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LIFESTYLE AS RISK FACTOR FOR CANCER: EVIDENCE FROM HUMAN STUDIES

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Abstract

It is increasingly appreciated that the chances of developing cancer are significantly affected by the choice of our lifestyle. There are several uncontrollable risk factors which account for the majority of cancers, but we can modify our lifestyle to reduce enhanced threat of cancer. Healthy lifestyle behaviors for cancer risk reduction include a healthy diet, weight management, regular exercise, reduction in alcohol consumption and smoking cessation. In this article, we present evidences on the association between certain lifestyle characteristics and their contribution for developing breast, prostate, lung and colon cancers, using information derived from human studies.

Keywords

Lifestyle; obesity; diet; alcohol; smoking

I. INTRODUCTION

It is increasingly appreciated that lifestyle could modify cancer risk factors. Cancer is a genetic disease in which tumor cells differ from their normal progenitors by genetic alterations that affect growth-regulatory genes. It has been recognized that malignant transformation occurs through successive mutations in specific cellular genes, leading to the activation of oncogenes and inactivation of tumor suppressor genes [1]. Compiling the most recent data on cancer incidence, mortality and survival based on incidence data from the National Cancer Institute, Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries and mortality data from the National Center for Health Statistics, the American Cancer Society estimated 1,479,350 number of new cancer cases and 562,340 deaths in the United States in the year 2009 [2]. The large differences in cancer rates among countries, striking changes in these rates among migrating populations, and rapid changes over time within countries indicate that some aspects of lifestyle and/or environmental factors are largely responsible for the common cancers which are more prevalent in Western countries. The great interest during the last several decades in

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diet and human cancer derives from the large variations in rates of specific cancers among countries, coupled with the dramatic changes in cancer incidence among populations immigrating to regions with different rates. Determining the mechanisms by which lifestyle patterns influence cancer risk will not only illustrate biological plausibility for the observed association but also provide evidence of causality to inform the optimal prescription to population at large for cancer risk reduction.

In this review, we focus on the evidences provided by human studies of the major modifiable risk factors to the cancer incidence and mortality for the cancers of breast, prostate, lung and colon. The major risk factors that can be modified to decrease risk for these cancers include improving diet, reducing tobacco use, controlling weight, limiting alcohol consumption and cessation of smoking. In recent years, there has been increasing interest in the use of dietary factors rich in chemopreventive substances. Several studies have shown that chemopreventive agents possess strong cancer-preventive properties that might interrupt different stages of cancer [3-5].

II. BREAST CANCER

Advances in early detection and improved treatment for breast cancer have led to a steady decrease in overall breast cancer mortality rate; however, it remains a significant cause of morbidity and mortality. That lifestyle changes can enhance/retard the risk of developing breast cancer is supported by several lines of evidence. First, rates of breast cancer incidence vary widely by geographic areas around the world. Only a small part of these differences could be explained based on genetics, predisposition to chemical or carcinogen exposures have also been linked to risk, but most of cases are therefore, due to individual health and lifestyle behaviors. Women may improve their overall health and thus perhaps minimize breast cancer risk by low fat consumption, maintaining a healthy weight, avoiding cigarettes, limiting alcohol consumption, getting regular exercise and avoiding non-diagnostic ionizing radiation.

(i). Obesity

Among the avoidable risk factors for breast cancer during a woman's life, overweight and obesity are important contributors (Table 1). Women with a body mass index (BMI) in the obese range had a three fold increased risk of breast cancer in a case-control study suggesting that obesity in postmenopausal women could increase risk of breast cancer [6]. A study was conducted in patients diagnosed with invasive breast cancer and received neoadjuvant chemotherapy before surgery. Obese patients were more likely to have hormone-negative tumors, stage III tumors and worse overall survival at a median follow-up time of 4.1 years. Higher BMI was associated with worse pathologic complete response to neoadjuvant chemotherapy [7]. In follow-up information from women with incident invasive breast cancer, increased risk of death for breast cancer emerged for BMI>/=30 compared to <25, or waist-to-hip ratio (WHR) >/= 0.85, compared to <0.80, and the strongest association was observed for women with BMI>/=30 and high WHR, compared to women with BMI<25 and low WHR [8]. In patients treated on prospective clinical trials, obese patients had a higher incidence of inflammatory breast cancer compared with overweight and normal/underweight groups. Patients with locally advanced breast cancer who were obese or overweight had a significantly worse median overall survival and recurrence-free survival and a higher incidence of visceral recurrence compared with normal/underweight patients [9]. A cohort of 14,709 patients was constituted and these patients were followed prospectively for a first unilateral invasive breast cancer without distant metastasis. Interaction analysis revealed a more important obesity effect in the presence of tumor estrogen receptors and among limited extent tumors and confirmed the prognosis role of obesity on one of the largest cohort by investigating several prognosis events [10]. A follow-

up study was conducted among a population-based sample of 1,508 women diagnosed with first, primary invasive and in situ breast cancer between 1996 and 1997. Obese women had increased mortality due to breast cancer compared with ideal weight women. Among women diagnosed with premenopausal breast cancer and gained more than 16 kg between age 20 years and 1 year before diagnosis had more than a 2-fold elevation in all-cause and breast cancer-specific mortality compared with those whose weight remained stable. Women diagnosed with postmenopausal breast cancer who gained more than 12.7 kg after age of 50 years up to the year before diagnosis had a 2- to 3-fold increased risk of death due to breast cancer [11].

(ii). Diet

Several studies have shown the association of breast cancer with the dietary patterns of individuals (Table 2). An association between high saturated fat intake and greater breast cancer risk was found for the highest quintile of saturated fat intake compared with the lowest quintile in cohort of European women. In menopausal women, the positive association with saturated fat was confined to nonusers of hormone therapy at baseline. There was weak positive association between saturated fat intake and breast cancer risk which was more pronounced for postmenopausal women who never used hormone therapy [12]. High fat intake was associated with increased risk of breast cancer and a positive association was found for oleic acid but not for linoleic acid or saturated fat. Risk was increased for women cooking with hydrogenated fats or vegetable/corn oil compared to women using olive/canola oil. [13]. Dietary intakes of total fat, monounsaturated fat (MUFA), polyunsaturated fat (PUFA) and saturated fat (SFA) were associated with breast cancer. Total fat, MUFA, PUFA or SFA were not associated with risk overall. However, women in the highest MUFA and PUFA quintile intake had a reduced breast cancer risk after age 50 years compared to women in the lowest quintile [14]. Women with a BMI>/= 25 were associated with a 58% increment in breast cancer risk compared to the lowest quartile. [15].Erythrocyte fatty acid concentrations were determined in specimens from women with histologically confirmed breast cancer and frequency age-matched control women. There was a significant direct association among palmitic, γ-linolenic, palmitoleic, and vaccenic acids and risk of breast cancer. Total n-3 fatty acids and eicosapentaenoic acid were associated with significantly lower risk of breast cancer [16].

(iii). Alcohol

In Norwegian European Prospective Investigation into Cancer and Nutrition cohort, there was a statistically higher risk of total cancer and breast cancer with high alcohol consumption. A significantly higher risk of total cancer with low intake of fatty fish in the alcohol group was also observed [17]. In a cohort study, the relative risks for breast cancer versus lifelong abstainers were at <1 drink per day, 1.21 at 1-2 drinks daily and 1.38 at 3 drinks daily. Increased breast cancer risk was concentrated in women with estrogen receptor positive tumors with no major disparity related to choice of wine, liquor, beer or type of wine. It was recently shown that with a threshold below 1-2 drinks daily, a hormone-related mechanism mediates a relation of alcohol drinking to an increased breast cancer risk [18].

In a cohort study, the relative risk of breast cancer was 2.30 for alcohol intake of 22-27 drinks per week, compared to 1-3 drinks per week. Among alcohol consumers, weekly alcohol intake increased the risk of breast cancer with 2% for each additional drink consumed. Weekend consumption increased the risk with 4% for each additional drink consumed on weekend. Binge drinking of 4-5 drinks the latest weekday increased risk with 55%, compared with consumption of one drink. [19]. In the European Prospective Investigation into Cancer and Nutrition study, during 6.4 years of follow up, 4,285 invasive cases of breast cancer were identified supporting previous findings that recent alcohol intake

increases the risk of breast cancer [20]. Moderate alcohol consumption over the life course increases breast cancer risk, particularly among women with low body mass index and those diagnosed with estrogen receptor positive tumors or with invasive rather than in situ disease in a large population-based study [21]. These studies are summarized in Table 3.

(iv). Radiation

In a pooled analysis of eight cohorts, breast cancer incidence rates after radiation exposure were described and compared. The nature of the exposures varied and ranged from a single or a small number of high-dose-rate exposures which include (i) Japanese atomic bomb survivors, (ii) U.S. acute post-partum mastitis patients, (iii) Swedish benign breast disease patients, (iv) U.S. infants with thymic enlargement (v & vi) two U.S. tuberculosis cohorts and (vii & viii) two Swedish skin hemangioma cohorts. The risk was attributed to age at exposure and supports the linearity of the radiation dose response for breast cancer suggesting a similarity in risks for acute and fractionated high-dose-rate exposures with much smaller effects from low-dose-rate protracted exposures. It was also concluded that women with some benign breast conditions may be at elevated risk of radiation-associated breast cancer [22]. A retrospective cohort of women diagnosed with spinal curvature was studied for risk of breast cancer by radiation dose to the breast after adjustment for established breast cancer risk factors. The dose response was significantly greater for women who reported a family history of breast cancer in first- or second-degree relatives [23]. The histories of chest X-ray exposures before age 30 in 138 breast cancer 1, early onset (BRCA1) human gene carriers with breast cancer were compared with women with breast cancer, but without a BRCA1 mutation. Affected carriers reported more frequent chest X-ray use before age 20 than affected non-carriers and had on average, 1.8 chest X-rays before age 30 compared to an average of 1.0 for affected non-carriers [24]. Increased risks for breast cancer were found for women who had radiotherapy for a previous cancer and diagnostic chest X-rays for tuberculosis or pneumonia. Risks were highest for women with a large number of exposures at a young age or exposed in earlier calendar years [25].

III. PROSTATE CANCER

Prostate cancer (PCa) is an increasing threat throughout the world. Environmental factors, such as diet and lifestyle have long been recognized as major contributors to the development of PCa. A dominant role for environment and lifestyle in the development of life-threatening PCa is further supported by ecological epidemiology data [26]. PCa incidence and mortality are well known to vary greatly in different geographic regions of the world, with low risks of PCa mortality characteristic of Asia and high risks of PCa mortality characteristic of the US and Western Europe. Furthermore, the fact that incidence rates increase significantly in groups who immigrate to North America indicates that life-style factors may be the major cause of life-threatening PCa in the US [27,28].

(i). Obesity

Obesity affects >30% of the population in USA and becoming a growing problem worldwide. It has recognized links with various chronic disease states, including diabetes, hypertension and cardiovascular disease [29]. Various studies have shown that obesity is also a factor in the causes of PCa (Table 1). Several hormonal alterations are associated with obesity which includes lower levels of sex hormone-binding globulin that might increase the fraction of biologically available testosterone. Obesity is associated with diabetes and hyperinsulinaemia; exposure to elevated levels of insulin and circulating insulin growth factor (IGF)-1 might facilitate the progression of PCa. Increased levels of leptin and decreased levels of adiponectin may also be important. The mitogenic effects of leptin on cancer cells, combined with increased expression of growth factors, might be more likely to

contribute to the progression of PCa. [30]. In the Physician's Health Study, overweight and obese men had significantly higher risk of PCa mortality compared with men of a healthy weight at baseline [31]. Obesity was not significantly associated with PCa risk in equal-access, clinic-based population without adjustment for clinical characteristics. However, obesity was associated with a 98% increased PCa risk after adjusting for the lower prostate-specific antigen (PSA) levels and the larger prostate size [32]. Neither weight loss nor weight gain was clearly associated with the incidence of all cancers combined, while high weight gain was inversely associated with PCa [33]. Obesity was associated with poorer tumor prognostic characteristics and decreased biochemical relapse-free survival, particularly in African-American men [34]. BMI was inversely related to PCa risk. Men with a BMI >29 kg/m^2 had the lowest risk of PCa and weight was also inversely associated with PCa risk [35]. The risk of PCa in men with a higher BMI was lower than that in men with a lower BMI but only if they were younger or had a family history of PCa. BMI had a weak, non-statistically significant positive association with PCa for groups with more sporadic cancers [36]. There was insignificant positive correlation between BMI and PCa incidence and a strong association between mortality and BMI, with a greater relative risk for a BMI of >26.2 kg/m^2 than for a normal BMI of <22.1 kg/m^2 suggesting that obese men with PCa might have biologically more aggressive disease [37].

(ii). Diet

The association of PCa with the diet is summarized in Table 2. Survival analysis among the men diagnosed with PCa revealed that those consuming fish more than or equal to 5 times/ week had a 48% lower risk of PCa death than did men consuming fish less than once weekly. A similar association was found between seafood n-3 fatty acid intake and PCa mortality [38]. Advanced PCa was directly related to total fat consumption primarily to animal fat, but not vegetable fat. Red meat represented the food group with the strongest positive association with advanced cancer. Fat from dairy products or fish was unrelated to risk. [39]. A high intake of dairy protein was associated with an increased risk of PCa. It was estimated that a 35g/ day increase in consumption of dairy protein was associated with 32% increase in the risk of PCa. The risk was positively associated with calcium from dairy products, but not calcium from other foods [40].

Consumption of processed meat, but not total meat or red meat, was associated with a possible increased risk of PCa. Higher intake of dairy foods, but not calcium was also positively associated with PCa [41]. It was shown that an elevated risk for metastatic PCa was observed with intake of red meat; this association was slightly attenuated after controlling for saturated and alpha-linolenic fatty acids. Processed meats as a main dish each contributed to an elevated risk of metastatic PCa. A high intake in both red meat and dairy product was associated with a statistically significant two-fold elevation in risk of metastatic PCa, compared to low intake of both products [42]. No association was found between meat type or specific cooking method and PCa risk. However, intake of well or very well done total meat was associated with a 1.26-fold increased risk of incident PCa and a 1.97-fold increased risk of advanced disease [43]. Eating fish more than three times per week was associated with a reduced risk of PCa and the strongest association was for metastatic cancer. Each additional daily intake of 0.5 g of marine fatty acid from food was associated with a 24% decreased risk of metastatic cancer [44].

IV. LUNG CANCER

Lung cancer is the leading cause of cancer-related death and thus a major health problem. More than 90% of patients with lung cancer die of this disease. About 17.8% of cancer deaths are attributed to pulmonary carcinoma and 5-year survival rates are less than 10% [45]. Tobacco use has been reported to be the main cause of 90% of male and 79% of female

lung cancers and about 90% of lung cancer deaths are estimated to be due to smoking [46]. The risk of the development of lung cancer in lifelong smokers is 20-40 times higher than non-smokers [47]. The risk of individual cancer development is determined by the balance between the metabolic activation and detoxification of the carcinogens in smoke. Metabolites occurring during the activation of carcinogens bind covalently with DNA and DNA adducts are formed which are regarded as an indicator of cancer risk in smokers [48]. Free radicals in cigarette smoke cause oxidative damage and mutations in DNA which leads to activation of oncogenes and inhibition of tumor suppressor genes.

(i). Obesity

The association of obesity with an increased risk for human lung cancer has been relatively well reported (Table 1). In a hospital-based case-control study, odds ratios for lung cancer by levels of BMI, ≥ 28 as the referent, showed an increasing linear trend with decreasing BMI for current smokers and ex-smokers of both sexes and for female never smokers [49]. An apparent positive association of a high WHR with lung cancer in the total cohort was found to be primarily accounted for by a higher WHR in current and former smokers. The inverse association of BMI with lung cancer can be explained by smoking status and the positive association of WHR with lung cancer can be explained by pack-years of smoking [50]. Baseline BMI was inversely associated with lung cancer in current smokers. BMI was inversely associated with lung cancer risk in both current smokers and former smokers when BMI and waist circumference were mutually adjusted and waist circumference was positively associated with risk. [51]. An inverse association between BMI and lung cancer was observed after adjustment for age and smoking in men and no association was found between BMI and lung cancer in women. [52]. To examine the association that leanness in adulthood may be a risk factor for lung cancer, data from the Canadian National Breast Screening Study was used. There was some evidence for inverse associations in current smokers and in former smokers, whereas in never-smokers, BMI was positively associated with lung cancer after adjustment for pack-years of smoking and other covariates [53].

(ii). Diet

Dietary lifestyle plays an important factor in the development of lung cancer (Table 2). In a case-control study, protective effects were observed for black tea among all non-smoking women, and physical exercise and vitamin supplements among all smoking women. Among all men, inverse associations were found in smokers between lung cancer risk and frequent intake of fruits and a direct association for fat foods among all men. In women, the intake of wine and physical exercise were inversely associated with the risk of both adenocarcinoma and small cell cancer, the intakes of fruits and vitamin supplements were inversely associated with the risk of squamous cell cancer. The intake of fat foods was directly associated with the risk of squamous cell cancer, while the frequent intake of apples was inversely associated with the risk of both squamous- and small cell cancers in men [54]. Linearly decreasing relative risks (RRs) were found for lung cancer with increased frequency of consumption of fish and shellfish but not with intake of dried/salted fish [55]. Frequent consumption of carrots significantly lowered the risk of lung cancer (squamous cell carcinoma, small cell carcinoma and adenocarcinoma) in women. The results also suggested that frequent consumption of carrots and margarine can have a protective influence against lung cancer irrespective of the number of cigarettes smoked and the amount of vodka drunk [56]. Protective effects against lung cancer were observed for high consumption of tomatoes, lettuce, carrots, margarine and cheese. High consumption of all carotenoids, beta-carotene and retinol had only weak protective effects. The excess risk associated with meat, butter and egg consumption was restricted to squamous and small cell carcinomas, but was not detected for adenocarcinomas [57]. There was significant dose-dependent reduction in risk for lung cancer with the consumption of greens, fresh fruits and

cheese, whereas whole milk was associated with a significant dose-dependent increase in risk. Vegetables, raw fruits and dairy products were associated with a reduction in risk among females and increased consumption of raw fruits and vegetables was associated with a reduced risk for lung cancer in men. [58]. Red meat, beef and fried meat caused a significant increase in risk of lung cancer, especially in squamous cell lung cancer suggesting a possible role of heterocyclic amines in lung carcinogenesis in a case-control study [59].

(iii). Alcohol

The possible role of alcohol intake is of particular importance in lung cancer risk because it is a modifiable behavior (Table 3). In a recently reported meta-analysis, consumption of beer, spirits and drinking regularly were associated with lung cancer risk [60]. It has been suggested that high consumption of beer and liquors may be associated with increased lung cancer risk, whereas modest wine consumption may be inversely associated with the risk [61]. An association was observed between recent hard-liquor consumption and lung cancer risk. An elevated lung-cancer risk was also observed for past liquor consumption [62]. A positive association between alcohol consumption and lung cancer risk confined to current smokers was found in a population-based prospective cohort study [63]. Alcohol consumption was not significantly associated with the risk of lung cancer in subjects who were light to moderate drinkers [64]. The association of ethanol intake at recruitment and mean lifelong ethanol intake with lung cancer was examined in the European Prospective Investigation into Cancer and Nutrition (EPIC). High mean lifelong ethanol intake tended to be related to a higher risk of lung cancer [65].

(iv). Smoking

It is estimated that cigarette smoking cause 85-90% of lung cancers in the USA. Lung cancer incidence and mortality is three times higher in men than in women worldwide [66]. The incidence rates of lung cancer by stratum of smoking use in men and women of the National Institutes of Health (NIH)-AARP cohort were compared recently. The findings suggested that women are not more susceptible than men to the carcinogenic effects of cigarette smoking in the lung. In smokers, there was modest difference in the incidence rates in men and women with comparable smoking histories and smoking was strongly associated with lung cancer risk in both men and women [67]. The effect of smoking on the carcinogenesis and progression of peripheral small lung adenocarcinomas was histologically examined. In smokers, small adenocarcinoma occurred frequently in the upper region of the lung, showed invasive features more frequently, and had greater progression and dedifferentiation than that in nonsmokers [68]. Tobacco smoking strongly increased the risk of lung cancer with the relative risk for current smokers compared with never smokers measuring around 4.4 for men and 2.8 for women [69]. A greater decrease in lung cancer mortality was found among those who quit smoking at younger ages. The risk was low in individuals who stop smoking earlier in life. Even at ages 60-69, the absolute rate substantially decreased after smoking cessation reflecting the high mortality rate among continuing smokers in the elderly [70]. Smoking cessation caused reduced risk of lung cancer mortality, with much greater benefits accruing to those quitting at younger ages [71]. Current and former cigarette smoking caused 52.2% and 14.8% of lung cancer deaths in males and 11.8% and 2.8% in females. The relative risk was strongly correlated with the intensity and duration of cigarette smoking in current male smokers. The largest population attributable risk were observed in those with 20-29 cigarettes per day, 40-59 pack-years and 20-22 years old at starting smoking. [72]. In a large population-based case-control study that was incorporated into a nationwide retrospective survey of mortality in China, tobacco smoking was associated with a large number of deaths from lung cancer. In male smokers aged 35-69 years, there were 54% of urban deaths, 51% of rural deaths and the average loss

of life expectancy per smoking-associated death at these ages was 18.3 years. In urban and rural smokers, there was 29% and 11% excess lung cancer mortality, respectively for women ages 35-69 years with an average loss of life expectancy per smoking-associated death of 21.3 years [73].

V. COLON CANCER

Colorectal cancer is one of the leading causes of premature death in people worldwide. Due to the fact that malignant conversion of normal colonic cells requires several steps and often proceeds over considerable time periods, primary prevention of this process should include several approaches, with optimization of nutrition and diet being among most important.

(i). Obesity

Increasing epidemiological evidence has demonstrated that obesity is associated with an increased risk of cancer, especially colon cancer [74,Table 1]. In a cross-sectional study, the prevalence of adenoma was higher among abdominal obese group with 45.6% had 1 or more adenoma and 9.0% of these had advanced adenoma, whereas among subjects with a normal waist circumference, only 25.7% had 1 or more adenomas. Abdominal obesity was associated with an increased risk of colorectal adenoma [75]. Short-term weight change in the prior 2 to 4 years and weight gain per 10 years since age 21 were significantly associated with risk of colon cancer. It was estimated that 29.5% of all colon cancer cases were attributable to BMI>22.5 [76]. A 5-unit increase in BMI was related to an increased risk of colon cancer in both men and women, but the association was stronger in men. Increasing waist circumference led to increased risk of colon cancer risk in both men and women and with increasing waist-hip in both and women [77]. A significant increase in the prevalence of colonic adenoma and of advanced polyps was found to occur with age in patients who underwent colonoscopy for cancer screening. The prevalence of adenoma and advanced polyps was higher in men in most age groups. A positive association between BMI and the prevalence of colonic adenoma and advanced polyps was shown in relatively young individuals of both gender and premenopausal women according to hormonal status [78]. Higher BMI was associated with an elevated risk of colorectal cancer, and the positive relationship was not altered by estrogen exposure among postmenopausal women [79]. Weight at baseline showed a significant positive association in women, while no such association was seen in men. There was also a significant trend of increasing risk with the increase in baseline-BMI among women. These data suggested that obesity and excessive weight gain are associated with the risk of colon cancer death in Japanese women but not in Japanese men [80].

(ii). Diet

The association between intakes of fish and n-3 fatty acids from fish and colorectal cancer risk in men enrolled in the Physicians' Health Study were examined. The results from this long-term prospective study suggested that intakes of fish and long-chain n-3 fatty acids from fish may decrease the risk for colorectal cancer [81]. Several studies show a strong association between per capita consumption of meat and colorectal cancer mortality [82,Table 2]. Various mechanisms have been proposed through which consumption of meat may increase cancer risk. Mutagenic heterocyclic amines and polycyclic aromatic hydrocarbons can be formed during the cooking of meat at high temperatures and nitrites and their related compounds found in smoked, salted and some processed meat products may be converted to carcinogenic *N*-nitroso compounds in the colon [83]. In men, high consumption of processed meat increased the risk of colon cancer in comparison with low consumption. Daily coffee drinkers had a reduced risk in comparison with individuals who never or rarely drank coffee in women [84]. Women who consumed >/=4 servings of high-

fat dairy foods/day including whole milk, full-fat cultured milk, cheese, cream, sour cream and butter had a multivariate rate ratio of colorectal cancer of 0.59 when compared with the women who consumed <1 serving/day. There was also a 13% reduction in the risk of colorectal cancer (CRC) cancer with each increment of 2 servings of high-fat dairy foods/day [85]. No association was found between the risk of CRC and intake of total meat and total fish. Eel, shrimp and shellfish consumption were positively associated with CRC risk. High egg intake and high intake of total cholesterol were also related to risk of CRC and milk intake was inversely associated with the risk of colon cancer [86]. High intake of red and processed meat was associated with higher risk of colon cancer after adjusting for age and energy intake but not after further adjustment for body mass index, cigarette smoking and other covariates. There was higher risk of distal colon cancer associated with processed meat when long-term consumption was considered. There was inverse association of both proximal and distal colon cancer with long-term consumption of poultry and fish. [87]. Animal fat was positively associated with the risk of colon cancer. There was increased risk of colon cancer with processed meats and liver, whereas fish and chicken without skin were related to decreased risk. There was also strong association of an increased incidence of colon cancer with the ratio of the intake of red meat to the intake of chicken and fish [88].

(iii). Alcohol

Alcohol consumption is a major risk factor in the development of colon cancer (Table 3). Alcohol consumption of >/=30.0 g/day (approximately 3 alcoholic drinks) was positively associated with the risk of CRC as compared to abstaining. Subjects who consumed equal amounts of alcohol 5 years before baseline also showed elevated risk estimates for consumers of >/=30.0 g of total alcohol per day. [89]. The association between alcohol consumption and colorectal cancer was examined by analyzing original data from five cohort studies that measured alcohol intake. The association between alcohol intake and cancer was evident for both the colon and the rectum. A significant positive association was also observed in women. One fourth of CRC cases were attributable to an alcohol intake of >/=23 g/day in men [90]. Both lifetime and baseline alcohol consumption increase colon and rectum cancer risk, with more apparent risk increases for alcohol intakes greater than 30 g/day [91]. Subjects who drank seven or more alcoholic drinks per week had a statistically significant, 72% increase in risk of CRC hazard ratio as compared with nondrinkers [92]. Alcohol consumption was found to be associated with a statistically significant increased risk of cancer of the distal colon and rectum, but not cancer of the proximal colon [93]. There was significantly increased risk of colon and rectal cancer by high alcohol intake, equivalent to a 15% increase of risk of colon or rectal cancer for an increase of 100 g of alcohol intake per week when comparing the highest with the lowest category of alcohol intake [94]. An increased risk of CRC was found in current drinkers and in those who drank >/= 4 days or >4 units weekly. The CRC risk was also found to decrease with increasing duration of drinking abstention. Current drinkers and those who drank regularly and heavily had increased CRC risk. Thus, it was shown that drinking cessation could be effective in reversing such increased risk in a duration-dependent manner [95].

(iv). Smoking

The current and former smokers had a significantly increased risk of CRC incidence and mortality, respectively, relative to nonsmokers in a comprehensive meta-analysis. The current smokers had a significantly increased risk of CRC incidence when CRC data were combined with colon/rectal cancer data. [96]. Smoking was associated with an absolute risk of CRC increase of 10.8 cases per 100,000 person-years. There was also a statistically significant dose-relationship with an increasing number of pack-years and cigarettes per day. However, the association was statistically significant only after 30 years of smoking. Smoking was associated with an absolute risk increase of 6.0 deaths per 100,000 person-

years. [97]. Significant positive associations were observed between most measures of cigarette smoking and risk of invasive CRC cancer. [98]. Age of CRC diagnosis was studied in two groups of patients, smokers with >10 pack-years and nonsmokers. Symptoms related to colorectal cancer were observed in smokers at an earlier mean age than nonsmokers. Tobacco smoking was the only independent risk factor of early onset of CRC according to multivariate analysis [99]. In a study population, cases and controls were drawn from a homogeneous cohort of Norwegian origin consisting of 133 cases and 334 controls and all tumors were sequenced in the mutation cluster region of the APC gene. A statistically significant association was found for all smoking parameters and duration of smoking >30 years. When cases were divided based on APC truncation mutation status, an association was detected in adenomas without APC mutation in relation to ever smoking. The smoking parameter starting smoking >/= 40 years ago was only associated with CRC cases with APC mutations [100]. The association between cigarette smoking and recurrence of colorectal polyps was investigated prospectively with data from the Polyp Prevention Trial. Current smokers had increased odds of hyperplastic polyps at follow-up compared to never smokers. Current smoking was associated with subsequent distal and rectal hyperplastic polyps, but not subsequent proximal hyperplastic polyps [101].

CONCLUSIONS AND PERSPECTIVES

Almost 1.5 million people in the USA are diagnosed with cancer every year and due to the substantial effect of the modifiable lifestyle factors, it has been estimated that 50% of cancers are preventable [98]. The burden of modern lifestyle diseases is enormous as the true unifying factor for most cancers seems to be lifestyle. The intervention with the modification of lifestyle factors seems to be a physiological and safe approach for the prevention and management of modern lifestyle diseases including cancer. Defining the precise role of diet and other lifestyle factors in cancer may require the elucidation of genetic susceptibility and genetic-environmental interactions. The balance between genetic predisposition and environmental factors, including nutritional components and lifestyle behaviors, determines individual susceptibility to develop cancer. The modifications in the diet along with secondary prevention measures may have a major impact on reducing the mortality from cancer. Continued focus on primary prevention of cancer, in combination with efforts aimed at screening and surveillance, will be vital in attaining the greatest possible progress against cancer.

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Table 1

Association of obesity with cancer risk in human studies.

Type of cancer	Epidemiological studies / Clinical trials	References
Breast Cancer	Three fold increased risk in women with a BMI in the obese range	[6]
	Obese patients more likely to have hormone-negative tumors, stage III tumors and worse overall survival	[7]
	BMI>/=30 or WHR >/= 0.85 associated with increased risk of death	[8]
	Increased mortality in obese women compared with ideal weight women	[11]
Prostate Cancer	Higher risk of PCa mortality in overweight and obese men compared with men of a healthy weight at baseline	[31]
	High weight gain was inversely associated with PCa	[33]
	Obesity was associated with poorer tumor prognostic characteristics and decreased biochemical relapse-free survival, particularly in African-American men	[34]
	BMI was inversely related to PCa risk	[35], [36]
	Positive correlation between BMI and PCa incidence	[37]
Lung Cancer	Positive association of a high WHR in current and former smokers	[50]
	Inverse association of BMI with lung cancer risk in both current smokers and former smokers	[51]
	Inverse association between BMI and lung cancer in men and no association was found in women	[52]
Colon Cancer	Abdominal obesity was associated with an increased risk of colorectal adenoma	[75]
	29.5% of all colon cancer cases were attributable to BMI>22.5	[76]
	A 5-unit increase in BMI was related to an increased risk of colon cancer in both men and women	[77]
	Higher BMI was associated with an increased risk of colorectal cancer	[79]

Table 2

Association of diet with cancer risk in human studies.

Type of cancer	Epidemiological studies / Clinical trials	References
Breast Cancer	High saturated fat intake and greater risk association was found for the highest quintile of saturated fat intake compared with the lowest quintile	[12]
	High fat intake of hydrogenated fats or vegetable/corn oil compared to olive/canola oil was associated with increased risk	[13]
	Increased risk associated with total fat, monounsaturated fat, polyunsaturated fat and saturated fat	[14]
	Women with a BMI>/= 25 were associated with a 58% increment in risk	[15]
	Direct association among palmitic, γ-linolenic, palmitoleic and vaccenic acids	[16]
Prostate Cancer	Consuming fish >/= 5 times/week had a 48% lower risk of PCa death than did men consuming fish <1 weekly	[38]
	Elevated risk with animal fat, especially fat from red meat	[39]
	An increase of 32% in the risk with 35g/day increase in dairy protein	[40]
	Consumption of processed meat and higher intake of dairy foods, but not total meat or red meat was associated with a possible increased risk	[41]
	Processed meats and high intake in both red meat and dairy product was associated with 2-fold elevation in risk, compared to low intake	[42]
	Intake of well or very well done total meat was associated with a 1.26-fold increased risk and a 1.97-fold increased risk of advanced disease	[43]
	Eating fish >3 times/ week was associated with a reduced risk, each additional daily intake of 0.5 g of marine fatty acid from food was associated with a 24% decreased risk of metastatic cancer	[44]
Lung Cancer	Direct association for fat foods and inverse associations between lung cancer risk and frequent intake of fruits were found in smokers	[54]
	Decreased risk with increased frequency of consumption of fish and shellfish but not with intake of dried/salted fish	[55]
	Protective influence by frequent consumption of carrots and margarine	[56]
	Protective effects were observed for high consumption of tomatoes, lettuce, carrots, margarine and cheese	[57]
	Reduction in risk with the consumption of greens, fresh fruits and cheese, whereas whole milk was associated with a significant increase in risk	[58]
	Increase in risk with red meat, beef and fried meat	[59]
Colon Cancer	Intakes of fish and long-chain n-3 fatty acids from fish may decrease the risk	[81]
	Strong association between per capita consumption of meat and CRC mortality	[82]
	In men, high consumption of processed meat increased the risk of colon cancer and daily coffee drinkers had a reduced risk	[84]
	Each increment of 2 servings of high-fat dairy foods/day caused 13% reduction in the risk of CRC	[85]
	Eel, shrimp and shellfish consumption were positively associated and milk intake was inversely associated with CRC risk. High egg intake and high intake of total cholesterol were also related to risk of CRC	[86]
	Red and processed meat was associated with higher risk whereas, inverse association with long-term consumption of poultry and fish	[87]
	Strong association of an increased incidence with ratio of the intake of red meat to the intake of chicken and fish	[88]

Table 3

Association of alcohol with cancer risk in human studies.

Type of cancer	Epidemiological studies / Clinical trials	References
Breast Cancer	High alcohol consumption cause higher risk	[17], [20]
	Threshold below 1-2 drinks daily, a hormone-related mechanism mediates a relation of alcohol drinking to an increased risk	[18]
	Weekly alcohol intake increased the risk with 2% and weekend consumption increased the risk with 4% for each additional drink consumed. Binge drinking of 4-5 drinks the latest weekday increased risk with 55%.	[19]
	In women with low BMI and those diagnosed with ER-positive tumors or with invasive rather than in situ disease, moderate consumption increased risk	[21]
Lung Cancer	Association of risk with regular consumption of beer, spirits	[60]
	High consumption of beer and liquors may be associated with increased risk, whereas modest wine consumption may be inversely associated with risk	[61]
	Association between recent hard-liquor and past liquor consumption with risk	[62]
	Positive association between alcohol consumption and risk confined to current smokers	[63]
	Alcohol consumption was not significantly associated with the risk	[64]
	High mean lifelong ethanol intake related to a higher risk	[65]
Colon Cancer	Alcohol consumption of >/=30.0 g/day was positively associated with the risk	[89]
	Association between alcohol intake and cancer was evident for both the colon and the rectum. One fourth of CRC cases were attributable to an alcohol intake of >/=23 g/day in men	[90]
	Both lifetime and baseline alcohol consumption increase colon and rectum cancer risk, with more apparent risk increases for alcohol intakes >30 g/day	[91]
	Drinking >/=7 alcoholic drinks/week increase risk of CRC hazard ratio by 72%	[92]
	Alcohol consumption associated with an increased risk of cancer of the distal colon and rectum, but not cancer of the proximal colon	[93]
	Increase in risk of colon or rectal cancer by 15% for an increase of 100 g of alcohol intake/week	[94]
	An increased risk of CRC in current drinkers and in those who drank >/= 4 days or >4 units weekly and decrease with increasing duration of drinking abstention	[95]