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Cancers Attributable to Modifiable Risk Factors: A Road Map for Prevention

Giulia Collatuzzo[1] and Paolo Boffetta[1,2]

[1]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; email: giulia.collatuzzo@studio.unibo.it

[2]Stony Brook Cancer Center, Stony Brook University, Stony Brook, New York, USA; email: paolo.boffetta@stonybrookmedicine.edu

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Keywords

avoidable cancer, prevention, attributable fraction, risk factors, cancer control, modifiable factors

Abstract

The implementation of primary and secondary preventive strategies is based on the evidence generated by cancer epidemiology, where the identification of risk factors and the description of their prevalence are fundamental to derive estimates on the burden of cancer from different etiologies, typically expressed as the population attributable fraction, which corresponds to the proportion of a cancer that may be prevented by controlling a given risk factor. However, even when cancer finds its etiology in modifiable factors, its prevention through the control of those factors is not always feasible, or it remains suboptimal despite the possibility of reducing the burden. We reviewed selected associations between modifiable risk factors and cancer, including tobacco smoking, occupational exposures, infections, air pollution, alcohol, and diet and obesity, and illustrated examples of both successes and failures in cancer control, underlying how current understanding of the avoidable causes of cancer is incomplete.

1. INTRODUCTION

Population attributable fraction (PAF): measures the burden of disease due to a risk factor; based on the strength of the association and the prevalence of the risk factors

Prevention represents the most cost-effective approach for controlling the burden of many cancers (112). To design and implement cost-effective cancer prevention strategies, researchers must couple knowledge on the determinants of cancer incidence and mortality, be they risk factors (primary prevention) or approaches for early detection (secondary prevention), with valid estimates of their distribution in the population. A widely used measure of the burden of cancer is the population attributable fraction (PAF), which depends on the strength of the association between the determinant and the cancer and on the distribution of the determinant in the population under study (82). This measure was first developed by Levin in 1953 for estimation of the "maximum proportion of lung cancer attributable to smoking" (93, p. 202). In the case of modifiable risk factors, the PAF provides the estimate of the proportion of cancers that could be avoided by modifying the existing exposure distribution into a counterfactual one.

One difficulty in interpreting the estimates of the cancer PAF stems from the different methodological approaches adopted in studies conducted in various populations (e.g., 5, 12, 17, 52, 113). This variation in approaches adds complexity when calculating the proportion of cases that could be avoided by removing a specific risk factor or implementing a preventive measure. Similarly, despite that several validated instruments, such as food frequency questionnaires (FFQ) for diet, have been developed, there are no standardized methods for the collection of data on several exposures (see the sidebar titled Food Frequency Questionnaires). In addition, most carcinogens exert their effect with a period of latency, the duration of which is variable and not fully known; these periods can be short (i.e., a few years) for hormonal factors, such as hormone replacement therapy as a risk factor of breast cancer, or long (i.e., several decades) for infectious agents or asbestos. Furthermore, there is no uniformity in the use of the reference population when calculating the relative risks (RRs) between exposures and cancers, which can also be affected by differences in ethnicity [e.g., effect of body mass in European versus Asian populations (121)], gender [e.g., RR of lung cancer from tobacco smoking in men and women (2)], life stage (e.g., risk factors for pre- and postmenopausal breast cancer), and genetic factors [e.g., aldehyde dehydrogenase 2 (ALDH 2) variants and risk of gastrointestinal cancer (37)].

Tables 1 and **2** provide the summary results for men and women, respectively, of the cancer PAF estimates for modifiable risk factors reported for selected high- and middle-income countries. Although the overall methodology was comparable in these studies, heterogeneity in the aspects mentioned above has likely contributed to the differences reported in these tables. We have aimed to review selected associations between modifiable risk factors and cancer, including circumstances that lead to both success and failure in cancer control and their implications in terms of PAFs.

FOOD FREQUENCY QUESTIONNAIRES

Food frequency questionnaires (FFQ) are data collection forms designed specifically to capture the dietary practices of a specific study population, accounting for ethnicity, cultural factors, and geographical factors. FFQ are complex tools picturing up to hundreds of food items usually consumed by a population recorded in times per day, week, month, and year, or as never, considering variations due to festivities and weekends. For the estimate of nutrients, recipes and complex foods are broken down into simple foods, which are then matched to food composition tables.

Table 1 Population attributable fraction for cancer in selected studies in men

Risk factor	China (113)	United States (52)	United Kingdom (17)	Brazil (5)	France[a] (12)
Tobacco smoking	32.9	24.0	17.7	14.7	33.4
Infectious agents	30.6	3.4	3.1	5.9	3.1
Alcohol drinking	12.3	4.8	3.1	2.1	9.4
Dietary factors	NA	5.2[b]	5.2[c]	17.3[d]	NA
Overweight, obesity	0.1	4.8	5.2	2.2	1.1
Physical inactivity	0.3	1.5	1.5	2.3	0.5
Occupation	NA	NA	5.0	2.4	3.7
UV radiation	NA	5.8	3.8	0.5	0.6
Environmental pollution	NA	NA	1.0	0.4	0.1
Ionizing radiation	NA	NA	1.7	NA	NA

Abbreviations: NA, not available; UV, ultraviolet.
[a]Mortality.
[b]Fruits/vegetables, red/processed meat, fiber, calcium.
[c]Fiber, processed meat.
[d]Fruits, vegetables, salt, red/processed meat.

Table 2 Population attributable fraction for cancer in selected studies in women

Risk factor	China (113)	USA (52)	UK (17)	Brazil (5)	France[a] (12)
Tobacco smoking	5.0	14.8	12.4	7.9	9.6
Infectious agents	24.1	3.3	4.3	13.8	4.4
Alcohol drinking	0.9	6.4	3.4	0.2	3.0
Dietary factors	NA	3.8[b]	4.5[c]	10.2[d]	NA
Overweight, obesity	0.8	10.9	7.5	3.5	2.3
Physical inactivity	0.2	4.4	0.5	7.7	3.2
Reproductive factors	1.0[e]	NA	1.5[f]	7.4	NA
Exogenous hormones	0.3	NA	1.3	0.7	2.2
Occupation	NA	NA	2.5	0.3	0.5
UV radiation	NA	3.7	3.7	0.5	0.8
Air pollution	NA	NA	1.0	0.4	0.3
Ionizing radiation	NA	NA	2.1	NA	NA

Abbreviations: NA, not available; UV, ultraviolet.
[a]Mortality.
[b]Fruits/vegetables, red/processed meat, fiber, calcium.
[c]Fiber, processed meat.
[d]Fruits, vegetables, salt, red/processed meat.
[e]Nulliparity, parity, % with age at first birth ≥30 years, and duration of breastfeeding.
[f]Breastfeeding.

2. EXAMPLES OF KNOWLEDGE ON RISK FACTORS THAT TRANSLATED INTO SUCCESSFUL PREVENTION

Several important human cancers have been prevented following the identification of a major risk factor and the development of an effective preventive strategy. In this section, we review, in detail, lung cancer from tobacco smoking, bladder cancer from occupational exposure, mesothelioma from asbestos exposure, and liver cancer from hepatitis B virus (HBV) infection. Additional

Supplemental Material >

examples, including cervical cancer from human papillomavirus (HPV) infection, are provided in the **Supplemental Discussion**.

2.1. Tobacco Smoking and Lung Cancer

Tobacco smoking is the main single cause of cancer incidence and mortality worldwide (67). It is a major cause of cancer of the lung, oral cavity, pharynx, nasal cavity, larynx, esophagus, stomach, pancreas, uterine cervix, kidney, and bladder, as well as of myeloid leukemia (47). In the United States in 2014, tobacco smoking was estimated to cause 19% of all cancers (52), a decline compared with earlier estimates (e.g., 35), due to the decreased prevalence of smoking, especially in men. In many middle- and low-income countries, the burden of tobacco-related cancer is still relatively low, given the more recent start of the epidemic of smoking; prevalence is increasing, however, and will result in a growing number of cancers in the future, in the absence of adequate intervention to control tobacco use.

The causal nature of the association between tobacco smoking and cancer, as well as other major nonneoplastic diseases, became clear in the 1960s and 1970s: This discovery was rapidly followed by interventions aimed at reducing the burden of tobacco-related disease. In addition to the advantages of avoiding tobacco initiation, research has shown a benefit from quitting tobacco smoking in adulthood for all major cancers causally associated with the habit. Smokers who stop around age 50 avoid more than 50% of overall excess mortality from all causes (36, 53, 81), from lung cancer (79), and from other tobacco-related cancers (14), and those who stop around age 40 or earlier avoid most of their tobacco-related cancer risk.

The decline in tobacco consumption that has taken place during the last half-century in North America and other high-income countries, in particular among men, resulted in decreased incidence of and mortality from lung cancer and other neoplastic and nonneoplastic conditions (59, 67). The decline was due primarily to an increasing rate of quitting smoking at young and middle ages and, secondarily, by avoidance of initiation. Precise estimates of this effect are sparse; in one such study, La Vecchia et al. (60) estimated that the decline in lung cancer mortality among men in the European Union, which was due primarily to reduction in tobacco use, led to the avoidance of an estimated 1,156,000 deaths from lung cancer between 1989 and 2021.

Despite growing efforts from medical and public health institutions and the growing involvement of governmental and nongovernmental organizations, the fight against the spread of tobacco smoking among women and in middle- and low-income countries, in particular in Asia, represents one of the biggest challenges for cancer prevention in the next few decades. Modeling suggests, however, that it will be difficult to achieve smoking rates below 10% within a 20-year time horizon (68). Notwithstanding many limitations, the decline in incidence and mortality from cancers of the lung and other organs attributable to tobacco control remains one of the most important examples of cancer prevention.

2.2. Occupational Exposure to Carcinogens and Bladder Cancer

Occupation-related cancers represent a paradigm of avoidable malignancies. Between 3% and 5% of all cancers among men are attributable to occupational agents (**Table 1**). This burden is mostly due to nonmelanoma skin cancer due to solar radiation; lung cancer related to more than 20 agents and mixtures; mesothelioma due to asbestos exposure; and urinary bladder cancer linked to different occupational carcinogens (30). In more developed countries, exposure to carcinogens was greatly reduced during the last five decades, which translated into the successful avoidance of occupation-related cancers.

Every year, more than 430,000 people are diagnosed with bladder cancer worldwide (55); this disease ranks sixth among the most common cancers in men (99). While tobacco smoking

accounts for 50% of cases, occupational exposures represent the second leading cause of bladder cancer. Aromatic amines, polycyclic aromatic hydrocarbons, and heavy metals represent the main occupational bladder carcinogens (111). In the past, the proportion of cases due to occupational exposure was estimated to have been up to 24% (111). After the wide elimination and control of most of these agents, it is not completely clear how many cases are still attributable to occupational carcinogens: In recent studies, the attributable fraction for occupation-related cases is reported to range between 2% and 8% (84).

Despite the elimination of exposure to known bladder carcinogens such as aromatic amines, cases of bladder cancer continue to occur in formerly exposed workers. For example, in a cohort of dyestuff workers exposed to aromatic amines between 1922 and 1972, the risk remained elevated for 35 or more years after cessation of exposure (29, 80). One hypothesis for the persistent risk, despite the cessation of exposure many years prior, is that aromatic amines induce gene mutations through a genotoxic action at a very early stage of the process of carcinogenesis, and an initiated cell may remain quiescent for a long time (74).

This pattern might not apply to all populations, however. A review on bladder cancer in China that evaluated the period between 1990 and 2017 found an increasing trend in incidence among men, which was due in part to a period effect (64). This effect can be interpreted as a result of industrialization, which may indeed have led to a higher likelihood of occupational exposure to bladder carcinogens among men. This finding contrasts with the general improvement in occupational health and increase in knowledge about risks that have taken place in more developed countries, which underlines the continuous need for occupational cancer prevention.

2.3. Asbestos Exposure and Mesothelioma

Mesothelioma is an aggressive, short-survival neoplasm that originates from the pleura, peritoneum, and pericardium. In more developed countries, ~80% of cases are caused by exposure to asbestos (83). This association is highly specific, but its magnitude is probably underestimated because of the difficulty in assessing past exposure. The incidence of mesothelioma varies by country, from less than 1 case per 100,000 to up to 4–5 cases per 100,000, based on the past presence of asbestos use in construction (22). Short-term exposure to amphibole asbestos (including amosite, crocidolite, anthophyllite, actinolite, and tremolite) is sufficient to cause mesothelioma, which may occur after a latency of three to four decades (91). For this reason, the disease mainly affects elderly people. In addition, the peak of incidence has not been observed yet in those countries where the control of asbestos was introduced more recently, as in Japan and Poland (1), compared with in the United States and Sweden, where control measures were implemented earlier and a decline in the incidence has been observed in the last 20 years. The downscale of mesothelioma is due largely to the introduction of measures limiting asbestos exposure at the workplace but is shown most prominently in young generations of workers, whose opportunity for occupational exposure was limited (11). In the case of long-latency carcinogens such as asbestos, the preventive effect becomes evident after several decades (11): While the incidence of mesothelioma is declining in the young, it may still be increasing in older populations of workers due to the long latency in the process of carcinogenesis. The latter supports a continued need for long-term follow-up after cessation of exposure. Thus, the offset of mesothelioma in recent years reflects the successful strategies introduced with the aim of preventing mesothelioma. This improvement was obtained, for the most part, by progressive bans on its use in materials and products through control of and oversight on engineering and work practices (62).

Classic studies on asbestos exposure and mesothelioma risk have been conducted among miners, manufacturers (asbestos-cement, textile, friction materials), and applicators (8). In addition,

population-based studies identified high risk of mesothelioma in other occupational groups, including construction workers, plumbers, seamen, mechanics, electrical workers, smelting workers, welders, and painters (83, 87). In particular, Rake et al. (87) estimated that 15,000 asbestos-related deaths may occur among carpenters by 2050 in Britain, corresponding with more than 1 in 10 deaths of carpenters born in the 1940s. Even if asbestos exposure has since been greatly reduced or eliminated, at least in more developed countries, the legacy of past exposure will extend the occurrence of the disease, given the long latency, causing a gap between very far exposure in time and mesothelioma occurrence (11). In fact, workers who have been exposed to asbestos remain at risk of developing mesothelioma (RR for 10-year interval since cessation of exposure = 1.02) (9).

2.4. Liver Cancer from HBV Infection

The development of vaccines has represented major medical progress. The perspective of preventing cancer through vaccination is as fascinating as it is challenging because it is based on the possibility of identifying infectious—thus potentially avoidable—carcinogens. Among biological carcinogens, the IARC (48) lists *Helicobacter pylori*, for noncardia gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach; HPV, for cancers of the cervix, oropharynx, oral cavity, larynx, anus, penis, vagina, and vulva; hepatitis B and C viruses (HBV and HCV), for hepatocellular carcinoma (HCC) and, for HCV, non-Hodgkin lymphoma; Epstein-Barr virus, for nasopharynx carcinoma, Hodgkin lymphoma, and Burkitt lymphoma; human T-cell lymphotropic virus for adult T-cell leukemia and lymphoma; human herpesvirus type 8 for Kaposi sarcoma; *Schistosoma haematobium*, for bladder carcinoma; and *Opisthorchis viverrini* and *Clonorchis sinensis*, for cholangiocarcinoma. Each of these microbial agents is a potentially preventable carcinogen. An estimated 2.2 million cancer cases diagnosed in 2018 were attributable to infectious agents worldwide (34). The availability of effective vaccines against HBV and HPV represents a strong and long-reaching weapon against cancer.

Liver cancer is the sixth most common cancer and the third most important cause of cancer death worldwide (99). The etiologic factors of HCC, the main form of liver cancer, are chronic HBV and HCV infection, heavy alcohol drinking, tobacco smoking, obesity, nonalcoholic fatty liver disease, and aflatoxin (58, 92). HBV infection represents the main cause of HCC on a global scale (40); its global prevalence is estimated to be on the order of 240 million people (115), and the proportion of infected people aware of their status is as low as 5% (115). Higher prevalence of seropositivity is reported in sub-Saharan Africa and East Asia, reaching 5–10% of the adult population. In these areas, mother to child is the main route of transmission (115). Subjects at high risk for adult transmission are intravenous drug users, homosexual men, HIV and HCV carriers, people having household contacts with HBV-seropositives, health care workers, and hemodialysis patients (63, 72, 90). Among the infected, the risk of developing HCC is associated with demographic (male sex, older age, Asian or African ancestry, family history of HCC), viral (high HBV replication levels; HBV genotype; duration of infection; HCV, HIV, or hepatitis D virus coinfection), clinical (cirrhosis), and environmental factors (exposure to aflatoxin, heavy intake of alcohol or tobacco) (58). In high-prevalence areas, chronic HBV infection is responsible for 60–90% of all HCC among adults and almost 100% of HCCs in children (43).

Vaccination is the most effective strategy to prevent HBV infection and HBV-related HCC, and the HBV vaccine represented the first example of primary prevention of an infection-related cancer. The goal of preventing HBV-related HCC can be reached by universal HBV vaccination, together with maternal antiviral prophylaxis and birth administration of hepatitis B immunoglobulin to seropositive mothers' newborns (92). In addition, secondary prevention can be obtained by using antiviral therapies in chronically infected subjects, reducing the risk of HCC development (58). Vaccines for HBV use hepatitis B surface antigen (HBsAg) to stimulate the production of

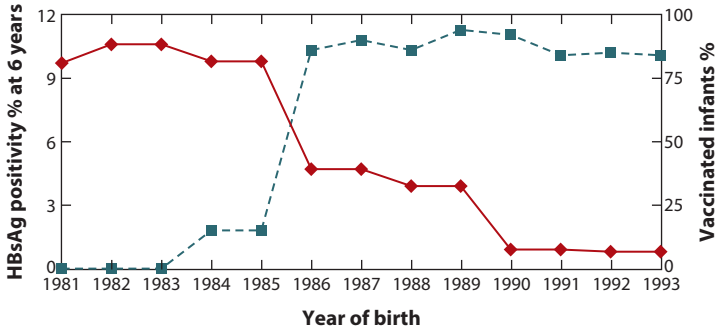

Figure 1

Trend in proportion of vaccinated children (*squares*) and in hepatitis B surface antigen (HBsAg) positivity at 6 years (*diamonds*) levels by year of birth in Taiwan (23, 25). Figure based on data from References 23 and 25.

antibodies for the virus. Immunocompetent subjects reach a protective antibody response in 90% (adults) to 95% (children) of subjects after the complete vaccination schedule (42, 90). Vaccination is also available for adults and recommended for high-risk categories, such as health care workers (44).

Vaccination schedules have been approved since 1982 and successfully came into use when the Advisory Committee on Immunization Practices (ACIP) published the first official recommendations on the use of the HBV vaccine (90). While at first the target population consisted of high-risk adults, universal vaccination in children has been established in many countries, leading to the reduction of virus reservoirs and high efficacy in reducing infection rates and incidences of related diseases (72, 90). In the United States, vaccination led to a 98% reduction in infected health care workers between 1983 and 2010 (90), as well as a 95% decline among dialysis patients since the vaccine's introduction (90).

Direct evidence of liver cancer prevention from HBV vaccination, however, is still limited. The strongest data come from Taiwan, a high-risk country, where a national vaccination program has been in place since the mid-1980s, shortly after the demonstration of the causal association between HBV infection and liver cancer (7). Between 1984 and 1986, the program targeted all newborns and later was expanded to other population groups. Early results showed a dramatic decline in the proportion of children belonging to the vaccinated cohort who were positive for HBV compared to the unvaccinated cohort (24) (**Figure 1**). As the first cohort of vaccinated subjects is now in the fourth decade of life, it is possible to observe the effect of the intervention on liver cancer incidence (23, 63) (**Table 3**). This story exemplifies the power of cancer prevention at the

Table 3 Relative risks of hepatocellular carcinoma according to vaccination status by birth cohort in Taiwan (adapted from 23)

Birth cohort (status of national HBV vaccination program)	Number of HCC cases	RR	95% CI
<1984 (prevaccination)	1,343	1.0	Reference category
1984–1986 (scaling-up)	59	0.45	0.34–0.57
1986–1992 (postvaccination)	76	0.26	0.21–0.33
1992–2005 (postvaccination)	31	0.12	0.08–0.17

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; RR, relative risk.

population level under circumstances in which a carcinogen plays a major role and an effective intervention is available and can be implemented.

GLOBOCAN: database maintained by the IARC comprising estimates of incidence, mortality, and prevalence of 36 types of cancers by sex and age groups in 185 countries and territories. Most recent estimates refer to the year 2020

Supplemental Material >

2.5. Examples of Successful Intervention: Conclusions

The examples of successful interventions to control cancer mentioned in the above sections and in the **Supplemental Discussion** share common points: Strong evidence of a causal association and high RRs and feasibility of the intervention despite difficulties (e.g., action of tobacco industry to counter control measures) are the principal characteristics. Moreover, a high prevalence of exposure to the carcinogen is of utmost importance for a preventive intervention to be highly impactful. For a cancer screening program, the latency between avoidance of exposure and effect plays an important role, as it justifies potential therapeutic actions and opens up opportunities for monitoring. Detailed knowledge of the trends in other risk or protective factors helps guide preventive recommendations and the development of targeted protocols, as well as the individuation of the subgroups of people who would benefit most from the preventive action. Thus, increased understanding of the interaction among different factors associated with cancer is a challenging but desirable objective in current research.

3. EXAMPLES OF RISK FACTOR KNOWLEDGE THAT HAS NOT TRANSLATED INTO SUCCESSFUL PREVENTION

Several known cancer risk factors remain poorly controlled, even if their carcinogenic role has long since been established. The problem of insufficient attention concerns not only carcinogens for low-incidence neoplasms, but also causes of widely spread cancers. For example, the IARC extended the number of cancers causally associated with obesity, establishing a risk for 13 different types, including colon, esophagus (adenocarcinoma), kidney (renal-cell), breast (postmenopausal), corpus uteri, gastric cardia, liver, gallbladder, pancreas, ovary, thyroid, multiple myeloma, and meningioma (61). Despite that obesity typically acts jointly with other causes, its burden in terms of malignant diseases is high because of its high prevalence: An estimated 544,300 cases, corresponding to 3.9% of all cancers, were attributable to excess body weight worldwide in 2012 (100). The association between obesity and cancer is considered in detail in the **Supplemental Discussion**.

The following section addresses some of the main modifiable agents for which the association with cancer has been defined but control remains suboptimal. Additional modifiable agents (e.g., alcohol drinking) are explored in the **Supplemental Discussion**.

3.1. *Helicobacter pylori* and Gastric Cancer

Helicobacter pylori (*Hp*) is the only oncogenic bacterium known so far. It is associated with gastric adenocarcinoma and gastric MALT lymphoma (48). It represents the first infective cause of cancer, with 810,000 attributable cases worldwide in 2018 (34). Only a minor fraction of gastric cancer (GC) occurs without *Hp*, making a preventive action toward the infection a powerful way to scale down one of the deadliest neoplastic diseases.

According to the last GLOBOCAN (**https://gco.iarc.fr/**) estimates, 1,089,103 GC cases were diagnosed in 2019 (5.6% of total cancer cases) and caused 768,793 deaths (7.7% of total cancer deaths), representing the fifth most common cause of cancer and the fourth most deadly cancer (99). While GC was the leading cause of cancer deaths in the United States until the 1930s, its incidence has seen a drastic and unexpected decrease since the 1950s decade (105). The trends suggest that GC is due largely to environmental factors (45), as confirmed by studies of migrant populations (105) and the high heterogeneity in its incidence among populations (6). The trend in

incidence concerns noncardia GC in particular and can be linked to the parallel declining prevalence in *Hp* infection, which is its main risk factor. Indeed, *Hp* is associated with 89% of cases of noncardia GC, corresponding with 78% of overall GC cases (46, 48). That the incidence is higher in less developed countries and among low socioeconomic population groups further confirms its strict link to modifiable factors. An interaction between *Hp* and other risk factors has also been reported (32).

Hp infection is typically acquired in childhood (18, 65, 76) and persists across the life span if left untreated, remaining asymptomatic in most subjects but possibly evolving in progressive damage over the long term (33). A screen-and-treat protocol for *Hp* would represent a powerful intervention to reduce the burden of GC (13, 31, 105). The earlier the eradication takes place (56), the greater is its effectiveness in preventing GC; the point of no return is thought to be represented by metaplastic transformation (13). Nevertheless, different controversies arise about which population should be targeted for eradication; the Kyoto consensus (98) recommends it for every infected subject, whereas other guidelines still exclude asymptomatic subjects (66).

The potential for eradicating this bacterium is proven by the long-term regression of the large majority of cases of first-stage MALT lymphoma of the stomach (71, 108, 118), also reported among patients affected by high-grade lymphoma (69, 78), making eradication a first-line therapy for this disease.

Different studies have been conducted to describe the potential benefit of a large eradication program in lowering GC incidence. A 35% reduction in GC risk has been hypothesized among treated subjects (39), as well as a 65% decrease in metachronous lesions (40). A recent placebo-controlled trial exploring the effectiveness of *Hp* eradication among first-degree relatives of GC patients found a RR equal to 0.45 of developing the neoplasm during a median of 9 years of follow-up (27).

While evidence on the benefit and the cost-effectiveness of *Hp* eradication for GC prevention is growing (89), more definite results would be provided by a community-based intervention trial currently ongoing in China (77), which includes about 185,000 *Hp*-positive adults.

The main concern is whether a population-based eradication strategy could be harmful. Indeed, *Hp* treatment can cause antibiotic-related adverse events in a minority of subjects (119), and widespread antibiotic administration would increase the burden of antimicrobial resistance (116). *Hp* eradication has also been reported to increase esophageal disease, including possibly esophageal cancer (77).

One alternative would be to target such interventions to high-risk subgroups, e.g., people with a family history of GC, symptomatic individuals, and those with multiple risk factors, as well as less affluent population groups who experience insecure access to health care services, have poor hygiene, and live in crowded settings. In that regard, clinical and genetic predictive models would be useful to individuate high-risk subjects (20, 54, 86, 102). Moreover, extensive animal studies addressed the formulation of a vaccine for *Hp* infection, but results to date are unsatisfactory due to its limited efficacy (97, 120), the difficulty of assessing the coverage duration, and determination of the age of administration.

3.2. Air Pollution and Lung Cancer

An association between exposure to air pollution and risk of lung cancer has been reported in cohort and case-control studies (49). Fine particulate matter (PM_{10} or $PM_{2.5}$) is considered the most relevant indicator of air pollution with respect to lung cancer risk (49). A meta-analysis of recent cohort studies estimated that the excess risk for an increase of 10 $\mu g/m^3$ $PM_{2.5}$ would be on the order of 16% (28).

Particulate matter (PM): solid carbonaceous particles or liquid droplets ("aerosol"); one of the main air pollutants, originating from incomplete combustion of organic matter, of either natural (e.g., volcans) or artificial (e.g., vehicles) sources

PM_{10}: inhalable particles up to 10 μm

$PM_{2.5}$: inhalable particles up to 2.5 μm in aerodynamic diameter (fine particles)

Some authors who reviewed the evidence linking exposure to air pollution and the risk of lung cancer, on the other hand, reached the conclusion that, although the causal nature of the association is plausible, the epidemiologic evidence suffers from limitations that complicate the quantification of the lung cancer burden attributable to it (10). Specifically, studies of cancer and other chronic health effects of air pollution ignore important lessons learned from studies of tobacco smoking and occupational carcinogens. These studies show that the entire history of exposure to toxins, including duration and intensity of exposure and age at first exposure, is an important determinant of disease risk (49). The biological rationale is that chronic diseases develop over a long period of time, typically decades, during which distinct biological events take place, and the relevant etiologic agents may have an impact on one or more steps in this process. It is therefore important to account for an adequate interval of time between exposure and outcome, a fact that is often overlooked in epidemiologic studies of the cancer risk from air pollution. When air pollution measurements at a single point in time are used for analyses, they should precede the outcome by an adequate latency. If latency is ignored but there is a strong correlation between current and past exposure levels, the qualitative interpretation of the results on the presence or absence of an association between air pollution and disease may or may not be invalidated. The quantitative results, however, would be biased upward because air pollution levels have been decreasing over recent years in most areas of the United States, European countries, and other high-income countries (26).

For these reasons, estimates of the proportion of cases of lung cancer that may be avoidable by reducing air pollution are subject to uncertainty. The overall reduction in air pollution that has taken place in more developed countries in the last several decades represents a positive trend that has not yet occurred to the same extent in less developed countries (50). In addition, indoor air pollution from heating coke and other low-efficiency fuels, such as animal dung, for cooking under poorly ventilated conditions represents an important cause of lung cancer in less developed countries and affects primarily women (94, 95). A Global Burden of Disease working group estimated that 15.1% of the lung cancer deaths that occurred globally in 2019 were attributable to ambient PM pollution, representing the second most important cause of lung cancer after tobacco smoking (41) (see the sidebar titled Global Burden of Disease). The burden was higher, and increasing, in less developed countries, compared to high-income countries, where the PAF had been declining since 1990.

Outdoor and indoor air pollution are avoidable causes of lung cancer: Their control would provide a benefit that would extend beyond cancer, as they are important causes of acute and chronic diseases, primarily of the respiratory and cardiovascular systems (19).

3.3. Dietary Factors and Colorectal Cancer

A very large body of literature has investigated the association between dietary factors and various cancer, most notably colorectal cancer (CRC) (4, 15, 85, 103, 110). While diet can be assessed at

GLOBAL BURDEN OF DISEASE

Global Burden of Disease is a project run by the Institute of Health and Metrics Evaluation established in Seattle, representing the most comprehensive epidemiological study worldwide. It examines the trends of 369 diseases and injuries over 204 countries and territories from 1990 to the present, including information on risk factors, and is continuously expanding. Indicators of disease burden include disability-adjusted life years (DALYs). One DALY represents the loss of one year of full health. DALYs for a disease are the sum of the years of life lost due to premature mortality and the years lived with a disability due to prevalent cases of the disease in a population.

different levels, the interest from the viewpoint of avoidable disease burden is mainly in individual food items, food groups, and dietary patterns, as they can be subject to recommendations. CRC illustrates the methodological issues involved in this area of research and its evaluation in terms of avoidable cancer. The World Cancer Research Fund (WCRF) (114) has conducted a series of systematic reviews of the evidence of the association between dietary factors and risk of cancer. The WCRF concluded that consumption of whole grains, foods containing dietary fibers, and dairy products probably decreases the risk of CRC, whereas consumption of red meat and processed meat probably or convincingly increases the risk. Despite many studies on the consumption of fresh fruits and vegetables, the evidence was not considered sufficient to draw a conclusion (except as contributors to dietary fibers, as mentioned above). It is therefore not surprising that estimates of the proportion of CRC that can be avoided through dietary modifications have been limited and quite heterogeneous.

While diet remains a potentially important target of cancer prevention, the impact of any such intervention remains elusive. The main problem refers to the lack of clear and strong association between food items, food groups, and dietary patterns and the disease. One peculiarity of diet is the fact that it can vary widely over an individual's lifetime; the same person may adopt different patterns in childhood compared to adulthood and older age and experience short-term changes in consumption. Quantification of the intake of different food items across the life span is therefore problematic. Changes in the composition of industrial foods and difficulties in the decomposition of complex foods represent additional challenges, which, coupled with recall bias, pose a challenge to the design and conduct of studies on diet and cancer. Estimating the PAF of diet-related CRC is, therefore, challenging and limits the ability to identify and quantify causal associations with specific dietary factors. Studies based on dietary patterns rather than on individual foods or nutrients have the potential to provide stronger evidence of dietary protective and risk behaviors, which can translate into recommendations for cancer prevention (117).

Several concomitant factors, both environmental and host related, are also likely to interact with diet. Among the latter is the microbiota, of high interest in relation to health and disease. Indeed, gut microbiota may be altered by fiber (103) and fat intake (21). Gut microbiota seems to have an effect on colorectal carcinogenesis through a shift in composition and activity (75), creating a local environment that promotes inflammation, proliferation, and neoplastic progression, without a predominant role of any single pathogen. Gut microbiota could thus mediate (96) the effect of dietary factors on the risk of CRC, for example through systemic inflammation, modulation of the immune and metabolic response, and an increase in bacterial production of secondary bile acids and other possible carcinogens (96).

In conclusion, the investigation of dietary factors, as well as dietary patterns, must take into account the opposite effect exerted by different food items on CRC as well as on several other cancers.

3.4. Examples of a Lack of Successful Interventions: Conclusions

Supplemental Material >

In the section above and in the **Supplemental Discussion**, we have illustrated some examples of tumors for which one or more risk factors have been identified but are still difficult to address with preventive measures. As previously discussed, *Hp* infection still lacks a standard test and treatment protocol because of such medical reasons as possible adverse events or antimicrobial resistance, as well as the lack of a vaccine. Air pollution and obesity face societal, economic, and political challenges because they require profound changes in lifestyle, with implications for food distribution, urban planning, and transportation, among other sectors. Other cancers are theoretically preventable but present barriers of social and cultural character, such as parity or age at first child with respect to breast cancer. For instance, if every woman had their first birth at a very young age, the

incidence of breast cancer would decline markedly. There is also a strong relationship between age at first pregnancy and breast cancer risk (73), but encouraging younger ages at first pregnancy collides with sociocultural values and would have an overall negative impact on women's well-being.

4. CONCLUSIONS: CAN WE REACH 100% PAF FOR CANCER?

For several important neoplasms, current knowledge on modifiable risk factors is very limited. As shown in **Table 4**, PAF estimates for prostate cancer and brain cancer are close to zero, and those for non-Hodgkin lymphoma are below 10%; the study from Brazil (5) is an exception,

Table 4 Estimated avoidable proportion of cancer cases (%, all modifiable risk factors combined) in selected countries

Risk factors	China (113)	United States (52)	United Kingdom (17)	Brazil[a] (5)	France[b] (12)
Oral cavity	68.9	77.9	46.3	94.0	85.5
Pharynx	79.7			14.4	
Nasopharynx	100.0	NA	85.0	89.2	NA
Esophagus, squamous cell carcinoma	45.8	73.2	58.6	70.1	74.2
Esophagus, adenocarcinoma				44.1	
Stomach, noncardia	85.3	56.1	54.2	86.4	38.2
Stomach, cardia	75.5			64.3	
Colon	14.6	54.6	54.3	37.1	18.8
Rectum	2.2				
Liver	80.9	71.2	48.5	25.2	64.4
Gallbladder	NA	35.5	19.9	16.2	0
Pancreas	24.6	25.3	31.5	29.7	21.2
Larynx	24.3	83.2	72.5	78.8	88.5
Lung	67.9	85.8	78.9	82.1	82.7
Mesothelioma	18.5	NA	94.4	29.5	74.4
Skin melanoma	NA	95.1	86.5	26.7	71.1
Breast, premenopause	14.8	28.7	23.0	11.2	30.8
Breast, postmenopause				17.3	
Cervix	100.0	100.0	99.8	100.0	100.0
Endometrium	14.7	71.0	34.0	44.8	17.8
Ovary	12.4	4.3	11.2	0.1	1.9
Bladder	36.7	46.9	48.9	22.2	51.5
Kidney	1.4	53.8	33.5	34.2	31.4
Prostate	0	0	0	0.1	0
Brain	NA	0	2.5	NA	0
Thyroid	NA	12.5	9.1	NA	0
Hodgkin lymphoma	24.7	5.3	40.4	61.8	40.0
Non-Hodgkin lymphoma	4.5	8.8	3.5	71.2	8.0
Multiple myeloma	NA	11.4	13.6	NA	0
Leukemia	12.3	15.1[c]	12.1	14.6	2.3
All cancers	57.4	42.0	37.7	34.3	35.0

Abbreviation: NA, not available.
[a]Derived from data in **Table 2** above.
[b]Mortality.
[c]Myeloid leukemia.

in which ~70% of cases were attributed to Epstein-Barr virus infection, despite the fact that this association is not considered causal (48). These three cancers represent 7.1%, 1.6%, and 2.8% of all cancers or more than 2 million cases each year (99). This disappointing picture is at odds with a large effort made by basic clinic and population researchers to identify preventable causes of these diseases. The reasons for this apparent failure are not fully understood and most likely are multiple and heterogeneous across cancers. First, genetics may play an important and still poorly understood role. In the case of prostate cancer, several genetic variants entailing an increased or decreased risk, alone or in combination with other neoplasms, have been identified, with marked ethnic differences (88). While few of these variants are responsible for a high risk of the disease, polygenic risk score approaches have identified population groups that are at substantial risk because of the combination of multiple intermediate- or low-risk variants (104). A second explanation for why researchers have found limited success in their attempts to identify avoidable causes may be related to the pathologic and molecular heterogeneity of these and other cancers. This heterogeneity is particularly apparent in the case of non-Hodgkin lymphoma, which represents a group of more than 10 major types and a large number of more rare types (101). The etiologic heterogeneity of non-Hodgkin lymphoma has been addressed in an analysis within the InterLymph Consortium, composed of 20 studies whose pooled data comprised more than 17,000 cases of non-Hodgkin lymphoma (70). This analysis provided important clues on the risk factors of specific subtypes and suggested that medical factors—including autoimmune diseases, HCV seropositivity, eczema, and blood transfusion, as well as family history of leukemia and multiple myeloma, alcohol consumption, cigarette smoking, and certain occupations—showed distinct patterns among subtypes, whereas more homogeneous results among subtypes were observed for family history of non-Hodgkin lymphoma, recreational sun exposure, hay fever, allergy, and socioeconomic status. For example, assuming a causal relationship, tobacco smoking would be responsible for ~5% of cases of follicular lymphoma, and HCV infection would be responsible for ~3% of cases of diffuse large B-cell lymphoma. These results offer important suggestions that need to be confirmed in independent populations, although these findings failed to identify major risk factors that would explain a large proportion of cases of non-Hodgkin lymphoma subtypes.

These considerations can be expanded to address a more fundamental question, namely whether research will be able to identify all avoidable causes of cancer, that is, whether PAF will reach 100% for all cancer, after accounting for nonmodifiable factors. Tomasetti et al. (106) recently argued that the combination of genetic and nongenetic risk factors accounts for one-third of human cancers, while the remaining proportion is due to random mutations arising spontaneously during replication of stem cells. While their approach is relatively crude, these authors stressed the importance of chance in the process of carcinogenesis. Therefore, a proportion of spontaneous cancer likely exists. Some empirical data suggest, however, that the estimate by these authors that one-third of human cancers are due to environmental or genetic factors is likely underestimated.

To identify avoidable causes of cancer, epidemiology and public health aim to identify associations between risk factors and diseases. However, associations are not necessarily causal because they may be due to chance, bias, or confounding. An example of a risk factor suspected to cause cancer based on associations that may not be causal is that of pesticides (3). Many of the difficulties in clarifying the carcinogenicity of pesticides arise because (*a*) pesticides are used mainly in complex mixtures, whose composition varies over time, and (*b*) multiple pesticide classes are often used, thus limiting the ability to identify the role of specific agents.

A concept that has been developed in recent decades is the exposome, which attempts to capture the combined effect of different environmental factors to which individuals are exposed throughout the life course (109). The exposome is an integrative approach to the current knowledge on specific risk factors and tries to explain the portion of cancer that is not yet attributable

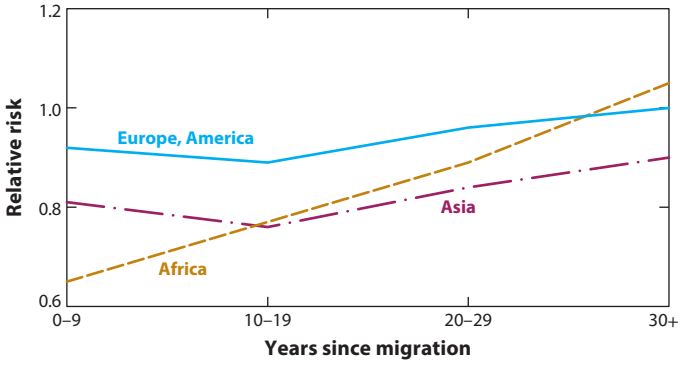

Figure 2

Relative risk of breast cancer among female migrants to Israel according to region of origin and years since migration. Figure based on data from Reference 51.

to a known cause. In the exposome approach, a panel of exposures is studied in relation to a certain phenotype. A particular advantage of this viewpoint is the effort put into identifying and describing the interactions between different chemicals and their mixtures. Although it is an appealing concept, the exposome has so far been helpful in addressing the variety of chemicals to which humans are potentially exposed rather than in providing new knowledge on the effect of these combined exposures across one's lifetime.

Studies of cancer risk in migrant populations offer very strong evidence of important differences in the incidence of many cancers following migration from a low-risk to a high-risk country (or vice versa) (57). These differences will be less pronounced for cancers whose risk factors appear to act early in life, such as nasopharyngeal carcinoma or GC, and more evident for cancers for which exposures are relevant throughout the life course, such as breast cancer. For example, **Figure 2** summarizes the results of a study of women migrating to Israel from countries with lower (North Africa, West Asia) or comparable (Europe, North America) risk of breast cancer (51). The risk of migrants from low-risk countries relative to that of Israeli-born women grew 3 times within 30 years of migration. These results cannot be explained only by known breast cancer risk factors, as they explain no more than 30% of the disease burden (**Table 4**) and suggest either that we underestimate the effect of known risk factors or that other modifiable determinants, yet to be identified, are at play in breast carcinogenesis. Similar results have been reported for other cancers and other migrant populations (57).

A second line of evidence is based on the consideration that the lowest cancer incidence rates reported across the world might approximate the burden of spontaneous cancer, and any excess above that level is attributable to preventable factors. This approach admittedly suffers from limitations, including the facts that it ignores differences in the genetic makeup of different populations and that underdiagnosis and underreporting of cancer are potential issues in populations with low incidence rates. **Figure 3** compares the age-adjusted incidence rate of selected cancers among US men with that of the populations at lowest risk among those included in the IARC's collection *Cancer Incidence in Five Continents* (16). This program includes population-based cancer registries that have been selected because they comply with high standards for completeness and quality of registration. For all cancers shown in **Figure 3**, the incidence in the United States is 15–150 times higher than that in the population at lowest risk. Similar ratios apply to cancer not shown in **Figure 3**, including those among women. Although some of the difference may be

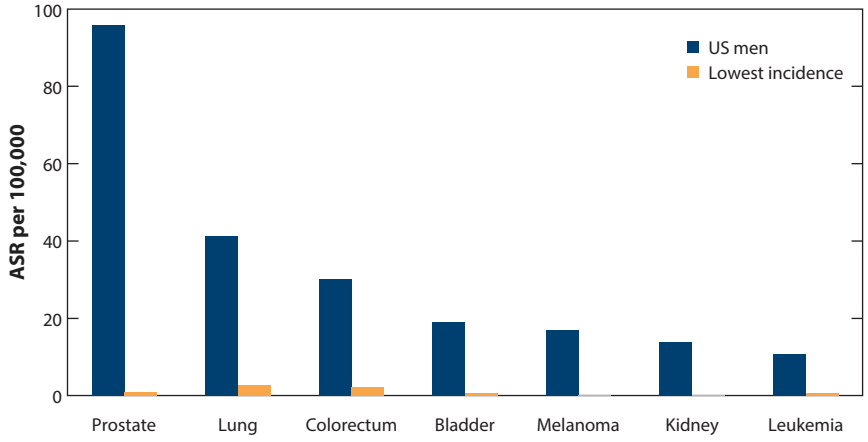

Figure 3

Age-standardized incidence rate of selected cancers among men in the United States and in the population-based cancer registry, with the lowest rate among those included in Bray et al. (16), men, 2008–2012. Abbreviation: ASR, age-standardized rate. Figure based on data from Reference 16.

attributed to under registration, despite IARC's effort to ensure high quality of data, most of it likely reflects differences in genetics and—to a larger extent—exposure to modifiable risk factors.

Evidence indicates that health policies have played a central role in cancer prevention; such policies have helped to reshape the incidence of several cancers attributable to causes mentioned above, including lung cancer following tobacco control regulations (38) and liver cancer following the implementation of HBV vaccination (92). In the future, other cancers may undergo a similar trend, including mesothelioma following asbestos bans and cervical cancer following HPV vaccination. Policies addressing individual behaviors that are associated with cancer, such as nutrition (e.g., overweight/obesity control, reduction in red meat intake), are more problematic because they are limited by cultural, social, and economic barriers. In addition, as cancer becomes a more controllable disease, disparities arise among disadvantaged subgroups, deepening the health gap due to poverty and a lack of literacy, both between countries (e.g., high cost of HPV vaccine in high-risk, less developed countries) and within countries (e.g., racial and ethnic minorities, uninsured subjects, migrants). Addressing disparities in cancer control needs to become a priority in future prevention policies.

These lines of evidence demonstrate that our understanding of the avoidable causes of cancer is incomplete. There are several possible explanations for this phenomenon. First, it is plausible that causes of cancer still need to be identified. Thus, these factors, which have not yet been associated with cancer, are difficult to study with currently available methods, such as large-scale cohort studies. Second, known risk factors are responsible for a larger proportion of cases than currently estimated because of misclassification and other biases in the underlying studies. Thus, the benefit of reducing or eliminating these exposures will be larger than projected. Finally, the causal pathways linking risk factors and cancers may be more complex than currently understood; most cases originate from interactions among exogenous risk factors and between exogenous and host factors and tumor characteristics, which cannot be adequately investigated with the available tools (107).

Despite these limitations, knowledge on avoidable causes of cancer has represented, and will continue to represent, a fundamental tool for cancer prevention. Identifying additional risk factors and implementing evidence into regulatory and behavioral interventions represent priorities for continuing research.

SUMMARY POINTS

1. Cancer control has been subject to large public health efforts, the success of which has been important but incomplete.
2. Prevention depends strictly on the knowledge of cancer epidemiology and on the magnitude of the relation between modifiable factors and cancers; magnitude of the association and prevalence of the exposure define the attributable fraction.
3. Next to lung cancer with tobacco control, the incidence of several occupation- and infection-related cancers (e.g., mesothelioma, bladder cancer, hepatocellular carcinoma, cervical cancer) has been successfully downscaled thanks to the avoidance of carcinogen exposure as well as to an increase in vaccinations.
4. Despite some modifiable risk factors that have been defined and connoted in their association with cancer (e.g., *Helicobacter pylori*, $PM_{2.5}$, PM_{10}, alcohol, diet, and obesity), the preventive interventions to reduce their prevalence have been suboptimal.
5. The rarity or heterogenicity of certain cancers (e.g., non-Hodgkin lymphomas) hinders the comprehension of their attributable fraction and, consequently, the possibility of their control.
6. Genetic factors, yet unknown causes, the understanding of the magnitude of known factors, and interactions among multiple causes could explain the current limitation of our knowledge. In addition, the role of chance in the occurrence of spontaneous cancer should be taken into account.

FUTURE ISSUES

1. The development of "-omics" research (including genomics, epigenomics, transcriptomics, metabolomics, proteomics, etc.), configuring the approach of multi-omics, is a promising area for cancer control.
2. Vaccine development, multidimensional analysis on dietary factors to guide interventions, design of new diagnostic tools and screening, and accurate study of the interaction between genetics, lifestyle, and environmental factors are possible avenues to improve our understanding of avoidable cancers.
3. Integration of research, implementation, and regulatory efforts will lead to more effective cancer prevention.

DISCLOSURE STATEMENT

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