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Latin American and the Caribbean Code Against Cancer 1st edition: Infections and cancer☆

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ABSTRACT

About 13% of all cancers around the world are associated with infectious agents, particularly in low-resource settings. The main infectious agents associated with cancer are *Helicobacter pylori (H. pylori),* that causes gastric cancer, human papillomavirus (HPV) that causes cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancer, hepatitis B and C viruses that cause liver cancer, and human immunodeficiency virus (HIV), associated with cancers of the cervix, Kaposi sarcoma (KS) and non-Hodgkin's lymphoma. In Latin America and the Caribbean (LAC), about 150,000 cancer cases are caused annually by infections. The LAC Cancer Code Against Cancer consists of a set of 17 evidence-based and individual-level cancer prevention recommendations targeted to the general population, suited to the epidemiological, socioeconomic, and cultural conditions of the region, and tailored to the availability and accessibility of health-care systems. The recommendations with respect to infection-driven malignancies include testing and treating for *H. pylori* in the context of specific public health programs, vaccination against HPV and Hepatitis B Virus (HBV) and detection and treatment of chronic infections with HBV, Hepatitis C virus (HCV) and HIV, in addition to the promotion of safe sex and use of condoms to prevent sexually transmitted infections (STI). Countries, policy makers, health care systems and individuals should consider the adoption of these recommendations to help reduce the incidence and mortality of infection-related cancers in LAC, to improve quality of life of individuals and reduce the costs of cancer care in the region.

1. Introduction

Estimates from the International Agency of Research on Cancer (IARC) indicate that about 13% of cancers around the world are associated with infectious agents, particularly in low-resource settings. In Latin America and the Caribbean (LAC), about 150,000 cancer cases are

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caused by infections every year [1]. The main infectious agents associated with cancer are *Helicobacter pylori (H. pylori)* that causes gastric cancer, human papillomavirus (HPV) that causes mainly cervical along with other anogenital and oropharyngeal cancers, hepatitis B virus (HBV) and hepatitis C virus (HCV) that cause liver cancer, and human immunodeficiency virus (HIV) which increases the risk of several cancers mainly through immunosuppression (e.g., Kaposi sarcoma (KS), non-Hodgkin's lymphoma, cervical cancer).

Latin America and the Caribbean Code against Cancer

Learn how to help prevent cancer in yourself and your family

Specialists on the subject and civil society representatives from Latin America and the Caribbean, convened by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) and the Pan American Health Organization (PAHO), have reviewed the scientific evidence and recommend the following 17 actions people can take to help prevent cancer:

1. Don't smoke or use any type of tobacco. If you do, quitting is possible, with professional help if needed. Don't use e-cigarettes either, as they lead to tobacco use.
2. Make your home a smoke-free place. Respect and promote laws that ensure smoke-free spaces to protect our health.
3. Achieve or maintain a healthy weight throughout your life to help prevent several types of cancer.
4. Get daily physical activity throughout your life and limit the time you spend sitting. Being a physically active person helps prevent several types of cancer.
5. Eat a healthy diet:
   - Eat as many fruits and vegetables as possible at each meal, and regularly include legumes such as beans and lentils.
   - Eat whole grains, such as whole-grain bread, corn tortillas, and brown rice, rather than refined grains such as white bread or rice.
   - Avoid sugar-sweetened beverages, drink water instead.
   - Limit your consumption of ultra-processed foods, such as sweets, sweetened breakfast cereals, salty snacks, pastries, and cookies, among others. Instead, eat natural foods or foods prepared at home.
   - Avoid processed meats, such as deli meats, sausages, or cured meats, and limit your consumption of red meat.
   - Limit your consumption of very hot beverages, such as tea, coffee, and *mate*. Wait a few minutes until the liquid no longer feels hot enough to burn your lips or tongue.
6. Avoid drinking alcoholic beverages. This helps prevent several types of cancer.
7. Breastfeed your baby—the more months the better—to help prevent breast cancer and excess weight in your baby.
8. Protect yourself from direct sun exposure during peak sunlight hours to help prevent skin cancer.
9. If you cook or heat your home with coal or firewood, make sure smoke doesn't build up inside your home.
10. If air pollution is high where you are, limit your time outdoors.
11. Find out if your job exposes you to substances that can cause cancer, and request and adopt the recommended protective measures.
12. Infection from *Helicobacter pylori* bacteria can cause stomach cancer. Check with health professionals to find out if you might benefit from screening and treatment for this bacterial infection.
13. Infection with viruses such as hepatitis B and C, human papillomavirus (HPV), and human immunodeficiency virus (HIV) can also cause cancer. Therefore:
    - Vaccinate children for hepatitis B virus in their first 24 hours of life. Vaccinate yourself and your family at any age if you have not yet done so.
    - Vaccinate girls and teens against the human papillomavirus (HPV), primarily to help prevent cervical cancer, as well as other types of cancer. Take this preventive measure at the ages recommended in your country. If available, vaccinate boys as well.
    - Talk to health professionals to see if you might benefit from screening and treatment for hepatitis B and C viruses to help prevent liver cancer.
    - Get tested for human immunodeficiency virus (HIV), and ask about the prevention and treatment programs available in your country.
    - Make sure to use condoms consistently and correctly, especially with new or casual partners.
14. Do not use hormone replacement for menopause unless directed to do so by your healthcare provider. Hormone replacement can cause breast cancer.

Cancer can be controlled and cured if it is detected and treated early:

15. If you are between the ages of 50 and 74, visit a health care provider and ask for an early detection test for colon and rectal cancer (fecal occult blood test or colonoscopy). Based on the results, follow your health professional's recommendations promptly.
16. If you are 40 years of age or older, visit a health care provider every two years for a clinical breast exam. From age 50 to 74, get a mammogram every two years. Based on the results, follow your health professional's recommendations promptly.
17. If you are between the ages of 30 and 64, visit a health care provider and ask for a molecular human papillomavirus (HPV) test at least every 5–10 years for early detection of cervical cancer. Ask if you can collect the sample yourself. If you don't have access to the HPV test, ask for the exam that is available in your country. Based on the results, follow your health professional's recommendations promptly.

Fig. 1. Latin America and the Caribbean Code Against Cancer 1st Edition: Recommendations for the general public.

Under the overall umbrella of a World Code Against Cancer Framework 6 [2,3], using the methodology established by IARC and the experience of the European Code Against Cancer (ECAC), the 1st edition of the LAC Code Against Cancer has been developed by cancer prevention experts from LAC, in collaboration with the Pan-American Health Organization (PAHO/WHO). The LAC Cancer Code Against Cancer consists of a set of 17 evidence-based and individual-level cancer prevention recommendations targeted to the general population, suited to the epidemiological, socioeconomic, and cultural conditions of the region, and tailored to the availability and accessibility of health-care systems [4](Fig. 1). The Code also includes a supplementary set of recommendations for policymakers (Supplementary material) and an online competency-based microlearning program on the topics covered by the recommendations. The aim of this learning program is to build primary healthcare professional's capacity to advice their patients and families on evidence-based actions for primary and secondary prevention of cancer [5].

In this article, we discuss general aspects of infectious agents associated with cancer, followed by a justification of each recommendation for the individual and the policy recommendations for the region.

2. *Helicobacter pylori*

H. pylori is a gram-negative bacterium that colonizes the human stomach. Infection is usually acquired in childhood, probably from infected parents or other children [6], and generally persists for life in the absence of specific antibiotic treatment. Crowding and poor hygienic conditions are the main determinants of *H. pylori* acquisition and transmission. In adult populations in LAC, *H. pylori* prevalence is ~60% (more than 200 million people), while the prevalence in younger cohorts is lower [7].

In most individuals, *H. pylori* infection produces asymptomatic chronic gastritis that can variably progress to premalignant lesions, including atrophic gastritis, intestinal metaplasia, and dysplasia. *H. pylori* infection is also associated with peptic ulcer and extra-gastric conditions, including thrombocytopenic purpura and iron deficiency anemia.

Diagnosis of *H. pylori* infection can be made with noninvasive tests, which do not require endoscopic collection of specimens (serology, urea breath test, PCR in feces), and invasive methods which are usually performed on tissue or specimens collected directly from the stomach (urease test, histology, culture)[8].

H. pylori is an IARC group 1 carcinogen [9]. Group 1 carcinogens are classified as such when there is enough evidence that they can cause cancer in humans. *H. pylori* is associated with gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. Specifically, the bacterium produces the CagA oncoprotein that deregulates several pathways implicated in carcinogenesis [10]. Both non-cardia (attributable fraction (AF), ~90%) and cardia (~60%) tumors are caused by chronic *H. pylori* infection [11,12].

Progression to cancer in infected individuals depends on host and environmental cofactors, including smoking, alcohol, and consumption of processed meats, excessive salt [12,13], overweight, some autoimmune diseases, family history, and some hereditary conditions [11,14]. Epstein-Barr virus-associated gastric carcinoma is a distinct subtype that accounts for ~9% of gastric adenocarcinomas [15,16].

Risk of gastric cancer varies across populations, with particularly high rates in East Asian countries (Korea, Japan) and LAC, with nearly 800,000 yearly deaths globally [17]. In LAC an estimated 70,000 cases and 53,000 deaths occurred in 2020. In LAC, the countries with the highest incidence are Perú, Haití , Chile, Colombia, Costa Rica, Ecuador, and Guatemala. Despite worldwide declines in incidence rates, IARC predicts a growing burden, because of population ageing and growth.

The long duration of the sequence of events leading to cancer allows multiple opportunities for early diagnosis or intervention with curative intention. Unfortunately, there are no specific biomarkers to identify population subgroups at high risk to target for screening programs.

Primary prevention of gastric cancer is based on *H. pylori* detection and eradication. Randomized clinical trials (RCT) mainly in high-risk Asian populations indicate that eradication reduces ~40% gastric cancer incidence and mortality [18]. Eradication reduces inflammation and degree of atrophy, but when intestinal metaplasia is present, there is limited benefit of eradication [19].

The current indications for *H. pylori* eradication are peptic ulcer, chronic use of non-steroidal anti-inflammatory drugs, treated gastric cancer, MALT lymphoma, *H. pylori*-associated dyspepsia, family history of gastric cancer, chronic gastritis, and some hematologic conditions [20]. Eradication treatment generally consists of combinations of antibiotics and proton-pump inhibitors. The efficacy of the different treatment schedules is variable and decreases in regions where antibiotic resistance is high. Ideally, selection of antibiotic combinations should be based on population studies of antibiotic resistance.

Secondary prevention is centered around detection of early cancers, for which treatment is relatively simple, and success is high. Population-based endoscopic screening has been implemented in high-incidence Asian countries, and mortality has declined in those populations [21]. The high cost and complexity of this approach makes it hard to implement it in the LAC region. A feasible alternative is the endoscopic follow-up of patients with intestinal metaplasia [22].

3. Hepatitis

Around 800,000 primary liver cancers are diagnosed yearly worldwide with more than 80% occurring in developing countries. In LAC, liver cancer is less common than in other regions (Age-adjusted incidence rate (AAIR) = 4,8 per 100,000) compared to 11,6 for Asia, the highest. The highest rates in LAC are in Central America, Caribbean, México, Bolivia and Perú [23].

Studies in LAC have shown that Hepatitis C, followed by alcohol consumption are the most common causes of liver cancer [24]. In Perú and the Amazon, the most common cause is HBV (Fig. 2). Several factors interact with hepatitis B and C in the development of hepatocellular carcinoma, including viral genotypes, coinfections with other hepatitis viruses, aflatoxins, alcohol, tobacco as well as obesity and other metabolic factors[25].

3.1. *Hepatitis B virus*

HBV is a DNA virus of the family *Hepadnaviridae* that only infects humans and is very common in the African and Western Pacific regions, with prevalence close to 6%. In LAC, around 0.7% of the population is infected, with higher prevalence in some areas of Central America (Guatemala, Honduras) and in South America, especially in the Amazon region. In LAC, an estimated 300,000 people are chronic carriers of HBV [26].

HBV is transmitted by blood (e.g., contaminated needles, tattooing or medical procedures) and other bodily fluids, including semen and vaginal secretions. It is more common in men who have sex with men (MSM) and sexual workers. Infected mothers transmit the virus to their offspring and infected children to other children [27].

Most infections are asymptomatic and some cause acute hepatitis that occasionally induces liver failure and death. Chronic infection develops in 5% of adult infections and up to 95% of infected newborns and small children. Conversely, acute manifestations are rare in children and occur in nearly 30% of adults [25].

HBV is an IARC group 1 carcinogen [25]. Chronic hepatitis B is characterized by serologic evidence of HBV surface antigen (HBsAg) for more than 6 months. Risk of progression to liver disease is associated with active viral replication as determined by HBV e Antigen (HBeAg) and the levels of circulating DNA. Cirrhosis is the main risk factor for progression to cancer, regardless of the underlying cause, with 30% of cases progressing to cancer. HBV carcinogenic mechanisms include viral

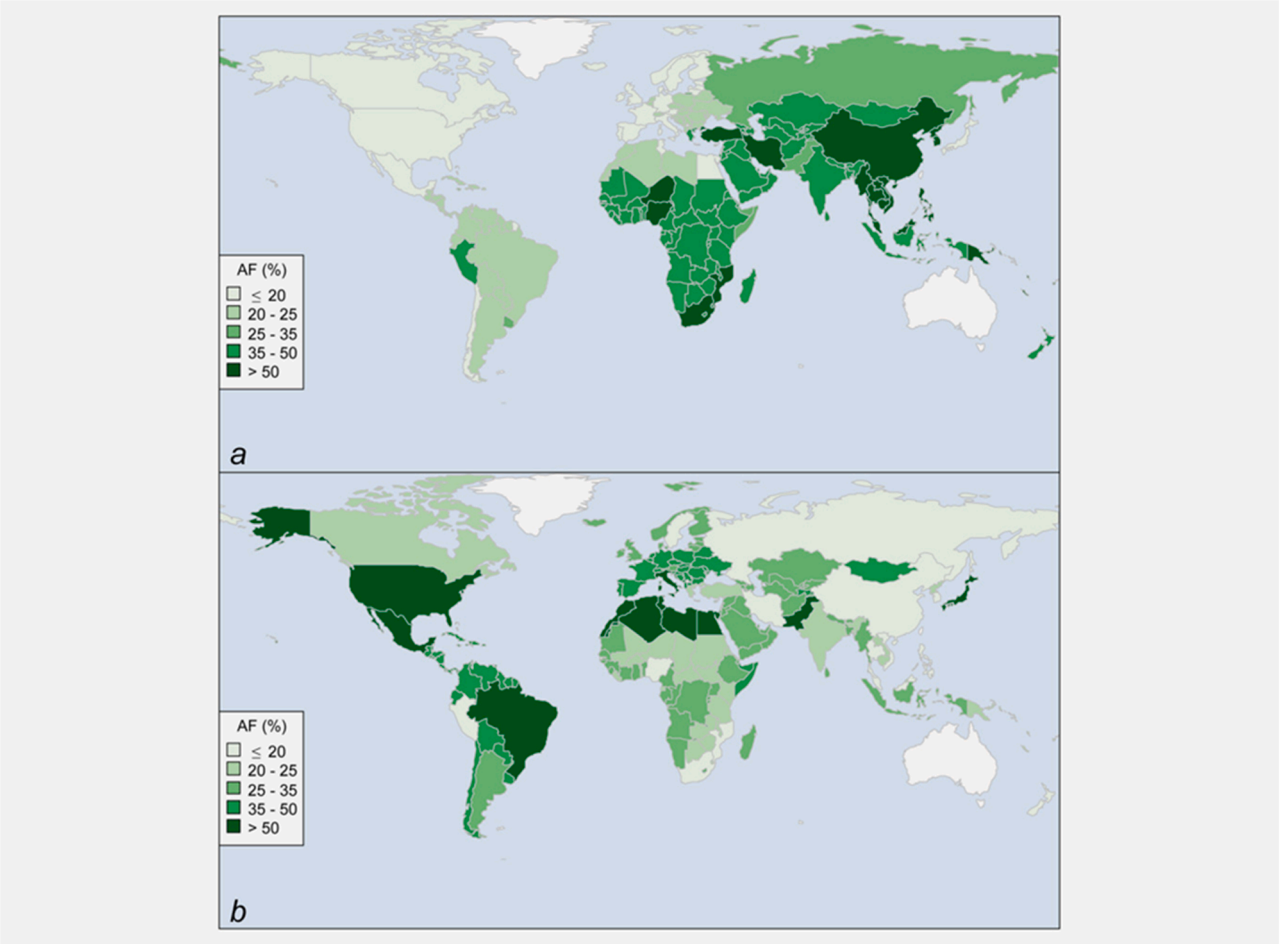

Fig. 2. Attributable fraction for liver cancers due to (a) HBV and (b) HCV chronic infection [109].

DNA integration in the host genome, altering endogenous gene function or inducing chromosomal instability and genetic damage associated with chronic inflammation or oxidative stress, with expression of viral proteins HBx and PreS/S [28]. The chronic inflammation, necrosis and scarring facilitates a mitogenic and mutagenic environment that can lead to cancer in the presence of cofactors.

The HBV vaccine is the basis of prevention of this disease and its sequelae. World Health Organization (WHO) recommends, since 1992, administering HBV vaccine to all newborns, ideally within 24 h after birth, to reduce mother to child transmission with an additional 2 doses 4 weeks apart [29].

HBV vaccines are made of highly purified recombinant preparations of the HBsAg adjuvanted with aluminum. Complete vaccination provides more than 95% protection in children and young adults against acute infection, chronic hepatitis and hepatocarcinoma, with a duration of more than 20 years and probably life-long [30–32].

WHO recommends vaccination of all unvaccinated children and adolescents as well as high-risk groups, which include health workers, patients in dialysis or requiring transfusion or blood products, transplant recipients, prisoners, drug users, carriers of other hepatitis viruses or people with high-risk sexual behavior or occupational exposure and travelers to endemic areas, taking into account the local epidemiology and the need to prevent acute HBV infection [33].

Chronic infection with HBV can be treated with antiviral agents that can delay evolution to cirrhosis, reduce incidence of liver cancer and improve survival. The currently recommended treatment is oral entecavir or tenofovir which are taken once a day and cause few adverse events [34,35].

Treatment of HBV does not cure infection in most people and needs to be maintained for life, priority is given to persons with advanced liver failure or cirrhosis or high circulating virus and signs of chronic inflammation.

Despite declining prices, in many low-income regions, access to treatment is still very limited. In 2016, only 10.5% (27 million people) of people infected knew they had the infection and only 16.7% of those diagnosed were on treatment [34,35].

3.2. *Hepatitis C virus*

HCV is an RNA virus of the *flavivirus* family. Global prevalence is ~ 2%, being more common in the Eastern Mediterranean and European regions. In most LAC countries the prevalence is between 1% and 2% with an estimated 5 million people infected. HCV is transmitted mainly by contaminated blood, and before screening of blood products, transfusions were the most common form of transmission. Currently, the most common source of infection is shared needles, diagnostic procedures, and medical interventions. Sexual and household transmission (direct through-the-skin exposure to the blood of an infected family member) can also occur [25].

HCV infection can be acute or chronic, but fulminant hepatitis C is very rare. Evolution to chronic infection with HCV occurs in about 85% of infected individuals regardless of age. Diagnosis is made by detection of antibodies with third generation ELISA methods or genomic detection by PCR and genotyping. HCV is an IARC group 1 carcinogen [25]. Its carcinogenic mechanisms are not fully elucidated but there is evidence of the role of inflammation and oxidative stress, as well as direct interaction of host factors and viral proteins. Among the specific mechanisms, induction of liver steatosis by HCV which increases

neo-synthesis of lipids in the liver has been reported. These factors induce a fibrogenic environment and genomic instability that after several years induces carcinogenesis. HCV is also associated with 10% of non-B-cell Hodgkin's lymphoma [25].

Prevention of hepatitis C requires screening donated blood, organs, and semen for this virus. Sterile syringes for intravenous drug users and proper sterilization can reduce HCV infections, but in some areas, risk from contaminated medical equipment persists. The circulating titers of HCV are lower than those of HBV or HIV and therefore transmission via contact with mucosae is less common, including vertical transmission. However, high-risk sexual behaviors, including anal sex, are associated with HCV transmission. Identification and treatment of infected subjects reduces transmission. Education programs on prevention are essential.

HCV infections are usually asymptomatic for decades until evidence of severe liver damage appears. Infection is diagnosed by detection of anti-HCV antibodies and viral ARN. HIV infected people have higher frequency of infection with HCV (~6%). In some people the immune response eliminates HCV, but when chronic infection is present, an 8–12 weeks course of oral pan-genotypic direct-action antivirals cures most infections in people over 12 years [36,37]. Despite availability of generics and improvements in access, treatment is still limited. An estimated 15% of the nearly 60 million people infected have been diagnosed and about 60% of those have been treated.

4. Human papillomavirus

HPV is a very common STI with an estimated 80% of men and women infected at some point in most regions of the world. Asymptomatic infection is acquired shortly after initiation of sexual activity and most infections clear spontaneously after several months or years. A small fraction of people develops persistent infections and squamous intraepithelial neoplasia which can progress to invasive cancer, usually after decades [38].

The prevalence of HPV infection of the cervix is strongly associated with age, with a peak in younger women and a subsequent decline, in Latin America to about 15% after age 30 [39,40]. In some populations in LAC and some African countries, a second peak of infection is noted after menopause, and in some areas, prevalence does not decline with age. People living with HIV have much higher HPV prevalence at all anatomic sites where HPV causes infection [39]. Several HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) have been classified as group 1 carcinogens by the IARC monographs program [25]. Persistent infection with HPV is associated with cancer of the cervix (100%), anus (100%), vagina (78%), vulva (25%), penis (53%) and oropharynx (30%) [1]. HPV 16 is the predominant type in all anatomic sites, but its predominance is stronger in cancers other than cervical. According to the Global Cancer Observatory (GLOBOCAN) estimates, about 600,000 cases and 340,000 deaths annually around the world are caused by HPV [23].

The mechanisms involved in HPV carcinogenesis are well known. The most important are inhibition of p53 by the E6 oncoprotein of HPV, and of the tumor suppressor protein retinoblastoma by E7. The first step in HPV carcinogenesis is a squamous intraepithelial lesion (SIL), which when classified as high-grade is considered precancerous, with potential to evolve into invasive cancer over several years. Cofactors for progression of HPV infections to precancer and cancer include HPV type, with HPV 16 being much more likely to progress, smoking, multiparity and prolonged use of hormonal contraception, in addition to immunosuppression (e.g., HIV co-infection)[25].

The main tool for prevention is the HPV vaccine, a recombinant subunit vaccine composed of L1 protein, the main component of the viral capsid, which self-assembles into virus-like particles (VLP). Currently available vaccines differ in the type of adjuvant and the number of HPV types. Bivalent, quadrivalent and nonavalent vaccines are available and new products are under evaluation. VLP-based vaccines have demonstrated high efficacy against type-specific infections and lesions in all anatomic sites where they have been evaluated (cervix, vulva, vagina, anus, penis and oral cavity) [41].

HPV vaccines generate a strong and long-lasting antibody response in practically all vaccinated subjects. Protection by the vaccines is close to 100% against type-specific HPV infections among individuals not infected at the time of vaccination and there is some cross protection against certain non-vaccine HPV types. The vaccine is prophylactic and has no effect on pre-established infections [42]. The initial clinical trials were conducted among women 15–26 years old, but the recommendation was extended to 9–26 years old women with immunobridging studies. The vaccines are considered very safe as recently documented by the WHO Global Advisory Committee on Vaccine Safety [43].

Vaccination against HPV started in 2006 in high-income countries, where the impact on reduction of infection, precancer and cancer has been demonstrated [44]. Globally, vaccination has limited coverage, with under 20% of girls having received the vaccine, but by 2020 most LAC countries had already introduced vaccination for adolescent girls as recommended by WHO (Fig. 3) [45]. Some countries are also including boys in the program. Despite important difficulties during the COVID-19 pandemic, vaccination is progressing in most areas. Secondary prevention of cervical cancer is achieved with screening programs traditionally with cytology and more recently HPV DNA testing[46].

5. Human immunodeficiency virus

HIV is a retrovirus that attacks the immune system, affecting its capacity to fight infections and some cancers. The main targets of HIV are the CD4 + T lymphocytes (LTCD4), which are destroyed by the virus. The advanced stage of HIV infection is the acquired immunodeficiency syndrome (AIDS), when LTCD4 decrease to levels under 200 cells/ml or when certain types of infections or cancers are present.

In 2020, an estimated 38 million people were living with HIV around the world, of which more than 25% were not receiving antiretroviral treatment, and there were 1.5 million new cases of HIV infection and 680,000 AIDS deaths [47]. The number of new HIV cases in Latin America is estimated to have increased by 21% since 2010, with approximately 120,000 new people infected in 2019. Conversely the Caribbean had a 29% reduction from 2010 to 2019, with an estimated 13,000 new cases in 2019 [48]. The populations most affected in LAC are MSM, transgender women and sexual workers.

HIV is transmitted sexually through semen and vaginal fluids. It can also be transmitted by blood, needle sharing or uncontrolled blood products and during delivery and breast feeding. HIV is diagnosed through nucleic acid amplification, antigens, and antibodies.

For the period 2016–2021, HIV prevalence in key populations in LAC was 1.5% in sexual workers, 13.9% in MSM, 1.5% in intravenous drug users, 23.6% in transgender people and 0.7% in prisoners [47]. Of 100, 000 new infections in Latin America, 92% were in vulnerable populations and their sexual partners, especially MSM. The prevalence in the general population is on average 0.4%.

HIV is an IARC group 1 carcinogen [25]. Although none of the HIV proteins has been unequivocally classified as oncogenic, some are associated with immunodeficiency, which is indirectly linked to carcinogenesis. The immune system can suppress oncogenic viruses and eliminate tumor cells (immune surveillance). HIV produces immunodeficiency, immune activation with a chronic pro-inflammatory condition and immune senescence. Low LTCD4 counts, especially < 200 cells/ml, a criterion for AIDS diagnosis increases risk of cancer, including tumors considered AIDS-defining (KS, cervix, and non-Hodgkin's lymphoma). Cancer risk is also increased by high frequency of coinfections with similar acquisition mechanisms (HPV, hepatitis, Epstein-Barr virus), and other cancer risk factors, like smoking and alcohol, which are frequently found in HIV-positive individuals [25]. In the antiretrovirals era, with extended survival, AIDS-defining cancers have declined, and non-AIDS-defining tumors have increased.

To reduce transmission of HIV, the main tools include provision of condoms and lubricants, pre/and post exposure prophylaxis, screening

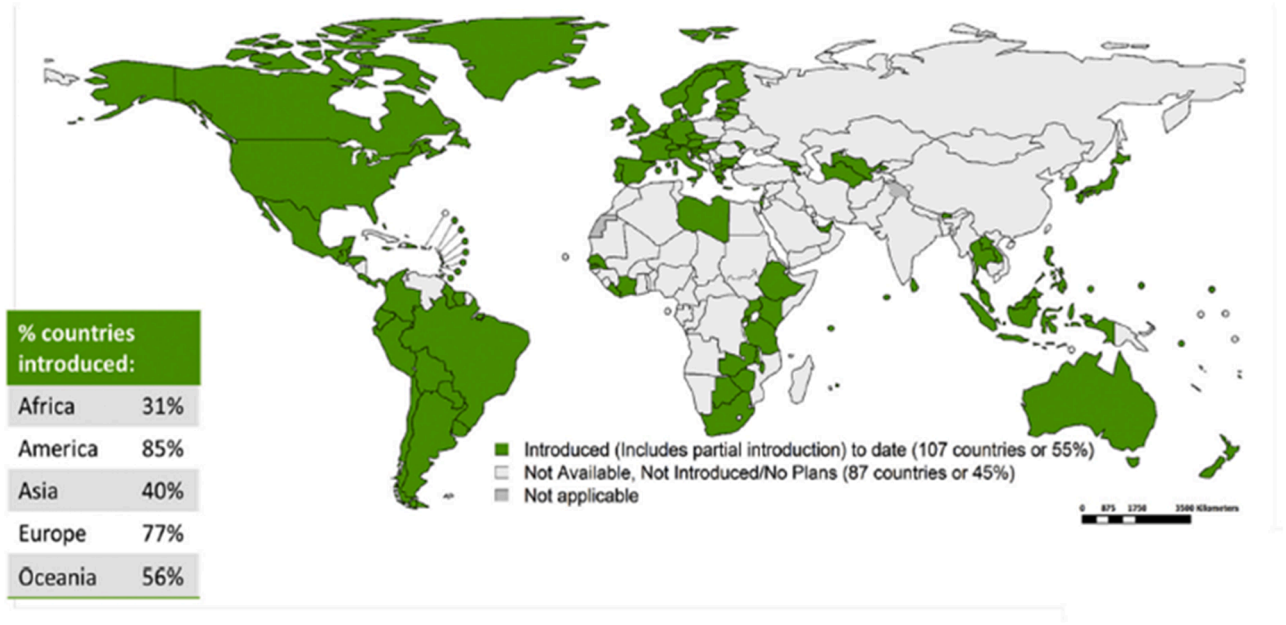

Fig. 3. WHO member states with HPV vaccination in their national immunization programs, as of June 2020. [45]

services, and detection and treatment of STIs in the context of sexual and reproductive health programs, in addition to prevention of use of contaminated needles and blood[49].

Treatment of HIV or antiretroviral therapy consists of a combination of drugs that suppress viral replication, to increase efficacy and prevent development of resistance. All persons with HIV should start treatment immediately as early treatment reduces morbidity, mortality, and further transmission [49].

Among people infected, diagnosis and initiation of treatment with antiretroviral therapy can reduce risk of cancer, together with reductions in exposure to oncogenic viruses, avoiding alcohol and tobacco and participating in vaccination and screening programs [50].

6. Justification of the LAC Code Against Cancer 1st edition recommendations for the individual and policymakers

The working group (WG) on infections, composed of experts from the region and using the ECAC as an initial model, reviewed and evaluated the latest evidence and proposed recommendations for the individual (Fig. 1) and public health recommendations for policy makers (supplementary material), following IARC guidance as described elsewhere [4]. For the first time a Code Against Cancer includes recommendations on screening and treatment on *H. Pylori*, hepatitis and HIV, and an intervention related to safe sex. This section discusses the main elements for the justification of the different recommendations.

In some instances, to support the discussions of the working group, a literature review was carried out by an external contractor. Briefly, according to the ECAC methodology [51], when evidence on the effectiveness of an intervention is not sufficient, a systematic review (SR) of the most recent evidence should be performed. Following the Cochrane Handbook for SRs of Interventions and adhering to the Preferred Reporting Items for SRs and Meta-Analysis (PRISMA) statement for the reporting [52], the reviews of the evidence consisted of two complementary approaches: a) an overview of SRs of randomized clinical trials or observational studies (comparative cohorts), prioritizing those that were more comprehensive and of higher quality, and b) a SR of individual studies: departing from the latest search date reported among the prioritized SR(s), we updated the evidence with individual studies not included in the previous reviews. We addressed the following questions: effectiveness of direct-acting antiviral treatment for HCV persisting infection (date of search October, 2021), use of condoms in the general population to prevent cancers associated to sexually transmitted infections (date of search November, 2021), cost effectiveness of *H.pylori* screening (screen and treat) in the general population (date of search November, 2021), antiretroviral treatment in people living with HIV effective in preventing the development of HIV associated cancers (date of search November, 2021), effectiveness of nucleotide analogue treatment for persistent HBV infection (date of search October, 2021) and effectiveness of the HPV vaccine in preventing cancer in healthy men (date of search October, 2021). The reviews included global data; they were not restricted to studies in the LAC region.

In addition, following a common syllabus developed for the LAC Code Against Cancer project [5], the WG prepared educational materials for primary care health workers that constitute the online competency-based program of the LAC Code Against Cancer.

Oral hygiene and gallbladder cancer were additional topics discussed by the WG, but the consensus was that there is not sufficient evidence to make a specific recommendation at this time, a brief summary is presented below.

7. Recommendation on *H.pylori* for the individual

The LAC Code Against Cancer indicates "**Infection from *Helicobacter pylori* bacteria can cause stomach cancer. Check with health professionals to find out if you might benefit from screening and treatment for this bacterial infection**". Several international clinical consensuses [53,54] have recommended the strategy of testing and treatment of *H. pylori* at the population level in areas of high gastric cancer incidence. More recently, the Maastricht VI/Florence consensus considers priority to implement public policies for diagnosis and treatment of *H. pylori* in populations with intermediate to high rates of gastric cancer [20], using antibiotic schedules achieving at least 90% eradication rates. Clarithromycin, one of the main antibiotics in eradication schemes should not be used where resistance is over 15% as is frequently the case in LAC [55]. Other modifiable risk factors include a healthy diet, limited consumption of salt and tobacco cessation.

A meeting convened by IARC in 2013 [56] concluded that implementation of testing and eradication of *H. pylori* for gastric cancer prevention at the population level has to consider local burden of disease, other health system priorities and cost effectiveness.

We conducted a new literature review on cost-effectiveness of *H. pylori* screening and eradication, including studies up to November 2021, as described above mainly for information to policy makers when deciding on the appropriateness of the intervention for their region. From the five SRs included [57–61], we identified a total of 18 economic evaluations (model-based studies) comprising populations from North America, Europe, East and Southeast Asia, and Oceania; only one study included Colombia's general population in the analysis [62]. In brief, for the strategy of one time screening and treating using serology test the incremental cost-effectiveness ratios (ICERs) varied from US$1560 (2005) in a Chinese men cohort [63] to US$25,881 (2006) per Quality-adjusted life year (QALY) for overall population in China [64]. The ICERs for urea breath tests (UBT) versus no screening were higher than those of serology screening, ranging from US$32,525 (2006) [65] to CA $50,400 (2009) [66]. For the alternative of screening with serology, treat, and confirmation of eradication with C-UBT, reported an ICER of US$90,712/QALY (2006) in men and US$130,239/QALY (2006) [67]. A recent review of modelling studies in Western countries, where gastric cancer incidence is relatively low, concluded that *H. pylori* test-and-treat is a potentially cost-effective strategy to reduce gastric cancer mortality in those regions but that it is too early for widespread implementation until more is known about the potential adverse impact of widespread antibiotic use on antibiotic resistance [58].

The working group considered that gastric cancer is a major public health problem in the region and the possibility of intervening with a proven effective intervention needs to be seriously considered by health authorities to reduce the burden of this deadly cancer.

8. Recommendation on Hepatitis, HPV and HIV for the individual

8.1. Hepatitis B and C

The LAC Code Against Cancer 1st edition recommends: "**Vaccinate children for hepatitis B virus in their first 24 h of life. Vaccinate yourself and your family at any age if you have not yet done so**" and "**Talk to health professionals to see if you might benefit from screening and treatment for hepatitis B and C viruses to help prevent liver cancer**".

HBV vaccination is well established in LAC with an estimated coverage of 87% for 3 doses in children under 1 year, despite regional differences. The elimination goal of reducing prevalence of HBsAg in children 4–6 years old to 0.1% has already been reached by several LAC countries [68]. However, the program goal of vaccination of 95% of newborns has been reached only by a few countries.

In 2016, the World Health Assembly (WHA) adopted the world strategy against viral hepatitis [69] with the ultimate objective of eliminating viral hepatitis as a public health problem. The worldwide goals are to reduce new infections by 90% and associated mortality by 65% by 2030. The working group considered that given the ambitious goals of the WHO and the recent availability of effective, safe, and relatively affordable treatments against HBV and HCV, countries should consider screening programs for specific population groups, all individuals should consult their providers to access such programs. WHO recommends screening of high-risk populations for HCV, and where the prevalence of HCV is high ($\geq$ 2% to $\geq$ 5%) to offer screening and treatment to all adults [70]. The U.S. Center for Disease Control and Prevention (CDC) recommends testing at least once in their lifetime all adults over 18 years of age, except in areas where prevalence is under 0.1% [71].

We reviewed the evidence on specific types of treatments for HCV and HBV chronic infection. Among patients with HCV, a meta-analysis [72] of 11 trials suggested that direct acting antivirals (DAAs) treatment reduces the risk of no sustained virological response (Rate ratio (RR) 0.44, 95% confidence interval 0.37–0.52).

For HBV chronic infection, when considering three observational studies that compared entecavir to no treatment or placebo, our pooled analysis suggested a 56% reduction of hepatocellular carcinoma cumulative incidence rates compared to not-treated patients (Hazard ratio (HR) 0.44; 95%CI 0.31–0.61) [73–75]. Regarding tenofovir, two retrospective observational studies compared it to no treatment or placebo, our pooled analysis suggested an adjusted Hazard ratio (aHR) of 0.42 (95%CI 0.29–0.63) for liver cancer incidence [76,77].

8.2. Human papillomavirus

For HPV, the LAC Code Against Cancer recommends "**Vaccinate girls and teens against the human papillomavirus (HPV), primarily to help prevent cervical cancer, as well as other types of cancers. Take this preventive measure at the ages recommended in your country. If available, vaccinate boys as well.**"

The Cervical Cancer Elimination Strategy, adopted by the World Health Assembly in 2020 has an ultimate goal of reducing cervical cancer to an incidence rate under 4 per 100,000 women. Its 3 pillars are vaccination of 90% of adolescent girls by age 15, screening of 70% of women and treatment of 90% of lesions detected [78].

Given current data that one dose of the HPV vaccine provides adequate protection against infection [79,80], the recent WHO position paper indicates that current evidence supports the recommendation that a 2-dose schedule be used in the primary target group from 9 years of age and for all older age groups for which HPV vaccines are licensed, and as an off-label option, a single-dose schedule can be used in girls and boys aged 9–20 years [43].

From our synthesis of evidence on the impact of HPV vaccines in males and a SR [81], the RCTs showed protection from external genital lesions and suggest protection against intraepithelial lesions but confidence intervals were broad. One RCT reported a better protection of quadrivalent HPV vaccine compared with control against penile or anal intraepithelial neoplasia at up to 3-year follow-up (RR 0.17, 95% CI 0.01–3.27), external genital lesions (HPV 6, 11, 16, or 18) (RR 0.10, 95% CI 0.03–0.31), penile, perianal, or perineal intraepithelial neoplasia grade 1 (RR 0.25, 95% CI 0.01–6.22), and penile, perianal, or perineal intraepithelial neoplasia grade 2 or 3 (RR 0.50, 95% CI 0.02, 14.80). One RCT reported protection of the quadrivalent HPV vaccine compared with control for males seronegative and PCR-negative at enrolment against anal intraepithelial neoplasia (AIN) grade 2 (Vaccine vs Control: 2/384.5 vs 9/418.6 person-years [82]. Regarding adverse events, RCTs showed HPV vaccines have more local-injection site reactions, such as pain at injection site and swelling; but little to no difference for systemic events and general symptoms or serious adverse events.

8.3. Human immunodeficiency virus

The LAC Code Against Cancer 1st edition recommends "**Get tested for human immunodeficiency virus (HIV) and ask about the prevention and treatment programs available in your country.**"

Based on the current international targets calling for 95% of people infected having a diagnosis, 95% of those diagnosed under treatment and 95% of those under treatment with viral suppression and considering the extensive efforts underway in the region to achieve these goals, for this recommendation the working group considered that recommending the test directly to the public was appropriate. According to the CDC, all people between 15 and 65 years of age should have an HIV test at least once in their life, people with other STIs and other high-risk populations more frequently, according to exposure. Pregnant women need to be screened to prevent vertical transmission [83].

Kelly et al. [84], reported that highly active antiretroviral therapy (HAART) had an uncertain association with anal cancer incidence when adjusted for years living with HIV in three studies (aHR 1.11, 95% CI 0.68–1.80; I^2 0%, p = 0.57). Among HAART users, those with a sustained undetectable HIV-viral load had 44% lower risk of anal cancer than those without (aHR 0.56, 95% CI 0.44–0.70; I^2 0%, p = 0.94) and

for each increase in nadir CD4 cell counts of 100 cells per μL, there was a 40% decrease in anal cancer incidence (HR 0.60, 95% CI 0.46–0.78; I^2 21.7%, p = 0.26).

Five systematic reviews [85–89] assessed the association of HAART with invasive cervical cancer. Kelly et al. reported that, in three studies among 15,846 women living with HIV, HAART was associated with a reduction in invasive cervical cancer incidence (HR 0.40, 95% CI 0.18–0.87). However, other two reviews reported uncertain association between HAART and cervical cancer, while Cobucci et al. [88] reported an increase in the risk for the development of invasive cervical cancer increased after the introduction of HAART (RR 1.46, 95% CI 1.09–1.94). In a systematic review, Bratcher et al. [89] in 2010 pointed out that the data revealed mixed findings, with some suggesting higher risk in the post-HAART era and others the opposite.

For KS, Hodgkin's, and non-Hodgkin's lymphoma the evidence from SRs suggested risk reduction for HAART use. Chang et al. [90] based on one study reported a reduction of KS incidence (adjusted incidence rate ratio (aIRR) 0.47, 95% CI: 0.38–0.58) early in the HAART era, along the same line, Cobucci et al. [88] reported that the risk for the development of KS decreased after the introduction of HAART (RR 0.30, 95% CI: 0.28–0.33). The only review examining Hodgkin's lymphoma [91], reported a lower SIR during the pre-HAART era, compared the HAART era (9.7 (95% CI 6.2–15) versus 19 (95% CI 13–27)). One review reported that the risk for the development of non-Hodgkin's lymphoma decreased after the introduction of HAART (RR 0.52, 95% CI 0.48–0.56)[88]. Most of the observational studies provided consistent results to the previous described reviews.

Helicobacter pylori[13]

- Define national policies on the screening and treatment of *Helicobacter pylori* infection according to the various at-risk population groups. Develop organized programs to implement these policies.
- Ensure the availability of the lab tests, treatment, follow-up, and diagnostic procedures required for these programs, and implement antibiotic resistance testing to ensure high eradication rates.

Viral infections[14,15, 16, 17, 18, 19, 20, 21]

- Ensure universal hepatitis B virus vaccination for boys and girls immediately after birth, and implement strategies to proactively find unvaccinated individuals in order to vaccinate them, preferably before they are sexually active (catch-up vaccination).
- Ensure access to diagnosis of hepatitis B and C, and availability of treatment for anyone diagnosed with these viral infections.
- Ensure the availability of HPV vaccines to sustain vaccination programs. Give one or two doses in vaccination programs, as recommended by WHO. Promote vaccination as a priority in girls 9–14 years of age and extend, if possible, to 18 years; include boys based on the availability of resources. Ensure WHO's global goal of vaccinating 90% of girls by age 15 by 2030.
- Establish a program to promote and facilitate HIV testing in the general population. Ensure treatment of at least 95% of people with the infection. Ensure that at least 95% of patients have suppressed viral load.
- Implement sex education programs. Ensure free and widespread access to condoms.

[13] Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou J-M, Schulz C, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. Gut. 2022;0:1-39. Available from: https://gut.bmj.com/content/71/9/1724.

[14] World Health Organization. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. Geneva: WHO; 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf?sequence=1&isAllowed=y.

[15] World Health Organization. Preventing perinatal hepatitis B virus transmission: a guide for introducing and strengthening hepatitis B birth dose vaccination. Geneva: WHO; 2017. Available from: https://apps.who.int/iris/handle/10665/208278.

[16] Weng MK, Doshani M, Khan MA, Frey S, Ault K, Moore K, et al. Universal Hepatitis B Vaccination in Adults Aged 19-59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep. 2022;71(13):477-483. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7113a1.htm.

[17] World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations. Geneva: WHO; 2022. Available from: https://apps.who.int/iris/bitstream/handle/10665/356579/WER9724-spa.pdf?sequence=27&isAllowed=y.

[18] World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem. Geneva: WHO; 2022. Available from: https://apps.who.int/iris/rest/bitstreams/1315304/retrieve.

[19] Pan American Health Organization. Plan of Action for the prevention and control of HIV and sexually transmitted infections 2016-2021. Washington, D.C.: PAHO; 2016. Available from: https://iris.paho.org/bitstream/handle/10665.2/34081/CD552017-eng.pdf.

[20] United Nations Population Fund, World Health Organization, Joint United Nations Programme on HIV/AIDS. Position statement on condoms and the prevention of HIV, other sexually transmitted infections and unintended pregnancy. Geneva: ONUSIDA; 2015. Available from: https://www.unaids.org/en/resources/presscentre/featurestories/2015/july/20150702_condoms_prevention.

[21] World Health Organization. WHO guideline on self-care interventions for health and well-being, 2022 revision. Geneva: WHO; 2022. Available from: https://www.who.int/publications/i/item/9789240052192.

Fig. 4. Latin America and the Caribbean Code Against Cancer 1st Edition: Recommendations for policymakers on infections.

9. Condom use

The LAC Code Against Cancer 1st edition recommends: "**Make sure to use condoms consistently and correctly, especially with new or casual partners**."

Condoms can reduce risk of acquisition of STIs (HPV, hepatitis, and HIV) that increase risk of cancer, as discussed above. The appropriate use of condoms has been estimated to reduce risk of transmission of many STIs, including HIV up to 94% [92], although it is less efficacious for prevention of HPV transmission.

WHO recommends the systematic and appropriate use of condoms to prevent transmission of HIV and other STIs (strong recommendation based on moderate amount of evidence) [92]. LAC countries have made a commitment to develop condom use programs to assure 90% of use during the most recent sexual activity among MSM, transgender women and sexual workers by 2020. However, the supply is generally not sufficient to cover the needs of the population and lubricants are not routinely provided.

PAHO recommends people in high-risk groups to use condoms appropriately and systematically, there has been an emphasis on high risk group and the programs for the general population are limited [92].

We found evidence from observational studies that suggest the use of condoms may decrease the risk of some cancers linked to STIs. The SR by Li et al. [93], identified three observational studies which reported an association between condom use and a decreased risk of cervical cancer (Odds ratio (ORs): 0.653, 0.447, and 0.18 respectively) without providing confidence intervals, number of subjects, or other relevant information. On the other hand, the SR by Manhart et al. [94], identified five studies, two of them showed a protective effect of the use of condom for invasive cervical cancer reporting an adjusted OR of 0.2 (95% CI, 0.1–0.6) and 0.5 (95% CI,0.2–1.0) respectively while the other three studies reported uncertain results.

The working group considered that prevention of STIs with the appropriate use of condoms can be beneficial to reduce the burden of several of the infection-related cancers, in addition to its other benefits in the context of sexual and reproductive health.

10. Recommendation for policies (Fig. 4)

The policy recommendation for *H.pylori* requires the elaboration and implementation of a country-specific intervention program with defined goals, target population, screening procedures, treatment and follow-up protocols, quality assurance, among others, to guide health professionals in their advice to patients. A national policy on screening and treatment of *H. pylori* infection focused on population groups at risk is recommended with corresponding organized programs to implement the policy. The selection of the target populations should be based on age, sex, socioeconomic status and cancer incidence statistics. In addition, the programs must assure availability of laboratory tests, treatment, follow-up, and diagnostic procedures and to implement studies of antibiotic resistance to guarantee high eradication rates [20]. A description of the protocol to verify success of treatment in the context of a population-based intervention needs to be included, together with local demonstration studies to assess implementation outcomes.

For Hepatitis B, the public health recommendation of the code is to guarantee universal vaccination against HBV for children at birth and to implement strategies for pro-active search of unvaccinated individuals to vaccinate them, preferably before initiation of sexual activity ("catch up vaccination"). In, addition, the policy should assure access to diagnosis of hepatitis B and C and availability of treatment for all individuals diagnosed with these infections [70,95,96].

For primary prevention of cervical and other HPV-related cancers, the recommendation is to assure availability of vaccines against HPV to maintain the vaccination programs as recommended by WHO. Specifically, to apply 1 or 2 doses in vaccination programs as recommended by WHO, giving priority to 9–14-year-old girls and expanding to 18 years and to boys according to availability of resources. The program should assure the global goal of reaching 90% of vaccinated girls by age 15 [97,98].

For HIV, establishing a program to promote and facilitate HIV testing in the general population, assuring diagnosis of 95% of those infected, treatment of at least 95% of HIV positive individuals and that 95% of individuals under treatment have suppressed viral load. Health professionals should advise their patients and relatives about the importance of knowing the diagnosis, contacting the health systems according to the local programs and assuring proper follow/up of people living with HIV [99].

For safe sex/condom use, the public health recommendation of the code is to implement sex education programs and to assure free and wide access to condoms.

11. Other topics discussed but not included as recommendation in the code

11.1. Oral and dental health

Oral and dental diseases affect 3.500 million people around the world, including caries, periodontal disease, oral cancer, trauma, among others. Dental caries is the most common non communicable disease, affecting about 2.000 million people [100,101]. Oral and dental diseases are increasing due to insufficient fluor exposure, high availability of sugar-rich products, limited access to dental services and aging of the population. Risk factors for oral and dental disease include sugar, tobacco, alcohol, poor hygiene, and social determinants. Dental treatment is expensive and not always included in health insurance. The 2021 74[a] World Health Assembly approved a resolution about oral and dental health, indicating the need for its inclusion in universal health coverage [101].

A metanalysis [102] including 57 studies (48 cohort studies) with more than 5 million participants, reported that periodontal disease and missing teeth are associated with higher risk of mortality from all causes, including cardiovascular and cerebrovascular disease and cancer.

There is increasing evidence that oral hygiene, periodontal disease and loss of teeth are associated with several types of cancers, mainly oral cavity and gastric [103]. However, it is not clear if this association is causal and if prevention or treatment can reduce cancer. Additional studies are needed to address these aspects. Microbiome alterations could contribute to carcinogenesis, in particular *Fusobacterium nucleatum* and *Porphyromonas gingivalis* associated with periodontal disease that can generate chronic local and systemic inflammation [103].

Among the preventive interventions that can contribute to better oral and dental health and prevent associated diseases are dental hygiene with twice a day brushing using fluoride tooth paste and dental floss, reductions in consumption of refined sugars, elimination of smoking and chewing tobacco, reduction of alcohol and supplementation with fluoride of water, salt, milk, and toothpaste. The current evidence did not warrant inclusion of a formal recommendation on oral hygiene for cancer prevention while more evidence accumulates.

11.2. Gallbladder cancer

Gallbladder cancer is a low incidence cancer worldwide, but is common in some areas of LAC, where overall incidence is twice as high as in US and Europe: LAC 1.2 / Europe 0.66 / North America 0.67 per 100,000 [23]. The LAC countries with the highest incidence are Bolivia (ASR=7.3 and 9.6 per 100,000 in males and females, respectively) and Chile (ASR=3.6 and 7.3 per 100,000). The main risk factors for gallbladder cancer are cholelithiasis, which is present in 70–90% of cases, overweight and obesity, female sex, ethnic background and other biliary tract conditions [104].

Cholecystectomy in people with stones prevents cancer development. However, most people with cholelithiasis are asymptomatic and

less than 5% of people with cholelithiasis develop cancer.

Cholelithiasis generates chronic inflammation in the gallbladder mucosa and inflammation can be enhanced by bacteria, especially chronic carriage of *Salmonella Typhi*, which has been associated with gallbladder cancer in LAC [105].

Amerindian populations are the most affected ethnic groups, particularly the Mapuche groups who also have high prevalence of cholelithiasis. Familial and genetic factors have also been identified, together with alcohol, smoking, diet high in fat, sugar and red meat, multiparity, autoimmune conditions and toxins, including aflatoxins, which are relatively common in LAC and are group I carcinogens [106].

Prevention of overweight and gallstones, in addition to a healthy diet and exercise are essential. Preventive cholecystectomy has been considered, but only a small fraction of people with gallstones develop cancer and this intervention is a large burden for the health system and not free of surgical complications. Recent studies have suggested that cholecystectomy could have long term adverse consequences, including metabolic alterations that could lead to fatty liver, obesity, insulin resistance and metabolic syndrome [107,108]. Giving priority to surgery for higher risk groups is a possible option (e.g., obese women in high-risk areas with large calculi), while an adequate biomarker becomes available.

12. Conclusions

A significant fraction of cancers in Latin America and the Caribbean are associated with infectious agents, and effective preventive and therapeutic interventions are available that could enormously reduce the burden of these cancers in the region.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102435.

References

[1] C. de Martel, D. Georges, F. Bray, J. Ferlay, G.M. Clifford, Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis, Lancet Glob. Health 8 (2) (2020) e180–e190, https://doi.org/10.1016/S2214-109X(19)30488-7.

[2] International Agency for Research on Cancer.WHO, European Code Against Cancer. https://cancer-code-europe.iarc.fr/index.php/en/. (Accessed March 19 2023).

[3] C. Espina, R. Herrero, R. Sankaranarayanan, E. Krug, C.P. Wild, J. Schuz, Toward the world code against cancer, J. Glob. Oncol. 4 (2018) 1–8, https://doi.org/10.1200/JGO.17.00145.

[4] C. Espina, A. Feliu, M. Maza, M. Almonte, C. Ferreccio, C. Finck, et al., Latin America and the Caribbean Code Against Cancer 1st Edition: 17 cancer prevention recommendations to the public and to policy-makers (World Code Against Cancer Framework), Cancer Epidemiol. S1 (2023), 102402, https://doi.org/10.1016/j.canep.2023.102402.

[5] A. Feliu, C. Finck, M. Lemos, A. Bahena Botello, F. de Albuquerque Melo Nogueira, A. Bonvecchio Arenas, et al., Latin America and the Caribbean Code Against Cancer 1st edition: Building capacity on cancer prevention to primary healthcare professionals, Cancer Epidemiol. S1 (2023), 102400, https://doi.org/10.1016/j.canep.2023.102400.

[6] M. Duan, Y. Li, J. Liu, W. Zhang, Y. Dong, Z. Han, M. Wan, M. Lin, B. Lin, Q. Kong, Y. Ding, X. Yang, X. Zuo, Y. Li, Transmission routes and patterns of helicobacter pylori, Helicobacter (2023), e12945, https://doi.org/10.1111/hel.12945.

[7] M.P. Curado, M.M. de Oliveira, M. de Araujo Fagundes, Prevalence of Helicobacter pylori infection in Latin America and the Caribbean populations: a systematic review and meta-analysis, Cancer Epidemiol. 60 (2019) 141–148, https://doi.org/10.1016/j.canep.2019.04.003.

[8] S. Redeen, F. Petersson, E. Tornkrantz, H. Levander, E. Mardh, K. Borch, Reliability of diagnostic tests for helicobacter pylori infection, Gastroenterol. Res Pr. 2011 (2011), 940650, https://doi.org/10.1155/2011/940650.

[9] International Agency for Research on Cancer, WHO, Monographs on the evaluation of carcinigenic risks to humans: Schistosomes, liver flukes and Helicobacter pylori, IARC Press, Lyon, France, 1994.

[10] M. Hatakeyama, Oncogenic mechanisms of the Helicobacter pylori CagA protein, Nat. Rev. Cancer 4 (9) (2004) 688–694, https://doi.org/10.1038/nrc1433.

[11] C. de Martel, D. Forman, M. Plummer, Gastric cancer: epidemiology and risk factors, Gastroenterol. Clin. North Am. 42 (2) (2013) 219–240, https://doi.org/10.1016/j.gtc.2013.01.003.

[12] L. Yang, C. Kartsonaki, P. Yao, C. de Martel, M. Plummer, D. Chapman, Y. Guo, S. Clark, R.G. Walters, Y. Chen, P. Pei, J. Lv, C. Yu, R. Jeske, T. Waterboer, G. M. Clifford, S. Franceschi, R. Peto, M. Hill, L. Li, I.Y. Millwood, Z. Chen, G. China Kadoorie Biobank Collaborative, 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 6 (12) (2021) e888–e896, https://doi.org/10.1016/S2468-2667(21)00164-X.

[13] World Cancer Research Fund/American Institute for Cancer Research, Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018.

[14] M. Song, G. Latorre, D. Ivanovic-Zuvic, M.C. Camargo, C.S. Rabkin, Autoimmune Diseases and Gastric Cancer Risk: A Systematic Review and Meta-Analysis, Cancer Res Treat. 51 (3) (2019) 841–850, https://doi.org/10.4143/crt.2019.151.

[15] G. Murphy, R. Pfeiffer, M.C. Camargo, C.S. Rabkin, Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location, Gastroenterology 137 (3) (2009) 824–833, https://doi.org/10.1053/j.gastro.2009.05.001.

[16] M. Hirabayashi, D. Georges, G.M. Clifford, C. de Martel, Estimating the global burden of epstein-barr virus-associated gastric cancer: a systematic review and meta-analysis, Clin. Gastroenterol. Hepatol. (2022), https://doi.org/10.1016/j.cgh.2022.07.042.

[17] International Agency for Research on Cancer.WHO.Global Cancer Observatory: Cancer Today. https://gco.iarc.fr/today/data/factsheets/cancers/7-Stomach-fact-sheet.pdf. (Accessed March 15 2023).

[18] A.C. Ford, E. Tsipotis, Y. Yuan, G.I. Leontiadis, P. Moayyedi, Efficacy of Helicobacter pylori eradication therapy for functional dyspepsia: updated systematic review and meta-analysis, Gut (2022), https://doi.org/10.1136/gutjnl-2021-326583.

[19] T. Rokkas, A. Rokka, P. Portincasa, A systematic review and meta-analysis of the role of Helicobacter pylori eradication in preventing gastric cancer, Ann. Gastroenterol. 30 (4) (2017) 414–423, https://doi.org/10.20524/aog.2017.0144.

[20] P. Malfertheiner, F. Megraud, T. Rokkas, J.P. Gisbert, J.M. Liou, C. Schulz, A. Gasbarrini, R.H. Hunt, M. Leja, C. O'Morain, M. Rugge, S. Suerbaum, H. Tilg, K. Sugano, E.M. El-Omar, H. European, G. Microbiota Study, Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report, Gut (2022), https://doi.org/10.1136/gutjnl-2022-327745.

[21] K. Mabe, K. Inoue, T. Kamada, K. Kato, M. Kato, K. Haruma, Endoscopic screening for gastric cancer in Japan: Current status and future perspectives, Dig. Endosc. 34 (3) (2022) 412–419, https://doi.org/10.1111/den.14063.

[22] P. Pimentel-Nunes, D. Libanio, R. Marcos-Pinto, M. Areia, M. Leja, G. Esposito, M. Garrido, I. Kikuste, F. Megraud, T. Matysiak-Budnik, B. Annibale, J. M. Dumonceau, R. Barros, J.F. Flejou, F. Carneiro, J.E. van Hooft, E.J. Kuipers, M. Dinis-Ribeiro, Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019, Endoscopy 51 (4) (2019) 365–388, https://doi.org/10.1055/a-0859-1883.

[23] International Agency for Research on Cancer. WHO. Global Cancer Observatory: Cancer Today, 2020. https://gco.iarc.fr/. (Accesed March 15 2023).

[24] F.J. Carrilho, D.C. Paranagua-Vezozzo, A.L. Chagas, R. Alencar, L.G. da Fonseca, Epidemiology of liver cancer in Latin America: current and future trends, Semin Liver Dis. 40 (2) (2020) 101–110, https://doi.org/10.1055/s-0039-3399561.

[25] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, Biological agents, B(Pt B), IARC Monogr. Eval. Carcinog. Risks Hum. 100 (2012) 1–441. B(Pt B), ⟨https://www.ncbi.nlm.nih.gov/pubmed/23189750⟩.
[26] GBD 2019 Hepatitis B Collaborators, Global, regional, and national burden of hepatitis B, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet Gastroenterol. Hepatol. 7 (9) (2022) 796–829, https://doi.org/10.1016/S2468-1253(22)00124-8.
[27] M. Umar, B. Hamama Tul, S. Umar, H.A. Khan, HBV perinatal transmission, Int J. Hepatol. 2013 (2013), 875791, https://doi.org/10.1155/2013/875791.
[28] M. Tarocchi, S. Polvani, G. Marroncini, A. Galli, Molecular mechanism of hepatitis B virus-induced hepatocarcinogenesis, World J. Gastroenterol. 20 (33) (2014) 11630–11640, https://doi.org/10.3748/wjg.v20.i33.11630.
[29] Centers for Disease Control and Prevention, Global progress toward universal childhood hepatitis B vaccination, 2003, MMWR Morb. Mortal. Wkly Rep. 52 (36) (2003) 868–870, ⟨https://www.ncbi.nlm.nih.gov/pubmed/12970620⟩.
[30] J.H. Kao, Hepatitis B vaccination and prevention of hepatocellular carcinoma, Best. Pr. Res Clin. Gastroenterol. 29 (6) (2015) 907–917, https://doi.org/10.1016/j.bpg.2015.09.011.
[31] R. Wang, C. Liu, T. Chen, Y. Wang, C. Fan, L. Lu, F. Lu, C. Qu, Neonatal hepatitis B vaccination protects mature adults from occult virus infection, Hepatol. Int 15 (2) (2021) 328–337, https://doi.org/10.1007/s12072-021-10156-z.
[32] J.E. Flores, A.J. Thompson, M. Ryan, J. Howell, The global impact of Hepatitis B vaccination on hepatocellular carcinoma, Vaccin 10 (5) (2022), https://doi.org/10.3390/vaccines10050793.
[33] World Health Organization, Hepatitis B vaccines: WHO position paper - July 2017, 92(27) (2017) 369–392.
[34] N.A. Terrault, A.S.F. Lok, B.J. McMahon, K.M. Chang, J.P. Hwang, M.M. Jonas, R. S. Brown Jr., N.H. Bzowej, J.B. Wong, Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance, Hepatology 67 (4) (2018) 1560–1599, https://doi.org/10.1002/hep.29800.
[35] European Association for the Study of the Liver. Electronic address, L. European Association for the Study of the, EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection, J. Hepatol. 67 (2) (2017) 370–398, https://doi.org/10.1016/j.jhep.2017.03.021.
[36] A.-I.H.G. Panel, Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection, Clin. Infect. Dis. 67 (10) (2018) 1477–1492, https://doi.org/10.1093/cid/ciy585.
[37] European Association for the Study of the Liver. Electronic address, C. Clinical Practice Guidelines Panel, E.G.B. representative, m. Panel, EASL recommendations on treatment of hepatitis C: Final update of the series(☆), J. Hepatol. 73 (5) (2020) 1170–1218, https://doi.org/10.1016/j.jhep.2020.08.018.
[38] M. Schiffman, J. Doorbar, N. Wentzensen, S. de Sanjose, C. Fakhry, B.J. Monk, M. A. Stanley, S. Franceschi, Carcinogenic human papillomavirus infection, Nat. Rev. Dis. Prim. 2 (2016) 16086, https://doi.org/10.1038/nrdp.2016.86.
[39] L. Bruni, M. Diaz, X. Castellsague, E. Ferrer, F.X. Bosch, S. de Sanjose, Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings, J. Infect. Dis. 202 (12) (2010) 1789–1799, https://doi.org/10.1086/657321.
[40] J. Valls, A. Baena, G. Venegas, M. Celis, M. Gonzalez, C. Sosa, J.L. Santin, M. Ortega, A. Soilan, E. Turcios, J. Figueroa, M. Rodriguez de la Pena, A. Figueredo, A.V. Beracochea, N. Perez, J. Martinez-Better, O. Lora, J. Y. Jimenez, D. Gimenez, L. Fleider, Y. Salgado, S. Martinez, Y. Bellido-Fuentes, B. Flores, S. Tatti, V. Villagra, A. Cruz-Valdez, C. Teran, G.I. Sanchez, G. Rodriguez, M.A. Picconi, A. Ferrera, L. Mendoza, A. Calderon, R. Murillo, C. Wiesner, N. Broutet, S. Luciani, C. Perez, T.M. Darragh, J. Jeronimo, R. Herrero, M. Almonte, E.s. group, Performance of standardised colposcopy to detect cervical precancer and cancer for triage of women testing positive for human papillomavirus: results from the ESTAMPA multicentric screening study, Lancet Glob. Health 11 (3) (2023) e350–e360, https://doi.org/10.1016/S2214-109X(22)00545-9.
[41] R. Herrero, P. Gonzalez, L.E. Markowitz, Present status of human papillomavirus vaccine development and implementation, Lancet Oncol. 16 (5) (2015) e206–e216, https://doi.org/10.1016/S1470-2045(14)70481-4.
[42] A. Hildesheim, R. Herrero, S. Wacholder, A.C. Rodriguez, D. Solomon, M. C. Bratti, J.T. Schiller, P. Gonzalez, G. Dubin, C. Porras, S.E. Jimenez, D.R. Lowy, Costa Rican HPV Vaccine Trial Group, Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial, JAMA 298 (7) (2007) 743–753, https://doi.org/10.1001/jama.298.7.743.
[43] World Health Organization, Human papillomavirus vaccines: WHO position paper(2022 update), 97(50) (2022) 645–672.
[44] M. Drolet, E. Benard, N. Perez, M. Brisson, HPV Vaccination Impact Study Group, Population-level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis, Lancet 394 (10197) (2019) 497–509, https://doi.org/10.1016/S0140-6736(19)30298-3.
[45] L. Bruni, A. Saura-Lazaro, A. Montoliu, M. Brotons, L. Alemany, M.S. Diallo, O. Z. Afsar, D.S. LaMontagne, L. Mosina, M. Contreras, M. Velandia-Gonzalez, R. Pastore, M. Gacic-Dobo, P. Bloem, HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019, Prev. Med. 144 (2021), 106399, https://doi.org/10.1016/j.ypmed.2020.106399.
[46] A. Baena, M. Paolino, C. Villarreal-Garza, G. Torres, L. Delgado, R. Ruiz, et al., Latin America and the Caribbean Code Against Cancer 1st Edition: Medical interventions including hormone replacement therapy and cancer screening, Cancer Epidemiol. S1 (2023), 102446, https://doi.org/10.1016/j.canep.2023.102446.
[47] UNAIDS, UNAIDS DATA 2021. https://www.unaids.org/en/resources/documents/2021/2021_unaids_data. (Accessed March 20 2023).
[48] Pan American Health Organization, HIV/AIDS. https://www.paho.org/es/temas/vihsida. (Accessed March 19 2023).
[49] Pan American Health Organization, Plan of Action for the prevention and control of HIV and sexually transmitted infections 2016–2021., 2017. https://iris.paho.org/handle/10665.2/34081.
[50] A.H. Borges, R. Dubrow, M.J. Silverberg, Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier combination antiretroviral therapy will alter this risk, Curr. Opin. HIV AIDS 9 (1) (2014) 34–40, https://doi.org/10.1097/COH.0000000000000025.
[51] S. Minozzi, P. Armaroli, C. Espina, P. Villain, M. Wiseman, J. Schuz, N. Segnan, European Code against Cancer 4th Edition: process of reviewing the scientific evidence and revising the recommendations, Cancer Epidemiol. 39 (Suppl 1) (2015) S11–S19, https://doi.org/10.1016/j.canep.2015.08.014.
[52] A.D. Higgins, J.P.T. Sterne, JAC,. Chapter 8: assessing risk of bias in included studies (updated March 2011), in: J.P.T. Higgins, S. Green (Eds.), Cochrane handbook for systematic reviews of interventions version 5.1.0, The Cochrane Collaboration, 2011.
[53] A. Rollan, J.P. Arab, M.C. Camargo, R. Candia, P. Harris, C. Ferreccio, C. S. Rabkin, J.C. Gana, P. Cortes, R. Herrero, L. Duran, A. Garcia, C. Toledo, A. Espino, N. Lustig, A. Sarfatis, C. Figueroa, J. Torres, A. Riquelme, Management of Helicobacter pylori infection in Latin America: a Delphi technique-based consensus, World J. Gastroenterol. 20 (31) (2014) 10969–10983, https://doi.org/10.3748/wjg.v20.i31.10969.
[54] K. Sugano, J. Tack, E.J. Kuipers, D.Y. Graham, E.M. El-Omar, S. Miura, K. Haruma, M. Asaka, N. Uemura, P. Malfertheiner, C. faculty members of Kyoto Global Consensus, Kyoto global consensus report on Helicobacter pylori gastritis, Gut 64 (9) (2015) 1353–1367, https://doi.org/10.1136/gutjnl-2015-309252.
[55] M.C. Camargo, A. Garcia, A. Riquelme, W. Otero, C.A. Camargo, T. Hernandez-Garcia, R. Candia, M.G. Bruce, C.S. Rabkin, The problem of Helicobacter pylori resistance to antibiotics: a systematic review in Latin America, Am. J. Gastroenterol. 109 (4) (2014) 485–495, https://doi.org/10.1038/ajg.2014.24.
[56] R. Herrero, J. Parsonnet, E.R. Greenberg, Prevention of gastric cancer, JAMA 312 (12) (2014) 1197–1198, https://doi.org/10.1001/jama.2014.10498.
[57] M. Areia, R. Carvalho, A.T. Cadime, F. Rocha Goncalves, M. Dinis-Ribeiro, Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies, Helicobacter 18 (5) (2013) 325–337, https://doi.org/10.1111/hel.12050.
[58] I. Lansdorp-Vogelaar, R.G.S. Meester, M. Laszkowska, F.A. Escudero, Z.J. Ward, J. M. Yeh, Cost-effectiveness of prevention and early detection of gastric cancer in Western countries, Best. Pr. Res Clin. Gastroenterol. 50–51 (2021), 101735, https://doi.org/10.1016/j.bpg.2021.101735.
[59] I. Lansdorp-Vogelaar, L. Sharp, Cost-effectiveness of screening and treating Helicobacter pylori for gastric cancer prevention, Best. Pr. Res Clin. Gastroenterol. 27 (6) (2013) 933–947, https://doi.org/10.1016/j.bpg.2013.09.005.
[60] A. Matsuda, K. Saika, R. Tanaka, Y. Ito, K. Fukui, K.I. Kamo, Simulation models in gastric cancer screening: a systematic review, Asian Pac. J. Cancer Prev. 19 (12) (2018) 3321–3334, https://doi.org/10.31557/APJCP.2018.19.12.3321.
[61] M. Sarmasti, M. Khoshbaten, F. Khalili, M. Yousefi, Cost-effectiveness of screening helicobacter pylori for gastric cancer prevention: a systematic review, J. Gastrointest. Cancer 53 (4) (2022) 1093–1103, https://doi.org/10.1007/s12029-021-00726-7.
[62] R.A. Harris, D.K. Owens, H. Witherell, J. Parsonnet, Helicobacter pylori and gastric cancer: what are the benefits of screening only for the CagA phenotype of H. pylori? Helicobacter 4 (2) (1999) 69–76, https://doi.org/10.1046/j.1523-5378.1999.98057.x.
[63] J.M. Yeh, K.M. Kuntz, M. Ezzati, S.J. Goldie, Exploring the cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer in China in anticipation of clinical trial results, Int J. Cancer 124 (1) (2009) 157–166, https://doi.org/10.1002/ijc.23864.
[64] F. Xie, N. Luo, G. Blackhouse, R. Goeree, H.P. Lee, Cost-effectiveness analysis of Helicobacter pylori screening in prevention of gastric cancer in Chinese, Int J. Technol. Assess. Health Care 24 (1) (2008) 87–95, https://doi.org/10.1017/S0266462307080117.
[65] F. Xie, N. Luo, H.P. Lee, Cost effectiveness analysis of population-based serology screening and (13)C-Urea breath test for Helicobacter pylori to prevent gastric cancer: a markov model, World J. Gastroenterol. 14 (19) (2008) 3021–3027, https://doi.org/10.3748/wjg.14.3021.
[66] F. Xie, D. O'Reilly, I.L. Ferrusi, G. Blackhouse, J.M. Bowen, J.E. Tarride, R. Goeree, Illustrating economic evaluation of diagnostic technologies: comparing Helicobacter pylori screening strategies in prevention of gastric cancer in Canada, J. Am. Coll. Radio. 6 (5) (2009) 317–323, https://doi.org/10.1016/j.jacr.2009.01.022.
[67] I.O. Wong, C.M. Schooling, B.J. Cowling, Cost-effectiveness of Helicobacter pylori screening and treatment for gastric cancer in Hong Kong: a decision analytic approach, Hong. Kong Med. J. 20 (Suppl 7) (2014) 13–15. ⟨https://www.ncbi.nlm.nih.gov/pubmed/25647818⟩.
[68] M.A. Espinal, M. Alonso, L. Sereno, R. Escalada, M. Saboya, A.M. Ropero, E. Bascolo, F. Perez, M. Vigilato, A. Soares, S. Luciani, A. Vicari, L.G. Castellanos, M. Ghidinelli, J. Barbosa, Sustaining communicable disease elimination efforts in

the Americas in the wake of COVID-19, Lancet Reg. Health Am. 13 (2022), 100313, https://doi.org/10.1016/j.lana.2022.100313.
[69] World Health Organization, Global health sector strategy on viral hepatitis 2016–2021. Towards ending viral hepatitis. World Health Organization. https://apps.who.int/iris/handle/10665/246177. (Accessed March 20 2023).
[70] World Health Organization, Guidelines for the screening,care and treatment of persons with chronic hepatitis C infection,Updated version, April 2016 https://apps.who.int/iris/handle/10665/205035. (Accessed March 24 2023 2023).
[71] S. Schillie, C. Wester, M. Osborne, L. Wesolowski, A.B. Ryerson, CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020, MMWR Recomm. Rep. 69 (2) (2020) 1–17, https://doi.org/10.15585/mmwr.rr6902a1.
[72] J.C. Jakobsen, E.E. Nielsen, J. Feinberg, K.K. Katakam, K. Fobian, G. Hauser, G. Poropat, S. Djurisic, K.H. Weiss, M. Bjelakovic, G. Bjelakovic, S.L. Klingenberg, J.P. Liu, D. Nikolova, R.L. Koretz, C. Gluud, Direct-acting antivirals for chronic hepatitis C, Cochrane Database Syst. Rev. 6 (6) (2017) CD012143, https://doi.org/10.1002/14651858.CD012143.pub2.
[73] G.L. Wong, H.L. Chan, C.W. Mak, S.K. Lee, Z.M. Ip, A.T. Lam, H.W. Iu, J.M. Leung, J.W. Lai, A.O. Lo, H.Y. Chan, V.W. Wong, Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis, Hepatology 58 (5) (2013) 1537–1547, https://doi.org/10.1002/hep.26301.
[74] T.H. Su, T.H. Hu, C.Y. Chen, Y.H. Huang, W.L. Chuang, C.C. Lin, C.C. Wang, W. W. Su, M.Y. Chen, C.Y. Peng, R.N. Chien, Y.W. Huang, H.Y. Wang, C.L. Lin, S. S. Yang, T.M. Chen, L.R. Mo, S.J. Hsu, K.C. Tseng, T.Y. Hsieh, F.M. Suk, C.T. Hu, M.J. Bair, C.C. Liang, Y.C. Lei, T.C. Tseng, C.L. Chen, J.H. Kao, C.T.S. group, C. the Taiwan Liver Diseases, Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients, Liver Int. 36 (12) (2016) 1755–1764, https://doi.org/10.1111/liv.13253.
[75] T. Yasunaka, F. Ikeda, N. Wada, Y. Morimoto, S. Fujioka, J. Toshimori, H. Kobashi, K. Kariyama, Y. Morimoto, H. Takayama, T. Seno, K. Takaguchi, A. Moriya, H. Miyatake, R. Okamoto, K. Yabushita, A. Takaki, K. Yamamoto, Entecavir reduces hepatocarcinogenesis in chronic Hepatitis B patients, Acta Med Okayama 70 (1) (2016) 1–12, https://doi.org/10.18926/AMO/53996.
[76] K. Liu, J. Choi, A. Le, T.C. Yip, V.W. Wong, S.L. Chan, H.L. Chan, M.H. Nguyen, Y. S. Lim, G.L. Wong, Tenofovir disoproxil fumarate reduces hepatocellular carcinoma, decompensation and death in chronic hepatitis B patients with cirrhosis, Aliment Pharm. Ther. 50 (9) (2019) 1037–1048, https://doi.org/10.1111/apt.15499.
[77] M.H. Nguyen, H.I. Yang, A. Le, L. Henry, N. Nguyen, M.H. Lee, J. Zhang, C. Wong, C. Wong, H. Trinh, Reduced incidence of hepatocellular carcinoma in cirrhotic and noncirrhotic patients with chronic Hepatitis B treated with tenofovir-A propensity score-matched study, J. Infect. Dis. 219 (1) (2019) 10–18, https://doi.org/10.1093/infdis/jiy391.
[78] M. Das, WHO launches strategy to accelerate elimination of cervical cancer, Lancet Oncol. 22 (1) (2021) 20–21, https://doi.org/10.1016/S1470-2045(20)30729-4.
[79] A.R. Kreimer, R. Herrero, J.N. Sampson, C. Porras, D.R. Lowy, J.T. Schiller, M. Schiffman, A.C. Rodriguez, S. Chanock, S. Jimenez, J. Schussler, M.H. Gail, M. Safaeian, T.J. Kemp, B. Cortes, L.A. Pinto, A. Hildesheim, P. Gonzalez, Costa Rica HPV Vaccine Trial (CVT) Group, Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies, Vaccine 36 (32 Pt A) (2018) 4774–4782, https://doi.org/10.1016/j.vaccine.2017.12.078.
[80] R.V. Barnabas, E.R. Brown, M. Onono, E.A. Bukusi, B. Njoroge, R.L. Winer, D. Donnell, D. Galloway, S. Cherne, K. Heller, H. Leingang, S. Morrison, E. Rechkina, R.S. McClelland, J.M. Baeten, C. Celum, N. Mugo, K.S.S. Team, Single-dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN SHE Study): study protocol for a randomized controlled trial, Trials 22 (1) (2021) 661, https://doi.org/10.1186/s13063-021-05608-8.
[81] H. Bergman, B.S. Buckley, G. Villanueva, J. Petkovic, C. Garritty, V. Lutje, A. X. Riveros-Balta, N. Low, N. Henschke, Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males, Cochrane Database Syst. Rev. 2019 (11) (2019), https://doi.org/10.1002/14651858.CD013479.
[82] T. Harder, O. Wichmann, S.J. Klug, M.A.B. van der Sande, M. Wiese-Posselt, Efficacy, effectiveness and safety of vaccination against human papillomavirus in males: a systematic review, BMC Med. 16 (1) (2018) 110, https://doi.org/10.1186/s12916-018-1098-3.
[83] K.A. Workowski, L.H. Bachmann, P.A. Chan, C.M. Johnston, C.A. Muzny, I. Park, H. Reno, J.M. Zenilman, G.A. Bolan, Sexually transmitted infections treatment guidelines, 2021, MMWR Recomm. Rep. 70 (4) (2021) 1–187, https://doi.org/10.15585/mmwr.rr7004a1.
[84] H. Kelly, A. Chikandiwa, L. Alemany Vilches, J.M. Palefsky, S. de Sanjose, P. Mayaud, Association of antiretroviral therapy with anal high-risk human papillomavirus, anal intraepithelial neoplasia, and anal cancer in people living with HIV: a systematic review and meta-analysis, Lancet HIV 7 (4) (2020) e262–e278, https://doi.org/10.1016/S2352-3018(19)30434-5.
[85] H. Kelly, H.A. Weiss, Y. Benavente, S. de Sanjose, P. Mayaud, Art, H.P.V.R. Group, Association of antiretroviral therapy with high-risk human papillomavirus, cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis, Lancet HIV 5 (1) (2018) e45–e58, https://doi.org/10.1016/S2352-3018(17)30149-2.
[86] G. Liu, M. Sharma, N. Tan, R.V. Barnabas, HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer, AIDS 32 (6) (2018) 795–808, https://doi.org/10.1097/QAD.0000000000001765.
[87] S. Menon, R. Rossi, N. Zdraveska, M. Kariisa, S.D. Acharya, D. Vanden Broeck, S. Callens, Associations between highly active antiretroviral therapy and the presence of HPV, premalignant and malignant cervical lesions in sub-Saharan Africa, a systematic review: current evidence and directions for future research, BMJ Open 7 (8) (2017), e015123, https://doi.org/10.1136/bmjopen-2016-015123.
[88] R.N. Cobucci, P.H. Lima, P.C. de Souza, V.V. Costa, C. Cornetta Mda, J. V. Fernandes, A.K. Goncalves, Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: a systematic review, J. Infect. Public Health 8 (1) (2015) 1–10, https://doi.org/10.1016/j.jiph.2014.08.003.
[89] L.F. Bratcher, V.V. Sahasrabuddhe, The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research, Infect. Agent Cancer 5 (2010) 8, https://doi.org/10.1186/1750-9378-5-8.
[90] E. Chang, S.R. Mapakshi, P. Mbang, N.K. El-Mallawany, J.R. Kramer, D.L. White, E.Y. Chiao, Impact of protease inhibitors on HIV-associated kaposi sarcoma incidence: a systematic review, J. Acquir Immune Defic. Syndr. 79 (2) (2018) 141–148, https://doi.org/10.1097/QAI.0000000000001798.
[91] M.S. Shiels, S.R. Cole, G.D. Kirk, C. Poole, A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals, J. Acquir Immune Defic. Syndr. 52 (5) (2009) 611–622, https://doi.org/10.1097/QAI.0b013e3181b327ca.
[92] Pan American Health Organization, Comprehensive Condom and Lubricant programming. https://www.paho.org/en/topics/combination-hiv-prevention/comprehensive-condom-and-lubricant-programming. (Accessed March 13 2023).
[93] X. Li, et al., Systematic literature review of risk factors for cervical cancer in the Chinese population, 1745506518816599. 14 Dec, Women'S. Health vol. 14 (2018), https://doi.org/10.1177/1745506518816599, 1745506518816599. 14 Dec.
[94] L.E. Manhart, L.A. Koutsky, Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis, Sex. Transm. Dis. 29 (11) (2002) 725–735, https://doi.org/10.1097/00007435-200211000-00018.
[95] World Health Organization, Preventing perinatal hepatitis B virus transmission: a guide for introducing and strengthening hepatitis B birth dose vaccination, Accessed March 25, World Health Organization,, 2023, ⟨https://apps.who.int/iris/handle/10665/208278⟩. Accessed March 25.
[96] M.K. Weng, M. Doshani, M.A. Khan, S. Frey, K. Ault, K.L. Moore, E.W. Hall, R. L. Morgan, D. Campos-Outcalt, C. Wester, N.P. Nelson, Universal Hepatitis B Vaccination in Adults Aged 19-59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022, MMWR Morb. Mortal. Wkly Rep. 71 (13) (2022) 477–483, https://doi.org/10.15585/mmwr.mm7113a1.
[97] Strategic Advisory Group of Experts (SAGE) on Inmunization, Meeting of the Strategic Advisory Group of Experts on Immunization, April 2022: conclusions and recommendations, WHO:Geneva,2022.
[98] World Health Organization, Global strategy to accelerate the elimination of cervical cancer as a public health problem., 2020. apps.who.int/iris/handle/10665/336583.
[99] UNAIDS/WHO, Position Statement on Condoms and HIV prevention. https://data.unaids.org/una-docs/condom-policy_jul04_en.pdf. (Accessed (Accesed March 20 2023.
[100] M.A. Peres, L.M.D. Macpherson, R.J. Weyant, B. Daly, R. Venturelli, M.R. Mathur, S. Listl, R.K. Celeste, C.C. Guarnizo-Herreno, C. Kearns, H. Benzian, P. Allison, R. G. Watt, Oral diseases: a global public health challenge, Lancet 394 (10194) (2019) 249–260, https://doi.org/10.1016/S0140-6736(19)31146-8.
[101] World Health Organization, Oral health, 2022. https://www.who.int/news-room/fact-sheets/detail/oral-health. (Accessed March 24 2023).
[102] M. Romandini, G. Baima, G. Antonoglou, J. Bueno, E. Figuero, M. Sanz, Periodontitis, edentulism, and risk of mortality: a systematic review with meta-analyses, J. Dent. Res 100 (1) (2021) 37–49, https://doi.org/10.1177/0022034520952401.
[103] M. Chung, B.R. York, D.S. Michaud, Oral health and cancer, Curr. Oral. Health Rep. 6 (2) (2019) 130–137, https://doi.org/10.1007/s40496-019-0213-7.
[104] M. Salazar, C. Ituarte, M.G. Abriata, F. Santoro, G. Arroyo, Gallbladder cancer in South America: epidemiology and prevention, Chin. Clin. Oncol. 8 (4) (2019) 32, https://doi.org/10.21037/cco.2019.07.12.
[105] P. Perez-Moreno, I. Riquelme, P. Garcia, P. Brebi, J.C. Roa, Environmental and lifestyle risk factors in the carcinogenesis of gallbladder cancer, J. Pers. Med 12 (2) (2022), https://doi.org/10.3390/jpm12020234.
[106] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans;, IARC: Lyon, France,2002; Volume 82, ISBN: 978–92-832–1582-0.
[107] Y. Chen, S. Wu, Y. Tian, Cholecystectomy as a risk factor of metabolic syndrome: from epidemiologic clues to biochemical mechanisms, Lab Invest 98 (1) (2018) 7–14, https://doi.org/10.1038/labinvest.2017.95.
[108] A. Di Ciaula, G. Garruti, D.Q. Wang, P. Portincasa, Cholecystectomy and risk of metabolic syndrome, Eur. J. Intern Med 53 (2018) 3–11, https://doi.org/10.1016/j.ejim.2018.04.019.
[109] D. Maucort-Boulch, C. de Martel, S. Franceschi, M. Plummer, Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide, Int J. Cancer 142 (12) (2018) 2471–2477, https://doi.org/10.1002/ijc.31280.