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Cancer Etiology

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Keywords

Causes
Substances and exposures that lead to cancer are called carcinogens. They may impact on DNA directly or indirectly by increasing the rate at which cells divide

Lifestyle
Lifestyle factors, including nutrition, physical activity and tobacco use are components of people live their lives in relation to the risk of chronic diseases

Tobacco
The nicotine-rich leaves of an American plant which, after curing, is smoked or chewed

Obesity
Obesity is defined by the World Health Organization as a body-mass index (BMI; a measure of adiposity) of 30 kg m^{-2}, or greater. The BMI is a measure of a person's body weight relative to their height

Causal
A causal relationship conveys the inference that changing a given factor will lead to a change in the population burden of disease. This may be either by reducing the number of cases or by making disease occur later than it would have

Prevention
The elimination of causes of disease from the population, or reducing exposure to them, so that the risk of disease is either reduced. Prevention thus aims to lower the risk of disease

Prospective cohort study
Epidemiological studies of people who either have or have not been exposed to a suspected risk factor, and who are subsequently observed over time for the development of the disease of interest. A link between the suspected risk factor and the disease is indicated when the exposed and unexposed participants have a significantly different frequency of future development of the disease

Risk (of disease)
The probability that a disease will develop in an individual during a specified time period

Understanding cancer etiology informs prevention. Given the recent explosion in understanding how genetics, lifestyle, individual behaviors, social environment, policy, and healthcare interventions can reduce the burden of cancer, new insights and an integration of knowledge can help to shape prevention strategies and lead to reductions in cancer incidence and improved population health. Inherited genetic predisposition may account for 5–10% of cancers. Currently, over 50% of cancers can be prevented on the basis of presently available knowledge. Age and gender show relations to most cancers, and race/ethnicity may be a marker for either genetic or lifestyle factors. Lifestyle (including smoking, diet, obesity, lack of exercise, alcohol, and excess sun exposure) contributes to the excess burden of cancer, while reproductive factors influence the risk of female cancer and occupational and environmental exposure also contribute to risk. Viruses and other infections also cause a large percentage of cancers in low- and middle-income countries. Further refinements in understanding the "molecular pathway" from lifestyle to cancer incidence will help to refine prevention priorities and guide policy and practice to reduce the burden of cancer.

1 Introduction

1.1 The Evolving Landscape of Cancer

At the start of 2012, approximately 13.7 million Americans had been diagnosed with cancer at some point in their lives. This number continues to increase, and an additional 1.65 million people are expected to be newly diagnosed with cancer in 2015 [1]. This already-large yet increasing burden of cancer is not just limited to the United States. Across the world in 2012, there were 14 million new cases of cancer with costs of diagnosis and treatment amounting to US$ 290 billion [2]. These global numbers are projected to rise to 22 million new cases in 2030, generating a monetary burden of US$ 458 billion. Already, more cases are diagnosed annually in low- and middle-income countries than in high-income countries [3]. The burden of cancer presents a major cause for concern among healthcare workers, public health researchers, and governments everywhere.

It has been for half a century that lifestyle, occupational, environmental and other external factors contribute significantly to the cancer burden. Occupational exposures have been largely regulated to reduce exposure and the disease burden experienced by workers. A 1964 report from a World Health Organization (WHO) panel of cancer prevention experts affirmed that "extrinsic factors" are a key contributor to the majority of cancers [4]. This report was the first official statement from experts to make the wide-ranging claim that cancer could be caused by external causes. But, with what is now known the panel's decision appears conservative in its estimates. Epidemiologists now agree that, given ideal conditions, at least 50% of cancers could be prevented [5, 6].

In addition to the WHO report, 1964 is well-known in public health for a landmark determination regarding smoking and lung cancer in the United States. Cigarette smoking became more widespread during the early 1900s with the inclusion of cigarettes in rations to soldiers in World War I and World War II. With much advertising increasing social acceptability

and pressure on society to smoke, cigarette smoking became highly prevalent in the US by the mid-twentieth century, when more than half of all adult men smoked. This rise in smoking was accompanied by a rise in scientific inquiry into the health effects of smoking. Studies performed during the 1950s had begun to link cigarette smoking and lung cancer, and in 1962 the British Royal College of Physicians released a report, "*Smoking and Health*," which stated that cigarette smoking is a cause of lung cancer [7]. Luther Terry, the Surgeon General of the United States from 1961 to 1965, created an American committee upon release of the British report to further explore the findings. In 1964, the Surgeon General's office released the *US Surgeon General's Report on Smoking and Health*, which concluded, based on seven prospective studies starting as early as 1951, that there is a causal relationship between smoking and lung cancer [8, 9]. This was not the first report to be produced by the US government highlighting this association [9], but it was by far the most famous. The release of the Surgeon's General report precipitated a nationwide movement reducing the use of cigarettes and tobacco and, as a consequence, sales of cigarettes were increasingly regulated by the government; indeed, starting in 1966 all cigarette packets were legally required to show a warning label. Cigarette smoking rates peaked in 1964, but have decreased steadily since that time (Fig. 1). While lung cancer remains a major public health issue (see Sect. 2.4), the tobacco-prevention efforts that started after publication of the 1964 Surgeon General's Report showed that to prevent the external causes of cancers could also be effective.

The risk of lung cancer increases in line with the number of cigarettes smoked per day. Among men and women who smoked 40 cigarettes per day, the relative risk of

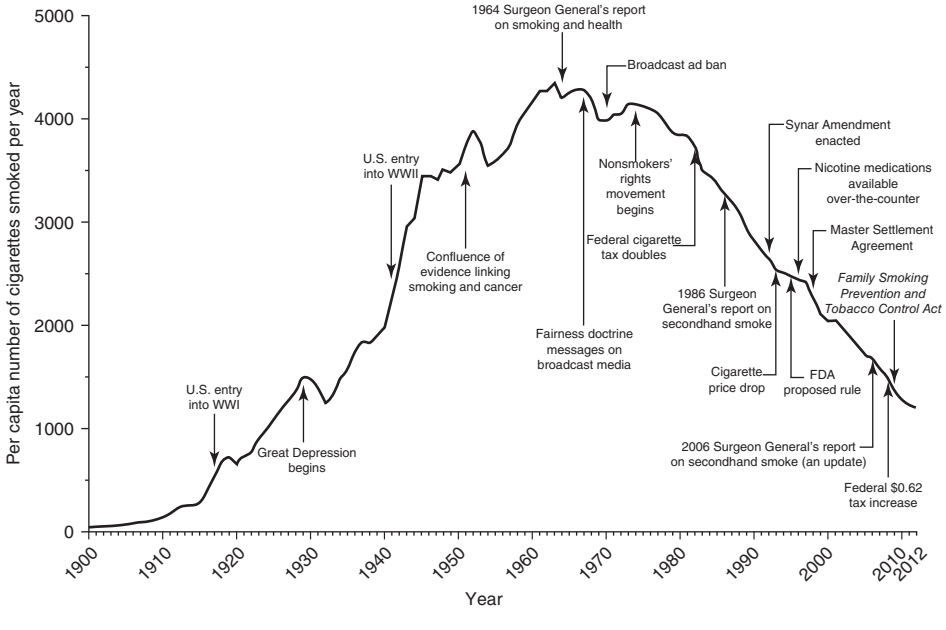

Fig. 1 Smoking rates in the United States during the twentieth century. Reproduced from Ref. [11].

lung cancer compared to "never-smokers" was 40 or more [10]. Whilst smoking causes 80–90% of all lung cancers, mortality due to lung cancer in the US has decreased by over 30% since peaking during the early 1990s; hence, prevention programs are clearly effective. Trends in lung cancer mortality have also shown that the time course between changes in a causal factor (e.g., smoking) and population changes in the cancer burden may be substantial, in part reflecting the timing of exposure in the pathway to carcinogenesis.

Updates to reports from the US Surgeon General continue to document the health effects of smoking and the benefits of quitting. More cancers have been added to the list of those caused by smoking, with reports summarizing the epidemiologic evidence, biologic mechanisms, carcinogenic products contained in tobacco smoke, and the population burden of cancer caused by smoking [11]. A review of the concepts of causal inference from epidemiologic data is presented in Chapter 1 of the 2004 US Surgeon General's report [12], while a history of the causal inference methods evolving from 1964 to 2014 is presented in Chapter 3 of the 2014 report [11]. These reviews, and the approach used by the International Agency for Research on Cancer (and the US Institute of Medicine), clearly support the use of terms such as "cause" for factors such as smoking, alcohol, lack of physical activity, estrogen plus progestin therapy, and other lifestyle factors that have been studied predominantly through observational epidemiologic investigations, as described in the following sections.

Programs and public health initiatives have substantially reduced the prevalence of smoking in the US, and a framework for ending the "tobacco epidemic" has been set forth. However, sustained public health programs are needed to achieve the potential reductions in cancer through tobacco control; unfortunately, these are beyond the scope of the present chapter but they have been clearly summarized elsewhere [13].

Beyond tobacco being the leading preventable cause of cancer, other occupational, environmental, lifestyle and social forces drive cancer risk. Evidence on the causes of cancer, and the potential mechanisms that link these causes to cancer and may inform prevention, are reviewed in the following sections.

1.2 The Cancer Burden

The incidence rates of several cancers in the United States from 2007 to 2011, and the projected number of new cases in 2015, are listed in Table 1 By a disproportionate amount, those cancers with the greatest burden on the United States population are (and continue to be) cancers of the breast, prostate, lung/bronchus and colon/rectum, which account for 50% or more of all cancer cases in men and women. Moreover, all of these cancers have established causes, many of which are modifiable and hence may provide pathways for their prevention.

2 The Leading Cancers

2.1 Breast Cancer

Breast cancer is one of the leading cancers diagnosed in women in the US and in women worldwide; in fact, it accounts for 25% of all cancers diagnosed among women worldwide. It is estimated that 12% of all women in the US will develop breast cancer at some point in their lifetimes, and that

Tab. 1 Recent incidence rates[a] and projected new cases[b] of leading cancers, USA.

Cancer	*Incidence rate per 100 000 (2007–2011)*		*Total new cases (projected) (2015)*
	Males	*Females*	*Both sexes*
Prostate	142.1	n/a	220 800
Breast (female)	n/a	122.8	231 840
Breast (male)			2 350
Lung/bronchus	78.6	54.6	221 200
Colorectal	50.0	37.8	132 700
Bladder	36.7	9.1	74 000
Melanoma	25.1	15.8	73 870
Non-Hodgkin lymphoma	23.2	16.1	71 850
Leukemia	16.6	10.2	54 270
Pancreas	13.8	10.8	46 420
Uterine corpus	n/a	25.0	48 960
Total	535.8	419.1	1 658 370

a) Standardized cancer incidence from Cancer in North America 2014 [14].
b) Case number projection from Ref. [15].

this percentage stands to increase. The incidence of breast cancer increases with age, rising rapidly through the premenopausal years, with dramatically slower increases after menopause. The major risk factors for breast cancer include reproductive factors (age at menarche, age at first birth, parity, and age at menopause), alcohol intake, ionizing radiation treatments, obesity, oral contraceptive use, and postmenopausal hormones [16, 17].

Breast cancer incidence rates among Asian, Hispanic and American Indian women in the US are considerably lower than those of (non-Hispanic) white women [18]. Migrant status often drives variation in risk; indeed, a large body of literature shows increases in breast cancer incidence following migration from a low-risk country to the US. For example, Ziegler *et al*. [19] noted a sixfold gradient in the risk of breast cancer among Asian women, depending on their time since migration. Asian American women with three or four grandparents born in the West were at highest risk, whereas women who had been born in rural areas of Asia and whose length of residence in the US was a decade or less were at lowest risk. These findings strongly suggest that factors associated with the lifestyle or environment of the destination country influence breast cancer risk, and are consistent with a positive relationship between the length of time in the destination country and adoption of that country's lifestyle. For example, among immigrants the fertility rate and average number of children born tend to converge to the rates of the destination country [20, 21].

Within the US, African American women have a higher breast cancer mortality than Caucasian women and a lower overall lifetime risk. Through the premenopausal years, African American women have a higher incidence of breast cancer and are more likely to be diagnosed with triple-negative or aggressive subtypes of breast cancer. The incidence is higher in African American women than Caucasian women [22].

Although a family history of breast cancer is an accepted risk factor, the proportion of breast cancer estimated as being due to rare, highly penetrant genes such as *BRCA1* and *BRCA2* is less than 10% [23], with currently documented mutations in *BRCA1* and *BRCA2* explaining 15% of all breast cancer familial risk [24]. Carriers of *BRCA1* mutations are estimated to have a 57% chance of developing breast cancer by the age of 70 years.

Percent mammographic density (PMD) is one of the strongest risk factors for breast cancer, and is predictive of breast cancer risk for at least 10 years in the future. Women with the highest mammographic density are at a four- to sixfold greater risk of breast cancer than those with the lowest density [25, 26].

Benign breast disease is related to the subsequent risk for breast cancer. Proliferative lesions carry approximately double the risk of normal breast tissue, while atypical hyperplasia on benign biopsy carries a four- to fivefold increase in risk that is bilateral [27]. In other words, these benign lesion serve as a marker of subsequent risk of breast cancer [28].

2.1.1 Obesity

Reflecting the global epidemic of obesity, an increasing proportion of breast cancers are due to adult weight gain and obesity after menopause. This effect of obesity on female breast cancer incidence varies according to the time point in a woman's life that she is obese. Obesity in childhood, adolescence, and young adult years is inversely related to the premenopausal incidence of breast cancer [29]. A higher body mass index (BMI) in childhood is related to lower peak height growth velocity and a lower lifetime risk for breast cancer [30, 31]. On the other hand, obesity after menopause leads to higher circulating estrogen levels and causes postmenopausal breast cancer [32], and also contributes to a poor prognosis for women with postmenopausal breast cancer [33].

Proposed mechanisms for the association of obesity with breast cancer center on hormones released by adipose tissue. The inverse association between obesity and breast cancer before menopause may be due to the effects of childhood adiposity, slower growth in height, lower breast density [34], and decreased risk through the premenopausal years. After menopause, adipose tissue is a major production source for estrogen, a driver of postmenopausal breast cancer. Adipose tissue, a major producer of sex steroids such as estrogen [35], contains high levels of the enzyme aromatase that produces estrogen; indeed, aromatase levels are increased in adipose tissue as a function of increasing age. Combined data acquired from prospective studies of estrogen levels have shown that high levels of estrogen are directly related to incidence, and that this is strongest for receptor-positive breast cancer [36]. Furthermore, in that analysis a strong relationship with hormone levels persisted, even after statistically controlling for BMI. Such an analysis points to estrogen being the mediator in the pathway from adiposity to breast cancer incidence. Further support for this pathway has been obtained from prevention trials with selective estrogen receptor modulators (e.g., tamoxifen and raloxifene) which block estrogen receptors and significantly reduce the risk of breast cancer [37].

More recently, other biologic pathways have emerged linking adipose tissue to breast cancer progression. One such theory centers on adiponectin, the hormone produced and secreted by adipocytes. The proposed mechanism states that adiponectin induces the expression of

growth factors such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), and enhances the migration of breast cancer cells [38]. Both, growth factor expression and cell migration contribute to the progression of breast cancer. Another proposed pathway derives from the chronic inflammation induced by obesity and the recruitment of inflammatory cells, which in turn promote to breast cancer [39]. These multiple pathways support the proposal that hormones secreted by fat cells are directly related to the progression of breast cancer. Local effects of adipose tissue in the breast producing estrone and estradiol also represent possible pathways for adiposity to impact on breast cancer etiology and progression.

A logical next question would be that, if the hormones produced by adipose tissue drive postmenopausal breast cancer, would a reduction in the volume of adipose tissue translate to a lower occurrence of breast cancer? Mechanistically, studies performed in mice have shown that calorie restriction decreases the inflammation seen with obesity [39]. Consequently, as inflammation is associated with several different cancers, it can be surmised that attempts to lose weight can indeed help in decreasing cancer progression. A prospective analysis based on the Nurses' Health Study cohort shows that sustained weight loss after menopause is associated with a reduced incidence of breast cancer [40]. In this case, women who lost 10 kg or more and maintained such loss halved their risk of breast cancer. Meta-analyses have also shown that bariatric surgery, which leads to substantial and sustained weight loss, is associated with lowered risks of breast cancer [41]. This suggests that the weight loss in and of itself – and not necessarily the method of achieving it – is protective against breast cancer.

2.1.2 Maternal Age and Menarche

The results of several epidemiological studies and statistical analyses have shown that breast cancer risk accumulation is modified by reproductive events, and their timing. These include: (i) having children at a young age; (ii) later-onset menarche; and (iii) earlier-onset menopause. A particular subtype of breast cancer, namely progesterone receptor (PR)-negative (PR–) cancer, shows a direct relationship between later age at first pregnancy and breast cancer risk [42]; PR+ cancers do not show this association, however. Age at menarche marks the onset of monthly cycling of female hormones; breast cancer incidence (or breast tissue aging in Pike's model) [43] is then increased by 8.5% per additional year between menarche and menopause [44]. This annual increase in risk slows to 2.5% per year after menopause, and is also slowed by pregnancy. In addition, the closer the pregnancies are together, the lower the lifetime risk [45, 46].

The mechanistic basis for these findings centers on breast tissue aging [43]. Rodent models have shown that pregnancy confers a protective effect against breast cancer by causing a differentiation of the breast tissue, making it less susceptible to carcinogenesis [47]. Subsequent studies have demonstrated molecular changes induced by pregnancy. Specifically, pregnancy induces decreases in the number of hormone-sensitive luminal cells and a downregulation of the Wnt signaling pathway in basal stem cells and/or progenitor cells in the FVB/NHanHsd mouse model, making breast tissue less susceptible to carcinogens [48]. Following a protocol-timed mating at 42 days with genetically homogeneous FVB/NHanHsd mice, mammary epithelial cell subpopulations were isolated from parous and age-matched virgin mice. A reduced expression of Wnt4 in the mammary cells from

parous mice corresponded to a decrease in the proportion of Wnt4-secreting estrogen/progesterone receptor-positive cells. Recombinant Wnt4 rescued the proliferation defect *in vitro*, supporting a causal link to parity-induced alterations of basal stem/progenitor cell properties and a long-term protection from first pregnancy [49]. Other studies have shown that human chorionic gonadotropin (hCG), a key hormone during pregnancy, mimics this protective effect, a finding also shown in women [50].

Chromosomal studies have added an additional layer of support for the differentiation of breast cells with first pregnancy. Nulliparous breast epithelial cells contain large, euchromatic nuclei, while parous breast cells contain smaller, heterochromatic (i.e., epigenetically silenced) nuclei [51]. Histone methylation, a well-known mechanism of gene silencing, is observed more in the breasts of parous women than in those of nulliparous women. Taken together, these molecular studies provide laboratory-based support for pathways between the interval from menarche to first pregnancy, parity, and the risk of breast cancer.

2.1.3 Alcohol Intake

Various epidemiological studies have shown conclusively that alcohol use is associated with an increased risk of breast cancer and, indeed, alcohol is classified by the International Agency for Research on Cancer as a breast carcinogen [52]. The risk of breast cancer increases directly with the amount of alcohol consumed, with even moderate alcohol consumption causing a clear increase [53, 54]. Mechanistically, randomized trials of alcohol feeding have shown increases in female hormones when taking alcohol compared to placebo (both in premenopausal and postmenopausal women) [55, 56]. An increased production of reactive oxygen species (ROS) such as hydroxyl radicals has also been proposed as an underlying factor [57]. Alcohol intake before the first pregnancy has also been shown to increase the risk of premalignant lesions, and the longer the interval from menarche to first birth the greater the adverse effect of alcohol intake [58]. While some evidence suggests that higher blood folate levels may counter the adverse effects of alcohol [59], this remains to be confirmed.

2.1.4 Postmenopausal Hormone Use

Exogenous hormones (i.e., hormone therapy), which is used for the relief of menopausal symptoms and to prevent osteoporosis, have also been purported to provide other health benefits among postmenopausal women. As noted above when discussing endogenous hormone levels in the context of obesity, estrogen is directly related to breast cancer risk, with the vast majority of prospective epidemiologic studies having shown that a longer duration of estrogen use alone increases the risk of both breast and endometrial cancer [60]. The collaborative reanalysis included individual patient data acquired from 51 epidemiological studies (over 50 000 breast cancer patients and 100 000 non-cancer women). Current use of hormone therapy, or its use within the previous four years, was associated with a significant increase in risk of breast cancer compared to women who had never used hormone therapy [60]. For those women who had stopped hormone therapy for more than five years, however, there was no significant excess risk of breast cancer. Importantly, the addition of progestins to counter the adverse effects of estrogen on the endometrium also increased the risk of breast cancer, as demonstrated in prospective epidemiologic

studies [61] and the Women's Health Initiative randomized trial [62]. Growing evidence has indicated that the timing of therapy initiation modifies the risk, with use closer to menopause (typical of traditional evidence from epidemiologic studies) and among lean women showing greater adverse effects [63]. Data from the Women's Health Initiative randomized trial, in which older women aged up to 79 years were randomized to hormone therapy, suggested that initiating use at an older age may not convey the same level of increased risk.

Many investigations have been conducted to elucidate the mechanistic basis for the link between progesterone and breast cancer. The main hypothesis is that progesterone exerts its carcinogenic effects through the receptor activator of NF-κB ligand (RANKL) [64]. The progesterone–RANKL axis is the main mediator of breast tissue proliferation in both mouse and human, and an inhibition of RANKL signaling has been shown to reduce the incidence of breast cancer metastasis [65, 66]. Therefore, RANKL represents a good short-term target for cancers caused by the use of progesterone as hormone replacement therapy (HRT), with a long-term goal being to eliminate progesterone as HRT entirely. Based not only on evidence acquired from studies conducted in women but also from biologic pathways, the International Agency for Research on Cancer classified combination estrogen plus progestin as a human carcinogen in 2007 [67].

2.1.5 Physical Activity

Many studies have now shown that women who are physically active throughout their lifetime have a lower risk of breast cancer. Indeed, women who routinely perform 3 h or more exercise each week have a 20% lower risk of breast cancer than those who are minimally active or inactive [68]. In the large Nurses' Health Study II, regular physical activity between the ages of 12 and 22 years was shown to provide the greatest protection against premenopausal breast cancer when compared to activity in older groups, with the most active women having a 25% lower risk of breast cancer through their premenopausal years. The IARC classifies a lack of physical activity as a cause of breast cancer [32].

2.1.6 Other Factors

Various other casual factors for breast cancer have been identified, the most common being ionizing radiation. Evidence acquired from the follow-up of atomic bomb survivors has pointed to the timing of exposure, and also age at exposure, as important when defining the magnitude of the adverse effect of exposure to this carcinogen [69]. Exposure to ionizing radiation in childhood and adolescence carries the greatest risk of breast cancer.

A current use of oral contraceptives is associated with a transient increase in the risk of breast cancer [70]. Lactation reduces the risk of breast cancer [71], and adolescent diets high in fruits, vegetables and fiber may also lower risk [72, 73]. Plasma markers of plant-based diets such as carotenoids are inversely related to the risk of breast cancer [74]. Cigarette smoking also increases the risk of breast cancer and death from the condition [11].

2.2 Colorectal Cancer

Colorectal cancer is the third most common cancer in the Western world [2], and the fourth most common in the US (Table 1). Only 10% of colon cancers are caused by genetic predispositions such as hereditary

non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP); the remaining 90% are caused by environmental and lifestyle factors, some of which are modifiable and include diet, cigarette smoking, obesity and physical activity, aspirin, and hormone therapy. Colon polyps, precursor lesions for colon cancer are often investigated to appreciate the time course of risk factors and thus the prevention of colon cancer.

2.2.1 Diet

Whilst eating a well-balanced diet is the optimal way of reducing the risk of several different types of cancer, specific factors have become associated with colon cancer.

Red Meat Intake Various studies have consistently demonstrated a positive association between a higher consumption of red or processed meat and an increased risk of colon cancer [75, 76]. Both, recent and long-term consumption of red meat confer an increased risk of developing colon cancer, especially when compared to poultry or fish intake [77]. In fact, there is an inverse association between the intake of fish and the incidence of colorectal cancers [78]. Proposed mechanisms for the association between red meat consumption and increased colon cancer include heme iron, nitrates from processed meats, and heterocyclic amine intake [79], all of which are known carcinogens. Heme iron in particular has been associated with DNA damage and a hyperproliferation of epithelial cells in the colon via a hydrogen peroxide mechanism [80]. Studies performed in rats have shown that fish intake is associated with less DNA damage and fewer inflammatory markers when compared to a controlled diet [81]. Together, these data indicate that red meat intake is a modifiable risk factor for colon cancer.

Calcium Several studies have demonstrated the benefits of sufficient dietary calcium with regards to the risk of colorectal cancer. Data obtained from the Nurses' Health Study and Health Professionals Follow-Up Study have indicated that calcium intakes of 700 mg per day or higher conferred protection against developing distal colorectal cancer but not necessarily from proximal colorectal cancer. Notably, the benefit was linear up to levels of about 700 mg per day, but leveled off at higher calcium intakes [82]. Subsequent studies corroborated this protective effect of calcium, particularly in the form of calcium supplements [83, 84]. Although the amount of calcium designated as "sufficient" remains uncertain, the pooled analysis of prospective cohort studies suggests that benefit decreases above 1200 mg per day [85]. In a randomized trial of patients who had undergone polyp removal, a daily supplement of 1200 mg calcium led to a significant reduction in the risk of subsequent polyps [86], and the benefit persisted when the supplementation was stopped [87].

The mechanism underlying calcium's chemopreventive effects most likely centers on the high sensitivity of colonic epithelial cells to calcium. Whereas, normal colonic epithelial cells will proliferate in the presence of trace amounts of calcium, higher levels of calcium (as are normal for most other tissues) cause the cells' proliferative machinery to shut down.

Vitamin D Whilst a dietary intake of vitamin D is known to be a protective factor against many cancers, studies from the IARC have indicated that vitamin D is most protective against the development of colon cancer [88]. In 2011, a meta-analysis conducted by the US Preventive Services Task Force confirmed this finding, where each 10 nmol l^{-1} increase in the blood level

of vitamin D was associated with a 6% decrease in colorectal cancer risk [89].

Mechanisms connecting vitamin D and decreased colon cancer risk are centered on the vitamin D receptor (VDR) which, when bound to vitamin D, interacts with DNA and signaling pathways [90]. In this case, the major pathway is the Wnt-Beta catenin pathway, which promotes colorectal oncogenesis. The suppression of beta-catenin signaling by VDR results in decreased oncogenesis [91]. Another pathway affected by VDR is the inflammatory pathway, and bowel inflammation (especially in conditions such as Crohn's disease) are a major risk factor for colon cancer. VDR suppresses the production of inflammatory markers and downregulates T_H1 types of T cells in favor of T_{reg} and T_H2 cells, which are less inflammatory [92]. While the epidemiology on the specifics of vitamin D levels and the magnitude of protection against colon cancer remains unclear, molecular biology studies have shown that claims for such a relationship have strong biologic basis.

Alcohol A long history of studies relates higher alcohol intake to an increased risk of colon cancer and to an increased risk of colorectal adenomas [93]. A dose–response relationship has been observed across several studies [94], with some evidence suggesting that even moderate drinkers (one drink per day) are at a higher risk of colon cancer than nondrinkers. These data have been extensively reviewed and summarized by the IARC [52], which has concluded that the association does not vary by alcoholic beverage type, gender, or smoking status. The effects of alcohol appear to be exacerbated by low levels of folate and methionine. In the Health Professionals Follow-Up Study, an increased risk of colon cancer was observed among both current and past drinkers, but only among those who also had low intakes of methionine or folate [95]. Because alcohol is an antagonist of methyl-group metabolism, it may imbalance DNA methylation, which may in turn contribute to the process of carcinogenesis.

Folate Folate is a vitamin found in green leafy vegetables, and low levels of folate intake have long been associated with colon and rectal cancers [93, 96]. Beneficial effects of folate supplementation were demonstrated through a reduction of dysplasia in patients with chronic ulcerative colitis, which is a risk factor for colon cancer [97]. Findings for a reduction in the risk of polyps, a precursor lesion for colon cancer, suggest that the timing of exposure may again be important for the prevention of colon cancer. Prospective data from the Nurses' Health Study and Health Professionals Follow-Up Study have shown that folate intake may be beneficial over decades before the diagnosis of colon cancer, but does not necessarily protect against colorectal cancer in the short term, which is consistent with protecting against early molecular changes [98]. Other studies, though typically much shorter in duration, have demonstrated a possible increased association between folate intake and colorectal adenomas [99]. Taken together, these data suggest that folate may play both a protective role against colorectal cancer and also a potential carcinogenic role. Further research is required to disentangle the mechanisms and timing of exposure.

2.2.2 Smoking

Smoking causes many cancers, and colorectal cancer is no exception. Prospective epidemiologic studies have shown that smokers have a higher incidence of colon and rectal cancers, with a higher risk of colon cancer than rectal cancer compared to

never-smokers [11, 100, 101]. Additionally, smokers of 40 cigarettes per day or more, have a 50% higher incidence of rectal cancer than those who have never smoked. Current smokers have a higher incidence of proximal colon cancer compared to distal colon cancer or rectal cancers. Importantly, timing matters again in the carcinogenesis of colorectal cancer. Exposure to smoking for decades before a diagnosis drives the risk, which is consistent with smoking acting as an initiator for colorectal cancer [102].

Mechanistically, the silencing of tumor suppressor genes through cigarette smoke has been proposed to link smoking to colon cancer incidence. Many colorectal cancers show a silencing of KRAS and BRAF, two major tumor suppressors, and this is also associated with cigarette smoking [103, 104]. As summarized in the Surgeon General's Report, other carcinogens have also been found in cigarette smoke [11]. In particular, polycyclic aromatic hydrocarbons and heterocyclic amines in cigarette smoke are associated with increased rates of tumorigenesis [105].

2.2.3 Obesity

Obesity appears to influence the development of adenomatous polyps, as well as the progression of polyps to malignancy. Both, men and women with excess body weight are at increased risk of polyps and colon cancer, though the magnitude of increased risk may be slightly higher among men than women [94, 106]. Men with high levels of abdominal fat appear to be at a particularly high risk [107].

The underlying mechanism for the relationship between obesity and colon cancer is unknown. However, it has been hypothesized that elevated insulin or other growth-related factors may be mediating the influence of obesity, and C-peptide (a marker of insulin secretion) has been shown to be directly related to risk in prospective blood studies [108]. Abdominal obesity, in particular, is a strong determinant of hyperinsulinemia, a condition which may promote colonic tumor growth.

2.2.4 Physical Activity

Regular physical activity is associated with decreased risks of colon cancer, as summarized in recent meta-analyses for both colon polyps and colon cancer [109, 110]. The level of physical activity is important as it is protective against colon cancer in a dose-dependent manner, with a higher activity leading to a lower risk [109]. The protective benefit of physical activity seems strong even in individuals who are obese, which suggests it is an independent factor for colon cancer unrelated to obesity.

Many different mechanisms have all been shown to support the idea that physical activity protects against colon cancer. One mechanism relates to insulin resistance, in that physical inactivity leads to insulin resistance where higher levels of insulin are needed to normalize blood glucose levels. Insulin and insulin-like growth factors (IGFs) in turn promote colorectal tumor growth by inducing mRNA expression of VEGF, which is responsible for the initiation and growth of several cancers, in the colon [111]. Consistent with this mechanism, prospective studies of glucose and insulin have demonstrated direct relationships to colon cancer incidence [108]. Exercise also limits the expression of inflammatory factors such as nitric oxide synthase [112], thereby reducing risk. Many more mechanisms have been proposed, related to prostaglandins, immune responses, and other biological factors [113]. Currently, research is ongoing to identify new possible pathways underlying the protective effects of physical activity against colon cancer,

potentially opening new pathways for chemoprevention.

2.2.5 Aspirin

Combined data from observational studies have shown that the use of aspirin is protective against colorectal cancer [114], and this finding has been supported by the follow-up of randomized trials [115]. A randomized trial of aspirin in carriers of hereditary risk (Lynch syndrome) showed a significant reduction in colorectal cancer risk of approximately 40% [115, 116].

2.2.6 Hormone Therapy

In women, the apparent smaller adverse effect of obesity is hypothesized to be due to higher estrogen levels. Data acquired from the randomized trial of hormone therapy (Women's Health Initiative) showed consistency with observational data [117] and a lower risk of colon cancer among those receiving hormone therapy [118].

2.3 Prostate Cancer

Prostate cancer is a leading cancer diagnosed among men, with the introduction of widespread screening leading to the detection of potentially nonlethal tumors. Today, investigations continue to focus and refine the present understanding of the factors that drive fatal prostate cancer. African American men are at a significantly higher risk than Caucasian men, and this is evident from the age of 35 years onwards, based on national estimates of age-specific incidence [119]. Several non-modifiable factors predispose men to higher risks of prostate cancer. One is genetics: men with *BRCA1* and *BRCA2* mutations, which are commonly associated with breast cancer, also have an increased risk of developing prostate cancer [120], and single nucleotide polymorphisms (SNPs) convey risk [121], including those in developmentally important genes such as *HOXB13* also increase risk for prostate cancer [122]. Yet, some risk factors are within the control of men that might modulate the risk of their developing prostate cancer, the most notable being diet (e.g., meat and tomato intake) and a high body weight. Despite extensive investigations, however, the evidence for modifiable risk factors in prostate cancer is less well established than for other cancers.

2.3.1 Meat Intake

Over the years, the intake of animal fat and meat has been shown to be associated with prostate cancer in several different prospective studies. In 2001, the risk for metastatic prostate cancer was shown to be increased with the intake of red meat and processed meats [123]. In subsequent studies, the possible contributory factors that would increase susceptibility to prostate cancer were narrowed down, with heme iron, nitrite/nitrate from meat, grilled/barbecued meat, and benzo(a)pyrene each being associated with elevated risks of advanced prostate cancer, in addition to red and processed meats. The same factors (except for nitrite/nitrate exposure) were also found to be associated with total prostate cancer [124]. Several mechanisms have been proposed as to how these compounds may contribute to prostate cancer. Heme iron has been suggested to cause free-radical damage in the prostate as well in other organs, which could contribute to the progression of prostate cancer [125]. *N*-nitroso compounds are also a possible contributor to the increased carcinogenesis that occurs with red meat consumption; the exogenous formation of these compounds results from the ingestion of nitrite-preserved meats, while their endogenous formation results from the heme iron content of red meat

[124]. Thus, limiting the consumption of meats and animal fats could curb the effects of chemicals causing prostate cancer.

2.3.2 Lycopene

Lycopene is found in tomatoes, and has potent anti-oxidant effects. Currently, it is widely believed that eating tomato products helps to protect against prostate cancer. Whereas, older studies yielded contradictory conclusions as to the protective effects of lycopene in prostate cancer, more recent data from prospective studies have indicated that larger amounts of lycopene are inversely associated with the incidence of both total and lethal prostate cancer [126]. The results of this prospective study showed that higher levels of lycopene intake were associated with lower levels of angiogenic markers. This, in turn, suggested that lycopene's protective effect against prostate cancer could be centered on preventing tumor angiogenesis, which is a separate mechanism from the antioxidant hypothesis.

2.3.3 Obesity

Obesity is a well-known risk factor for prostate cancer mortality, as demonstrated by several meta-analyses [127]. Consistent with excess mortality, obesity is associated with more aggressive prostate cancers [128, 129].

Endocrine factors are responsible for the association between obesity and prostate cancer. A comparison of the serum of lean and obese men showed the latter to contain higher levels of leptin and other factors, that led to an increased proliferation, invasion, and migration of tumors, as well as an increased activity of proteins needed for epithelial–mesenchymal transition [130]. These characteristics of metastatic tumors support the relationship between obesity and increased tumor aggression.

2.4 Lung Cancer

Smoking is the primary cause of lung cancer, accounting for up to 90% of all cases, though other factors such as nutritional intake also play a role. As noted in Sect.1, lung cancer incidence is decreasing across the US due to reductions in smoking rates.

2.4.1 Smoking

The link between cigarette smoking and lung cancer is undisputed. Numerous studies have demonstrated the strong association between cigarette smoking or secondhand smoke ("passive" smoking) and lung cancer [11, 131]. Cigar smoking and other forms of smoking have also been shown to lead to lung cancer [132].

There are myriad mechanisms by which cigarette smoking leads to lung cancer. Carcinogens found in tars in cigarettes or in cigarette smoke, including compounds such as benzo[a]pyrene and nitrosamines [133], lead to DNA damage. Cigarette carcinogens are also associated with mutations or the silencing of important tumor suppressor genes, such as *TP53*, *KRAS*, and *P16* [134]. There is also a genetic component to lung cancer, with some smokers or even nonsmokers being more likely to develop lung cancer if they have mutations in genes such as *CYP1A1* and *GSTM1* [135]. Others genes that play a role in lung cancer have been reviewed in reports of the US Surgeon General.

As discussed in Sect. 1, since the mid-1960s cigarette smoking rates have declined in men, and lung cancer deaths have declined in the US by one-third since the early 1990s. The delay between these two effects reflects in part the dual impact of smoking on lung cancer, namely that: (i) the age when starting to smoke modifies the risk [136]; and (ii) the risk declines steadily

over many years after stopping [137]. These characteristics of the relationships between smoking and lung cancer highlight the importance of considering where in the pathway a lifestyle factor might operate to increase cancer risk, and where preventive efforts should be focused [138].

2.4.2 Fruit/Vegetable Intake

An increased consumption of fruits and vegetables is associated with a decreased risk of lung cancer [139]. Mechanisms proposed for this relationship include beta-carotene, a vitamin found in carrots, pumpkins, and other fruits and vegetables. While dietary studies have shown this relationship with fruits and vegetables consistently, the use of a supplement in a chemoprevention trial such as CARET (a randomized controlled trial comparing beta-carotene supplementation with a placebo) failed to show any benefit of the supplementation. A combined analysis of four chemoprevention trials demonstrated an increase in lung cancer risk among current smokers who were randomized to beta-carotene supplementation [140]. Baseline fruit and vegetable intake before randomization was related to a lower risk of lung cancer during the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial. This again highlights the challenges of timing a preventive intervention to reduce the risk [141]. Other insights on this issue have arisen from a nutritional prevention trial in China, where the benefits were most evident among men who were younger at randomization. This suggested that intervening in the pathway to cancer at an early stage of carcinogenesis could reduce risk but that, among older men, where a greater risk had already accumulated, the nutritional intervention did not produce any benefit [142].

3 Medical Interventions Interrupting Pathways to Cancer

Medical interventions based on insights from etiology typically use drugs to interrupt a pathway to carcinogenesis. Alternatively, for infectious causes of cancer, vaccines, or drugs to treat infections can reduce risk. These are discussed in turn.

As noted in Sect. 2.1, selective estrogen receptor modulators reduce the incidence of breast cancer by half in women who are at high risk of the disease, or who are eligible for the prevention of osteoporosis. Likewise, aspirin has been shown to significantly reduce the incidence of colon cancer in patients at high genetic risk [116]. Observational data support the prevention benefits of aspirin across a number of cancer sites beyond colon. The benefits for colon and other cancer risk reduction over 20 or more years of aspirin use are substantial [143]. Although oral contraceptives increase the risk of breast cancer among current users, they provide a long-term reduction in the risks of ovarian cancer and endometrial cancer.

Infections cause approximately 7% of cancers in high-income countries, and approximately 25% of cancers in low and middle-income countries [144]. The IARC has classified numerous infectious agents as carcinogens for humans [145], including:

- Stomach: *Helicobacter pylori*
- Liver cancer: Hepatitis B virus, hepatitis C virus (HCV), *Opisthorchis viverrini*, *Clonorchis sinensis*
- Cervix uteri: Human papillomavirus (HPV), with or without HIV
- Anogenital: (penile, vulva, vagina, anus): HPV with or without HIV
- Nasopharynx: Epstein–Barr virus (EBV)
- Oropharynx: HPV with or without tobacco or alcohol consumption

- Kaposi's sarcoma: Human herpesvirus type 8 with or without HIV
- Non-Hodgkin lymphoma: *H. pylori*, EBV with or without HIV, HCV, human T-cell lymphotropic virus type 1
- Hodgkin's lymphoma: EBV with or without HIV
- Bladder: *Schistosoma haematobium*.

Hepatitis B vaccination reduces the incidence of liver cancer when compared to vaccinated and unvaccinated birth cohorts [146]. Currently, HPV vaccination is recommended for the prevention of cervical cancer and anal cancer, and conveys long-term protection against these cancers caused by viruses [147].

3.1 Balancing Risks and Benefits with Chemoprevention

Breast cancer chemoprevention demonstrates the ability to counter the estrogen stimulation of breast cancers through selective estrogen receptor modulators and aromatase inhibitors that reduce estrogen production. The balance of risks and benefits for chemoprevention depends on several factors, including a woman's age, race, and risk of breast cancer; whether she has a uterus; and the type of medication (tamoxifen or raloxifene) [148]. Tamoxifen increases the risk of endometrial cancer, stroke, pulmonary embolism, deep-vein thrombosis and cataracts, but decreases the risk of bone fractures [149]. Compared with tamoxifen, raloxifene (which is only approved for postmenopausal women) has a lower risk of endometrial cancer, cataracts and thromboembolic events [37]. In white women under the age of 50 years, the benefits of tamoxifen are likely to outweigh the risks when the five-year risk of breast cancer is at least 1.5% [150]. Younger black women at high risk of breast cancer also benefit from tamoxifen, although black women aged 40–50 years may need a higher level of breast cancer risk to derive a net benefit. In women aged 50 years or more, the benefit/risk ratio tends to be better for raloxifene than for tamoxifen among women with a uterus, and similar for the two drugs among women without a uterus [148]. The level of breast cancer risk that is required to derive a net benefit increases with age, and also tends to be higher for black women than for white women [148].

Aspirin (see Sect. 2.2.5) also demonstrates these issues, with increased bleeding complications occurring in a subset of users. Again, this risk must be balanced against the drug's long-term use to achieve protection against colon cancer [151].

4 Conclusions

Multiple modifiable risk factors have been identified that together account for the majority of cancers as experienced in high-income countries [152]. Tobacco and obesity account for approximately 30% each. While the US Surgeon General Reports on smoking and health set out clear criteria for causal relations between smoking and cancer, the number of cancers caused by smoking often surprises. The 2014 report [11] lists the following cancers as caused by smoking;

- Lung
- Bladder
- Cervix
- Colorectal
- Esophagus
- Renal cell and renal pelvis
- Liver

- Acute myeloid leukemia
- Larynx
- Oral cavity and pharynx
- Pancreas
- Gastric

Notably, smoking reduces the risk of endometrial cancer.

Obesity accounts for up to 20% of all cancer deaths, but for a higher proportion of incident cancers. Cancers of the breast, endometrium, esophagus, kidney, and colon [32], of the thyroid gland, liver, gallbladder and pancreas, as well as hematologic malignancies, are directly related to overweight and obesity [153].

Diet, physical activity, occupational factors, alcohol, reproductive factors and ionizing radiation each also contribute as preventable causes of cancer. Ionizing radiation drives lung cancer and melanoma risk, which is a rapidly increasing cancer among white populations worldwide. Importantly, infection has a greater impact on cancer incidence in low- and middle-income countries, but as these economies evolve to higher standards of living the incidences of many of the cancers associated with obesity, lack of physical activity and smoking will increase. Clearly, an understanding of the pathways and mechanisms involved is necessary to inform prevention methods, to guide the timing of interventions across a patient's lifetime, and to stratify risk so that interventions which carry both risks and benefits can be targeted to high-risk subgroups, so that the benefits may outweigh the risks.

The location of the causes of cancer during the time course of disease development, from its early initiation to the late promotion of tumor growth, has major implications for prevention and the time over which reductions in incidence will be observed after preventive programs have been implemented, and these issues have been addressed in greater detail elsewhere [138, 152]. A further refinement of the present understanding of molecular pathways from lifestyle to cancer incidence will help to identify new pathways for prevention, to refine prevention priorities, and to guide policy and practice in order to reduce the worldwide burden of cancer.

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