

Chapter 2

Lifestyle, Genes, and Cancer

Yvonne M. Coyle

Abstract

It is estimated that almost 1.5 million people in the USA are diagnosed with cancer every year. However, due to the substantial effect of modifiable lifestyle factors on the most prevalent cancers, it has been estimated that 50% of cancer is preventable.

Physical activity, weight loss, and a reduction in alcohol use can strongly be recommended for the reduction of breast cancer risk. Similarly, weight loss, physical activity, and cessation of tobacco use are important behavior changes to reduce colorectal cancer risk, along with the potential benefit for the reduction of red meat consumption and the increase in folic acid intake. Smoking cessation is still the most important prevention intervention for reducing lung cancer risk, but recent evidence indicates that increasing physical activity may also be an important prevention intervention for this disease. The potential benefit of lifestyle change to reduce prostate cancer risk is growing, with recent evidence indicating the importance of a diet rich in tomato-based foods and weight loss. Also, in the cancers for which there are established lifestyle risk factors, such as physical inactivity for breast cancer and obesity for colorectal cancer, there is emerging information on the role that genetics plays in interacting with these factors, as well as the interaction of combinations of lifestyle factors. Integration of genetic information into lifestyle factors can help to clarify the causal relationships between lifestyle and genetic factors and assist in better identifying cancer risk, ultimately leading to better-informed choices about effective methods to enhance health and prevent cancer.

Key words: Cancer prevention, diet, lifestyle, obesity and overweight, physical activity, smoking, tobacco.

1. Introduction

It is estimated that almost 1.5 million people in the USA are diagnosed with cancer every year (1). There is also evidence that lifestyle factors increase cancer risk and, if modified, could significantly reduce the cancer burden (2). This chapter reviews

the current epidemiological evidence on the contributions of the major modifiable risk factors to cancer incidence and mortality for the most common cancers diagnosed in the USA and developed world—breast, colorectal, lung, and prostate cancer (3). Due to the substantial effect of modifiable lifestyle factors on the most prevalent cancers, it has been estimated that 50% of cancer is preventable (4). Current recommendations for the major risk factors that can be modified to decrease risk for these cancers include reducing tobacco use, increasing physical activity, controlling weight, improving diet, and limiting alcohol consumption (5). When defining the cancer prevention strategies used to modify these risk factors, it is also important to integrate genetic information that may play a role in determining the effectiveness for modifying these factors.

2. Breast Cancer

Breast cancer is the most common cancer in women, with nearly 180,000 women diagnosed with breast cancer in the USA annually (1). The fact that lifestyle changes can decrease the risk for developing breast cancer is supported by several lines of evidence. First, studies indicate that as populations migrate from the low- to the high-risk geographical areas for breast cancer, the incidence of breast cancer approaches that of the host country in one to two generations (6–8). Second, only a small part of breast cancer risk is linked to genetic inheritance and environmental exposures from chemicals or physical agents. Third, modification in lifestyle due to behavior change has been shown to be associated with a lower breast cancer risk in population studies. Last, experimental animal and human models provide confirmation that several lifestyle behaviors have a positive effect on breast biology. The major modifiable risk factors for breast cancer are physical inactivity, obesity and the overweight condition, alcohol use, and possibly diet (9).

2.1. Physical Activity

A recent systemic review that included all cohort and case-control studies that assessed total and leisure time activities in relation to the occurrence or mortality of breast cancer indicated that there was strong evidence for an inverse association between physical activity and breast cancer risk (10). The risk reduction for the cohort studies with a higher quality score ranged from 21% to 39%. Evidence for an inverse dose-response relationship was seen in all but one of the cohort studies. The risk reduction for the case-control studies ranged from 23% to 65%, and evidence for a dose-response was noted in most of the case-control studies.

A lower risk breast cancer was also noted for both premenopausal and postmenopausal breast cancer in nearly all of the studies in which this relationship was assessed. Several of these studies quantified the level of physical activity required to reduce breast cancer risk, finding that this risk reduction was on the average about 30% lower for women who exercised for 3–4 hours per week at moderate and vigorous levels. In addition, most studies have been conducted in non-Hispanic white women, although data from some studies suggest that physical activity is associated with a lower risk for breast cancer in women of diverse races and ethnicities (11–15). Physical activity at adolescence has also been observed to be associated with a delayed age at breast cancer onset among women with mutations in the tumor suppressor genes (TSGs), *BRCA1* and *BRCA2*, which substantially increase the risk for breast cancer (16). Likewise, the benefit of physical activity has been apparent among breast cancer survivors in recent studies (17, 18). In one study that involved 2,987 women diagnosed with stage I, II, and III breast cancer, the age-adjusted risk of death from breast cancer was inversely associated with physical activity after the diagnosis of breast cancer (17). In this study, the greatest benefit was noted in women who performed the equivalent of walking 3–5 hours per week at an average pace. In another study, among 1,264 women ages 20 to 54 years, it was found that recreational physical activity undertaken in the year before a diagnosis of breast cancer was associated with a lower all-cause mortality at the 8–10 year follow-up (18). Thus, it appears that physical activity may play an important role in preventing breast cancer in women with and without a personal history of breast cancer, as well as delaying the onset of breast cancer in women with genetic susceptibility.

It is thought that the relationship between physical activity and breast cancer risk may have a hormonal mechanism. Increased physical activity measured through self-report has been found to be associated with lower estrogen levels in premenopausal and postmenopausal women (19, 20). Exercise interventions have also been shown to decrease estrogen levels and increase sex hormone-binding globulin (SHBG) levels in postmenopausal women (21, 22). A recent pooled analysis of nine cohort studies showed that the risk for breast cancer in postmenopausal women increased significantly with increasing concentrations of total estradiol, free estradiol, and estrone (23). In addition, lower concentrations of SHBG, which binds to estradiol, is associated with a higher risk for breast cancer (23). Other findings from epidemiological studies further support the etiologic role of estrogen in breast cancer, showing that breast cancer risk is associated with early menarche, late menopause, low parity, and the use of exogenous estrogens, all of which are linked to prolonged or extensive exposure of breast tissue to estrogen

stimulation (24). High endogenous estrogen levels have also been shown to be associated with shortening of the disease-free interval in postmenopausal women with breast cancer recurrence (25). Finally, a number of clinical trials have shown that estrogen ablation increases survival after a diagnosis of breast cancer (26). In addition, estrogens can increase the production of insulin-like growth factor (IGF)-I (27), and higher estrogen and IGF-I levels have both been shown to be associated with increased mammographic density (28). Mammographic density is a strong risk factor for breast cancer, and reflects proliferation of the breast epithelium and stroma (29). Several epidemiological studies have shown that IGF-I is positively associated with breast cancer risk, especially in premenopausal women (30–33). Thus, several randomized studies with exercise interventions have been performed to identify the potential benefit of aerobic exercise or strength training for reducing IGF-I levels. These studies have shown that aerobic training produces a decrease in mean serum IGF-I levels in prepubertal girls (34), adolescent female subjects (35), and postmenopausal breast cancer survivors (36). However, most of the weight training intervention studies that involved premenopausal postmenopausal women or premenopausal and postmenopausal breast cancer survivors reported no change in IGF-I levels (37–39).

There is also growing evidence that estrogens play a dual role in the etiology of breast cancer by not only stimulating cell proliferation (40), but by silencing genes implicated in breast carcinogenesis (41–43). For breast cancer, as well as many other cancers, promoter region hypermethylation of TSGs is an early and frequent event in carcinogenesis and occurs in conjunction with transcriptional silencing of these genes. The mechanism driving promoter hypermethylation is unknown, however, it has been noted in tissues where there is chronic exposure to carcinogens that a continuum of increasing gene promoter hypermethylation occurs from hyperplasia through invasive carcinoma (44). The process of promoter hypermethylation has been referred to as “epigenetic” and is potentially reversible (45). DNA methylation of promoter CpG islands of genes prevents them from being transcribed for apoptosis, senescence, and other important physiological processes in cells, which makes cells that have accumulated DNA methylation prone to becoming tumor cells (45). Although the relationship between estrogen, which has been shown to have carcinogenic effects in human breast epithelial cells (46), and the methylation of genes is unknown, there is some evidence that estrogen alters the methylation patterns of genes. Studies in mice have shown that diethylstilbestrol (DES) (47) and estradiol (48) elicit genetic methylation changes that result in heavier uteri (47) and uterine tumors (48). Recently, it was demonstrated that estradiol and DES induced promoter

hypermethylation of the putative TSGs, *E-cadherin* and *p16*, in human breast epithelial cells (42).

There is direct evidence that promoter hypermethylation of several putative TSGs, including *APC*, *RASSF1A*, and *RAR β 2*, are associated with breast carcinogenesis (45, 49–56). In a recent study that included women with and without a personal history of breast cancer, it was shown that promoter hypermethylation of *APC*, *RASSF1A*, and *RAR β 2* in nonmalignant breast tissue was associated with epidemiological markers of breast cancer risk (56). More specifically, *APC* and *RASSF1A* were positively associated with breast cancer risk, as defined by the Gail mathematical risk model (57); whereas promoter hypermethylation of *RAR β 2* was positively associated with a personal history of breast cancer (57). Several studies (51, 52, 58–60) have shown that treatment of breast cancer cells with promoter hypermethylation of the putative TSGs, *RASSF1A* and *RAR β 2*, with the DNA methyltransferase inhibitor 5-Aza-2'-deoxycytidine has led to their demethylation and re-expression. Thus, promoter hypermethylation of TSGs can be reversed by small molecules, making them promising targets for cancer prevention interventions. Alternatively, it is thought that lifestyle changes, such as physical activity, may reverse promoter methylation of TSGs. A recent cross-sectional study was conducted to determine the association of lifetime physical activity with promoter hypermethylation of *APC* and *RASSF1A* in nonmalignant breast tissue, among premenopausal and postmenopausal women without breast cancer (61). This study provided evidence to support the hypothesis that physical activity is inversely associated with promoter hypermethylation of TSGs, such as *APC*, in nonmalignant breast tissue (61).

In summary, observational studies have shown that there is a strong inverse association between moderate or vigorous physical activity and breast cancer risk, in which there may be a hormonal mechanism, particularly involving estrogen and its related effect on IGF-I.

2.2. Obesity and Overweight

The association of the overweight condition and obesity with breast cancer risk has been well studied. Extensive data from cohort and case-control studies provide convincing evidence that there is a 30–50% greater risk of postmenopausal breast cancer from the overweight condition and obesity, and a larger twofold increase in risk for adult weight gain (62, 63). Estimates from a meta-analysis of cohort studies found gradual increases in risk of postmenopausal breast cancer up to a body mass index (BMI) of 28, after which the risk did not increase further, with the relative risk (RR) of 1.26 for a BMI of 28 compared with a BMI of less than 21 (64). However, risk estimates vary by age at diagnosis, history of hormone-replacement therapy (HRT), and estrogen receptor (ER) status of the tumor. Another meta-analysis,

involving prospective cohort and population-based case-control studies, found that this increased risk for postmenopausal breast cancer corresponded to a 12% increase for overweight women and a 25% increase for obese women (65). In fact, in a prospective cohort study among premenopausal and postmenopausal women, there was an even stronger association for adult weight gain, with a doubling of risk among women who have never used HRT and who gained over 20 kg from age 18 years (66). A meta-analysis of cohort studies found an inverse association between BMI and premenopausal breast cancer, with a RR reduction of 46% for women with a BMI greater than 31 compared with a BMI of less than 21 (64).

There are several plausible mechanisms linking adiposity to breast cancer risk. These mechanisms have evolved from a focus on estrogen excess, to the combined effect of estrogen and progesterone, and most recently, to attempts to understand the factors defining the bioavailability and effects of estrogens and androgens and their metabolites on specific end organs. Increases in obesity have been associated with increases in androgens, triglycerides, and insulin; and decreases in SHBG. These hormonal changes increase the bioavailability of estradiol and its metabolites and may also directly promote tumor growth (67–73). The bioavailability of estradiol is dependent on the degree and strength of binding to several protein carriers. SHBG is the predominant protein carrier of estradiol and the percentage of free estradiol is inversely related to the level of SHBG (23). Increases in free fatty acids, such as triglycerides, has been reported to increase the level of free estradiol by displacing estradiol from SHBG (23). Therefore, both decreases in SHBG and increases in triglycerides may result in increases in free estradiol. Key and Pike (74, 75) first hypothesized that the effect of adiposity on the estrogen bioavailability was modulated by menopausal changes in estrogen and progesterone production, and as a result explained the contradictory findings for premenopausal and postmenopausal breast cancer. Before menopause, ovarian production of estrogen overwhelms changes in estrogen metabolism related to the overall level of adiposity. As a result, estradiol in ovulatory cycles does not differ significantly in obese compared with lean women. However, estradiol levels are reduced in anovulatory cycles that are more frequent in obese than lean premenopausal women. In addition, obese premenopausal women have been found to have markedly reduced progesterone levels, both due to anovulation and decreased production during the luteal phase of the menstrual cycle. After menopause, the lower risk associated with premenopausal obesity diminishes over time. In addition, in postmenopausal women, the overall level of adiposity results in increased estrogenic activity due to an increase in estrogen production from the aromatization of higher levels of androgens

in adipose tissue (76), decreased estrogen binding (77) due to decreases in SHBG (70, 72, 78), and increases in triglycerides (72). Furthermore, insulin and insulin-like growth factors have been found to promote cancer cell growth, and their production can be increased by estrogen (79). However, although five studies have shown that higher IGF-I levels are associated with a higher risk for breast cancer (80–84), only one of these studies found this association to be statistically significant (81). In addition, published studies, thus far, have not found an association between IGF-I and postmenopausal breast cancer (81, 83, 85). Similarly, one of two published studies found C-peptide, a marker of hyperinsulinemia, to be associated with breast cancer risk (85, 86). Data on the association between IGF-I and BMI or fat mass in men and women are also mixed (87), with some studies showing no association and others an inverse association. Therefore, it has been hypothesized that IGF-I is positively associated with muscle mass, which may explain the increased premenopausal breast cancer risk among tall and lean women. Another hormonal hypothesis is that leptin, a hormone that reflects total fat mass, may be positively related to breast cancer risk. Leptin has been characterized as a growth factor for breast cancer (88–91). Thus far, one study has been published that has examined this relationship among premenopausal women finding nonsignificant lower levels of leptin in breast cancer cases compared with controls (92), which is consistent with an inverse association between BMI and premenopausal breast cancer. No published studies have examined the relationship of leptin to breast cancer risk in postmenopausal women. Thus, current studies do not provide convincing data to support a link between insulin, IGF-I, or leptin with breast cancer risk. However, one study found that there was a multiplicative interaction between adult exercise and sports activity and BMI, with inactive women in the upper BMI quartile being at increased risk compared with their lean and active counterparts (93).

2.3. Alcohol

The literature over the last 2½ decades provides convincing evidence that alcohol consumption has a modest impact on breast cancer risk (94). That is, the RR associated with alcohol consumption is not great, since it has been found to be associated with an approximately 10% increase in risk for an increase in average consumption of one drink per day (95). However, because of the high prevalence of alcohol consumption, the attributable risk is likely to exceed 10% in those who consume alcohol regularly (96). The dose-response relationship between alcohol and breast cancer risk is well demonstrated in the results of a meta-analysis by Smith-Warner and colleagues (95), where breast cancer risk rose by 7% for every 10-g increase in daily alcohol consumption. However, there is also some evidence that this risk does not

substantially increase until a threshold of 15 g/day of alcohol is reached. Furthermore, there is little evidence that this risk is modified by menopausal status (97, 98).

One plausible explanation for an etiologic association between alcohol and breast cancer carcinogenesis is that it increases circulating estrogen levels. Circulating estrogens originate from ovarian synthesis or from peripheral conversion (aromatization) pathways involving androgens, such as testosterone. For premenopausal women, alcohol intake has been associated with higher concentrations of estrogens and androgens, as well as decreases in follicle-stimulating hormone levels (99–106). It has also been found that in postmenopausal women not using HRT, moderate alcohol intake can lead to increased estrogen and androgen levels, although the findings have been variable (107–109). Studies have shown that alcohol is associated with mammographically dense breast tissue (110–115), which is also positively associated with levels of estrogen and IGF-I (27, 116). As previously mentioned, estrogen can increase the production of IGF-I (27). The dense patterns seen on mammography are associated with atypical hyperplasia and/or carcinoma in situ (117) and with cytological atypia in nipple aspirates (118), which may be a result of mitogenesis or mutagenesis in the breast (119).

In addition, whether dietary and genetic factors modify the effect of alcohol use in breast cancer risk has been of interest. Zhang and colleagues reported that women consuming more than 15 g of alcohol per day and whose intake of folate was less than 300 µg/day had a higher risk for breast cancer, compared with women who had the same level of alcohol consumption, along with folate levels greater than 300 µg/day (120). Other reports (121–123) confirm this relationship. It is important to note, however, that low-to-moderate alcohol consumption, in contrast to heavy drinking, may not result in folate depletion (124–127). Thus, it is thought that in combination with low folate intake, ethanol and/or its primary metabolite acetaldehyde may alter folate or methionine metabolism so that an imbalance in DNA methylation or in DNA repair processes results; leading to DNA instability or aberrant gene expression (128–132). Alcohol consumption also has been associated with decreased blood levels of β-carotene, lutein/zeaxanthin, and vitamin C, which are thought to be cancer protective (133, 134). Thus, these studies collectively suggest that alcohol consumption, particularly at higher levels, may be associated with increased breast cancer risk, in part because of the negative impact of alcohol intake on the dietary factors that are thought to be cancer protective. There is also some evidence that the relationship between alcohol and breast cancer risk could differ according to the genotype of several metabolizing enzymes. Park and colleagues have found that premenopausal women that consume alcohol and lack

the glutathione-*S*-transferase genes (*GSTM1* and *GSTT1*) were at 5.3-fold greater risk for developing breast cancer compared with women with these genes, suggesting that the lack of these genes potentiates the adverse effects of alcohol on the breast due to the decreased capacity to detoxify alcohol (135).

2.4. Diet

Fat is the dietary component that has most often been found to relate to the risk of cancer in general (136). In a pooled analysis of case-control studies, a highly significant and positive association was seen between dietary fat and breast cancer risk (137). However, prospective studies have consistently shown no association (138). In a pooled analysis of large prospective studies, breast cancer risk for a higher total fat intake was minimal (RR = 1.03) (139). Similarly, the largest randomized controlled dietary cancer prevention intervention study to date, which involved 48,800 postmenopausal women, found only a modest statistically nonsignificant 9% decrease in invasive breast cancer in those who consumed a low-fat diet (140).

Early epidemiological studies suggested that vegetables and fruits may lower breast cancer risk (141). However, a pooled analysis of eight prospective cohort studies involving 351,825 women found no association between the intake of vegetables and fruits and breast cancer risk (142). A recent prospective study in which 285,526 women participated, ages 25–70 years, found no significant association between vegetable and fruit intake and breast cancer risk, adjusting for potentially important confounders, such as menopausal status (143). Although these studies collectively indicate that vegetables and fruits may not modify breast cancer risk, it is possible that specific genotypes may interact with vegetable and fruit intake to lower breast cancer risk. A recent large case-control study was performed to assess the effect of different variants of myeloperoxidase (MPO), an antimicrobial enzyme in the breast that generates reactive oxygen species, on breast cancer risk. This study showed that specific variants of MPO were associated with a lower breast cancer risk among premenopausal and postmenopausal women who consumed higher amounts of vegetables and fruits that was not noted among the lower consumption group (144).

Soy products contain phytoestrogens, which can act as weak estrogens and as estrogen antagonists, depending on the hormonal milieu of the host. Epidemiological data suggest that the consumption of soy products may reduce breast cancer risk (145, 146). However, recent evidence suggests that a component of soy, genistein, may promote the growth of some estrogen-sensitive tumors and reduce the efficacy of tamoxifen, emphasizing the need to perform additional studies to determine whether soy products are safe for women with breast cancer or at high risk for breast cancer (147, 148).

Several epidemiological studies have investigated the association between dietary and supplement intakes of various vitamins and minerals and the risk of breast cancer. Those micronutrients that have been found to be potentially associated with a lower risk for breast cancer include the carotenoids, folate (particularly in association with alcohol intake), calcium, vitamin D, and vitamin C (*141, 149–151*).

3. Colorectal Cancer

Colorectal cancer is the second most commonly occurring cancer in the USA and was estimated to affect over 150,000 men and women in 2005 (*1*). Based on epidemiological studies, there is convincing data that obesity is an important risk factor for colorectal cancer (*152*), and that a high level of physical activity is a strong protective factor for colorectal cancer, which may reduce its risk by 50% (*153, 154*). Convincing data from epidemiological studies also support tobacco use as significant risk factor for colorectal cancer. Another potential risk factor for colorectal cancer is the consumption of red meat. However, the numerous studies with both cohort and case-control designs have not consistently supported a positive association between the consumption of red meat and colorectal cancer. On the other hand, a dietary factor that may be related to colorectal cancer risk is the micronutrient, folate, which has an inverse association.

3.1. Physical Activity

Colorectal cancer is one of the most commonly studied cancers with respect to physical activity. Numerous case-control and cohort studies have found an inverse association between physical activity and colon cancer risk (*152, 155–159*). This relationship has been observed in men and women of all age groups, in various racial and ethnic groups, and in diverse geographic areas around the world. In some of these studies, the effect of physical activity on colon cancer risk is attenuated in women compared with men, the reason for which is unknown. In most of the cohort studies described in a past review (*152*), as well as several more recent cohort studies (*155–159*), the risk of colon cancer was decreased in the highest physical activity compared with the lowest category, with risk reductions ranging from 10% to 60%. In addition, adjustment for potential confounding factors, such as age, diet, and obesity, did not reduce the strength of the associations between physical activity and colon cancer risk (*152, 155–159*). However, with regard to rectal cancer, these studies as a whole did not support an inverse association between physical activity and rectal cancer risk (*152, 155–159*). There is also some evidence

that physical activity reduces neoplastic growth in the colon and rectum. In a recent prospective cohort study among African-American women, higher levels of physical activity were inversely associated with risk for the development of colorectal adenomas (160), which are thought to be precursors to most colon and rectal cancers (161). In another recent study, a 12-month moderate-to-vigorous intensity aerobic exercise intervention resulted in a significant decrease in colon crypt cell proliferation indices in men who exercised ≥ 250 min/week or whose cardiopulmonary fitness, as measured by VO_2 max, increased by $\geq 5\%$ (162). In this study, patients with colon cancer and persons with an elevated risk for colon cancer (history of sporadic adenoma, ulcerative colitis, familial polyposis, family history of colon cancer, age, etc.) exhibited in macroscopically normal colon mucosa both an increased epithelial cell proliferation rate and an extension of the normal zone of epithelial cell proliferation extending from the base to the luminal portion of the colonic crypt (163).

Biological mechanisms for the effect of physical activity on colon and perhaps rectal cancer risk are unknown. However, several biologically plausible mechanisms have been proposed, including alterations in the immune system, reduced bowel transit time (increasing exposure to fecal carcinogens), higher prostaglandin levels, and bile acid secretion, as well as higher levels of insulin and insulin-like growth factors (164). Although studies are limited in number, there is convincing data to support the latter of these mechanisms, in that both insulin and IGF-I are potent mitogens of colonic carcinoma cells. Several studies have now shown that high levels of IGF-I increase the risk for colorectal cancer, whereas high levels of insulin-like growth factor binding protein (IGFBP)-3, which can reduce IGF-I levels, are associated with a reduced risk for colorectal cancer (165, 166). Likewise, the interaction of physical activity with inherited genetic polymorphisms or mutations in colorectal tumors is limited. Although the interaction of gene polymorphisms and physical activity are unavailable, there is evidence that mutations in the genes *APC*, *p53*, and *Ki-ras* may be inversely associated with physical activity. These genes are thought to regulate cell growth and apoptosis, with mutations in these genes resulting in tumor growth (155). *APC* mutations are thought to be an early event in the carcinogenic process, with other gene mutations occurring afterward (155). Studies have not been done to determine the association of physical activity with *APC* mutations, but other studies have suggested that *p53* and *Ki-ras* mutations in tumors may be inversely related to physical activity (167, 168). Another study examined physical activity with colorectal adenomas and reported that people who were more active were more likely to have *Ki-ras*-negative rather than *Ki-ras*-positive tumors (169).

3.2. Obesity and Overweight

Numerous cohort and case-control studies have consistently demonstrated a positive relationship between body size and colorectal cancer. This relationship has been observed in men and women, with the risk being stronger for men than women (152). In these studies, this relationship is stronger for those who are obese as compared with those who are overweight. In general, this relationship has also been proven to be stronger for cancer of the colon than the rectum, and for the distal rather than the proximal colon. Body size has also been shown to influence colorectal carcinogenesis: BMI has been found to be associated with colorectal adenoma, a precursor lesion of colorectal cancer, and large adenomas of the distal colon and rectum in several epidemiological studies (170–177). There is also evidence to suggest that abdominal or visceral adiposity is a risk factor for colorectal cancer independent of BMI. Recent studies have shown that higher waist-to-hip ratio (WHR) increases the risk for colorectal cancer (178–180).

The understanding of the biological mechanisms linking body size to colorectal cancer is evolving. One plausible mechanism is that a high BMI causes insulin resistance, which promotes colon carcinogenesis. The term insulin resistance refers to a state of cellular unresponsiveness to the effects of insulin, with higher levels of insulin required to normalize plasma glucose, which is associated with a high BMI (181). Diabetes mellitus type 2 is a disease that occurs when insulin resistance coincides with impaired pancreatic secretion of insulin, and is positively associated with colorectal cancer. Type 2 diabetic patients have a threefold increased risk for colorectal cancer compared with nondiabetic patients (182), and in general, non-obese colorectal cancer patients exhibit clinical manifestations of insulin resistance, with higher insulin and glucose levels compared with their control patients (183). Furthermore, serum levels of C-peptide (the cleaved product of proinsulin and a marker of insulin secretion), glycated hemoglobin, and glucose have all been positively associated with colorectal neoplasia (184–188). In addition, plasma levels of IGF-I, which can be increased by insulin, has been positively associated with colorectal cancer (189). Furthermore, several metabolic disturbances resulting from the insulin-resistant state, including hyperinsulinemia, hyperglycemia, hypertriglyceridemia, and increased levels of non-esterified fatty acids, have been found to be positively associated with colorectal cancer risk among fasting participants in prospective studies (190, 191). At least three mechanisms exist through which insulin resistance may cause colorectal cancer. The first is that insulin promotes the growth of colorectal tumors. Specifically, insulin has been shown to stimulate cellular proliferation and reduce cellular apoptosis in colorectal cancer cell lines (192, 193), and it promotes colorectal cancer growth in animal models (194–196). Second, insulin increases IGF-I levels, and high circulating levels of IGF-I have been associated with colorectal cancer risk (189, 197,

198). IGF-I has also been shown to promote the growth of colon cancers in a mouse model (199). In addition, obesity is associated with a state of chronic inflammation, thought to be induced by high circulating levels of lipids and glucose, both of which create a proinflammatory environment that contains a high free radical content (200, 201). It is well known that inflammatory bowel disease increases the risk for colorectal cancer (202). In addition, randomized clinical trials have shown that the use of the nonsteroidal anti-inflammatory drugs, celecoxib and aspirin, reduce colorectal cancer risk (203, 204), where a 45% risk reduction was noted with the use of aspirin for adenoma recurrence (204). Finally, there is some evidence that the association of body size with colorectal cancer may be mediated through other disease pathways. One study reported that an elevated BMI was associated with a mutation of *Ki-ras* in colorectal tumors, which was more likely to occur in women than men (205).

3.3. Diet

Although not entirely consistent, numerous case-control and cohort studies have reported a positive association between red meat consumption and processed meat in particular, with colon cancer risk that was not noted with poultry and fish intake. Red meat intake is thought to increase the risk for colorectal cancer due to its higher heme content compared with the white meats, poultry and fish (206, 207). Heme damages the colonic mucosa and stimulates epithelial cell proliferation in animal studies (207). Both the ingestion of red meat and heme iron supplementation have been found to increase fecal concentrations of *N*-nitroso compounds (208) and DNA adducts in human colonocytes (208, 209). The central role for DNA adducts in carcinogenesis has been established and confirmed as a biological fact for over 50 years (210). Nitrosamines have also been detected in foods with added nitrates or nitrites, such as processed meat (211, 212). A meta-analysis of case-control and cohort studies that were published during 1973–1999 assessed the hypothesis that the consumption of red meat and processed meat increases colorectal cancer risk. This study indicated that the RR (higher versus lowest category) for red meat was 1.27 and for processed meat was 1.59 (213). A recent prospective cohort study that included 148,610 adults also assessed the effect of long-term red meat and processed meat, as well as poultry and fish, consumption on colorectal cancer risk (214). In this study, the risk of distal colon cancer was positively associated with the consumption of processed meat (RR = 1.50), and the risk of rectal cancer was positively associated with the consumption of red meat (RR = 1.71). In contrast, a lower risk of proximal and distal colon cancer was noted with the long-term consumption of poultry and fish in this study (213).

Folic acid deficiency has long been known to cause tumors in animals, which is thought to be the result of altering gene expression through DNA methylation or by increasing the incorporation of uracil in DNA (215). There is considerable evidence

from case-control and cohort studies that supports an inverse association between folate intake and colon cancer risk (216), with this association being stronger among alcohol users (217). A recent study indicated that the inverse association between dietary folate intake and colon cancer risk was stronger for ever smokers compared with never smokers (218). A positive association between a functional polymorphism in the folic acid metabolizing gene, methylene tetrahydrofolate reductase, and the incidence of colon cancer adds support to the potential casual relationship between folic acid deficiency and colon cancer (219).

3.4. Tobacco

In 2004, the US Surgeon General recently concluded that the evidence for the relationship of smoking with colorectal cancer was suggestive but not sufficient to infer a causal relationship (220). At the time of this report, 3 prospective cohort studies (221–223) and 13 case-control studies (224–235), with the exception of the study by Kato and colleagues, identified the RR estimates between smoking and colorectal adenomatous polyps to be between 1.5 and 3.8, after adjusting for age and other important covariates (236). However, in a more recent study (237), the tobacco use of 4,383 subjects with histologically verified benign (hyperplastic or adenomatous) polyps of the distal colon were compared with the tobacco use among 33,667 subjects who were endoscopy negative for distal colon tumors in the screening arm of a randomized trial of flexible sigmoidoscopy. In this study, the risk estimated by the odds ratio (OR) was 4.4 for hyperplastic polyps, 1.8 for adenomas polyps only, and 6.2 for both hyperplastic and adenomatous polyps, which provides stronger support for this relationship.

Prospective studies that have investigated the relationship between smoking and colon cancer have generally reported RR estimates of 1.2–1.4 for colon cancer and 1.4–2.0 for rectal cancer (238–244). To date, there has not been a meta-analysis that has evaluated this relationship across all studies that controlled for factors that influence colorectal cancer risk.

Recent studies indicate that variants of the metabolizing genes, *NAT1*, *CYP1A1*, *GSTM1*, and *GSTT1*, may interact with smoking to increase the risk of colorectal cancer (245–247).

4. Lung Cancer

Lung cancer is the leading cause of cancer death for men and women in the USA; 85% of patients who develop lung cancer will die from it within 5 years of diagnosis (248). Although more than 80% of lung cancer cases are attributable to cigarette smoking, recent studies have noted a protective effect for lung cancer with

physical activity in men and women after adjusting for smoking (5). Past case-control and large cohort studies among men and women were encouraging as to the potential benefit of vegetable and fruit consumption reducing lung cancer risk (5), however, this inverse relationship has not held up in more recent studies (249). Thus, there is likely a major benefit for men and women for modifying their lifestyle related to cigarette exposure, and possibly physical activity and fruit and vegetable intake.

4.1. Tobacco

Cigarette smoking is more strongly associated with lung cancer than with any other cancer type. Cigarette smoking is also the strongest risk factor for lung cancer, increasing the risk of this disease by at least 10-fold and as much as 20-fold, depending on smoking habits and the medical history. There is also a dose-response relationship between smoking and lung cancer that relates to the number of cigarettes smoked, the deepness of the inhalation of cigarette smoke, and the duration of smoking (250). The median delay between the initiation of smoking and death from lung cancer is approximately 50 years (251). Cigarette smoking is more strongly associated with squamous and small cell lung carcinomas, but is increasingly becoming associated with adenocarcinoma and large cell carcinomas that are usually located in the periphery of the lung (252). The incidence of adenocarcinoma has increased in many industrialized countries since the 1970s, which is thought to be due to the introduction of filter-tip cigarettes and reconstructed tobacco in the 1950s (252). There is also increasing evidence suggesting that there are significant differences in lung cancer susceptibility and histological type between the sexes. It appears that women may be more susceptible to lung cancer development than men with and without cigarette smoke exposure, and that the histological distribution of lung cancer differs between men and women, with adenocarcinoma being more common in women than men. Studies are underway to determine if genetic variation, as well as biological factors, may play a role in these differences between the sexes related to lung cancer histological type and overall risk (253).

Tobacco products contain a diverse array of chemical carcinogens, which are responsible for the development of lung cancer and other cancers. More than 60 known carcinogens have been detected in cigarette smoke (254). These include polycyclic aromatic hydrocarbons (PAH); tobacco-specific nitrosamines and other nitrosamines; aromatic amines; aldehydes; volatile hydrocarbons such as benzene, 1,3-butadiene, and ethylene oxide; and inorganic compounds (254). Tobacco carcinogens and their metabolically activated forms induce gene mutations through the formation of DNA adducts, which disrupt cell cycle checkpoints and cause genetic instability that predisposes to the development of malignancy (255). It has been shown that activation of tobacco carcinogens via multiple forms of the cytochrome P450 enzyme system, which detoxifies drugs and

toxic compounds primarily in the liver, leads to DNA adduct-forming intermediates that are detoxified further by additional steps in metabolism. Metabolizing genes that have been shown to activate or deactivate tobacco smoke constituents are: *CYP1A1*, *GSTM1*, *GSTT1*, *NAT2*, and *GSTP1* (256). Therefore, large studies have been undertaken to investigate the role of functional polymorphisms in these genes in lung cancer development (257). Also, as an extension of this approach, research is ongoing on the role of functional polymorphisms in DNA repair genes in the development of lung cancer (258). Furthermore, research is ongoing to determine whether the interaction of cigarette smoke with these genes increases the risk for lung cancer (259).

4.2. Vegetable and Fruit Consumption

Although an inverse relationship between high levels of consumption of fruits and vegetables and the risk of lung cancer has been observed in both case-control and large cohort studies (260), a recent meta-analysis that included more than 3,000 incident cases of lung cancer in men and women did not confirm these results (249). It is thought that this inverse relationship may have been due to counting an inverse association with one or a few foods as support for the benefit of fruits and vegetables, when this may have been the result of chance due to multiple comparisons. However, it is still possible that biologically active substances in fruits and vegetables do exist but in doses too small and not possible to estimate using food frequency questionnaires, and that measuring blood levels of candidate substances would be best for assessing these dietary exposures (261).

4.3. Physical Activity

A recent meta-analysis that evaluated the relationship between physical activity and lung cancer found that this was a statistically inverse relationship, in which several studies were able to adjust for smoking (262). The ORs were 0.87 for moderate leisure-time physical activity and 0.70 for high physical activity, with the inverse association occurring for both sexes, although it was somewhat stronger for women. Four more recent prospective cohort studies, which all adjusted for smoking, yielded mixed results; with three out of the four studies showing an inverse relationship between physical activity and lung cancer risk (263–266). In the study that only included women ($n = 36,929$), physical activity was only inversely related to lung cancer risk in former and never smokers (266).

5. Prostate Cancer

Prostate cancer is the most common and second deadliest cancer in US men (267). Clinical prostate cancer usually presents late in life, leaving much opportunity for preventive interventions.

Although microscopic evidence of prostate cancer occurs in more than 70% of all men by age 70 years (268), the progression to clinically manifest cancer of the prostate is significantly more frequent in regions such as North America when compared with Asian countries (269). There is also an increased incidence of clinical prostate cancer in Asian men who emigrate to the USA compared with men who remain in Asian countries (270, 271). This feature of this disease suggests that environmental factors are contributors to the progression of prostate cancer. Preventive measures for this disease are not established, however, there is evidence that lifestyle modification that includes a diet rich in tomato products and controlling weight may reduce the risk for prostate cancer progression.

5.1. Diet

Several reports have noted an inverse association between a diet rich in tomato products and prostate cancer risk. The key component in tomatoes that is believed to be responsible for this effect is lycopene, which is a carotenoid and is the most effective antioxidant of all of the carotenoids (272). As is the case with other micronutrients, most of the evidence for the protective effect of lycopene in humans is derived from observational studies. A recent review of the published epidemiological evidence suggested that there was a potential benefit of lycopene against the risk of prostate cancer, particularly the more aggressive forms of this cancer. Five of these studies supported a 30% to 40% reduction in this risk, and three were consistent with a 30% reduction in risk, but the results of these studies were not statistically significant, and seven studies were not supportive of an association between lycopene and prostate cancer risk (273). The largest dietary prospective cohort study, which was conducted in male professionals, found that the consumption of two to four servings of tomato sauce per week was associated with nearly a 35% risk reduction of prostate cancer and a 50% reduction of advanced (extraprostatic) prostate cancer. Of the three blood-based prospective cohort studies, all demonstrated an inverse association between lycopene and prostate cancer risk, however, this association was only statistically significant related to aggressive prostate cancers. Thus, although not definitive, the data from these observational studies collectively suggests that lycopene may be protective for prostate cancer, particularly for the aggressive form.

5.2. Obesity and Overweight

In a recent meta-analysis that involved case-control and cohort studies, obesity was found to be positively associated with an increased risk of prostate cancer, particularly in the advanced stage tumors. In these studies, the association was small, 5% on the average, across the categories for BMI, and the range of RR was 0.66–2.28. A similar risk was seen for height and prostate cancer incidence, but only among the cohort studies. There were also weak positive associations with height and waist circumference,

but no notable relationship between WHR and the risk of prostate cancer. A methodological issue for many of the studies represented in this meta-analysis was recall bias due to study subjects recalling their height and weight (274). However, in a recent large prospective cohort study, BMI and adult weight gain was positively associated with prostate cancer mortality, with a RR of 2.12 for the highest BMI category (≥ 35 kg/m²) (275).

Despite the lack of an association between markers of obesity and prostate cancer from the above epidemiological studies, several biological markers that are related to obesity suggest an association of these markers with prostate cancer risk. Leptin, an adipocyte-derived hormone that regulates satiety and energy expenditure, has been shown to increase prostate cancer risk (276). In addition, higher serum insulin levels increase prostate cancer risk, independent of abdominal obesity (277). A meta-analysis of published studies on hormonal markers of prostate cancer risk also found that men with serum IGF-I levels in the upper quartile of the population distribution had a twofold higher prostate cancer risk (278). However, how BMI may play a role in the association of these markers with prostate cancer is complex and not well understood.

6. Summary and Conclusions

Although the underlying mechanisms that are operative in the association between lifestyle and these cancers has not been established (**Table 2.1**), there is now overwhelming evidence that lifestyle factors affect breast, colorectal, lung, and, likely, prostate cancer risk. Physical activity, weight loss, and a reduction in alcohol use can strongly be recommended for the reduction of breast cancer risk. In addition, weight loss, physical activity, and cessation of tobacco use are important behavior changes to reduce colorectal cancer risk, along with the potential benefit for the reduction of red meat consumption and the increase in folic acid intake. Smoking cessation is still the most important prevention intervention for reducing lung cancer risk, but recent evidence indicates that increasing physical activity may also be an important prevention intervention for this disease. The potential benefit of lifestyle change to reduce prostate cancer risk is growing, with recent evidence indicating the importance of a diet rich in tomato-based foods and weight loss. Also, in the cancers for which there are established lifestyle risk factors, such as physical inactivity, obesity, and tobacco use for colorectal cancer, there is emerging information on the role that genetics plays in interacting with these factors, as well as the interaction of combinations

Table 2.1
Biological mechanisms that may be involved in the association of lifestyle, genes, and cancer

Cancer	Possible mechanisms
Breast	<p><i>Physical activity</i></p> <p>Decreased circulating estrogen levels due to a decrease in SHBG levels Prevents silencing of tumor suppressor genes, such as <i>APC</i>, in breast tissue due to gene promoter hypermethylation Reduced production of IGF-I that promotes cancer cell growth, due to lower circulating levels of estrogen</p> <p><i>Obesity and overweight</i></p> <p>Aromatization of high levels of androgens in adipose tissue leading to higher circulating estrogen levels Higher estrogen levels increase the production of insulin-like growth factors, such as IGF-I, which increases cancer cell growth</p> <p><i>Alcohol</i></p> <p>Higher estrogen levels increase the production of insulin-like growth factors, such as IGF-I, which increases cancer cell growth The combination of alcohol consumption and folate deficiency may alter folate metabolism that causes an imbalance in the DNA repair processes that promote cancer cell growth Polymorphisms in the metabolizing genes for alcohol, <i>GSTM1</i> and <i>GSTT1</i>, in combination with alcohol consumption may promote cancer cell growth</p>
Colorectal	<p><i>Physical activity</i></p> <p>Increases bowel transit time, which may reduce mucosal exposure to fecal carcinogens Decreases levels of insulin-like growth factors, such as IGF-I, which increases cancer cell growth May prevent mutations of genes that regulate cell growth and apoptosis, such as <i>APC</i>, <i>p53</i>, and <i>Ki-ras</i></p> <p><i>Obesity and overweight</i></p> <p>May increase levels of leptin and insulin-like growth factors, such as IGF-I, which increase cancer cell growth Obesity produces a state of chronic inflammation that increases the production of free radicals that may lead to gene mutations that promote cancer cell growth Obesity may cause mutations in genes involved in regulating cell growth and apoptosis, such as <i>Ki-Ras</i>, which increases cancer cell growth</p> <p><i>Folic acid deficiency</i></p> <p>Folic acid deficiency may alter gene expression through DNA methylation or by increasing the incorporation of uracil in DNA causing cancer cell growth</p>

(continued)

Table 2.1
(continued)

Cancer	Possible mechanisms
	<p><i>Tobacco</i></p> <p>Tobacco carcinogens in combination with specific polymorphisms of the metabolizing genes, <i>NAT2</i>, <i>CYP1A1</i>, <i>GSTM1</i>, and <i>GSTT1</i>, may increase the risk for initiating colorectal cancer</p>
Lung	<p><i>Tobacco</i></p> <p>Tobacco carcinogens initiate lung cancer by inducing gene mutations and genetic instability through the production of DNA adducts</p> <p>Specific polymorphisms of the genes that metabolize tobacco carcinogens, <i>NAT2</i>, <i>CYP1A1</i>, <i>GSTM1</i>, and <i>GSTT1</i>, may increase the risk for tobacco-induced lung cancer</p>
Prostate	<p><i>Lycopene</i></p> <p>Lycopene may reduce the production of free radicals that may lead to gene mutations that promote cancer cell growth</p> <p><i>Obesity and overweight</i></p> <p>May increase levels of leptin, insulin, and insulin-like growth factors, such as IGF-I, which increase cancer cell growth</p>

SHBG, Sex hormone-binding globulin; *IGF-I*, Insulin-like growth Factor

of lifestyle factors. Integration of genetic information into lifestyle factors can help to clarify the causal relationships between lifestyle and genetic factors and assist in better identifying cancer risk, ultimately leading to better informed choices about effective methods to enhance health and prevent cancer.

References

1. Cancer Facts and Figures 2007. (2007) National Home Office, American Cancer Society, Inc., 1599 Clifton Road, NE, Atlanta, GA 30239–34251.
2. Stein CJ, Colditz GA. (2004) Modifiable risk factors for cancer. *Brit J Cancer*. 90, 299–303.
3. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. (2002) Selected major risk factors and global and regional burden of disease. *Lancet*. 360, 1347–1360.
4. Colditz GA, DeJong W, Hunter DJ, Trichopoulos D, Willet WC (eds). (1996) Harvard report on cancer prevention. *Cancer Causes Control*. 7(Suppl), S1–S55.
5. Curry SJ, Byers T, Hewitt M. (2003) Fulfilling the Potential of Cancer Prevention and Early Detection. The National Academies Press, 500 Fifth Street, NW, Washington, DC 20001.
6. Parkin DM, Pisani P, Ferlay J. (1999) Estimates of the worldwide incidence of 25

- major cancers in 1990. *Int J Cancer*. 80, 827–841.
7. Lacey JV, Devesa SS, Brinton LA. (2002) Recent trends in breast cancer incidence and mortality. *Environ Mol Mutagen*. 39, 82–88.
8. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. (2001) *Lancet*. 2, 133.
9. McTiernan A. (2003) Behavioral risk factors in breast cancer, can risk be modified? *The Oncologist*. 8, 326–334.
10. Monninkhof EM, Elias SG, Vlems FA, van der Tweel I, Schuit AJ, Voskuil DW, et al. (2007) Physical activity and breast cancer: a systematic review. *Epidemiol*. 18, 137–157.
11. Ueji M, Ueno E, Osei-Hyiaman D, Takahashi H, Kano K. (1997) Physical activity and the risk of breast cancer, a case-control study of Japanese women. *J Epidemiol*. 8(2), 115–122.
12. Adams-Campbell LL, Rosenberg L, Rao RS, Palmer JR. (2001) Strenuous physical activity and breast cancer risk in African-American women. *J Natl Med Assoc*. 93(7/8), 267–275.
13. Matthews CE, Shu XO, Jin F, Dai Q, Hebert JR, Ruan ZX, et al. (2001) Lifetime physical activity and breast cancer risk in the Shanghai Breast Cancer Study. *Br J Cancer*. 84(7), 994–1001.
14. Yang D, Bernstein L, Wu AH. (2003) Physical activity and breast cancer risk among Asian-American women in Los Angeles. *Cancer*. 97(10), 2565–2575.
15. John EM, Horn-Ross PL, Koo J. (2003) Lifetime physical activity and breast cancer risk in a multiethnic population, The San Francisco Bay Area Breast Cancer Study. *Cancer Epidemiol Biomarkers Prev*. 12, 1143–1152.
16. King MC, Marks JH, Mandell JB. (2003) Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science*. 302, 643.
17. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. (2005) Physical activity and survival after breast cancer diagnosis. *JAMA*. 293(20), 2479–2486.
18. Abrahamson PE, Gammon MD, Lund MJ, Britton JA, Marshall SW, Flagg EW, et al. (2006) Recreational physical activity and survival among young women with breast cancer. *Cancer*. 107, 1777–1785.
19. Nelson ME, Meredith CN, Dawson-Hughes B, Evans WJ. (1988) Hormone and bone mineral status in endurance-trained and sedentary postmenopausal women. *J Clin Endocrinol Metab*. 66, 927–933.
20. Jasienska G, Ziolkiewicz A, Thune I, Lipson SE, Ellison PT. (2006) Habitual physical activity and estradiol levels in women of reproductive age. *Eur J Cancer Prev*. 15, 439–445.
21. Cauley JA, Gutai JP, Kuller LH, LeDonne D, Powell JG. (1989) The epidemiology of serum sex hormones in postmenopausal women. *Am J Epidemiol*. 129, 1120–1131.
22. McTiernan A, Tworoger SS, Ulrich CM, Yasui Y, Irwin ML, Rajan KB, et al. (2004) Effect of exercise on serum estrogens in postmenopausal women, a 12-month randomized trial. *Cancer Res*. 64, 2923–2928.
23. The Endogenous Hormones and Breast Cancer Collaborative Group. (2002) Endogenous sex hormones and breast cancer in postmenopausal women, reanalysis of nine prospective studies. *J Natl Cancer Inst*. 94, 606–616.
24. McTiernan A (Ed.) *Cancer Prevention and Management Through Exercise and Weight Control*. Boca Raton, CRC Press, Taylor & Francis Group, LLC, 2006.
25. Lønning PE, Helle SI, Johannessen DC, Ekse D, Adlercreutz H. (1996) Influence of plasma estrogen levels on the length of the disease-free interval in postmenopausal women with breast cancer. *Breast Cancer Res Treat*. 29, 335–341.
26. Combined Hormone Trialists' Group and the European Organization for Research and Treatment of Cancer. (2001) Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer, a meta-analysis of four randomized trials. *J Clin Oncol*. 19, 343–353.
27. Clemons M, Gross P. (2001) Mechanisms of disease, estrogen and the risk of breast cancer. *NEJM*. 344, 276–285.
28. Byrne C, Colditz GA, Willet WC, Speizer FE, Pollak M, Hankinson SE. (2000) Plasma insulin-like growth factor (IGF) I, IGF-binding protein 3, and mammographic density. *Cancer Res*. 60, 3744–3748.
29. McCormack VA, dos Santos Silva I. (2006) Breast density and parenchymal patterns as markers of breast cancer risk, a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 15, 1159–1169.
30. Peyrat JP, Bonnetterre J, Hecquest B, Vennin P, Louchez MM, Fournier C, Lefebvre J, Demaille A. (1993) Plasma insulin-like growth-factor (IGF-I) concentrations in human breast cancer. *Eur J Cancer*. 29A, 492–497.

31. Bruning PF, Van Doorn J, Bonfrer JMG, Van Noord PA, Korse CM, Linders TC, Hart AA. (1995) Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. *Int J Cancer*. 62, 266–270.
32. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M. (1998) Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet*. 351, 1393–1396.
33. Bohlke K, Cramer DW, Trichopoulos D, Manziros CS. (1998) Insulin-like growth factor-I in relation to premenopausal ductal carcinoma in situ of the breast. *Epidemiology*. 9, 570–573.
34. Eliakim A, Scheett TP, Newcomb R, Mohan S, Cooper DM. (2001) Fitness, Training, and the Growth Hormone→Insulin-like Growth Factor I Axis in Prepubertal Girls. *J Clin Endocrinol Metab*. 86, 2797–2802.
35. Eliakim A, Brasel JA, Mohan S, Barstow TJ, Berman N, Cooper DM. (1996) Physical fitness, endurance training, and the growth hormone-insulin-like growth factor I system in adolescent females. *J Clin Endocrinol Metab*. 81, 3986–3992.
36. Fairey AS, Courneya KS, Field CJ, Bell G, Jones LW, Macky JR. (2003) Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors, a randomized controlled trial. *Cancer Epidemiol Biomarkers Prev*. 12, 721–727.
37. Milliken LA, Going SB, Houtkooper LB, Flint-Wagner HG, Figueroa A, Metcalfe LL, Blew RM, Sharp SC, Lohman, TG. (2003) Effects of exercise training on bone remodeling, insulin-like growth factors, and bone mineral density in postmenopausal women with and without hormone replacement therapy. *Calcif Tissue Int*. 72, 478–484.
38. Schmitz KH, Ahmed RL, Hannan PJ, Yee D. (2005) Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. *Cancer Epidemiol Biomarkers Prev*. 14, 1672–1680.
39. Schmitz KH, Ahmed RL, Yee D. (2002) Effects of a 9-month strength training intervention on insulin, insulin-like growth factor (IGF)-I, IGF-binding protein (IGFBP)-1, and IGFBP-1 in 30–50-year-old women. *Cancer Epidemiol Biomarkers Prev*. 11, 1597–1604.
40. Russo J, Hu Y-F, Yang X, Russo IH. (2000) Chapter 1, Developmental, cellular, and molecular basis of human breast cancer. *J Natl Cancer Inst Monogr*. 27, 17–37.
41. Klein CB, Costa M. (1997) DNA methylation, heterochromatin and epigenetic carcinogens. *Mutation Res*. 386, 163–180.
42. Klein CB, Leszczynska J. (2005) Estrogen-induced DNA methylation of E-cadherin & p16 in non-tumor breast cells. *Proc Amer Assoc Cancer Res*. 46, 2744.
43. Fernandez SV, Wu Y-Z, Russo IH, Plass C, Russo J. (2006) The role of DNA methylation in estrogen-induced transformation of human breast epithelial cells. *Proc Amer Assoc Cancer Res*. 47, 1590.
44. Shames DS, Minna JD, Gazdar AF. (2007) DNA methylation in health, disease, and cancer. *Curr Mol Med*. 7, 85–102.
45. Widschwendter M, Jones PA. (2001) DNA methylation and breast carcinogenesis. *Oncogene*. 21, 5462–5482.
46. Russo J, Russo IH. (2006) The role of estrogen in the initiation of breast cancer. *J Steroid Biochem Mol Biol*. 102, 89–96.
47. Li S, Ma L, Chiang TC, Burow M, Newbold RR, Negishi M, Barrett JC, McLachlan JA. (2001) Promoter CpG methylation of Hox-a10 and Hox-a11 in mouse uterus not altered upon neonatal diethylstilbestrol exposure. *Mol Carcinogenesis*. 32, 213–219.
48. Alworth LC, Howdeshell KL, Ruhlen RL, Day JK, Lubahn DB, Huang TH, Besch-Williford CL, vom Saal FS. (2002) Uterine responsiveness to estradiol and DNA methylation are altered by fetal exposure to diethylstilbestrol and methoxychlor in CD-1 mice, effects of low versus high doses. *Toxicol Appl Pharmacol*. 183, 10–22.
49. Jin Z, Tamura G, Tsuchiya T, Sakata K, Kashiwaba M, Osakabe M, Motoyama T. (2001) Adenomatous polyposis coli (APC) gene promoter hypermethylation in primary breast cancers. *Br J Cancer*. 85(1), 69–73.
50. Virmani AK, Rathi A, Sathyanarayana UG, Padar A, Huang CX, Cunningham HT, Farinas AJ, Milchgrub S, Euhus DM, Gilcrease M, Herman J, Minna JD, Gazdar AF. (2001) Aberrant methylation of the adenomatous polyposis coli (APC) gene promoter 1A in breast and lung carcinomas. *Clin Cancer Res*. 7, 1998–2004.
51. Burbee DG, Forgacs E, Zochbauer-Muller S, Shivakumar L, Fong K, Gao B, Randle D, Kondo M, Virmani A, Bader S, Sekido Y, Latif F, Milchgrub S, Toyooka S, Gazdar AF, Lerman MI, Zabarovsky E, White M,

- Minna JD. (2001) Epigenetic inactivation of RASSF1A in lung and breast cancers and malignant phenotype suppression. *J Natl Cancer Inst.* 93, 691–699.
52. Dammann R, Yang G, Pfeifer GP. (2001) Hypermethylation of the CpG island of ras association domain family 1A (RASSF1A), a putative tumor suppressor gene from the 3p21.3 locus, occurs in a large percentage of human breast cancers. *Cancer Res.* 61, 3105–3109.
 53. Honorio S, Agathangelou A, Schuermann M, Pankow W, Viacava P, Maher ER, Latif F. (2003) Detection of RASSF1A aberrant promoter hypermethylation in sputum from chronic smokers and ductal carcinoma in situ from breast cancer patients. *Oncogene.* 22, 147–150.
 54. Pu RT, Laitala LE, Alli PM, Fackler MJ, Sukumar S, Clark DP. (2003) Methylation profiling of benign and malignant breast lesions and its application to cytopathology. *Mod Pathol.* 16(11), 1095–1101.
 55. Fackler MJ, McVeigh M, Mehrotra J, Blum MA, Lange J, Lapides A, Garrett E, Argani P, Sukumar S. (2004) Quantitative multiplex methylation-specific PCR assay for the detection of promoter hypermethylation in multiple genes in breast cancer. *Cancer Res.* 64, 442–452.
 56. Lewis CM, Cler LR, Bu DW, Zochbauer-Muller S, Milchgrub S, Naftalis EZ, Leitch AM, Minna JD, Euhus DM. (2005) Promoter hypermethylation in benign breast epithelium in relation to predicted breast cancer risk. *Clin Cancer Res.* 11, 166–172.
 57. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, Mulvihill JJ. (1989) Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst.* 81, 1879–1886.
 58. Sirchia SM, Ferguson AT, Sironi E, Subramanyan S, Orlandi R, Sukumar S, Sacchi N. (2000) Evidence of epigenetic changes affecting the chromatin state of the retinoic acid receptor $\beta 2$ promoter in breast cancer cells. *Oncogene.* 19, 1556–1563.
 59. Yang Q, Shan L, Yoshimura G, Nakamura M, Nakamura Y, Suzuma T, Umemura T, Mori I, Sakurai T, Kakudo K. (2002) 5-aza-2'-deoxycytidine induces retinoic acid receptor beta 2 demethylation, cell cycle arrest and growth inhibition in breast carcinoma cells. *Anticancer Res.* 22, 2753–2756.
 60. Widschwendter M, Berger J, Hermann M, Muller HM, Amberger A, Zeschnigk M, Widschwendter A, Abendstein B, Zeimet AG, Daxenbichler G, Marth C. (2000) Methylation and silencing of the retinoic acid receptor- $\beta 2$ gene in breast cancer. *J Natl Cancer Inst.* 92, 826–832.
 61. Coyle YM, Xie X-J, Lewis CM, Bu D, Milchgrub S, Euhus D. (2006) Role of physical activity in modulating breast cancer risk as defined by APC and RASSF1A promoter hypermethylation in non-malignant breast tissue. *Cancer Epidemiol Biomarkers Prev.* 16, 192–196.
 62. IARC Working Group on the Evaluation of Cancer-Preventive Agents. (2002) Weight Control and Physical Activity, IARC Handbooks of Cancer Prevention, Volume 6. Lyon, France, IARC.
 63. Friedenreich CM. (2001) Review of anthropometric factors and breast cancer risk. *Eur J Cancer Prev.* 10, 15–32.
 64. van den Brandt PA, Spiegelman D, Yaun SS, Adami HO, Beeson L, Folsom AR, et al. (2000) Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol.* 152, 514–527.
 65. Bergstrom A, Pisani P, Tenet V, Wolk A, Adami HO. (2001) Overweight as an avoidable cause of cancer in Europe. *Int J Cancer.* 91, 421–430.
 66. Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, Hennekens CH, Rosner B, Speizer FE, Willett WC. (1997) Dual effects of weight and weight gain on breast cancer risk. *JAMA.* 278, 1407–1411.
 67. Evans DJ, Hoffman RG, Kalkhoff RK, Kissebah AH. (1984) Relationship of body fat topography to insulin sensitivity and metabolic profiles in premenopausal women. *Metabolism.* 33, 68–75.
 68. Haffner SM, Katz MS, Stern MP, Dunn JF. (1989) Relationship of sex hormone binding globulin to overall adiposity and body fat distribution in a biethnic population. *Int J Obes.* 13, 1–9.
 69. Kirschner MA, Samojlik E, Drejka M, Szmaj E, Schneider G, Ertel N. (1990) Androgen-estrogen metabolism in women with upper body versus lower body obesity. *J Clin Endocrinol Metab.* 70, 473–479.
 70. Kaye SA, Folsom AR, Soler JT, Prineas RJ, Potter JD. (1991) Associations of body mass and fat distribution with sex hormone concentrations in post menopausal women. *Int J Epidemiol.* 20, 151–156.
 71. Bruning PF, Bonfrer JM, van Noord PA, Hart AA, Jong-Bakker M, Nooijen WJ.

- (1992) Insulin resistance and breast-cancer risk. *Int J Cancer*. 52, 511–516.
72. Bruning PF, Bonfrer JM, Hart AA, van Noord PA, van der Hoeven H, Collette HJ, Battermann JJ, Jong-Bakker M, Nooijen WJ, de Waard F. (1992) Body measurements, estrogen availability and the risk of human breast cancer, A case-control study. *Int J Cancer*. 51, 14–19.
 73. Potischman N, Swanson CA, Siiteri P, Hoover RN. (1996) Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *J Natl Cancer Inst*. 88, 456–758.
 74. Key TJ, Pike MC. (1988) The dose-effect relationship between “unopposed” oestrogens and endometrial mitotic rate, its central role in explaining and predicting endometrial cancer risk. *Br J Cancer*. 57, 205–212.
 75. Key TJ, Pike MC. (1988) The roles of oestrogens and progestagens in the epidemiology and prevention of breast cancer. *Eur J Cancer Clin Oncol*. 24, 29–43.
 76. Kirschner MA, Ertel N, Schneider G. (1981) Obesity, hormones and cancer. *Cancer Res*. 41, 3711–3717.
 77. Bruning PF. (1987) Endogenous estrogens and breast cancer a possible relationship between body fat distribution and estrogen availability. *J Steroid Biochem*. 27, 487–492.
 78. Moore JW, Key TJ, Bulbrook RD, Clark GM, Allen DS, Wang DY, Pike MC. (1987) Sex hormone binding globulin and risk factors for breast cancer in a population of normal women who had never used exogenous sex hormones. *Br J Cancer*. 56, 661–666.
 79. Clayton SJ, May FE, Westley BR. (1997) Insulin-like growth factors control the regulation of oestrogen and progesterone receptor expression by oestrogens. *Mol Cell Endocrinol*. 128, 57–68.
 80. Peyrat JP, Bonnetterre J, Hecquet B, Vennin P, Louchez MM, Fournier C, Lefebvre J, Demaille A. (1993) Plasma insulin-like growth factor-1 (IGF-1) concentrations in human breast cancer. *Eur J Cancer*. 29A, 492–497.
 81. Bruning PF, Van Doorn J, Bonfrer JM, van Noord PA, Korse CM, Linders TC, Hart AA. (1995) Insulin-like growth-factor-binding protein 3 is decreased in early-stage operable pre-menopausal breast cancer. *Int J Cancer*. 62, 266–270.
 82. Del Giudice ME, Fantus IG, Ezzat S, McKewon-Eyssen G, Page D, Goodwin PJ. (1998) Insulin and related factors in pre-menopausal breast cancer risk. *Breast Cancer Res Treat*. 47, 111–120.
 83. Hankinson SE, Willett WC, Colditz GA, Hunter DJ, Michaud DS, Deroot B, Rosner B, Speizer FE, Pollak M. (1998) Circulating concentrations of insulin-like growth factor-I risk of breast cancer. *Lancet*. 351, 1393–1396.
 84. Toniolo B, Bruning PF, Akhmedkhanov A, Bonfrer JM, Koenig KL, Lukanova A, Shore RE, Zeleniuch-Jacquotte A. (2000) Serum insulin-like growth factor-1 and breast cancer. *Int J Cancer*. 88, 828–832.
 85. Jernstrom H, Barrett-Connor E. (1999) Obesity weight change, fasting insulin, proinsulin, C-peptide and insulin-like growth factor-1 levels in women with and without breast cancer, The Rancho Bernardo Study. *J Womens Health Gend Based Med*. 8, 1265–1272.
 86. Yang G, Lu G, Jin F, Dai Q, Best R, Shu XO, Chen JR, Pan XY, Shrubsole M, Zheng W. (2001) Population-based, case-control study of blood C-peptide level and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 10, 1207–1211.
 87. Yu H, Rohan T. (2000) Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst*. 92, 1472–1489.
 88. Hu X, Juneja SC, Maible NJ, Cleary MP. (2002) Leptin-a growth factor in normal and malignant breast cells and for normal mammary gland development. *J Natl Cancer Inst*. 94, 1704–1711.
 89. Laud K, Gourdou I, Pesseme L, Peyrat JP, Djiane J. (2002) Identification of leptin receptors in human breast cancer, functional activity in the T47-D breast cancer cell line. *Mol Cell Endocrinol*. 188, 219–226.
 90. Dieudonne MN, Machinal-Quelin F, Serazin-Leroy V, Leneveu MC, Pecquery R, Giudicelli Y. (2002) Leptin mediates a proliferative response in human MCF7 breast cancer cells. *Biochem Biophys Res Commun*. 293, 622–628.
 91. Okumura M, Yamamoto M, Sakuma H, Kojima T, Maruyama T, Jamali M, Cooper DR, Yasuda K. (2002) Leptin and high glucose stimulate cell proliferation in MCF-7 human breast cancer cells, reciprocal involvement of PKC-alpha and PPAR expression. *Biochimica et Biophysica Acta*. 1592, 107–116.
 92. Mantzoros CS, Bolhke K, Moschos S, Cramer DW. (1999) Leptin in relation to carcinoma in situ of the breast, a study of pre-menopausal cases and controls. *Int J Cancer*. 80, 523–526.

93. Malin A, Matthews CE, Shu XO, Cai H, Dai Q, Jin F, Gao YT, Zheng W. (2005) Energy balance and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 14(6), 1496–1501.
94. Singletary KW, Gapstur SM. (2001) Alcohol and breast cancer, review of epidemiologic and experimental evidence and potential mechanisms. *JAMA.* 286, 2143–2151.
95. Smith-Warner SA, Spiegelman D, Yaun SS, Van Den Brandt PA, Folsom AR, Gold-bohm A, Graham S, Holmberg L, Howe GR, Marshall JR, Miller AB, Potter JD, Speizer FE, Willet WC, Wolk A, Hunter DJ. (1998) Alcohol and breast cancer in women. A pooled analysis of cohort studies. *JAMA.* 270, 535–540.
96. Mezzetti M, La Vecchia C, Decarli A, Boyle P, Talamini R, Franceschi S. (1998) Population attributable risk for breast cancer, diet, nutrition and physical exercise. *J Natl Cancer Inst.* 90, 389–394.
97. Byers T, Funch DF. (1982) Alcohol and breast cancer. *Lancet.* 1, 799–800.
98. Baumgartner KB, Annegers JF, McPherson RS, Frankowski RF, Gilliland FD, Samet JM. (2002) Is alcohol intake associated with breast cancer in Hispanic women? The New Mexico Women's Health Study. *Ethn Dis.* 12, 460–469.
99. Reichman ME, Judd JT, Longcope C, Schatzkin A, Clevidence BA, Nair PP, et al. (1993) Effects of alcohol consumption on plasma and urinary hormone concentrations in pre-menopausal women. *J Natl Cancer Inst.* 85, 722–727.
100. Muti P, Trevisan M, Micheli A, Krogh V, Bolelli G, Sciajno R, et al. (1998) Alcohol consumption and total estradiol in premenopausal women. *Cancer Epidemiol Biomarkers Prev.* 7, 189–193.
101. Sarkola T, Makisalo H, Fukunaga T, Eriksson C. (1999) Acute effect of alcohol on estradiol, estrone, progesterone, prolactin, cortisol and luteinizing hormone in premenopausal women. *Alcohol Clin Exp Res.* 23, 976–982.
102. Dorgan JF, Reichman ME, Judd JT, Brown C, Longcope C, Schatzkin A, et al. (1994) The relation of reported alcohol ingestion to plasma levels of estrogens and androgens in pre-menopausal women (Maryland, United States). *Cancer Causes Control* 1994. 5, 53–60.
103. Sarkola T, Fukunaga T, Makisalo H, Eriksson C. (2000) Acute effect of alcohol on androgens in pre-menopausal women. *Alcohol Alcohol.* 35, 84–90.
104. Verkasalo P, Thomas H, Appleby P, Davey G, Key T. (2001) Circulating levels of sex hormones and their relation to risk factors for breast cancer, a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). *Cancer Causes Control.* 12, 47–59.
105. Martin C, Mainous A, Curry T, Martin D. (1999) Alcohol use in adolescent females, correlated with estradiol and testosterone. *Am J Addict.* 8, 9–14.
106. Stevens R, Davis S, Mirick D, Kheifets L, Kaune W. (2000) Alcohol consumption and urinary concentration of 6-sulfatoxymelatonin in healthy women. *Epidemiology.* 11, 660–665.
107. Purohit V. (1998) Moderate alcohol consumption and estrogen levels in postmenopausal women, a review. *Alcohol Clin Exp Res.* 22, 994–997.
108. Dorgan JF, Baer DJ, Albert PS, Judd JT, Brown ED, Corle DK, et al. (2001) Serum hormones and the alcohol-breast cancer association in postmenopausal women. *J Natl Cancer Inst.* 93, 710–715.
109. Longnecker M, Tseng M. (1998) Alcohol, hormones and postmenopausal women. *Alcohol Health Res World.* 22, 185–189.
110. Boyd N, McGuire V, Fishell E, Kuriov V, Lockwood G, Trichtler D. (1989) Plasma lipids in premenopausal women with mammographic dysplasia. *Br J Cancer.* 59, 766–771.
111. Herrington L, Saftlas A, Stanford J, Brinton L, Wolfe J. (1993) Do alcohol intake and mammographic densities interact in regard to the risk of breast cancer? *Cancer.* 71, 3029–3035.
112. Funkhouser E, Waterbor J, Cole P, Rubin E. (1993) Mammographic patterns and breast cancer risk factors among women having elective screening. *South Med J.* 86, 177–180.
113. Boyd NF, Connelly P, Byng J, Yaffe M, Draper H, Little L, et al. (1995) Plasma lipids, lipoproteins and mammographic densities. *Cancer Epidemiol Biomarkers Prev.* 4, 727–733.
114. Vachon C, Kushi L, Cerhan J, Kuni C, Sellers T. (2000) Association of diet and mammographic breast density in the Minnesota Breast Cancer Family cohort. *Cancer Epidemiol Biomarkers Prev.* 9, 151–160.
115. Vachon C, Kuni C, Anderson K, Anderson V, Sellers T. (2000) Association of mammographically defined breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control.* 11, 653–662.

116. Byrne C, Colditz G, Willett W, Speizer F, Pollak M, Hankinson S. (2000) Plasma insulin-like growth factor (IGF)-1, IGF-binding protein 3 and mammographic density. *Cancer Res.* 60, 3744–3748.
117. Boyd N, Jensen H, Cooke G, Han N, Lockwood G, Miller A. (2000) Mammographic densities and the prevalence and incidence of histological types of benign breast disease, Reference Pathologists of the Canadian National Breast Screening Study. *Eur J Cancer Prev.* 9, 15–24.
118. Lee M, Petrakis N, Wrensch M, King E, Miike R, Sickles E. (1994) Association of abnormal nipple aspirate cytology and mammographic pattern and density. *Cancer Epidemiol Biomarkers Prev.* 3, 33–36.
119. Boyd N, Lockwood G, Byng J, Trichler D, Yaffe M. (1998) Mammographic densities and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 7, 1133–1144.
120. Zhang S, Hunter DJ, Hankinson SE, Giovannucci EL, Rosner BA, Colditz GA, et al. (1999) A prospective study of folate intake and the risk of breast cancer. *JAMA.* 281, 1632–1637.
121. Rohan T, Jain M, Howe G, Miller A. (2000) Dietary folate consumption and breast cancer risk. *J Natl Cancer Inst.* 92, 266–269.
122. Negri E, LaVecchia C, Franceschi S. (2000) Dietary folate consumption and breast cancer risk. *J Natl Cancer Inst.* 92, 1270–1271.
123. Sellers T, Kushi L, Cerhan J, et al. (2001) Dietary folate mitigates alcohol associated risk of breast cancer in a prospective study of postmenopausal women. *Epidemiology.* 12, 420–428.
124. Hillman R, Steinberg S. (1982) The effects of alcohol on folate metabolism. *Annu Rev Med.* 33, 345–354.
125. Jacques P, Sulsky S, Hartz S, Russell R. (1989) Moderate alcohol intake and nutritional status in nonalcoholic elderly subjects. *Am J Clin Nutr.* 50, 875–883.
126. Bailey L. (1990) Folate status assessment. *J Nutr.* 120(suppl 11), 1508–1511.
127. Giovannucci E, Stampfer M, Colditz G, Rimm E, Trichopoulos D, Rosner B, et al. (1993) Folate, methionine and alcohol intake and risk of colorectal adenoma. *J Natl Cancer Inst.* 85, 875–884.
128. Choi S, Mason J. (2000) Folate and carcinogenesis, an integrated scheme. *J Nutr.* 130, 129–132.
129. Kim Y. (1999) Folate and carcinogenesis, evidence, mechanisms and implications. *J Nutr Biochem.* 10, 66–88.
130. Duthie S. (1999) Folic acid deficiency and cancer, mechanisms of DNA instability. *Br Med Bull.* 55, 578–592.
131. Fenech M, Aitken C, Rinaldi J. (1998) Folate, vitamin B12, homocysteine status and DNA damage in young Australian adults. *Carcinogenesis.* 19, 1163–1171.
132. Smith S, Crocitto L. (1999) DNA methylation in eukaryotic chromosome stability revisited, DNA methyltransferase in the management of DNA conformation space. *Mol Carcinog.* 25, 1–9.
133. Drewnowski A, Rock CL, Henderson SA, Shore AB, Fischler C, Galan P, et al. (1997) Serum beta-carotene and vitamin C as biomarkers of vegetable and fruit intakes in a community-based sample of French adults. *Am J Clin Nutr.* 65, 1706–1802.
134. Forman MR, Beecher GR, Lanza E, Reichman ME, Graubard BI, Campbell WS, et al. (1995) Effect of alcohol consumption on plasma carotenoid concentrations in premenopausal women, a controlled dietary study. *Am J Clin Nutr.* 62, 131–135.
135. Park SK, Yoo KY, Lee SJ, Kim SU, Ahn SH, Noh DY, et al. (2000) Alcohol consumption, glutathione S-transferase M1 and T1 genetic polymorphisms and breast cancer risk. *Pharmacogenetics.* 10, 301–309.
136. Willett WC. (2001) Diet and cancer, one view at the start of the millennium. *Cancer Epidemiol Biomarkers Prev.* 10, 3–8.
137. Howe GR, Hirohata T, Hislop TG, Iscovich JM, Yuan JM, Katsouyanni K, et al. (1990) Dietary factors and risk of breast cancer, combined analysis of 12 case-control studies. *J Natl Cancer Inst.* 82, 561–569.
138. Hunter DJ, Spiegelman D, Adami HO, Beeson L, van den Brandt PA, Folsom AR, et al. (1996) Cohort studies of fat intake and the risk of breast cancer, a pooled analysis. *N Eng J Med.* 334, 356–361.
139. Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, et al. (2001a) Types of dietary fat and breast cancer, a pooled analysis of cohort studies. *Int J Cancer.* 92, 767–774.
140. Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, Margolis KL, Limacher MC, Manson JE, et al. (2006) Low-fat dietary pattern and risk of invasive breast cancer; the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA.* 295, 629–642.
141. World Cancer Research Fund Panel (Potter JD Chair). Food, Nutrition and the Prevention of Cancer, a Global Perspective. Washington, DC, American Institute for Cancer Research, 1997.

142. Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, et al. (2001) Intake of fruits and vegetables and risk of breast cancer, a pooled analysis of cohort studies. *JAMA*. 285, 769–776.
143. van Gils CH, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Lahmann PH, Clavel-Chapelon F, et al. (2005) Consumption of vegetables and fruits and risk of breast cancer. *JAMA*. 293(2), 183–193.
144. Ahn J, Gammon MD, Santella RM, Gaudet MM, Britton JA, Teitelbaum SL, Terry MB, Neugut AI, Josephy PD, Ambrosone CB. (2004) Myeloperoxidase genotype, fruit and vegetable consumption and breast cancer risk. *Cancer Res*. 64(20), 7634–7639.
145. Wu AH, Ziegler RG, Nomura AM, West DW, Kolonel LN, Horn-Ross PL, et al. (1998) Soy intake and risk of breast cancer in Asians and Asian Americans. *Am J Clin Nutr*. 68(suppl 6), 1437S–1443S.
146. Greenwald P. (2002) Cancer prevention clinical trials. *J Clin Oncol*. 20(suppl 18), 14S–22S.
147. Jones JL, Daley BJ, Enderson BL, Zhou JR, Karlstad MD. (2002) Genistein inhibits tamoxifen effects on cell proliferation and cell cycle arrest in T47D breast cancer cells. *Am Surg*. 68, 575–577.
148. JU YH, Doerge DR, Allred KF, Allred CD, Helferich WG. (2002) Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. *Cancer Res*. 62, 2474–2477.
149. Dorgan JF, Sowell A, Swanson CA, Potischman N, Miller R, Schussler N, et al. (1998) Relationships of serum carotenoids, retinol, alpha-tocopherol and selenium with breast cancer risk, results from a prospective study in Columbia, Missouri (United States). *Cancer Causes Control*. 9, 89–97.
150. Hulten K, Van Kappel AL, Winkvist A, Kaaks R, Hallmans G, Lenner P, et al. (2001) Carotenoids, alpha-tocopherols and retinol in plasma and breast cancer risk in northern Sweden. *Cancer Causes Control*. 12, 529–537.
151. Sato R, Helzlsouer KJ, Alberg AJ, Hoffman SC, Norkus EP, Comstock GW. (2002) Prospective study of carotenoids, tocopherols and retinoid concentrations and the risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*. 11, 451–457.
152. IARC. (2002) Weight control and physical activity. IARC Handbooks of Cancer Prevention, vol. 6. Lyon, France, IARC Press.
153. Colditz GA. (1997) Epidemiology-future directions. *Int J Epidemiol*. 26(4), 693–697.
154. Marrett LD, Theis B, Ashbury FD. (2000) Workshop report, physical activity and cancer prevention. *Chronic Dis Can*. 21(4), 143–149.
155. Slattery M. (2004) Physical activity and colorectal cancer. *Sports Med*. 34, 239–252.
156. Calton BA, Lacey JV Jr, Schatzkin A, Schairer C, Colbert LH, Albanes D, Leitzmann MF. (2006) Physical activity and the risk of colon cancer among women, a prospective cohort study (United States). *Int J Cancer*. 119, 385–291.
157. Larsson SC, Rutegard J, Bergkvist L, Wolk A. (2006) Physical activity, obesity and risk of colon and rectal cancer in a cohort of Swedish men. *Eur J Cancer*. 42, 2590–2597.
158. Friedenreich C, Norat T, Steindorf K, Boutron-Ruault MC, Pischon T, Mazuir M, et al. (2006) Physical activity and risk of colon and rectal cancers, the European prospective investigation into cancer and nutrition. *Cancer Epidemiol Biomarkers Prev*. 15(12), 2398–2407.
159. Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S. (2007) Physical activity and risk of colorectal cancer in Japanese men and women, the Japan Public Health Center-based prospective study. *Cancer Causes Control*. 18, 199–209.
160. Rosenberg L, Boggs D, Wise LA, Palmer JR, Roltsch MH, Makambi KH, Adams-Campbell LL. (2006) A follow-up study of physical activity and incidence of colorectal polyps in African-American women. *Cancer Epidemiol Biomarkers Prev*. 15(8), 1438–1442.
161. Hill MJ, Morson BC, Bussey HJ. (1978) Aetiology of adenoma-carcinoma sequence in large bowel. *Lancet*. 1, 245–247.
162. McTiernan A, Yasui Y, Sorensen B, Irwin ML, Morgan A, Rudolph RE, Surawicz C, Lampe JW, Ayub K, Potter JD, Lampe PD. (2006) Effect of a 12-month exercise intervention on patterns of cellular proliferation in colonic crypts, A randomized controlled trial. *Cancer Epidemiol Biomarkers Prev*. 15(9), 1588–1597.
163. Bostick RM, Fosdick L, Lillemoe TJ, Overn P, Wood JR, Grambsch P, et al. (1997) Methodological findings and considerations in measuring colorectal epithelial cell proliferation in humans. *Cancer Epidemiol Biomarkers Prev*. 6, 931–842.
164. Quadriatero J, Hoffman-Goetz L. (2003) Physical activity and colon cancer, A systematic

- review of potential mechanisms. *J Sports Med Phys Fitness.* 43, 121–138.
165. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, et al. (2000) Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst.* 92(19), 1592–1600.
 166. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, et al. (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding proteins-3. *J Natl Cancer Inst.* 91(7), 620–625.
 167. Slattery ML, Curtin K, Ma K, Edwards S, Schaffer D, Anderson K, et al. (2002) Diet activity and lifestyle associations with p53 mutation in colon tumors. *Cancer Epidemiol Biomarkers Prev.* 11(6), 541–548.
 168. Slattery ML, Anderson K, Curtin K, Ma K, Schaffer D, Edwards S, et al. (2001) Lifestyle factors and Ki-ras mutations in colon cancer tumors. *Mutat Res.* 483(12), 73–81.
 169. Martinez ME, Maltzman T, Marshall JR, Einspahr J, Reid ME, Sampliner R, et al. (1999) Risk factors for Ki-ras protooncogene mutation in sporadic colorectal adenomas. *Cancer Res.* 59(20), 5181–5185.
 170. Boutron-Ruault MC, Senesse P, Meance S, Belghiti C, Faivre J. (2001) Energy intake, body mass index, physical activity and the colorectal adenoma-carcinoma sequence. *Nutr Cancer.* 39, 50–57.
 171. Neugut AI, Lee WC, Garbowski GC, Waye JD, Forde KA, Treat MR, et al. (1991) Obesity and colorectal adenomatous polyps. *J Natl Cancer Inst.* 83, 359–361.
 172. Shinchi K, Kono S, Honjo S, Todoroki I, Sakurai Y, Imanishi K, et al. (1994) Obesity and adenomatous polyps of the sigmoid colon. *Jpn J Cancer Res.* 85, 479–484.
 173. Davidow AL, Neugut AI, Jacobson JS, Ahsan H, Garbowski GC, Forde KA, et al. (1996) Recurrent adenomatous polyps and body mass index. *Cancer Epidemiol Biomarkers Prev.* 5, 313–315.
 174. Giovannucci E, Colditz GA, Stampfer MJ, Willett WC. (1996) Physical activity, obesity and risk of colorectal adenoma in women (United States). *Cancer Causes Control.* 7, 253–263.
 175. Bird CL, Frankl HD, Lee ER, Haile RW. (1998) Obesity, weight gain, large weight changes and adenomatous polyps of the left colon and rectum. *Am J Epidemiol.* 147, 670–680.
 176. Kono S, Handa K, Hayabuchi H, Kiyohara C, Inoue H, Marugame T, et al. (1999) Obesity, weight gain and risk of colon adenomas in Japanese men. *Jpn J cancer Res.* 90, 801–811.
 177. Lukanova A, Bjor O, Kaaks R, Lenner P, Lindahl B, Hallmans G, Stattin P. (2006) Body mass index and cancer. Results from the northern Sweden health and disease cohort. *Int J Cancer.* 118, 458–466.
 178. Moore LL, Bradlee ML, Singer MR, Splan-sky GL, Proctor MH, Ellison RC, et al. (2004) BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int J Obes Relat Metab Disord.* 28, 559–567.
 179. MacInnis RJ, English DR, Hopper JL, Haydon AM, Gertiz DM, Giles GG. (2004) Body size and composition and colon cancer risk in men. *Cancer Epidemiol Biomarkers Prev.* 13, 553–559.
 180. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, et al. (2006) Body size and risk of colon and rectal cancer in the European prospective investigation into cancer and nutrition (EPIC). *J Natl Cancer Inst.* 98, 920–931.
 181. Gunter MJ, Leitzmann MF. (2006) Obesity and colorectal cancer, epidemiology, mechanisms and candidate genes. *J Nutr Biochem.* 17, 145–156.
 182. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. (2004) Preliminary communication, glycated hemoglobin, diabetes and incident colorectal cancer in men and women, a prospective analysis from the European prospective investigation into cancer. Norfolk study. *Cancer Epidemiol Biomarkers Prev.* 13, 915–919.
 183. Yam D, Fink A, Mashia A, Ben-Hur E. (1996) Hyperinsulinemia in colon, stomach and breast cancer patients. *Cancer Lett.* 104, 129–132.
 184. Nilsen TI, Vatten LJ. (2001) Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI, exploring the hyperinsulinaemia hypothesis. *Br J Cancer.* 84, 417–422.
 185. Platz EA, Hankinson SE, Rifai N, Colditz GA, Speizer FE, Giovannucci E. (1999) Glycosylated hemoglobin and risk of colorectal cancer and adenoma (United States). *Cancer Causes Control.* 10, 379–386.
 186. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Dechaud H, et al. (2000) Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins, and colorectal cancer risk in women. *J Natl Cancer Inst.* 92, 1592–1600.

187. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. (2005) Fasting serum glucose level and cancer risk in Korean men and women. *JAMA*. 293, 194–202.
188. Saydah SH, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. (2003) Association of markers of insulin and glucose control with subsequent colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*. 12, 412–418.
189. Ma J, Pollak MN, Giovannucci E, Chan JM, Tao Y, Hennekens CH, et al. (1999) Prospective study of colorectal cancer risk in men and plasma levels of insulin-like growth factor (IGF)-I and IGF-binding protein-3. *J Natl Cancer Inst*. 91, 620–625.
190. Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashiwara H, et al. (1998) Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. *Int J Epidemiol*. 27, 794–798.
191. Schoen RE, Tangen CM, Kuller LH, Burke GL, Cushman M, Tracy RP, et al. (1999) Increased blood glucose and insulin, body size and incident colorectal cancer. *J Natl Cancer Inst*. 91, 1147–1154.
192. Koenuma M, Yamori T, Sururo T. (1989) Insulin and insulin-like growth factor I stimulate proliferation of metastatic variants of colon carcinoma 26. *Jpn J Cancer Res*. 80, 51–58.
193. Wu X, Fan Z, Masui H, Rosen N, Mendelsohn J. (1995) Apoptosis induced by an anti-epidermal growth factor receptor monoclonal antibody in a human colorectal carcinoma cell line and its delay by insulin. *J Clin Invest*. 95, 1897–1905.
194. Bjork J, Nilsson J, Hultcrantz R, Johansson C. (1993) Growth-regulatory effects of sensory neuropeptides, epidermal growth factor, insulin, and somatostatin on the non-transformed intestinal epithelial cell line IEC-6 and the colon cancer cell line HT 29. *Scand J Gastroenterol*. 28, 879–884.
195. Tran TT, Medline A, Bruce WR. (1995) Insulin promotion of colon tumors in rats. *Cancer Epidemiol Biomarkers Prev*. 5, 1013–1015.
196. Corpet DE, Jacquinet C, Peiffer G, Tache S. (1997) Insulin injections promote the growth of aberrant crypt foci in the colon of rats. *Nutr Cancer*. 27, 316–320.
197. Giovannucci E. (2001) Insulin, insulin-like growth factors and colon cancer, a review of the evidence. *J Nutr*. 131, 3109S–3120S.
198. DeLellis K, Rinoldi S, Kaaks FJ, Kolonel LN, Henderson B, Le Marchand L. (2004) Dietary and lifestyle correlates of plasma insulin-like growth factor-I (IGF-I) and IGF binding protein-3 (IGFBP-3), The Multi-ethnic Cohort. *Cancer Epidemiol Biomarkers Prev*. 13(9), 1444–1451.
199. Wu Y, Yakar S, Zhao L, Hennighausen L, LeRoith D. (2002) Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis. *Cancer Res*. 62, 1030–1035.
200. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, et al. (2002) Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans, role of oxidative stress. *Circulation*. 106, 2067–2072.
201. Mohanty P, Hamouda W, Garg R, Aljada A, Ghanim H, Dandona P. (2000) Glucose challenge stimulates reactive oxygen species (ROS) generation by leukocytes. *J Clin Endocrinol Metab*. 85, 2970–2973.
202. Eaden JA, Abrams KR, Mayberry JF. (2001) The risk of colorectal cancer in ulcerative colitis, a meta-analysis. *Gut*. 48, 526–535.
203. Steinbach G, Lynch PM, Phillips RK, Wallace M, Hawk E, Gordon G, et al. (2000) The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *New Engl J Med*. 342, 1946–1952.
204. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. (2003) A randomized trial of aspirin to prevent colorectal adenomas. *New Engl J Med*. 348, 891–899.
205. Slattery ML, Anderson K, Curtin K, Ma KN, Schaffer D, Edwards S, Samowitz W. (2001) Lifestyle factors and Ki-ras mutation in colon cancer tumors. *Mut Res*. 483, 73–81.
206. Cross AJ, Pollock JRA, Bingham SA. (2003) Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res*. 63, 2358–2360.
207. Sesink AL, Termont DS, Kleibeuker JH, Van der Meer R. (1999) Red meat and colon cancer: the cytotoxic and hyperproliferative effects of dietary heme. *Cancer Res*. 59, 5704–5709.
208. Hughes R, Pollock JRA, Bingham S. (2002) Effect of vegetables, tea, and soy on endogenous N-nitrosation, fecal ammonia, and fecal water genotoxicity during a high meat diet in humans. *Nutr Cancer*. 42, 70–77.
209. Hughes R, Cross AJ, Pollock JRA, Bingham S. (2001) Dose-dependent effect of dietary meat on endogenous colonic N-nitrosation. *Carcinogenesis* 22, 199–202.

210. Miller JA. (1994) Research in chemical carcinogenesis with Elizabeth Miller a trail of discovery with our associates. *Drug Metabol Dispos.* 26, 1–36.
211. Scanlan RA. (1983) Formation and occurrence of nitrosamines in food. *Cancer Res.* 43, 2435S–2440S.
212. Hothckiss JH. (1989) Preformed N-nitroso compounds in foods and beverages. *Cancer Surv.* 8, 295–321.
213. Norat T, Lukanova A, Ferrari P, Riboli E. (2002) Meat consumption and colorectal cancer risk, dose-response meta-analysis of epidemiological studies. *Int J Cancer.* 98, 241–256.
214. Chao A, Thun MJ, Connell CJ, McCullough ML, Jacobs EJ, Flanders WD, et al. (2005) Meat consumption and risk of colorectal cancer. *JAMA.* 293(2), 172–182.
215. Blount BC, Ames BN. (1994) Analysis of uracil in DNA by gas chromatography-mass spectrometry. *Anal Biochem.* 219, 195–200.
216. Giovannucci E. (2002a) Epidemiologic studies of folate and colorectal neoplasia, A review. *J Nutr.* 132, 2350S–2355S.
217. Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. (1995) Alcohol, low-methionine-low-folate diets and risk of colon cancer in men. *J Natl Cancer Inst.* 87, 265–273.
218. Larsson SC, Giovannucci E, Wolk A. (2005) A prospective study of dietary folate intake and risk of colorectal cancer, Modification by caffeine intake and cigarette smoking. *Cancer Epidemiol Biomarkers Prev.* 14(3), 740–743.
219. Jiang Q, Chen K, Ma X, Li Q, Yu W, Shu G, Yao K. (2005) Diets, polymorphisms of methylenetetrahydrofolate reductase, and the susceptibility of colon cancer and rectal cancer. *Cancer Detection and Prev.* 29, 146–154.
220. Department of Health and Human Services. (2004) The Health Consequences of Tobacco Use, A Report of the Surgeon General. Atlanta, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
221. Giovannucci E, Colditz GA, Stampfer MJ, Hunter D, Rosner BA, Willett WC, et al. (1994) A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. *J Natl Cancer Inst.* 86, 192–199.
222. Giovannucci E, Rimm EB, Ascherio A, Colditz GA, Spiegelman D, Stampfer MJ, et al. (1999) Smoking and risk of total and fatal prostate cancer in United States health professionals. *Cancer Epidemiol Biomarkers Prev.* 8, 277–282.
223. Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T, Matsushita S. (1999) Cigarette smoking, alcohol use, and colorectal adenoma in Japanese men and women. *Dis Colon Rectum.* 42, 337–342.
224. Kikendall JW, Bowen PE, Burgess MB, Magnetti C, Woodward J, Langenberg P. (1989) Cigarettes and alcohol as independent risk factors for colonic adenomas. *Gastroenterology.* 97, 660–664.
225. Cope GF, Wyatt JJ, Pinder IF, Lee PN, Heatley RV, Kelleher J. (1991) Alcohol consumption in patients with colorectal adenomatous polyps. *Gut.* 32, 70–72.
226. Monnet E, Allemand H, Farina H, Carayon P. (1991) Cigarette smoking and the risk of colorectal adenoma in men. *Scand J Gastroenterol.* 26, 758–762.
227. Zahm S, Cocco P, Blair A. (1991) Tobacco smoking as a risk for colon polyps. *Am J Public Health.* 81, 846–849.
228. Longnecker MP, Chen MJ, Probst-Hensch NM, Harper JM, Lee ER, Frankl HD, et al. (1996) Alcohol and smoking in relation to the prevalence of adenomatous colorectal polyps at sigmoidoscopy. *Epidemiology.* 7, 275–280.
229. Olsen J, Kronborg O. (1993) Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine. *Int J Epidemiol.* 22, 398–402.
230. Boutron MC, Faivre J, Dop MC, Quipourt V, Senesse P. (1995) Tobacco, alcohol and colorectal tumors, a multistep process. *Am J Epidemiol.* 141, 1038–1046.
231. Breuer-Katschinski B, Nemes K, Marr A, Rump B, Leiendecker B, Breuer N, et al. (2000) Alcohol and cigarette smoking and the risk of colorectal adenomas. *Dig Dis Sci.* 45, 487–493.
232. Almendingen K, Hofstad B, Trygg K, Hoff G, Hussain A, Vatn MH. (2000) Smoking and colorectal adenomas, a case-control study. *Eur J Cancer Prev.* 9, 193–203.
233. Hisako I, Chikako K, Tomomi M, Sachiko S, Emiko T, Koichi H, et al. (2000) Cigarette smoking, CYP1A1 MspI and GSTM1 genotypes, and colorectal adenomas. *Cancer Res.* 60, 3749–3752.
234. Martinez ME, McPherson RS, Annegers JF, Levin B. (1995) Cigarette smoking and alcohol consumption as risk factors for colorectal adenomatous polyps. *J Natl Cancer Inst.* 87, 274–279.

235. Potter JD, Bigler J, Fosdick L, Bostick RM, Kampman E, Chen C, et al. (1999) Colorectal adenomatous and hyper-plastic polyps, smoking and N-acetyltransferase 2 polymorphisms. *Cancer Epidemiol Biomarkers Prev.* 8, 69–75.
236. Kato I, Tominaga S, Matsuura A, Yoshii Y, Shirai M, Kobayashi S. (1990) A comparative case-control study of colorectal cancer and adenoma. *Jpn J Cancer Res.* 81, 1101–1108.
237. Ji BT, Weissfeld JL, Chow WH, Huang WY, Schoen RE, Hayes RB. (2006) Tobacco smoking and colorectal hyperplastic and adenomatous polyps. *Cancer Epidemiol Biomarkers Prev.* 15(5), 897–901.
238. Chute C, Willet W, Colditz G, Stampfer MJ, Baron JA, Rosner B, et al. (1991) A prospective study of body mass, height, and smoking and risk of colorectal cancer in women. *Cancer Causes Control.* 2, 117–224.
239. Chyou P-H, Nomura A, Stemmermann G. (1996) A prospective study of colon and rectal cancer among Hawaii Japanese men. *Ann Epidemiol.* 6, 276–282.
240. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. (1994) Mortality in relation to smoking, 40 years' observations on male British doctors. *BMJ.* 309, 901–911.
241. Engeland A, Andersen A, Haldorsen T, Tretli S. (1996) Smoking habits and risk of cancers other than lung cancer, 28 years' follow-up of 26,000 Norwegian men and women. *Cancer Causes Control.* 7, 497–506.
242. Heineman E, Zahm S, McLaughlin J, Vaught J. (1994) Increased risk of colorectal cancer among smokers, results of a 26-year follow-up of US veterans and a review. *Int J Cancer.* 59, 728–738.
243. Nyren O, Bergstrom R, Nystrom L, Engholm G, Ekblom A, Adami HO, et al. (1996) Smoking and colorectal cancer, a 20-year follow-up study of Swedish construction workers. *J Natl Cancer Inst.* 88, 1302–1307.
244. Tverdal A, Thelle D, Stensvold I, Leren P, Bjartveit K. (1993) Mortality in relation to smoking history, 13 years' follow-up of 68,000 Norwegian men and women 35–49 years. *J Clin Epidemiol.* 46, 475–487.
245. Slattery ML, Samowitz W, Ma K, Murtaugh M, Sweeney C, Levin TR, Neuhausen S. (2004) CYP1A1, cigarette smoking and colon and rectal cancer. *Am J Epidemiol.* 160, 842–852.
246. Huang K, Sandler RS, Milikan RC, Schroeder JC, North KE, Hu J. (2006) GSTM1 and GSTT1 polymorphisms, cigarette smoking and risk of colon cancer, a population-based case-control study in North Carolina (United States). *Cancer Causes Control.* 17, 385–394.
247. van der Hel OL, de Mesquita HBB, Sandkuijl L, van Noord PA, Pearson PL, Grobbee DE, et al. (2003) Rapid N-acetyltransferase 2 imputed phenotype and smoking may increase risk of colorectal cancer in women (Netherlands). *Cancer Causes Control.* 14, 293–298.
248. Report of the Lung Cancer Progress Review Group. National Cancer Institute. Publication No. 01-5025. August 2001.
249. Smith-Warner S, Spiegelman D, Yaun S-S, Albanes D, Beeson W, van den Brandt PA, et al. (2003) Fruits, vegetables and lung cancer, a pooled analysis of cohort studies. *Int J Cancer.* 107, 1001–1011.
250. US Department of Health and Human Services. (2004) The Health Consequences of Tobacco Use, A Report of the Surgeon General, Atlanta, US Department of Health and Human Services, Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health.
251. Thun M, Henley S, Calle E. (2002) Tobacco use and cancer, an epidemiologic perspective for geneticists. *Oncogene.* 21, 7307–7325.
252. Thun M, Lally C, Flannery J, Calle E, Flanders W, Heath C. (1997b) Cigarette smoking and changes in the histopathology of lung cancer. *J Natl Cancer Inst.* 89, 1580–1586.
253. Patel JD. (2005) Lung cancer in women. *J Clin Oncol.* 23, 3212–3218.
254. Hecht SS. (2003) Tobacco carcinogens, their biomarkers and tobacco-induced cancer. *Nature Rev Cancer.* 3, 733–744.
255. Osada H, Takahashi T. (2002) Genetic alterations of multiple tumor suppressors and oncogenes in the carcinogenesis and progression of lung cancer. *Oncogene.* 21, 7421–7434.
256. Smits KM, Benhamou S, Garte S, Weijenberg MP, Alamanos Y, Ambrosone C, et al. (2004) Association of metabolic gene polymorphisms with tobacco consumption in healthy controls. *Int J Cancer.* 110, 266–270.
257. Kiyohara C, Otsu A, Shirakawa T, Fukuda S, Hopkin JM. (2002) Genetic polymorphisms and lung cancer susceptibility, a review. *Lung Cancer.* 37, 241–256.
258. Goode EL, Ulrich CM, Potter JD. (2002) Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol Biomarkers.* 11, 1513–1530.
259. Christiani DC. (2000) Smoking and the molecular epidemiology of lung cancer. *Clinics Chest Med.* 21(1), 87–93.
260. World Cancer Research fund and American Institute for Cancer Research, 1997. Food,

- nutrition and prevention of cancer, A global prospective. Washington, DC, American Institute for Cancer Research.
261. Kristal AR, Potter JD. (2006) Not the time to abandon the food frequency questionnaire, Counterpoint. *Cancer Epidemiol Biomarkers Prev.* 15(10), 1759–1764.
 262. Tardon A, Lee WJ, Delgado-Rodriguez M, Dosemeci M, Albanes D, Hoover R, Blair A. (2005) Leisure-time physical activity and lung cancer, a meta-analysis. *Cancer Causes Control.* 16, 389–397.
 263. Alfano CM, Klesges RC, Murray DM, Bowen DJ, McTiernan A, Vander Weg MW, et al. (2004) Physical activity in relation to all-site and lung cancer incidence and mortality in current and former smokers. *Cancer Epidemiol Biomarkers Prev.* 13(12), 2233–2241.
 264. Bak H, Christensen J, Thomsen BL, Tjorneland A, Overvad K, Loft S, Raaschou-Nielsen O. (2005) Physical activity and risk for lung cancer in a Danish cohort. *Int J Cancer.* 116, 439–445.
 265. Steindorf K, Friedenreich, Linseisen J, Rohrmann S, Rundle A, Veglia F, et al. (2006) Physical activity and lung cancer risk in the European prospective investigation into cancer and nutrition cohort. *Int J Cancer.* 119, 2389–2397.
 266. Sinner P, Folsom AR, Harnack L, Eberly LE, Schmitz KH. (2006) The association of physical activity with lung cancer incidence in a cohort of older women. The Iowa women's health study. *Cancer Epidemiol Biomarkers Prev.* 15, 2359–2363.
 267. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, et al. (2005) Cancer statistics. *CA Cancer J Clin.* 55, 10–30.
 268. Breslow N, Chan CW, Dhom G. (1977) Latent carcinoma of prostate of autopsy in seven areas. *Int J Cancer.* 20, 680.
 269. Dhom G. (1983) Epidemiologic aspects of latent and clinically manifest carcinoma of the prostate. *J Cancer Res Clin Oncol.* 106, 210.
 270. Haenszel W, Kurihara M. (1968) Studies of Japanese migrants. I. Mortality from cancer and other diseases among Japanese in the United States. *J Natl Cancer Inst.* 40, 43.
 271. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. (1991) Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. *Br J Cancer.* 63, 963.
 272. Di Mascio P, Kaiser S, Sies H. (1989) Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys.* 274, 532.
 273. Giovannucci E. (2002) A review of epidemiologic studies of tomatoes, lycopene and prostate cancer. *Exp Biol Med.* 227, 852–859.
 274. MacInnis RJ, English DR. (2006) Body size and composition and prostate cancer risk, systematic review and meta-regression analysis. *Cancer Causes Control.* 17, 989–1003.
 275. Wright ME, Chang S-C, Schatzkin A, Albanes D, Kipnis V, Mouw T, et al. (2007) Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. *Cancer.* 109, 675–684.
 276. Hsing AW, Chua S Jr, Gao YT, Gentzschein E, Chang L, Deng J, et al. (2001) Prostate cancer risk and serum levels of insulin and leptin, a population based study. *J Natl Cancer Inst.* 93, 783–789.
 277. Mantzoros CS, Tzonou A, Signorello LB, Stampfer M, Trichopoulos D, Adami HO. (1997) Insulin-like growth factor I in relation to prostate cancer and benign prostatic hyperplasia. *Br J Cancer.* 76, 1115–1118.
 278. Shaneyfelt T, Husein R, Bubley G. (2000) Hormonal predictors of prostate cancer, a meta-analysis. *J Clin Oncol.* 18, 847–853.



<http://www.springer.com/978-1-60327-491-3>

Cancer Epidemiology

Volume 2, Modifiable Factors

Verma, M. (Ed.)

2009, XIV, 484 p., Hardcover

ISBN: 978-1-60327-491-3

A product of Humana Press