

Cancer Risks

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This is just for your information.

As scientific research progresses, the evidence that dietary patterns, foods, nutrients, and other dietary constituents are closely associated with the risk for several types of cancer becomes more compelling. And while it is not yet possible to provide quantitative estimates of the overall risks, it has been estimated that 35 percent of cancer deaths may be related to dietary factors. The recommendations for dietary change currently before the American public are based on years of scientific research and offer potential for an effective public health approach to cancer prevention. Currently available research shows that diets low in fat and high in fiber, fruits, vegetables, and grain products are associated with reduced risks for many cancers.

Dietary Fats

Diets high in fat have been linked to increased risk of various cancers, particularly breast, colon, prostate, and possibly pancreas, ovary, and endometrium. Studies of populations in countries consuming high-fat diets compared to low-fat diets have consistently shown higher incidence and mortality rates for breast, colon, and prostate cancer. There is substantial, but not conclusive, evidence that the international association between fat intake and the risk of breast and colon cancer is much stronger for total fat intake compared to the specific type of fat, i.e., saturated, monounsaturated, or polyunsaturated fat. However, a combined analysis of 12 case-control studies showed a significant positive association between breast cancer risk and saturated fat intake in postmenopausal women. Recent studies in the same population of U.S. women reported that increased intakes of total saturated and monounsaturated fats were associated with increased colon cancer but not breast cancer.

Fat consumption in the United States is much higher than that needed to meet the physiological needs for energy and essential fatty acids. The average U.S. diet is estimated to contain approximately 37 percent of calories from fat. Dietary recommendations are to decrease total fat intake to 30 percent of calories. The major sources of fat in the American diet are added fats and oils used as spreads, cooking fats, and salad oils as well as the fat in meats and whole milk dairy products.

Because dietary fat intake is highly correlated with calorie intake, the question has been raised as to whether fat intake or calorie intake is the major dietary factor affecting cancer risk. However, the few studies that have addressed the relative importance of fat intake versus calorie intake suggest that both fat and calorie intake have independent effects. Dietary fat is the most concentrated source of energy of all the nutrients and supplies nine calories per gram compared to four calories per gram from either carbohydrate or protein. In general, a reduction in dietary fat intake is accompanied by a decrease in total calorie intake and body weight.

Dietary Fiber

Dietary fiber falls into two categories, water-soluble fiber and water-insoluble fiber, and is generally defined as those components of food plants resistant to the enzymes produced by the human digestive tract.

Increasing evidence suggests that diets high in fiber-containing foods are associated with a reduced risk for cancer, especially cancer of the colon. A few studies have also shown a reduced risk for cancers of the breast, rectum, oral cavity, pharynx, stomach, and other sites with diets rich in fruits, vegetables and grain products. Because these foods contain other nutrients as well as fiber, and are usually lower in fat, it has not been possible to determine whether the protective effect is attributable to dietary fiber.

Fruits and Vegetables

Populations consuming diets high in fruits and vegetables tend to have a lower cancer risk. Fruits, vegetables, and grains contain a number of nutrients, including carotenoids, vitamin A, and vitamin C. The cancers for which there is evidence of a protective effect include those of the lung, colon and rectum, breast, oral cavity, esophagus, stomach, pancreas, uterine cervix, and ovary. For most cancer sites, especially epithelial cancers of the respiratory and digestive tracts, persons with low fruit and vegetable intake had about twice the risk of cancer as those with high intake.

Carotenoids and Vitamin A

Numerous studies have found evidence that carotenoids reduce the risk of some cancers. The evidence is particularly strong for lung cancer, even after taking smoking into account. Every study that examined the role of carotene-rich foods found reduced lung cancer risk with higher intake, and about 20 of 25 studies yielded statistically significant results. Five of six studies of blood carotenoids found that persons with higher levels had reduced risk. There is no question that smoking is the strongest risk factor, and quitting smoking is the most important step to reduce risk. It appears, however, that there may be additional benefit to increasing the consumption of foods containing carotenoids.

Carotenoids are found in dark yellow/orange vegetables and fruits such as carrots, sweet potatoes, and cantaloupe and in deep green leafy vegetables such as broccoli, spinach, and collard greens. There are many different carotenoids in such foods, including beta-carotene, alpha-carotene, and lutein.

While the current dietary recommendation is for five servings of fruit and vegetables a day, Americans fall somewhat short of this goal. A recent survey showed that only 23 percent of the population is achieving this goal; the average daily intake is about three and a half servings of fruits and vegetables.

Vitamin C

Vitamin C is found in fruits, particularly citrus fruits and juices, and in green vegetables, as well as in some fortified foods. Of a group of epidemiologic studies investigating the role of vitamin C, three-fourths found that vitamin C, or fruit rich in vitamin C, provides significant protection. The evidence is most consistent for cancers of the esophagus, oral cavity, and stomach, but protective effects have been reported for cancers of the pancreas, rectum, and cervix. There is increasing evidence for a role in lung cancer, and an analysis combining results of studies of diet and breast cancer found that vitamin C had a strong and significant negative association.

Other Nutrients

Fruits, vegetables, and grains contain other vitamins and minerals associated with a protective effect against cancer.

Vitamin E has inhibited tumors in experimental animals and been linked to reduced risks of oral, stomach, and other cancer in epidemiologic studies. Selenium also may have a protective effect. In a recent randomized large-population trial testing the effectiveness of vitamin/mineral supplementation among persons in high risk areas of China, those who received daily supplements with a combination of beta-carotene, vitamin E, and selenium for 5 years had a significantly lower cancer death rate. The findings do not automatically translate to Western populations--in that the Chinese population studied was chronically deficient in a number of nutrients--but offer a hopeful sign that certain vitamins and minerals may lower risk of some cancers. However, two other recent large randomized trials of supplements, one testing the effect of supplemental beta-carotene or alpha-tocopherol in the prevention of lung cancer among smokers and the other testing the effect of supplemental beta-carotene and vitamins C and E in the prevention of adenomatous polyps (a precursor lesion for colorectal cancer), suggest that supplemental use of these nutrients does not reduce the risk of either lung or colorectal cancer. In the study of the effect of beta-carotene or alpha-tocopherol on lung cancer among smokers, dietary intake of these nutrients from foods was associated with a reduced risk for lung cancer. Some studies suggest that calcium may play a protective role in colon cancer. A 19-year prospective study in men showed the risk for colon cancer was lower in those with the highest calcium intake. In addition to dairy products, certain vegetables are good sources of calcium, notably roots, okra, and dark green leafy vegetables such as collard greens.

Tobacco use, particularly in the form of cigarette smoking, is the single most preventable cause of excess mortality in the United States. Each year, more people die prematurely from smoking than die from automobile accidents, drug abuse, AIDS, and alcohol combined. An estimated 434,000 Americans died as a result of their smoking last year alone. Former Surgeon General C. Everett Koop has called cigarette smoking "...the chief, single, avoidable cause of death in our society and the most important public health issue of our time".

A series of authoritative reports by the U.S. Public Health Service and other international scientific organizations has conclusively documented a causal relationship between cigarette smoking and cancer of at least eight major sites. These reports have uniformly identified smoking as a major cause of cancers of the lung, larynx, oral cavity, and esophagus--that is, cigarette smoking is responsible for a majority of the cases and deaths from cancer of these sites. These reports have also demonstrated that smoking substantially elevates the death rates for cancers of the bladder, kidney, and pancreas in both men and women, and, possibly, cervical cancer in women. A number of published reports have suggested an association between smoking and other cancers, including cancer of the stomach, liver, prostate, colon, and rectum.

Recent evidence published by investigators at the National Cancer Institute and the American Cancer Society conclusively demonstrates that the cancer risks among current cigarette smokers are greater today than at the time of the first Surgeon General's report in the early 1960s. Table 1 reports the relative risks of early cancer mortality for the eight major smoking-associated cancer sites among smoking men and women compared to nonsmokers. These data are taken from the large American Cancer Society

Cancer Prevention Study II of more than 1.2 million individuals (685,748 women and 521,555 men) followed prospectively since 1982. This study clearly shows that, for each site, mortality risks among current smokers are higher than those among nonsmokers. Mortality risks in former smokers are lower than in those who continue to smoke, but higher than in those subjects who had never smoked.

The risk of developing any of the smoking-related cancers is dose-related; that is, the more cigarettes consumed daily, the younger the age at which one initiates smoking, and the more years one smokes, the greater the risk.

Among male cigarette smokers, the risk of lung cancer is more than 2,000 percent higher than among male nonsmokers; for women, the risks were approximately 1,200 percent greater. Lung cancer is the single largest cause of cancer mortality among both men and women and accounts for more than one in every four cancer deaths nationally in the U.S.

In addition to cigarette smoking as a cause of cancer in smokers, environmental tobacco smoke (ETS) (also called involuntary or passive smoking) is now recognized as a significant cause of lung cancer in nonsmokers. Nonsmokers who live or work with smokers experience a 30 to 50 percent elevated risk for lung cancer. An estimated 3,000 to 6,000 nonsmoker lung cancer deaths annually are attributed to ETS. While the number of ETS related lung cancer deaths may seem small when compared to the number attributed to active smoking, the number is actually quite large when compared to other indoor and outdoor environmental pollutants, many of which are regulated by the U.S. Environmental Protection Agency. By way of comparison, two British scientists have estimated that exposure to asbestos fibers among people who live or work in asbestos-containing buildings carries an annual risk of lung cancer of less than 1 in 1 million. Notwithstanding this small risk, great efforts are made to remove asbestos from work sites, schools, and other public buildings because the risks are deemed to be unacceptable. Yet, according to these same investigators, the relative risk for lung cancer due to ETS "is more than 100 times higher than the estimated effects of 20 years' exposure to the amount of chrysotile asbestos normally found in asbestos-containing buildings".

Smokeless tobacco users are at increased risk for cancers of the oral cavity, particularly cancers of the cheek and gum, and evidence also suggests an association between use of smokeless tobacco and cancers of the larynx and esophagus.

Pipe and cigar smokers experience substantially elevated risks for cancers of the oral cavity, larynx, pharynx, and esophagus, which equal and often exceed the risks observed in regular cigarette smokers. Pipe and cigar smokers experience a slightly increased risk for lung cancer; however, among pipe and cigar smokers who inhale, the risk of lung cancer is on the same order of magnitude found in cigarette smokers.

The total magnitude of the cancer burden caused by smoking is staggering. Of the 514,000 cancer deaths expected to occur this year in the United States, slightly over 164,000, or nearly one-third, are directly linked to cigarette smoking. An additional 14,000 deaths can reasonably be attributed to pipe and cigar smoking among men. In all, it is estimated that cigarette smoking causes approximately 23 percent of all cancer deaths in women, but the combination of pipe, cigar, and cigarette smoking is responsible for 42 percent of all male cancer deaths. If cancer deaths associated with tobacco use were excluded from national cancer mortality figures, we would be witnessing a substantial downturn in both overall cancer deaths and rates.

In short, all forms of tobacco use are hazardous, but the hazards are magnified when smoke from the tobacco is inhaled. Furthermore, the nicotine in tobacco is addictive, which makes it extremely difficult for most users to stop the behavior once it has been adopted as part of their lifestyle.

What's in Cigarette Smoke to Cause so Many Diseases?

Tobacco smoke contains literally thousands of chemical agents, including 60 constituents which are known carcinogens, cocarcinogens, or tumor promoters. Because the average smoker consumes about 30 cigarettes daily, the smoker is being subjected to a constant barrage of hazardous agents. After many years of smoking, it is not surprising that smokers die many years prematurely from cancer, heart disease, emphysema, bronchitis, and other chronic and debilitating diseases at rates substantially higher than persons who never smoke.

The Health Benefits of Quitting Smoking

Quitting smoking greatly reduces the risks for all these diseases. For example, within a year of quitting, a former smoker's risk of heart disease is reduced by nearly 50 percent compared to someone who continues to smoke. Unfortunately, the risks for lung cancer do not decrease as rapidly, but the sooner one quits smoking, the quicker one begins to benefit. Usually, after 10 to 15 years off cigarettes, most former smokers' health status is not significantly different from that of a lifelong nonsmoker. Any residual risk following cessation is strongly dependent on total previous exposure to cigarette smoke, length of time off cigarettes, and the health status of the individual at the time of cessation.

Most cancers are caused by a variable mix of heredity and environment. While an inherited defect can lead to cancer clusters in multiple members of certain families, the age at which cancers first appear will differ among these relatives, due in part to environmental triggers. Other cancers, such as lung cancers in cigarette smokers, while caused primarily by external factors, are still influenced by genes which modify an individual's risk of disease. To further our understanding of cancer etiology and risk factors, scientists are currently studying the complex ways in which genes and environment interact.

Some ethnic groups apparently possess traits that protect them against specific cancers. For example, chronic lymphocytic leukemia is extremely rare among Asians; Ewing's sarcoma, skin cancers, and testicular cancer are very rare among blacks.

Family clusters have been reported for virtually every form of cancer. In general, close relatives of a cancer patient have twice the usual risk for developing the same type of cancer, but among different cancer families the level of excess risk can vary widely. Familial cancer clusters are often due to inherited factors, but environmental influences, chance association, or a combination of these factors also must be considered. The effect of chance is considerable; within the U.S. population there is approximately a 45 percent lifetime risk of developing cancer, including the common nonmelanoma skin cancers. Thus, it is not unusual for most families to have at least some individuals with a history of cancer.

An inherited susceptibility often becomes apparent when cancers of the same body site or organ occur in multiple blood relatives. These cancers tend to occur at earlier ages

than usual, and often develop in more than one site in a particular organ, e.g., two primary breast cancers in the same breast or one in each breast. Hereditary cancers can also arise in multiple organs, as seen in the Li-Fraumeni syndrome, a disorder characterized by the early onset of breast cancer in mothers of children with leukemia and/or bone and soft tissue sarcomas. In addition, cancer can occur as part of a non-cancerous hereditary disease with diverse features, such as neurofibromatosis.

In familial cancers that are triggered by environmental carcinogens, patient education regarding the avoidance of harmful exposures can help prevent or delay the onset of cancer. For example, members of melanoma-prone families who avoid significant ultraviolet radiation exposure can reduce substantially their risk of melanoma.

Recent laboratory findings have emphasized the importance of studying cancer-prone families. New methods in molecular biology have been used to identify several human cancer genes and to reveal a new class of cancer genes, called tumor suppressor genes or antioncogenes. These genes normally function by inhibiting the development of cancer. However, when they are damaged they lose their protective effect and cancer arises with greater frequency. The first such inherited cancer susceptibility gene to be discovered was that for retinoblastoma (RB1), a malignant eye tumor which occurs in children.

Several additional tumor suppressor genes have been identified, predominantly through studies of cancer-prone families with hereditary cancers. For example, inherited alterations in the p53 gene have been found in the Li-Fraumeni Syndrome. The WT1 gene for Wilms' tumor, the APC gene for colon cancers associated with familial adenomatous polyposis coli, the NF1 and NF2 genes for neurofibromatosis, types 1 and 2, the p16 gene found in some melanoma families and the VHL gene for renal cancer and other tumors associated with von Hippel-Lindau disease have all been recently identified and characterized.

Major discoveries within the last year include the identification of BRCA1, a gene for hereditary breast and ovarian cancer, the localization of BRCA2, another breast cancer gene, and mismatch repair genes--such as MLH1 and MSH2 for hereditary nonpolyposis colorectal cancer. (The function of mismatch repair genes is to prevent DNA from making errors during replication.) Approximately 5 percent of breast or colon cancer patients might carry one or more inherited susceptibility genes. The discovery of these genes has increased greatly the numbers of cancer susceptibility gene carriers who can possibly be identified.

The primary purpose of identifying gene carriers would be to promote earlier detection of cancer and, since prognosis is correlated closely with stage of disease at diagnosis, increased survivability. However, identifying gene carriers in cancer-free populations is a new concept with many clinical, ethical, legal and psychosocial implications yet to be explored. Predisposition testing presents certain advantages when prevention and early detection measures are available. On the other hand, there is a great potential for harm—from loss of insurability and employability, psychological stress, social stigmatization and other adverse consequences. As more and more inherited susceptibility genes are identified, their clinical relevance will require careful evaluation. The challenge to research is to identify testing procedures and guidelines that maximize benefits while minimizing harm.

The concept that viruses cause human cancer dates back to the first decade of the 20th century, when experiments on animals showed that tumors could be induced in chickens by an agent that could pass through a filter. This pioneering work by Francis Peyton Rous in the United States was recognized more than 50 years later with the 1972 Nobel Prize that he shared with Howard Temin and David Baltimore, who characterized the molecular biology of retroviruses, first detected in Rous's experiments. Over the last decade, the new tools of molecular biology have led to profound discoveries about the role of viruses in human cancer and the mechanisms of disease causation.

Viruses are a type of infectious agent that must invade living cells in order to reproduce. The two major types of viruses have either DNA or RNA as their genetic material. Viruses often invade cells by attaching to receptors on the surface of the target cell. Once inside the cell, they often integrate their genetic material into that of the host and alter the cell in ways that predispose to cancer through a variety of mechanisms. In some cases, the virus is thought to induce cancer directly; in other cases, indirect effects of the virus (e.g., immunodeficiency) predispose to malignancy. The major classes of viruses that are linked to cancer are retroviruses, herpes viruses, papilloma viruses, hepadnaviruses (hepatitis B), and flavaviruses (hepatitis C). In addition, genes called oncogenes, first discovered as part of the genetic material of acutely transforming retroviruses but now recognized as part of the normal genetic makeup of the cell, have been identified as critical factors in the oncogenic process.

The first human retrovirus, discovered by Robert C. Gallo of the National Cancer Institute, is called human lymphotropic virus type I (HTLV-I). This prototype human retrovirus is strongly associated with malignant lymphomas of T-lymphocytes, first recognized in Southern Japan and called adult T-cell leukemia/lymphoma. A characteristic feature of these tumors is the monoclonal integration of the viral genome in the tumor tissue. Because the leukemia may occur years to decades after infection--which often occurs at birth--it is hypothesized that other factors play a role in pathogenesis. However, viral genes have the capacity to turn on genes of the host cell, promoting cell growth that may lead to uncontrolled cell proliferation. Recently, HTLV-I has been linked to a chronic neurologic syndrome called HTLV-associated myelopathy, which, because of demyelination, bears some resemblance to multiple sclerosis. The HTLV-I virus also causes a pediatric immunodeficiency syndrome called infective dermatitis and adult autoimmune diseases such as polymyositis and arthritis. Because of these immunologic effects of HTLV-I, it has been hypothesized that some more common cancers might be enhanced by HTLV-I infection through indirect mechanisms such as immunodeficiency. The closely related HTLV-II virus has not been definitively linked to cancer, although it was first isolated from a patient with a rare form of T-lymphocyte leukemia. The recent discovery that HTLV-II occurs naturally among some native American populations has created new opportunities to determine whether this "orphan" virus contributes in any way to cancer or other disease causation. Since 1990, the American blood supply has been screened for HTLV-I. As a consequence, numerous donors have been identified as seropositive and have sought counseling concerning the health implications of this infection. While disease risk is not fully characterized, experts agree that the risk of leukemia and other complications is low, with an estimated lifetime risk of approximately 3 to 5 percent for an HTLV-associated disease.

The emergence of an epidemic of Kaposi's sarcoma in the United States among gay men, first recognized in 1981, was soon linked to the epidemic of acquired immunodeficiency syndrome, and an infectious agent postulated. The techniques pioneered by Robert C. Gallo were critical to the isolation of human immunodeficiency

virus by Gallo and Luc Montagnier of The Institut Pasteur in Paris. This class of virus has as its major effect the induction of profound immunodeficiency through its ability to infect T-lymphocytes and cause their destruction. While the process of HIV-associated immunodeficiency is complex, including direct killing effects of the virus on T-lymphocytes, lymphokine-mediated immune perturbations, and "autoimmune" mechanisms, the end result is a progressive depletion of CD-4 positive T-helper lymphocytes. This depletion results in heightened susceptibility of the infected individual to a variety of "opportunistic" pathogens as well as numerous cancers.

Kaposi's sarcoma is a cancer of the lining of blood vessels which can occur on the skin, or be more widely disseminated in vital organs. Before the AIDS-associated epidemic, Kaposi's sarcoma was a rare tumor reported largely among older men, often of Mediterranean ancestry, and in residents of central Africa. The epidemic form is largely seen among gay men and is much more rare in other groups at risk of HIV infection. Some epidemiologic data suggest that an infectious agent may be involved and studies are under way to search for such an agent. Recently, a novel herpesvirus has been implicated in the pathogenesis of AIDS-related body-cavity-based lymphomas. The other major tumor type is non-Hodgkin's lymphoma, which occurs in all risk groups and appears strongly related to profound immunodeficiency .

The pattern of tumor types and the high frequency of lymphomas of the central nervous system mirror the pattern of lymphomas associated with congenital and transplantation-associated immunosuppression. In one recent analysis, it was estimated that between 8 percent and 10 percent and up to 25 percent of all lymphomas in the United States will be AIDS-associated in coming years. Molecular studies have suggested that these lymphomas are linked to the Epstein-Barr virus (EBV), often with the pattern of oncogene translocation associated with Burkitt's lymphoma, which is a type of virally associated cancer originally described by Sir Dennis Burkitt in the 1960s. Thus, AIDS-associated cancers may represent examples of a process of immunosuppression allowing other oncogenic viruses such as EBV or the more recently discovered human herpes virus 6 (HHV-6) to be expressed as cancer.

It is likely that some other virally-associated cancers will show increases among HIV-positive immunosuppressed persons. For example, preliminary data suggest that human papilloma viruses may be increased in HIV-infected persons, with the potential for enhancing induction of associated tumors.

As noted above, Epstein-Barr virus has been linked to Burkitt's lymphoma as well as other lymphomas, Hodgkin's disease, and nasopharyngeal carcinoma. Intervention studies with an EBV vaccine are now under way in hopes of preventing some of these cancer types.

Worldwide, hepatocellular carcinoma is a leading cause of death. A role for hepatitis B in the etiology of this tumor is well established. For example, very large studies of persons from populations where hepatitis B is frequent have shown an exceptional risk for cancer among antigen carriers who have not developed an adequate antibody response to the virus. Vaccine trials are also under way with this virus in order to prevent infections and associated hepatocellular cancer. The recently discovered hepatitis C, has also been linked to hepatocellular carcinoma. Given the very different nature of these two viruses, important clues about the role of viruses that cause liver damage and cancer will emerge as more is learned.

The decade of the 1990s is exciting because of the advances in techniques for detecting and characterizing oncogenic viruses. It is likely that new agents that cause cancer will be discovered, and cancers of unknown cause linked to known and yet to be discovered agents.

Hormones, substances produced in the body, have regulatory effects on specific organs. Estrogens and progesterone are two hormones produced predominantly in the ovary of the female. Estrogens control the development of feminine body characteristics, and both estrogens and progesterone regulate the menstrual cycle and pregnancy. Androgens, which are produced predominantly in the male, determine masculine body characteristics. These hormones, or synthetic chemicals that have similar effects, are used as drugs for a variety of purposes.

Many women take "replacement" estrogens to relieve the hot flashes, vaginal dryness, and itching that may develop at menopause when ovarian function decreases. They are also taken by older women to retard bone loss. The most frequently prescribed estrogen in the United States is Premarin, a natural estrogen. Between 1962 and 1975, there was a four-fold increase in the use of estrogens for menopausal symptoms in the United States. This was followed by a parallel increase in the incidence of cancer of the endometrium, the lining of the uterus. An explanation for the rise in incidence came from several studies which showed nine- to 14-fold increases in the risk of endometrial cancer associated with long-term use of menopausal estrogens. Subsequent studies have confirmed these earlier findings and suggest that risk is greatest among current and recent users. There is also a fairly rapid decline in risk after cessation of use, although a small increase in risk remains for former users.

Numerous studies have shown a slightly increased risk of breast cancer in different subgroups of women who have used estrogens for a long period or at relatively high doses. A number of other studies, however, have found no increased risk associated with duration or dose, making it difficult to draw firm conclusions about the risk of breast cancer associated with the use of estrogen replacement therapy.

Most evidence suggests no overall association between menopausal estrogen use and risk of ovarian cancer, although further research is needed to determine whether replacement estrogens increase risk of specific types of ovarian tumors. Of two studies that have examined the relationship between menopausal estrogens and eye melanoma, one found no association, and the other found a two-fold increase in risk associated with menopausal estrogen use. Several studies suggest that menopausal estrogens protect against large bowel cancer, while others do not.

With the recognition in the early 1980s that use of progesterone or its derivatives (collectively called progestins) may offset the increased risk of endometrial cancer associated with estrogen use, it has become increasingly common to prescribe progestins in conjunction with estrogens during a portion of the monthly cycle.

The most frequently prescribed progestin in the United States is Provera (medroxy-progesterone acetate), a derivative of progesterone. While the addition of progestins to estrogen replacement therapy appears to have definite beneficial effects on endometrial cancer risk, further epidemiologic studies are needed to determine the optimal regimen needed to counteract the adverse effects of estrogens, particularly after prolonged use. Data regarding the effect of estrogen/progestin replacement therapy on risk of breast cancer are limited and inconsistent. Early studies reported a

protective effect of the estrogen/progestin combination, but a recent study reported an increased risk of breast cancer in long-term users of estrogens and progestin in combination. Further studies are needed to clarify this issue.

In contrast to the natural estrogens most commonly used in estrogen replacement therapy, the estrogens used in oral contraceptives are synthetic. The most effective and widely used oral contraceptives are "combination" pills, taken for 21 days, that contain a fixed amount of estrogen and progestin. These "combination" oral contraceptives actually reduce a woman's risk of some cancers. Studies have uniformly shown a risk reduction of 40 to 50 percent for ovarian and endometrial cancers in women who ever used combined pills. The risk decreases with increasing duration of use, and some protective effect appears to persist for at least 10 to 20 years after discontinuation of use (Stanford, 1993, Rosenberg, 1994). However, sequential oral contraceptives, in which estrogen alone is taken during the first 14 to 16 days of the monthly cycle followed by an estrogen-progestin combination during the last five or six days, have been associated with increases in the risk of endometrial cancer.

The relationship between oral contraceptive use and risk of breast cancer remains unresolved despite numerous studies. Although many studies have found that oral contraceptive use does not increase risk of breast cancer in most women, most, but not all, studies have reported that long-term use at an early age increases risk in women under the age of 45 years. Prolonged use of oral contraceptives has also been linked to an increased risk of cervical cancer, but some doubt remains as to the causality of this association. Substantial increases in the risk of liver cancer have also been associated with oral contraceptive use in developed countries where this cancer is very rare. However, no such elevation in risk has been detected in countries where hepatitis B virus is endemic and liver cancer rates are high. Present evidence suggests that there is no causal link between oral contraceptive use and cutaneous melanoma, cancers of the kidney, the colon, the gallbladder, or tumors of the pituitary.

Depot-medroxyprogesterone acetate (DMPA), a long-acting progestational injectable contraceptive, has been approved for contraceptive use in more than 90 countries, including the United States. However, concern that DMPA might increase the risk of breast cancer in women delayed its approval in the United States until 1992. Although data are limited, there appears to be no overall increase in breast cancer risk among women who have used this form of contraception. However, a two-fold increase in the risk of breast cancer in women who started using DMPA in the previous five years has been reported, suggesting that DMPA may accelerate the growth of preexisting tumors. Data on DMPA use and risk of other cancers are also limited, but suggest no association with cervical or ovarian cancer, or liver cancer, and a protective effect against endometrial cancer.

DES (diethylstilbestrol), a synthetic chemical with estrogenic properties, has also been linked to risk of cancer. It was used for the prevention of miscarriage and late complications of pregnancy during the late 1940s and 1950s. Following several studies in the late 1950s that reported no beneficial effect of DES, use of the drug gradually tapered off. In 1971, prenatal DES exposure was linked in young women to clear-cell adenocarcinoma of the vagina, a rare form of cancer. Subsequent studies have also linked prenatal DES exposure to clear-cell adenocarcinoma of the cervix. Results from a number of studies suggest that a woman exposed to DES in utero has about a one in 1,000 chance of developing a clear-cell adenocarcinoma of the vagina or cervix by the

age of 34 years. There is little evidence, however, that prenatal exposure to DES increases risk of other types of cervical or vaginal cancers.

Studies have shown that males exposed to DES in utero have a greater frequency of abnormalities of the reproductive tract than those not exposed. One of these abnormalities, failure of the testes to descend into the scrotum, is known to increase the risk of testicular cancer. In several studies, a higher proportion of males with testicular cancer were also exposed to DES in utero compared to study subjects without testicular cancer.

Studies of breast cancer in women who were themselves treated with DES to prevent abortion have yielded inconsistent results and further studies are needed to determine whether the possible association is causal. Data on development of other types of cancer in women exposed to DES during pregnancy are too limited to draw firm conclusions.

Synthetic androgens are used in the treatment of renal conditions, various types of anemias, endocrine disorders, and generalized weakness. They are also used by athletes and body builders to enhance development of skeletal muscles. Individual cases of liver cancer have been linked to the use of these substances, but well-designed studies are needed to confirm or refute a causal relationship with oral contraceptives.