. In addition, the AF of cancer related to infection in the Italian population is similar to that of less developed countries such as Brazil [16] and Vietnam [11]. This is largely because of the high proportion of gastric cancer from Hp infection and liver cancer from HBV and HCV infection in those countries and in Italy, and to the high HPV prevalence in Brazil and Vietnam [16, 11].

Our estimates are based on infectious agents with sufficient evidence for a causal role in cancer occurrence. Other infectious agents suspected to cause cancer in humans include Mt [7] for lung cancer and Pf for Burkitt lymphoma [8]. In addition, established carcinogenic agents might cause cancers other than those included in our analysis, such as EBV for gastric cancer [35]. The number and types of cancers due to EBV are still to be defined [35], with increasing evidence reporting an association with gastric cancer [36]. Assuming these associations are causal, we estimated that a small number of cancers would be attributable to these additional agents. For example, the proportion of lung cancers attributable to infection with Mt, based on a reported prevalence of latent infection of 2.1% [37] and a RR of lung cancer equal to 1.76 [38], would be 0.16%, corresponding to 54 deaths and 65 cases.

The inclusion of these agents may be worthwhile in studies conducted in high-risk populations for these infections (e.g., from middle- and low-income countries).

The proportion of cancer caused by infectious agents is a dynamic indicator, depending on temporal changes in the prevalence of relevant agents. Some of these changes are the result of preventive measures (e.g., HPV vaccination), while others occur without planned interventions (e.g., a decrease in the prevalence of Hp infection [39]). Moreover, it is difficult to estimate the proportion of cancers due to coinfections, which is particularly relevant for liver cancer, due to concomitant HBV and HCV. To this purpose, potential interactions between multiple infectious agents in determining the risk of a specific cancer need to be accounted for, but data on the patterns of interaction are limited [40-44]. Precise and updated estimates of the proportion of HBV–HCV coinfection prevalence in Italy are scarce [45, 46]; we, therefore, assumed independence of effect of the two infections and estimated that 6.3% of liver cancers were attributable to HBV–HCV coinfection. Similarly, when considering anal cancer, we calculated that 10% of the cases were attributable to concomitant HIV–HPV infections [47]. The change in infection prevalence heavily impacts the number of cancers, implying a large potential of prevention. This particularly concerns infections for neoplasms for which therapies and/or vaccines are available. Hp can be easily detected with noninvasive diagnostic tests [48], and first-line eradication therapies have more than 80% of effectiveness [49, 50]. HBV vaccination is mandatory in all Italian newborns since 1991, and all those born since 1980 were vaccinated at age 12 [51]. The current therapies are able to control liver disease from both HBV and HCV infection [52-54]. Moreover, both HBV and HCV are screened on a regular basis in some high-risk settings such as hospitals through healthcare workers' surveillance [55-57] and prisons [58-60]. The fact that the prevalence of major infectious agents is progressively declining leads to a continuous change in the AF, which indeed deserves to be periodically updated to have the most representative estimates for a certain country in a certain time frame.

Regarding HPV, vaccination coverage rates remain suboptimal in Italy [61], with a decreasing trend in the last few years for different birth cohorts and both sexes, which was further impacted by the Coronavirus Disease 2019 (COVID-19) pandemic [62]. The proportion of cancers attributable to HPV in Italy reflects the lack of vaccination in women born before 1996, with a birth-cohort effect due to the introduction of HPV vaccination. Further, we have to consider the higher risk of cervical cancer observed in Italy among recently immigrated women (representing about 9% of women living in

Italy) who have different rates of HPV infection, cervical screening, and vaccination coverage [63].

The cultural and lifestyle heterogeneity due to Italian geographical areas (i.e., northern, central, and southern, including major islands), next to the environmental differences between these areas, determines the distinct patterns of risk factors, and different incidence and mortality rates of cancer [64]. Participation in the available cancer screenings in the different Italian areas varied between 62% and 90%, considering planned and private screening for cervical cancer [65].

At the same time, head-and-neck HPV-related cancers in Italy are increasing, consistently with other countries [66].

The higher rates in men likely reflect different lifestyle habits by sex, and consequent exposure to infection hazards, including the use of injective drugs and men who have sex with men, given the potential transmission of the infection through blood and sexual contact [67-69]. This applies also to HIV- and HHV8-related cancers, observed mainly in men.

Hp infection accounted for the largest AF of infection-related cancers in Italy. Our study allowed us to translate common knowledge on Hp etiological link to gastric cancer with objective proportions and numbers, also drawing possible figures by cancer subsite. In particular, 21% of cardia cancer deaths were caused by Hp infection, corresponding to 300 deaths in 2017. These summed up to the 5500 deaths from non-cardia gastric cancer, and 57 deaths from MALT of the stomach, making Hp responsible for up to 3.3% of deaths from cancer in 2017 in Italy. Noticeably, the knowledge on the role of Hp in gastric cancer subtypes is evolving as increasing evidence underlines its causal role in both cardia and non-cardia cancer with the latter showing a stronger association than the former, as commonly known. A large analysis that has been recently conducted within the China Kadoorie Biobank found a significant association of 3.06 between Hp and cardia gastric cancer [70], higher than that we adopted based on more comprehensive data [9]. If on the one side, the link between Hp and either anatomical subsite of gastric cancer has been reported of higher magnitude in the Chinese population than in the European one, previous studies may have missed to identify the relationship with cardia cancer because of the issues related to the methods of detection, as discussed by the

authors [70]. Therefore, our results could be a conservative estimate of the number of cardia cancers attributable to Hp infection.

To date, no standardized and organized screening program for Hp infection exists [71] despite the noninvasive diagnostic tests and the antibiotic therapies available for the infection. Most population-based studies on Hp testing and treatment have been conducted in Asian countries, given the high incidence of gastric cancer and the diffusion of virulent Hp strains [72-75]. Recently released Italian guidelines for the management of Hp infection states with a moderate level of evidence and high grade of recommendation that the testing and treatment of Hp should be performed in dyspeptic subjects younger than 50, and in subjects using nonsteroidal anti-inflammatory drugs or aspirin with a history of the peptic ulcer [76]. Our analysis calls for intervention to control Hp infection in Italy on a broader scale.

Infectious agents are heterogeneously distributed in the population. Many studies have described a higher prevalence of infection, including Hp [77], HBV [78], HCV [79], HPV [80], and HIV [81], in less affluent subgroups, including immigrants and less educated subjects. Indeed, infectious-related cancers are characterized by social disparities [82-86]. As more deprived subgroups of the population have suboptimal access to healthcare interventions, despite the public nature of the healthcare system in Italy can limit this phenomenon, specific plans should be developed to enhance their involvement in ongoing prevention programs, such as HPV and HBV vaccination [87,88]; also, deprived subgroups could be targeted with new potential preventive interventions.

A possibility is that high-risk subjects should be identified, during general health visits, or occupational surveillance [89-91], and recommended to undergo specific tests of screening for infection status and, when possible, to be targeted with available interventions. In fact, given the long latency, a high proportion of cancer could be avoided by eradicating the infected, with benefit also for the young generations through the reduction in the infection reservoir. The benefit would also be projected within the household, where the transmission is more likely, with benefits for the new generations. Moreover, vaccination for HBV [92] and HPV [93, 94] should be made available and strongly recommended in unvaccinated subjects of both sexes. The eradication and vaccination against the mentioned infections would help shape the AF of related cancers in the future generations, reducing the reservoir of infection and interrupting the routes of transmissions [95].

Our study has a few limitations. First, some of the data we used were not derived from representative samples of the general Italian population. This especially regards less prevalent infectious agents. We were also unable to consider geographical differences within the country of infection-related cancer by geographical areas, given the heterogeneous availability of data from different regions. Moreover, mortality data for some specific cancers were not available and were then derived from incidence data, as described in the Appendix. Further, we used RR derived from studies conducted in other countries, which did not comprehensively account for potential background factors and the virulence of the infectious agents, which vary across the countries. The use of a single source to estimate the prevalence of infections does not take into account its temporal trend, and the latency chosen between infection and cancer diagnosis or death is subject to uncertainty. Despite accounting for coinfections, we also assumed no interaction among the agents, possibly introducing some bias in both directions (overestimating cases if the interactions were more than multiplicative and underestimating cases if they were less than multiplicative). Finally, we did not account for the uncertainties around the AF point estimates. Such uncertainties depend on the statistical precision of the data on prevalence and the RR, as well as on the accuracy of these data to the national Italian population.

This study also has several strengths. First, we provided for the first time an estimate of the burden of cancer related to infections in Italy using recent mortality and incidence data.

All the main known oncogenic infectious agents with a substantial prevalence in Italy were included, in association with all the cancers they are known to cause. The AF was calculated using standardized methodology, based on data from recent systematic reviews and meta-analyses and cancer registries. We also accounted for the latency period between infection and cancer occurrence, to draw an accurate picture of infection-related cancer in Italy.

In conclusion, our results provide a systematic assessment of infection-associated cancer risk in Italy. The AF of cancer due to infections appears high. These results indicate that

most of the cancer burden related to infections in Italy is due to two agents for which vaccinations are available, namely HPV and HBV, and two other agents for which screening and treatment are possible, Hp and HCV. A better management and prevention of relevant infections may lead to a better control of the burden of infection-related cancers in Italy, for example, through vaccination and screening campaigns in schools and at the workplace, as well as public health campaigns targeting high-risk populations [96].

A large portion of infection-related cancers are avoidable by preventive program, including screening for infection, vaccination (also in adults), and therapies as appropriate.

Updated estimates should be provided in the future for the Italian population, allowing us to draw the trends of infectious-related cancer in time based on the variation of the prevalence of the infections.

References

1- Momin B, Richardson L. An analysis of content in comprehensive cancer control plans that address chronic hepatitis B and C virus infections as major risk factors for liver cancer. J Community Health. 2012 Aug;37(4):912-6.
2- Szymonowicz KA, Chen J. Biological and clinical aspects of HPV-related cancers. Cancer Biol Med. 2020 Nov 15;17(4):864-878
3- Farrell PJ. Epstein-Barr Virus and Cancer. Annu Rev Pathol. 2019 Jan 24;14:29-53.
4- Zheng J, Shi Y, Feng Z, Zheng Y, Li Z, Zhao Y et al.Oncogenic effects of exosomes in γ-herpesvirus-associated neoplasms. J Cell Physiol. 2019 Nov;234(11):19167-19179
5- Alipour M. Molecular Mechanism of Helicobacter pylori-Induced Gastric Cancer. J Gastrointest Cancer. 2021 Mar;52(1):23-30
6- Arora N, Kaur R, Anjum F, Tripathi S, Mishra A, Kumar R et al.Neglected Agent Eminent Disease: Linking Human Helminthic Infection, Inflammation, and Malignancy. Front Cell Infect Microbiol. 2019 Dec 6;9:402.
7- Hwang SY, Kim JY, Lee HS, Lee S, Kim D, Kim S et al.Pulmonary Tuberculosis and Risk of Lung Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2022 Jan 30;11(3):765.
8- Ellis T, Eze E, Raimi-Abraham BT. Malaria and Cancer: a critical review on the established associations and new perspectives. Infect Agent Cancer. 2021 May 13;16(1):33.
9- de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health. 2020 Feb;8(2):e180-e190.
10- Xiang W, Shi JF, Li P, Wang JB, Xu LN, Wei WQ et al.Estimation of cancer cases and deaths attributable to infection in China. Cancer Causes Control. 2011 Aug;22(8):1153-61.
11- Nguyen TP, Luu HN, Nguyen MVT, Tran MT, Tuong TTV, Tran CTD et al.Attributable Causes of Cancer in Vietnam. JCO Glob Oncol. 2020 Feb;6:195-204.
12- Shin A, Park S, Shin HR, Park EH, Park SK, Oh JK et al. Population attributable fraction of infection-related cancers in Korea. Ann Oncol. 2011 Jun;22(6):1435-1442.
13- Inoue M, Hirabayashi M, Abe SK, Katanoda K, Sawada N, Lin Y et al.Burden of cancer attributable to modifiable factors in Japan in 2015. Glob Health Med. 2022 Feb 28;4(1):26-36.
14- Boffetta P, Tubiana M, Hill C, Boniol M, Aurengo A, Masse R et al.The causes of cancer in France. Ann Oncol. 2009 Mar;20(3):550-5.
15- Brown KF, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A et alThe fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 2018 Apr;118(8):1130-1141.

16- Azevedo E Silva G, de Moura L, Curado MP, Gomes Fda S, Otero U, Rezende LF et al.The Fraction of Cancer Attributable to Ways of Life, Infections, Occupation, and Environmental Agents in Brazil in 2020. PLoS One. 2016 Feb 10;11(2):e0148761.

17- Brown HE, Dennis LK, Lauro P, Jain P, Pelley E, Oren E. Emerging Evidence for Infectious Causes of Cancer in the United States. Epidemiol Rev. 2019 Jan 31;41(1):82-96.

18- Tybjerg AJ, Friis S, Brown K, Nilbert MC, Morch L, Køster B. Updated fraction of cancer attributable to lifestyle and environmental factors in Denmark in 2018. Sci Rep. 2022 Jan 11;12(1):549.

19- Levin ML: The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* 1953, 9:531–541.

20- https://www.cancer.org/healthy/cancer-causes/general-info/known-and-probable-human-carcinogens.html

21- Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. Gut. 2001 Sep;49(3):347-53.

22- Palli D, Decarli A, Cipriani F, Sitas F, Forman D, Amadori D et al.Helicobacter pylori antibodies in areas of Italy at varying gastric cancer risk. Cancer Epidemiol Biomarkers Prev. 1993 Jan-Feb;2(1):37-40. PMID: 8420610.

23- Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ et al.Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018 Jan;68(1):31-54.

24- Sagnelli E, Sagnelli C, Pisaturo M, Macera M, Coppola N. Epidemiology of acute and chronic hepatitis B and delta over the last 5 decades in Italy. World J Gastroenterol. 2014 Jun 28;20(24):7635-43.

25- Buscarini E, Tanzi E, Zanetti AR, Savi E, Sbolli G, Civardi G et al. High prevalence of antibodies to hepatitis C virus among family members of patients with anti-HCV-positive chronic liver disease. Scand J Gastroenterol. 1993 Apr;28(4):343-6.

26- Ronco G, Giorgi-Rossi P, Carozzi F, Dalla Palma P, Del Mistro A, De Marco L et al. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. Lancet Oncol. 2006 Jul;7(7):547-55.

27- Ronco G, Segnan N, Giorgi-Rossi P, Zappa M, Casadei GP, Carozzi F, et al. New Technologies for Cervical Cancer Working Group. Human papillomavirus testing and liquid-based cytology: results at recruitment from the new technologies for cervical cancer randomized controlled trial. J Natl Cancer Inst. 2006 Jun 7;98(11):765-74.

28- Serraino D, Toma L, Andreoni M, Buttò S, Tchangmena O, Sarmati L et al. A seroprevalence study of human herpesvirus type 8 (HHV8) in eastern and Central Africa and in the Mediterranean area. Eur J Epidemiol. 2001;17(9):871-6.

29- Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016 Sep;4(9):e609-16.
30- Mentzer AJ, Brenner N, Allen N, Littlejohns TJ, Chong AY, Cortes A et al. Identification of host-pathogen-disease relationships using a scalable multiplex serology platform in UK Biobank. Nat Commun. 2022 Apr 5;13(1):1818.
31- Vescio MF, Gallo P, Farchi F, Avellis L, Spadea T, Giuliani M et al.Prevalence and attitudes to HIV testing among adults visiting public outpatient clinics in Rome: results of the MeDi (Measuring health Disparities in HIV prevention) survey. Part 1. Ann Ist Super Sanita. 2020 Jan-Mar;56(1):19-29.
32- https://www.registri-tumori.it/cms/pubblicazioni/i-numeri-del-cancro-italia-2020
33- Di Maso M, Bravi F, Polesel J, Negri E, Decarli A, Serraino D et al. Attributable fraction for multiple risk factors: Methods, interpretations, and examples. Stat Methods Med Res. 2020 Mar;29(3):854-865.
34- Wijaya WA, Liu Y, Qing Y, Li Z. Prevalence of Merkel Cell Polyomavirus in Normal and Lesional Skin: A Systematic Review and Meta-Analysis. Front Oncol. 2022 Mar 22;12:868781.
35- Ozoya OO, Sokol L, Dalia S. EBV-Related Malignancies, Outcomes and Novel Prevention Strategies. Infect Disord Drug Targets. 2016;16(1):4-21.
36- Saito M, Kono K. Landscape of EBV-positive gastric cancer. Gastric Cancer. 2021 Sep;24(5):983-989.
37- Coppeta L, Pietroiusti A, Neri A, Janni A, Baldi S, Papa F et al. Prevalence and Risk Factors for Latent Tuberculosis Infection among Healthcare Workers in a Low Incidence Country. Open Respir Med J. 2019 Apr 30;13:1-4
38- Cabrera-Sanchez J, Cuba V, Vega V, Van der Stuyft P, Otero L. Lung cancer occurrence after an episode of tuberculosis: a systematic review and meta-analysis. Eur Respir Rev. 2022 Jul 27;31(165):220025.
39- Burucoa C, Axon A. Epidemiology of Helicobacter pylori infection. Helicobacter. 2017 Sep;22 Suppl 1.
40- Abdelaal R, Yanny B, El Kabany M. HBV/HCV Coinfection in the Era of HCV-DAAs. Clin Liver Dis. 2019 Aug;23(3):463-472.
41- Cho J, Lee SS, Choi YS, Jeon Y, Chung JW, Baeg JY et al.Occult hepatitis B virus infection is not associated with disease progression of chronic hepatitis C virus infection. World J Gastroenterol. 2016 Nov 14;22(42):9427-9436.
42- Mak LY, Wong DK, Pollicino T, Raimondo G, Hollinger FB, Yuen MF. Occult hepatitis B infection and hepatocellular carcinoma: Epidemiology, virology, hepatocarcinogenesis and clinical significance. J Hepatol. 2020 Oct;73(4):952-964.

43- Dreyer G. Clinical implications of the interaction between HPV and HIV infections. Best Pract Res Clin Obstet Gynaecol. 2018 Feb;47:95-106.
44- Guidry JT, Scott RS. The interaction between human papillomavirus and other viruses. Virus Res. 2017 Mar 2;231:139-147.
45- Fabris P, Baldo V, Baldovin T, Bellotto E, Rassu M, Trivello R et al.Changing epidemiology of HCV and HBV infections in Northern Italy: a survey in the general population. J Clin Gastroenterol. 2008 May-Jun;42(5):527-32.
46- Stroffolini T, Sagnelli E, Sagnelli C, Smedile A, Furlan C, Morisco F et al.The burden of HBV infection in HCV patients in Italy and the risk of reactivation under DAA therapy. Dig Liver Dis. 2019 Mar;51(3):434-437.
47- Rovelli C, Poli A, Galli L, Cernuschi M, Tamburini AM, Racca S et al.Presence of multiple genotypes in subjects with HPV-16 infection is highly associated with anal squamous intraepithelial lesions in HIV-1 infected males. PLoS One. 2017 Oct 31;12(10):e0186367. This study is from S.Raffaele, and talks about coinfections. Should we instead cite the study based on which we calculated a 10% of coinfections in Italy?
48- Best LM, Takwoingi Y, Siddique S, Selladurai A, Gandhi A, Low B et al.Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev. 2018 Mar 15;3(3):CD012080.
49- Fiorini G, Zullo A, Saracino IM, Gatta L, Pavoni M, Vaira D. Pylera and sequential therapy for first-line Helicobacter pylori eradication: a culture-based study in real clinical practice. Eur J Gastroenterol Hepatol. 2018 Jun;30(6):621-625.
50- Zullo A, Fiorini G, Scaccianoce G, Portincasa P, De Francesco V, Vassallo R et al.Sequential therapy for first-line Helicobacter pylori eradication: 10- or 14-day regimen? J Gastrointestin Liver Dis. 2019 Mar;28(1):11-14.
51- Stroffolini T, Morisco F, Ferrigno L, Pontillo G, Iantosca G, Cossiga V et al.Effectiveness of Hepatitis B Vaccination Campaign in Italy: Towards the Control of HBV Infection for the First Time in a European Country. Viruses. 2022 Jan 26;14(2):245.
52- Juan J, Feld JJ. Hepatitis B virus and hepatitis C virus treatment and management in patients receiving immune-modifying agents. Curr Opin Rheumatol. 2014 Jul;26(4):395-403.
53- Lanini S, Ustianowski A, Pisapia R, Zumla A, Ippolito G. Viral Hepatitis: Etiology, Epidemiology, Transmission, Diagnostics, Treatment, and Prevention. Infect Dis Clin North Am. 2019 Dec;33(4):1045-1062.
54- Stella L, Santopaolo F, Gasbarrini A, Pompili M, Ponziani FR. Viral hepatitis and hepatocellular carcinoma: From molecular pathways to the role of clinical surveillance and antiviral treatment. World J Gastroenterol. 2022 Jun 7;28(21):2251-2281.
55- Bianchi FP, Vimercati L, Mansi F, De Nitto S, Stefanizzi P, Rizzo LA et al. Compliance with immunization and a biological risk assessment of health care

workers as part of an occupational health surveillance program: The experience of a university hospital in southern Italy. Am J Infect Control. 2020 Apr;48(4):368-374.

56- Barchitta M, Basile G, Lopalco PL, Agodi A. Vaccine-preventable diseases and vaccination among Italian healthcare workers: a review of current literature. Future Microbiol. 2019 Jun;14:15-19.

57- https://www.ccm-network.it/documenti_Ccm/prg_area1/Inf_Oss/Normativa_naz/Circolare52_1985.pdf

58- Fiore V, De Matteis G, Ranieri R, Saderi L, Pontali E, Muredda A et al. HCV testing and treatment initiation in an Italian prison setting: A step-by-step model to micro-eliminate hepatitis C. Int J Drug Policy. 2021 Apr;90:103055.

59- Fiore V, Rastrelli E, Madeddu G, Ranieri R, De Vito A, Giuliani R et al. HCV spread among female incarcerated population and treatment pathways to viral elimination in Italian prison settings: clinical perspectives and medico legal aspects. BMC Infect Dis. 2022 Jul 7;22(1):601.

60- Masarone M, Caruso R, Aglitti A, Izzo C, De Matteis G, Attianese MR et al. Hepatitis C virus infection in jail: Difficult-to-reach, not to-treat. Results of a point-of-care screening and treatment program. Dig Liver Dis. 2020 May;52(5):541-546.

61- https://www.europeancancer.org/resources/199:hpv-vaccine-tracker.html

62- https://www.quotidianosanita.it/allegati/allegato660418.pdf

63- Campari C, Fedato C, Iossa A, Petrelli A, Zorzi M, Anghinoni E et al. Cervical cancer screening in immigrant women in Italy: a survey on participation, cytology and histology results. Eur J Cancer Prev. 2016 Jul;25(4):321-8.

64- https://www.salute.gov.it/imgs/C_17_notizie_5681_0_file.pdf

65- https://www.epicentro.iss.it/passi/dati/ScreeningCervicale

66- Boscolo-Rizzo P, Zorzi M, Del Mistro A, Da Mosto MC, Tirelli G, Buzzoni C et al. The evolution of the epidemiological landscape of head and neck cancer in Italy: Is there evidence for an increase in the incidence of potentially HPV-related carcinomas? PLoS One. 2018 Feb 7;13(2):e0192621.

67- Bendinelli B, Palli D, Assedi M, Facchini L, Grioni S, Agnoli C et al. Alcohol, smoking and rectal cancer risk in a Mediterranean cohort of adults: the European Prospective Investigation into Cancer and Nutrition (EPIC)-Italy cohort. Eur J Gastroenterol Hepatol. 2020 Apr;32(4):475-483.

68- Varì R, Scazzocchio B, D'Amore A, Giovannini C, Gessani S, Masella R. Gender-related differences in lifestyle may affect health status. Ann Ist Super Sanita. 2016 Apr-Jun;52(2):158-66.

69- Millarini V, Caini S, Allamani A, Ermini I, Querci A, Masala G et al. Prevalence and co-occurrence of unhealthy lifestyle habits and behaviours among secondary school students in Tuscany, central Italy. Public Health. 2019 Jan;166:89-98.

70- Yang L, Kartsonaki C, Yao P, de Martel C, Plummer M, Chapman D et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with

Helicobacter pylori infection in China: a case-cohort study. Lancet Public Health. 2021 Dec;6(12):e888-e896.
71- Eusebi LH, Telese A, Marasco G, Bazzoli F, Zagari RM. Gastric cancer prevention strategies: A global perspective. J Gastroenterol Hepatol. 2020 Sep;35(9):1495-1502.
72- Ding SZ, Du YQ, Lu H, Wang WH, Cheng H, Chen SY et al. Chinese Consensus Report on Family-Based *Helicobacter pylori* Infection Control and Management (2021 Edition). Gut. 2022 Feb;71(2):238-253.
73- Ma J, Yu M, Shao QQ, Yu XC, Zhang C, Zhao JB et al. Both family-based Helicobacter pylori infection control and management strategy and screen-and-treat strategy are cost-effective for gastric cancer prevention. Helicobacter. 2022 Aug;27(4):e12911.
74- Gotoda T, Kusano C, Suzuki S, Horii T, Ichijima R, Ikehara H. Clinical impact of vonoprazan-based dual therapy with amoxicillin for H. pylori infection in a treatment-naïve cohort of junior high school students in Japan. J Gastroenterol. 2020 Oct;55(10):969-976.
75- Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut. 2020 Dec;69(12):2113-2121.
76- Romano M, Gravina AG, Eusebi LH, Pellegrino R, Palladino G, Frazzoni L et al. Management of Helicobacter pylori infection: Guidelines of the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED). Dig Liver Dis. 2022 Sep;54(9):1153-1161.
77- Varga MG, Butt J, Blot WJ, Le Marchand L, Haiman CA, Chen Y et al. Racial Differences in *Helicobacter pylori*CagA Sero-prevalence in a Consortium of Adult Cohorts in the United States. Cancer Epidemiol Biomarkers Prev. 2020 Oct;29(10):2084-2092.
78- Morisco F, Stroffolini T, Lombardo FL, Guarino M, Camera S, Cossiga V et al. Prevalence of and risk factors for HBV infection in a metropolitan Southern Italian area: Evidence for the effectiveness of universal Hepatitis B vaccination. Dig Liver Dis. 2017 Nov;49(11):1257-1261.
79- Pan CQ, Rabinovich C, Gayam V, Normatov M, Fidman B, Wang D. Late presenters among minority patients with chronic hepatitis C infection in the USA. Int J Public Health. 2020 Sep;65(7):1181-1191.
80- Olusola P, Banerjee HN, Philley JV, Dasgupta S. Human Papilloma Virus-Associated Cervical Cancer and Health Disparities. Cells. 2019 Jun 21;8(6):622.
81- Probst C, Simbayi LC, Parry CDH, Shuper PA, Rehm J. Alcohol Use, Socioeconomic Status and Risk of HIV Infections. AIDS Behav. 2017 Jul;21(7):1926-1937.
82- Collatuzzo G, Teglia F, Boffetta P. Role of Occupation in Shaping Cancer Disparities. Cancers (Basel). 2022 Aug 31;14(17):4259.

83- Pike LRG, Royce TJ, Mahal AR, Kim DW, Hwang WL, Mahal BA et al. Outcomes of HPV-Associated Squamous Cell Carcinoma of the Head and Neck: Impact of Race and Socioeconomic Status. J Natl Compr Canc Netw. 2020 Feb;18(2):177-184.

84- Olusola P, Banerjee HN, Philley JV, Dasgupta S. Human Papilloma Virus-Associated Cervical Cancer and Health Disparities. Cells. 2019 Jun 21;8(6):622.

85- Gupta S, Tao L, Murphy JD, Camargo MC, Oren E, Valasek MA et al. Race/Ethnicity-, Socioeconomic Status-, and Anatomic Subsite-Specific Risks for Gastric Cancer. Gastroenterology. 2019 Jan;156(1):59-62.e4.

86- Giorgi Rossi P, Baldacchini F, Ronco G. The Possible Effects on Socio-Economic Inequalities of Introducing HPV Testing as Primary Test in Cervical Cancer Screening Programs. Front Oncol. 2014 Feb 10;4:20.

87-Adjei Boakye E, Tobo BB, Rojek RP, Mohammed KA, Geneus CJ, Osazuwa-Peters N. Approaching a decade since HPV vaccine licensure: Racial and gender disparities in knowledge and awareness of HPV and HPV vaccine. Hum Vaccin Immunother. 2017 Nov 2;13(11):2713-2722.

88- Scognamiglio P, Girardi E, Fusco M, Piselli P, Spena SR, Maione C et al.Lack of implementation of Hepatitis B Virus (HBV) vaccination policy in household contacts of HBV carriers in Italy. BMC Infect Dis. 2009 Jun 7;9:86.

89- Collatuzzo G, Fiorini G, Vaira B, Violante FS, Farioli A, Boffetta P. The role of the occupational physician in controlling gastric cancer attributable to *Helicobacter pylori*infection: A review. Prev Med Rep. 2021 Aug 18;24:101527.

90-Leone Roberti Maggiore U, Scala C, Toletone A, Debarbieri N, Perria M, D'Amico B et al. Susceptibility to vaccine-preventable diseases and vaccination adherence among healthcare workers in Italy: A cross-sectional survey at a regional acute-care university hospital and a systematic review. Hum Vaccin Immunother. 2017 Feb;13(2):470-476.

91- Napolitano F, Pelullo CP, Della Polla G, Angelillo IF. HPV Vaccination Attitudes and Behaviors among General Practitioners in Italy. Vaccines (Basel). 2021 Jan 19;9(1):63.

92- Lu PJ, Hung MC, Srivastav A, Grohskopf LA, Kobayashi M, Harris AM et al.Surveillance of Vaccination Coverage Among Adult Populations -United States, 2018. MMWR Surveill Summ. 2021 May 14;70(3):1-26.

93- Garbuglia AR, Lapa D, Sias C, Capobianchi MR, Del Porto P. The Use of Both Therapeutic and Prophylactic Vaccines in the Therapy of Papillomavirus Disease. Front Immunol. 2020 Feb 18;11:188.

94- Du J, Ährlund-Richter A, Näsman A, Dalianis T. Human papilloma virus (HPV) prevalence upon HPV vaccination in Swedish youth: a review based on our findings 2008-2018, and perspectives on cancer prevention. Arch Gynecol Obstet. 2021 Feb;303(2):329-335.

95- Douglas R. Lowy; John T. Schiller. Reducing HPV-Associated Cancer Globally. *Cancer Prev Res (Phila)* (2012) 5 (1): 18–23.
96- Choi SE, Choudhary A, Huang J, Sonis S, Giuliano AR, Villa A. Increasing HPV vaccination coverage to prevent oropharyngeal cancer: A cost-effectiveness analysis. Tumour Virus Res. 2022 Jun;13:200234.

Ethical statement

No request was sought from an Ethical Committee because the study is based on publicly available data.

Acknowledgments/Funding

This work was conducted with the contribution of the AIRC Foundation for Cancer Research (IG grant N. 22987).

Conflict of interest

All authors have declared no conflicts of interest.

Data availability statement

The data that support the findings of this study are openly available from the authors upon reasonable request.

Authors' contribution

Conceptualization: GC, PB; coordination: GC, PB. Investigation: all the authors. Methodology: PB, GC, CLV; writing the main draft: GC, PB; statistical analyses: PB, GC. Funding: EN. Writing review and editing: all authors. All authors reviewed and approved the final version of the manuscript.

Table 1- Relative risks (RR) and prevalence of exposure to infectious agents used in the calculation of attributable fractions

Agent	Prevalence %	Cancer	RR	Reference RR	Reference prevalence
Hp	0.45	Cardia gastric	1.6	de Martel 2020 [9]/ /HCCG	Palli 1993 [22
		Non-cardia gastric	5.9	2001 [21]	
HBV	0.01	Liver	23.4	Islami 2018* [23]	Sagnelli 201
				Islami 2018* [23]	[24]
HCV	0.02	Liver	27.6	Islami 2018* [23]	Buscarini 199
		NHL	1.78	Islami 2018* [23]	[25]
HPV	0.06	Cervix	∞	Islami 2018* [23]	Ronco 2006 a
		Oral cancer	1.94	Islami 2018* [23]	**[26,27]
		Pharynx	8.6	Islami 2018* [23]	
		Anus	6.7	Islami 2018* [23]	
		Vagina	10.9	Islami 2018* [23]	
		Vulva	4.4	Islami 2018* [23]	
		Penis	5.3	Islami 2018* [23]	
HHV-8	0.19	Kaposi sarcoma	∞	Islami 2018* [23]	Serraino 200
					[28]
EBV	0.95	HL	3.7	Plummer 2016 [29]	Mentzer 201
		Nasopharyngeal	10.14	Plummer 2016 [29]	[30]
HIV	0.02	NHL	15	Islami 2018* [23]	Vescio 2020 [3
		HL	11	Islami 2018* [23]	
		Anus	32	Islami 2018* [23]	
		Cervix	5	Islami 2018* [23]	
		Kaposi sarcoma	1584	Islami 2018* [23]	

Notes: Helicobacter pylori [Hp]; hepatitis B and C viruses [HBV and HCV]; human papillomavirus [HPV]; human herpesvirus-8 [HHV8]; Epstein–Barr virus [EBV]; and human immunodeficiency virus [HIV]

HL= Hodgkin lymphoma; NHL= non-Hodgkin lymphoma; MALT= mucosa-associated lymphoid tissue

HCCG= Helicobacter and Cancer Collaborative Group.

*See references for specific agents in Supporting Table 3 of [23].

**Weighed average of two age groups; prevalence in women used for both sexes.

Table 2-Number of deaths from selected cancers in 2017 and of cases of selected cancers in 2020 in Italy

Site	ICD 10	Male		Female	
		Deaths	Cases	Deaths	Cases
Oral cavity	C00-C06	1056	2177	656	1314
Nasopharynx	C11	183	377	76	152
Pharynx	C09, C10, C12-C14	669	1379	199	398
Gastric cardia	C16	828	1269	583	915
Gastric non-cardia	C16	4690	7189	3306	5183
Anus	C21	180	398	255	588
Liver	C22	6156	8978	3107	4034
Kaposi Sarcoma	C46.1	495	669	191	258
Vulva	C51	-	-	214	1024
Vagina	C52	-	-	45	218
Cervix	C53	-	-	494	2365
Penis	C60	168	371	-	-
HL	C81	441	1222	357	929
NHL	C82-86	2479	7011	2041	6171
Gastric MALT	C88.4	45	126	37	111
All cancers	C00-97	100,123	194,754	79,962	181,857

Notes: HL= Hodgkin lymphoma; NHL= non-Hodgkin lymphoma; MALT= mucosa-associated lymphoid tissue.

Table 3-Total number of cancer deaths in 2017 and cancer cases in 2020 attributable to infectious agents in Italy by sex and infectious agent

Infectious agent	N deaths, males	N deaths, females	Total N deaths	N cases, males	N cases, females	Total N cases
HPV						
Oral cavity	56	35	91	116	70	186
Pharynx	209	62	271	432	125	557
Anus	46	65	111	102	150	252
Cervix	-	494	494	-	2365	2365
Vulva	-	36	36	-	174	174
Vagina	-	17	17	-	81	81
Penis	17	-	17	76	-	76
Total	328	709	1037	726	2965	3691
% total cancer	0.3	0.9	0.6	0.4	1.6	1.0
HP						
Gastric cardia	176	124	300	270	194	464
Gastric non-cardia	3227	2274	5501	4946	3566	8512
Gastric MALT	31	26	57	89	78	167
Total	3434	2424	5858	5305	3838	9143
% total cancer	3.4	3.0	3.3	2.7	2.1	2.4
HBV						
Liver	1127	569	1696	1643	738	2381
% total cancer	1.1	0.7	0.9	0.8	0.4	0.6
HCV						
Liver	2138	1079	3217	3118	1401	4519
Non-Hodgkin lymphoma	38	31	69	108	95	203
Total	2176	1110	3286	3226	1496	4722

% total cancer	2.2	1.4	1.8	1.7	0.8	1.3
EBV						
Nasopharynx	146	61	259	302	122	424
Hodgkin lymphoma	159	129	288	440	334	774
Total	305	190	495	742	456	1198
% total cancer	0.3	0.2	0.3	0.4	0.3	0.3
HIV						
Anus	69	98	167	152	224	376
Kaposi sarcoma	480	185		649	250	899
Hodgkin lymphoma	73	60	133	204	155	359
Non-Hodgkin lymphoma	572	471	1043	1534	1350	2884
Total	1194	814	2008	2539	1979	4518
% total cancer	1.2	1.0	1.1	1.3	1.0	1.2
HHV8						
Kaposi sarcoma	495	191	686	669	258	927
% total cancer	0.5	0.2	0.4	0.3	0.1	0.2

Notes: Helicobacter pylori [Hp]; hepatitis B and C viruses [HBV and HCV]; human papillomavirus [HPV]; human herpesvirus-8 [HHV8]; Epstein–Barr virus [EBV]; and human immunodeficiency virus [HIV].

Table 4-Total number of cancer deaths in 2017 and cancer cases in 2020 attributable to infectious agents in Italy by cancer sex and cancer site.

Cancer site	N deaths, males	N deaths, females	Total N deaths	N cases, males	N cases, females	Total N cases
Oral cavity	56	35	91	116	70	186
Nasopharynx	146	61	207	302	122	424
Pharynx	209	62	271	432	125	557
Gastric cardia	176	124	300	270	194	464
Gastric non-cardia	3227	2274	5501	4946	3566	8512
Gastric MALT	31	26	57	89	78	167
Anus	97	138	235	215	318	533
Liver	2873	1450	4323	4190	1883	6073
Kaposi sarcoma	495	191	686	669	258	927
Vulva	-	36	36	-	174	174
Vagina	-	17	17	-	81	81
Cervix	-	494	494	-	2365	2365
Penis	34	-	34	72	-	72
HL	206	167	373	570	434	1004
NHL	572	471	1043	1618	1424	3024
All cancers N	8,124	5,546	13,670	13,493	11,091	24,584
All cancers AF	8.1 %	6.9%	7.6%	6.9%	6.1%	6.5%

Notes: HL= Hodgkin lymphoma; NHL= non-Hodgkin lymphoma; MALT= mucosa-associated lymphoid tissue; N= number; AF=attributable fraction.

Table 5. Population-attributable fraction of cancer deaths related to infectious agents in selected countries by sex.

Sex	**Italy (present study)**	**China [10]**	**Vietnam [11]**	**United States [20]**	**United Kingdom [15]**	**Brazil [16]**	**France [14]**	**Denmark [18]**
Men (%)	8.1%	30.6	34.7	3.4	3.1	5.9	3.1	2.3%
Women (%)	6.9%	24.1	22.1	3.3	4.3	13.8	4.4	3.6%

Highlights

- Infectious agents are responsible for a high proportion of cancer in Italy.
- Helicobacter pylori is the main cancer-related infectious agent.
- Most infectious-related cancers are preventable.

Authors' contribution

Conceptualization: GC, PB; Coordination: GC, PB. Investigation: all the authors; Methodology: PB, GC, CLV; Writing the main draft: GC, PB; Statistical analyses: PB, GC. Funding: EN. Writing rewiew and editing: all authors All authors reviewed and approved the final version of the manuscript.

Conflict of interest

All authors have declared no conflicts of interest.

Prof. Paolo Boffetta, MD
Stony Brook University, NY, US
University of Bologna, Bologna, Italy