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Incidence of infection-associated cancers in Italy and prevention strategies

Incidenza dei tumori di origine infettiva in Italia e linee di prevenzione

Silvio De Flora,[1,6] Emanuele Crocetti,[2] Paolo Bonanni,[3,7] Antonio Ferro,[4] Francesco Vitale,[5] and the Vaccines and Cancer Prevention/Screening Working Groups of the Italian Society of Hygiene, Preventive Medicine and Public Health (SItI)

[1]Dip. Scienze della salute, Università di Genova, Italy; [2]Istituto per lo studio e la prevenzione oncologica, Firenze, Italy; [3]Dip. Scienze della salute, Università di Firenze, Italy; [4]ULSS Verona, Italy; [5]Dip. Scienze per la promozione della salute e materno-infantile "G. D'Alessandro", Università di Palermo, Italy; [6]coordinator of the Cancer Prevention/Screening WG; [7]coordinator of the Vaccines WG

Corresponding author: Silvio De Flora; e-mail: sdf@unige.it

Abstract

Chronic infections and infestations represent major causes of cancer. Overall, *Helicobacter pylori*, HPV, HBV, and HCV are estimated to account for 15% of all human cancers. We have estimated that cancers associated with 6 pathogens in Italy account for 31,000 yearly cases, 42.0% of which is attributable to *H. pylori*, 34.7% to HBV and HCV, 19.8% to HPV, 2.9% to KSHV, and 0.2% to EBV. These figures represent 8.5% of all incident cases of cancer in Italy.

The implementation of anti-HBV vaccination programs in countries with high endemicity resulted in a significant impact on the incidence of hepatocellular carcinoma, and the availability of antiviral drugs is a real opportunity to drastically reduce the cases attributable to HCV.

Primary prevention of cervical cancer mainly involves HPV vaccination; two vaccines (bivalent and quadrivalent) are available and a new vaccine (9-valent) has recently been approved by the FDA. Secondary prevention is based on screening programs that include Pap smear cytology and/or HPV test.

To reduce the burden of HIV-associated cancers, prevention programs include primary prevention of HIV infection, early diagnosis and treatment, restoration of immune function, reduction in the prevalence of associated infections and risk factors, and secondary prevention.

To date, anti-HBV and anti-HPV vaccinations, eradication of *H. pylori* infection, treatment of HCV and HIV carriers with antivirals, and HPV-related cancer screening prove to be the most effective strategies for the prevention of infection-associated cancers.

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Key words: infection-associated cancers, incidence data in Italy, hepatitis B and C viruses, human papillomaviruses, human immunodeficiency virus

Riassunto

Le infezioni e infestazioni croniche sono associate con una proporzione rilevante dei tumori umani. *Helicobacter pylori*, HPV, HBV e HCV sono complessivamente responsabili del 15% dei tumori nel mondo. In Italia, abbiamo stimato che i tumori associati con 6 agenti patogeni incidano per 31.000 casi all'anno, il 42,0% dei quali è attribuibile a *H. pylori*, il 34,7% a HBV e HCV, il 19,8% a HPV, il 2,9% a KSHV e lo 0,2% a EBV. Nel complesso, questi valori rappresentano l'8,5% di tutti i casi incidenti di tumore in Italia.

L'applicazione della vaccinazione anti-HBV in Paesi a elevata endemia ha determinato un notevole impatto anche sul carcinoma epatocellulare primitivo e la disponibilità di farmaci antivirali rappresenta una concreta possibilità di ridurre l'incidenza di questo tumore, specie quello attribuibile ad HCV.

La prevenzione primaria del carcinoma cervicale si basa principalmente sulla vaccinazione anti-HPV mediante due vaccini (bivalente e quadrivalente); recentemente, l'FDA ha approvato un nuovo vaccino (nove-valente). La prevenzione secondaria si basa su programmi di screening che utilizzano Pap-test e HPV-test.

Per ridurre l'incidenza dei tumori HIV-correlati sono stati promossi programmi di prevenzione incentrati sulla prevenzione primaria dell'infezione da HIV, diagnosi precoce di sieropositività, riduzione della prevalenza di infezioni e fattori di rischio concomitanti e sulla prevenzione secondaria.

Nel complesso, le vaccinazioni contro HBV e HPV, l'eradicazione dell'infezione da *H. pylori*, il trattamento con antivirali dei portatori di HCV e HIV e gli screening oncologici per HPV rappresentano oggigiorno le armi più efficaci per la prevenzione dei tumori di origine infettiva.

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Parole chiave: tumori di origine infettiva, incidenza in italia, virus dell'epatite B e C, papillomavirus umani, virus dell'immunodeficienza umana

GLOBAL BURDEN OF INFECTION-ASSOCIATED CANCERS

Chronic infections and infestations represent major causes of cancer. In the population of individual countries, the incidence of cancers attributable to infectious agents, as evaluated in studies published between 1981 and 2005, varied between 3.6% and 29.4%.[1] In the world population, taking into account the infections categorized in Group 1 by the International Agency for Research on Cancer (IARC), the attributable fraction was estimated to be 15.6% in 1990,[2] 17.8% in 2002,[3] and 16.1% in 2008.[4]

There are large geographical differences in the incidence of infection-associated cancers, with 26.3% of cases occurring in developing countries and 7.7% in developed countries.[3] These regional disparities depend on the different endemic burden of infections and infestations associated with cancer, on the different age composition of the populations of the various countries, as well as on the uneven application of both primary and secondary prevention strategies.

OVERVIEW OF CHRONIC INFECTIONS AND INFESTATIONS ASSOCIATED WITH HUMAN CANCERS

Table 1 provides a list of the pathogenic agents, including DNA viruses, RNA viruses, bacteria, protozoa, and trematodes, that are known or suspected to play a role in the epidemiology of human cancers, along with the main associated cancers. Eleven of these pathogens are classified in IARC Group 1, three in Group 2A, and four in Group 2B. Three viral or bacterial infections share a particularly heavy burden. *Helicobacter pylori* was estimated to be responsible for 90% of non-cardia gastric cancer cases and 5.2%[4] or 5.5%[3] of all human cancers. Persistent infection with HPV is associated with virtually 100% of cervical cancer cases and with a variety of other cancers in both men and women, thereby accounting for an estimated 4.8%[4] or 5.2%[3] of all human cancers. Worldwide, chronic infections with HBV and HCV were estimated to be associated with 54.4% and 31.1% of hepatocellular carcinoma cases, respectively.[3] These hepatotropic viruses are responsible for 4.9%[3] or 4.7%[4] of all human cancers. Thus, collectively, the above chronic infections (*H. pylori*, HPV, HBV, and HCV) are associated with approximately 15% of all human cancers. Other epidemiologically relevant cancers are those associated with the herpesviruses EBV (0.9%[4] or 1.0%[3]) and KSHV (0.3%[4]).

INCIDENCE OF INFECTION-ASSOCIATED CANCERS IN ITALY

We estimated the incidence of cancers associated with 6 infectious agents, all of them classified as IARC Group 1, in the general Italian population. We did not estimate HIV-related cancers in order to avoid the risk of counting the cancers caused by immunodeficiency together with the cases directly related to this infection.

The incidence data for malignant neoplasms of the liver, cervix uteri, and Kaposi's sarcoma refer to the year 2014.[5] For cancers of the oral cavity, oropharynx, nasopharynx, and larynx we used estimates from Globocan 2012.[6] For anal and non-cardia gastric cancers we applied each cancer's sex-specific proportion according to Italian cancer registries[7] to the estimates for Italy in 2014.[5] For vulvar and vaginal cancers we considered their relative ratio to cervix uteri according to Italian cancer registries.[5] To estimate penile carcinoma we applied its ratio to all cancer sites but skin according to Italian cancer registries[7] to the estimate of all sites but skin for Italy in 2014.[5] To estimate Burkitt's and MALT lymphomas we applied the age- and sex-specific incident rates (2000-2012) from SEER to the Italian population.[8]

Population attributable fractions (PAFs) for head and neck squamous cell carcinomas, including oral cavity, oropharyngeal, nasopharyngeal, and laryngeal carcinomas,[9] for HPV-related cancers, including vaginal, vulvar, and anal carcinomas[10] and penile carcinoma,[11] as well as for non-cardia gastric cancer, MALT, cervical cancer, and Kaposi's sarcoma[4] were estimated in the world population. The PAF for Burkitt's lymphoma was estimated in the US and European populations.[4] The PAF for nasopharyngeal carcinoma was estimated in low-incidence Regions.[4] PAFs for malignant neoplasms of the liver were estimated in the Italian population.[12]

The results of our estimates are shown in table 2. Overall, the cancers associated with the considered infectious agents account for more than 31,000 incident cases (almost 18,000 in males and more than 13,000 in females), 42.0% of which is attributable to *H. pylori*, 34.7% to HBV and HCV, 19.8% to HPV, 2.9% to KSHV, and 0.2% to EBV. These figures represent 8.5% of all incident cases of cancers in Italy (excluding skin carcinomas) during the same period, which have been estimated to be 365,000.[5] Clearly, these estimates are just tentative, due to the uncertainties in assessing both the incidence of cancer and the PAFs.

GENERAL STRATEGIES AIMED AT PREVENTING INFECTION-ASSOCIATED CANCERS

In principle, the primary prevention of infection-related cancers is more easily affordable than prevention of other types of cancer: not only will the prevention of an infectious disease result in the primary prevention of the associated cancer, but even its therapy, such as eradication of *H. pylori* infection or use of anti-HIV, anti-HBV, or anti-HCV drugs, will avoid evolution towards malignancy.[13]

As reported below, certain infection-associated cancers provide paradigmatic examples of primary prevention and oncological screening.[13] Subsequently, after the onset of cancer and its therapy, it is still possible to apply tertiary prevention, for instance by means of antiangiogenic agents.[14]

PREVENTION OF HEPATOCELLULAR CARCINOMA ASSOCIATED WITH HBV AND HCV INFECTIONS

Mechanistic considerations

There are multiple, diversified mechanisms leading to primary hepatocellular carcinoma (HCC) in chronic HBV carriers. Liver fibrosis followed by cirrhosis occurs in 20-30% of chronic HBsAg carriers within 20-30 years, and this is a pre-

[IARC Group*] Pathogens	Main associated human cancers
DNA viruses	
papillomaviridae	
[1] human papillomaviruses (HPV), alpha types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59	■ cervical cancer, cancers of the anogenital region, head and neck cancers, colorectal cancer
[2A] HPV, alpha type 68	
[2B] HPV, alpha types 26, 30, 34, 53, 66, 67, 69, 70, 73,82, 85, 97, and beta types 5 and 8	
[3] HPV, alpha types 6 and 11, other beta and gamma types	
herpesviridae	
[1] Epstein-Barr virus (EBV, HHV4)	■ Burkitt's lymphoma, sinonasal angiocentric T-cell lymphoma, immunosuppressor-related non-Hodgkin's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma
[1] Kaposi's sarcoma virus (KSHV, HHV8)	■ Kaposi's sarcoma, primary effusion lymphoma
polyomaviridae	
[3] simian virus 40 (SV40)	■ malignant mesothelioma?
[2A] Merkel cell virus (MCV)	■ Merkel cell carcinoma
[2B] BK virus (BKV)	■ no specific target detected
[2B] JC virus (JCV)	■ no specific target detected
hepadnaviridae	
[1] hepatitis B virus (HBV)	■ hepatocellular carcinoma
RNA viruses	
flaviviridae	
[1] hepatitis C virus (HCV)	■ hepatocellular carcinoma, B-cell non-Hodgkin's lymphoma
defective virus	
[3] hepatitis D virus (HDV)	
retroviridae	
[1] human T-cell leukemia virus-I (HTLV-I)	■ adult T-cell leukemia-lymphoma
[3] human T-cell leukemia virus-II (HTLV-II)	
[1] human immunodeficiency virus-1 (HIV-1)	■ Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, cervical cancer, anal cancer, conjunctival cancer
[2B] human immunodeficiency virus-2 (HIV-2)	
[NA] human endogenous retrovirus (HERV-K)	■ breast cancer?
[NA] xenotropic murine leukemia virus-related virus (XMRV)	■ prostate cancer?
Bacteria	
[1] *Helicobacter pylori*	■ non-cardia gastric cancer, MALT lymphoma
[NA] *Salmonella typhi*	■ gallbladder carcinoma?
[NA] *Streptococcus bovis*	■ colorectal cancer?
[NA] *Clamydophila pneumonia*	■ lung cancer?
[NA] *Mycobacterium tubercolosis*	■ lung cancer?
[NA] Bartonella species	■ vascular tumors?
Protozoa	
[2A] *Plasmodium falciparum*	■ Burkitt's lymphoma (+EBV)
[NA] *Trichomonas vaginalis*	■ prostate cancer?
Trematodes	
[1] *Schistosoma haematobium*	■ urinary bladder cancer
[2B] *Schistosoma japonicum*	■ colorectal and liver cancer
[3] *Schistosoma mansoni*	
[1] *Opistorchis viverrini*	■ cholangiocarcinoma
[3] *Opistorchis felineus*	
[1] *Chlonorchis sinensis*	■ cholangiocarcinoma

* Group 1: sufficient evidence of carcinogenicity to humans; Group 2A: probably carcinogenic; Group 2 B: possibly carcinogenic; Group 3: inadequate evidence of carcinogenicity to humans; NA: not available.

Table 1. Pathogenic agents and main associated human cancers. / **Tabella 1.** Agenti patogeni e principali tumori umani associati.

cursor condition for development of 80%-90% of HCC cases.[15] HBV-DNA is also able to integrate into the hepatocyte DNA, and several alterations can occur in the host genome, such as HBx gene expression, chromosomal deletions, fusion transcripts, translocations, DNA amplification, and genomic instability, which independently contribute to HCC development.[13] Interactions between HBV infection and chemical hepatocarcinogens are also of crucial importance in the pathogenesis of HCC.[16] On the other hand, HCV lacks reverse transcriptase activity, and is thus unable to integrate its genome into the host cell DNA, while viral protein expression has a critical role in hepatocarcinogenesis by altering signal transduction pathways;[15] this has two important implications:

- HCV-induced cirrhosis is the necessary mechanism for its carcinogenesis;
- due to the lack of DNA integration into the host genome, antiviral drugs have the potential to achieve a "sterilizing" effect in chronically infected subjects.[17]

Prevention programs

Avoiding viral infection through **primary prevention** measures is crucial in order to obtain a dramatic decrease in HCC incidence. Regarding HBV, universal vaccination programs of newborns/infants have been introduced in 183 world countries, with 81% coverage overall with 3 doses.[18] There is clear evidence on the impact of immunization on HCC in countries where such programs have been implemented for a long time, as was first demonstrated in cohorts of Taiwanese children aged 6-14 years[19] and, later, in adolescents aged 16-19 years.[20] Similar results are reported from Thailand, China, Singapore, Korea, Japan, and Alaska, and are expected to be available from Gambia in the coming years.[21]

No vaccine is presently available for HCV due to the high variability of envelope proteins. Primary prevention of HCV infection is based upon identification of infectious blood donors through anti-HCV detection and NAT (nucleic acid testing), careful application of universal precautions for blood-borne infections, and adequate sterilization of non-disposable medical equipment. Of course, the same measures represent an important complement to hepatitis B vaccination for the prevention of HBV-related HCC.

With regard to HCC **secondary prevention**, data on the impact of IFN (interferon) therapy for HBV-related cancers are conflicting, due to the lack of pre-treatment patient stratification for relevant cancer predictors and exclusion of patients at higher risk of developing HCC, such as those unfit to receive IFN owing to advanced hepatitis. The advent of user-friendly oral NUC (nucleoside/nucleotide analogs) allowed for a broader and safe access of patients to effective anti-HBV therapy. HCC was prevented in patients with chronic hepatitis but not in those with cirrhosis, and in general in patients that could not achieve complete virological suppression. The re-analysis of outcomes following patient stratification for risk factors of HCC helped shed light on an association between NUC therapy and a reduced HCC risk only in non-cirrhotic patients.[22]

As regards to HCV antiviral therapy, a meta-analysis of 30 observational studies of patients treated with interferon demonstrated a more than 70% reduction of HCC risk occurring independently of severity of the underlying liver fibrosis. The residual risk for HCC in SVR (sustained virologic response) patients might reflect persistence of cirrhosis following virus sterilization. The same factors predicting HCC in viremic patients, such as advanced age, portal hypertension, advanced fibrosis, and elevated alpha-fetoprotein levels, act as independent predictors of HCC in SVR patients, too. This further emphasizes the clinical advantages of treating patients early during infection.[22] IFN-free, DAA (direct acting antiviral)-based regimens, such as sofosbuvir + ribavirin with a 24-week course, can also eliminate HCV infection in two-thirds of patients awaiting liver transplantation or already transplanted, with obvious positive consequences on their short- and long-term prognoses (**tertiary prevention**).[23]

PREVENTION OF HPV-ASSOCIATED CANCERS

Foreword

Worldwide epidemiological studies indicate that 12 different high-risk HPVs, namely 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59, are associated with cervical cancer; they are therefore classified in IARC Group 1 (table 1).

A subset of anal, penile, vulvar, vaginal, and oropharyngeal cancers have been attributed to infection with high-risk HPVs, mainly to HPV 16.[24] Prevention of cervical cancer includes both primary prevention, through HPV vaccination and education about safe sexual practices, and secondary prevention through cervical cancer screening.

Primary prevention

Two vaccines (bivalent and quadrivalent) are available to protect against HPV types 16 and 18, which are responsible for approximately 50% and 20% of cervical cancers, respectively. In addition, the quadrivalent vaccine offers protection against HPV 6 and 11, which cause over 90% of genital warts. Vaccination programs are being widely implemented, primarily targeting adolescent girls, and efficacy has been widely demonstrated for both vaccines by showing a 93%-100% of vaccine efficacy in preventing cervical pre-cancers due to HPV 16 or 18. Millions of doses have been distributed worldwide so far, and all randomized controlled clinical trials of both vaccines provide evidence for an excellent safety profile.[25,26] In some Italian Regions, vaccination programs have recently been extended to 12-year old boys, as recommended by the *2014 lifetime immunization schedule approved by the Italian scientific societies*.[27] Although this strategy is still debated, recent evidence shows a trend toward better results in cost-effectiveness of universal vaccination versus girls-only vaccination.[28,29]

The convenience of extending the anti-HPV vaccination to males is also supported by the estimates reported in the present study. As inferred from the data available in table 2, HPV-related cancers in males appear to account for 38% of all the cases estimated in the Italian population. With regard to the issue of extending the HPV vaccination recommendation to older women, an economic modeling study regarding 330,000 25-year old women in Italy showed that immunization with the HPV vaccine is fully economically justified, with an ICER (incremental cost-effectiveness ratio) = € 33,918/QALY (quality adjusted life years) using the vaccine prices of 2011 (prices have gone down since then). The same analysis showed that a public health program of HPV vaccination would be justified (ICER < € 50,000/QALY) until 30 years without cross-protective effects of the vaccine, and up to 35 years considering cross-protection.[30] Moreover, a new vaccine (9-valent) has recently been approved by the FDA. It is indicated in girls and women 9 through 26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.[31]

Secondary prevention

Secondary prevention involves screening asymptomatic patients or carrying out definitive tests in symptomatic or screen-positive patients to pick up precancerous lesions before they turn into cancer. Observational studies have shown that introduction of any regular cervical cancer screening program results in a drop

Cancer site or morphology	ICD 10	Infectious agent	PAF (%)	Sex	Estimated annual incident cases	Estimated incidence attributable to infectious agents
oral cavity	C00-C08	HPV	23.5	M	2,283	537
				W	1,524	358
				P	3,807	895
oropharyngeal (including hypo pharynx and pharynx)	C09-C10, C12-C14	HPV	35.6	M	1,214	432
				W	348	124
				P	1,589	566
nasopharyngeal	C11	EBV	80.0	M	315	252
				W	124	99
				P	439	351
laryngeal	C32	HPV	24.0	M	3,714	891
				W	335	80
				P	4,049	972
Burkitt's lymphoma	C83.7	EBV + *Plasmodium falciparum*	20.0	M	200	40
				W	100	20
				P	300	60
non-cardia gastric cancer	C16.1-C16.9	*Helicobacter pylori*	90.0	M	7,500	6,750
				W	5,500	4,950
				P	13,000	11,700
MALT (stomach)	C88.4	*Helicobacter pylori*	86.0	M	700	602
				W	850	731
				P	1,550	1,333
malignant neoplasms of liver	C22	HBV, HCV	86.8	M	8,600	7,465
				W	3,800	3,298
				P	12,400	10,763
anal carcinoma	C21.0	HPV	84.3	M	450	379
				W	650	548
				P	1,100	927
penile carcinoma	C60	HPV	46.9	M	182	85
uterine cervix cancer	C53	HPV	100	W	2,200	2,200
vulvar cancer	C51	HPV	40.4	W	900	364
vaginal cancer	C52	HPV	60.9	W	200	122
Kaposi's sarcoma	C46	HHV8	100	M	600	600
				W	300	300
				P	900	900
all the above tumors				M	25,758	18,034
				W	16,831	13,194
				P	42,589	31,238

Table 2. Estimated number of cancers attributable to 6 infectious agents in Italy. Cancer site, International classification for diseases-10 (ICD-10) codes, infectious agent, population-attributable fraction (PAF), estimated annual number of incident cases and estimated number of cases attributable to infectious diseases, by sex (M: men, W: women, P: people).

Tabella 2. Stima del numero di tumori attribuibili a 6 agenti infettanti in Italia. Sede del cancro, codici dell'International classification for diseases-10 (ICD-10), agenti infettanti, frazione attribuibile alla popolazione (PAF), numero annuale stimato di casi incidenti attribuibile a malattie infettive, distinto per sesso (M: uomini, W: donne, P: uomini + donne).

in the incidence of invasive cervical cancer and cancer deaths. Different methods are available for cervical cancer screening: cervical cytology (Pap test) is the globally preferred screening method and has been shown to reduce the incidence of invasive cervical cancer by up to 80%.

Two types of tests for HPV DNA are currently in use; one is a nucleic acid hybridization assay with signal amplification for the qualitative detection of high risk HPV types in cervical specimens, whereas the other is a polymerase chain reaction based assay. Testing for HR (high risk)-HPV has been investigated as a primary screening test in several randomized clinical trials. Cross-sectional as well as longitudinal studies have consistently demonstrated the superiority of HPV testing, compared with Pap testing, to prevent invasive cervical cancer by detecting high-grade precancerous lesions. However, HPV testing is also associated with a lower specificity, especially in younger women.[32]

By 2018, screening programs in Italy will rely more on HPV testing than cytology, with the following schedule: at 25-30/35 years Pap smear as a primary test and triage ASCUS (squamous cells of undetermined significance) with HPV test every 3 years; at >30/35 years HPV test as a primary test and triage with Pap smear every 5 years. Moreover, HPV testing will be the approach to follow up women treated for CIN-2 (cervical intraepithelial neoplasia-2) and with cytological abnormalities and negative colposcopy. The 5-year interval will lead to cost savings, and using the HPV test as the primary test will be key to improving uptake of cervical screening programs.[33]

PREVENTION OF CANCERS ASSOCIATED WITH HIV INFECTION

Foreword

The association between HIV/AIDS and cancer is still unclear, although HIV is classified as a Group 1 IARC carcinogen[34] and several authors have associated an increased cancer risk with HIV-related immunodeficiency, chronic immune activation/inflammation, and immune dysfunction/senescence.[35]

Epidemiological evidence suggests that the increased cancer risk observed among HIV-infected patients could be, at least in part, attributed to co-infection with other cancer-related viruses, such as KSHV, EBV, HPV, HBV, and HCV, and to a higher exposure to lifestyle risk factors for cancer, including smoking and alcohol use.[35,36] Furthermore, the use of highly active antiretroviral therapy (HAART) has dramatically improved survival, and most HIV-infected patients live several decades after their diagnosis.

In most developed countries, effective treatment of HIV has contributed to increase the prevalence of HIV infection, thereby leading to a higher clinical impact of long-term morbidities, including cancers.[37] For instance, in Italy people living with HIV increased from 78,000 in 1990 to 120,000 in 2013 (http://www.who.int/gho/hiv/en/).

Prevention programs

Research programs aimed at understanding, preventing, and treating HIV-related cancers have been promoted.[38] These programs are based on the following five pillars:

- **Primary prevention of HIV infection**. Preventing HIV infection or, at least, limiting the number of HIV-infected cells and viral load would greatly contribute to the reduction of associated cancers.[39] For this reason, the development of effective vaccines against HIV may be one of the biggest challenges for medical science. Unfortunately, to date, no fully effective HIV vaccine is available and prevention strategies should therefore be based on the promotion of counselling for HIV testing in high-risk populations and implementation of behavioural measures aimed at controlling HIV transmission via sexual intercourse, blood and other body fluids, and perinatal exposure of fetuses and children.[13]
- **Early diagnosis and treatment of HIV infection, and restoration of immune function**. Early diagnosis of HIV infection, linkage to and retention in care, and adherence to antiretroviral therapy are crucial in reducing the cancer burden in HIV-infected subjects.[40] In addition, evidence from in vitro and in vivo model systems indicates that antiretroviral agents may have antitumor activity independent of their antiviral effect.[41]
- **Reduction in the prevalence of non-communicable risk factors**. A number of cancers observed among HIV subjects are attributable to exposure to tobacco smoking (e.g., cancers of the lung, head and neck, bladder), alcohol consumption (e.g., cancers of liver and head and neck) and ultraviolet radiation (non-melanoma skin cancer).[42] Accordingly, programs to encourage HIV-infected individuals to quit tobacco smoking and alcohol consumption and minimize unnecessary sun exposure should be a priority for public health authorities.
- **Primary prevention of concomitant cancer-related viral infections**. As previously discussed, prevention of chronic infections with other cancer-related viruses, such as HBV and HPV infections, should be optimized. Cancers caused by EBV and KSHV may be in principle preventable with vaccines, with early candidate vaccines for EBV showing promise.[43] Finally, encouraging HIV-infected people to limit the number of their sexual partners may reduce their risk of acquiring new HBV and HPV infections.
- **Secondary prevention**. Limited data exist regarding harms and benefits of cancer screening interventions specifically targeted to HIV-infected persons. For some cancers, performance of screening programs may be sufficiently different in HIV-infected individuals to warrant modified approaches. Thus, cancer screening interventions that have no evidence of benefit in the general population (e.g., anal, skin, and liver cancer screening[42]) may be of value in HIV-infected individuals because of their different cancer risk profiles. However, the decision to screen HIV-infected persons for cancer is complex and should include considerations about the risk of the particular cancer, the life expectancy of the patient, and the specific benefits and harms that may stem from the screening interventions.[44]

CONCLUSIONS

A high proportion of cancers are associated, with a variety of mechanisms, with chronic infections and infestations. In Italy, cancers associated with the 6 main pathogens appear to be responsible for almost 1 out of 10 cancers, with a total of 31,000 yearly cases, the large majority of which are attributable to either *H. pylori* (42.0%), HBV and HCV (34.7%), or HPV (19.8%).

The major strategies for the prevention of these cancers involve a variety of measures, including large-scale vaccinations against HBV and HPV, eradication of *H. pylori* infection, treatment of HCV-positive and HIV-positive subjects in order to avoid chronic infections, control of both concomitant infections and exposure to synergistically-acting lifestyle and environmental risk factors, and secondary prevention of the associated cancers, with special emphasis on cancer screening for HPV.

Conflicts of interest: none declared

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