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NON-INTRINSIC CANCER RISK FACTORS

*S. Yıldırım-Kahrıman**
Demiroglu Bilim University, Istanbul 34394, Turkey

Our knowledge about the etiology of cancer is increasing. Many studies show that non-intrinsic factors such as environment or lifestyle are the main risk factors for the occurrence of cancer. On the other hand, there are studies showing that the main risk factors in the occurrence of cancer are caused by DNA replication errors (known as the intrinsic factors). This view limits highly the possibility of protection from cancer. However, the findings obtained from the literature show that non-intrinsic factors contribute substantially to cancer risk and that cancer should be considered as a preventable disease. This review is aimed to examine the factors known as non-intrinsic cancer risk factors in the light of recent research.
Key Words: **cancer, non-intrinsic risk factors, cancer prevention.**

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INTRODUCTION

The International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO), estimates that 18.1 million people were diagnosed with cancer in the world in 2018 and 9.6 million died due to cancer [1]. According to the estimates of the WHO in 2015, in the deaths seen before the age of 70, cancer takes the first or second place in 91 of 172 countries and occupies the third or fourth place in 22 countries. Cancer is a disease whose incidence and mortality increase rapidly all over the world. It can be said that the most important factors that lead to this situation are the prolongation of life expectancy and the increase in the frequency of being affected by risk factors, many of which are related to socioeconomic development [2].

Cancer incidences differ among different populations around the world. If environmental and/or behavioral factors responsible for these differences can be identified and changed, it can be thought that cancer is largely preventable [3].

The main and specific causes of some cancers are known, for example, smoking in lung cancer, sunlight in skin cancer, human papilloma virus infection in cervical cancer, *Helicobacter pylori* infection in gastric cancer and viral hepatitis in hepatocellular carcinoma. However, the causes of some other common cancers such as prostate and colorectal cancer are not yet fully understood [3, 4].

It is possible to examine the main risk factors that play a role in the emergence of cancer in two categories as intrinsic and non-intrinsic factors. Unmodifiable intrinsic factors are DNA replication errors that occur spontaneously in the cell. Non-intrinsic factors are modifiable exogenous factors and partially modifiable endogenous factors associated with individual characteristics [4]. Exogenous factors can be listed under the headings of tobacco and tobacco products use, diet-related factors, radiation, medical carcinogens, occupational carcinogens and environmental pollution. Endogenous factors can be summarized as infections, reproductive and hormonal factors and genetic susceptibility. In this review, the non-intrinsic risk factors listed above will be examined one by one.

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*Correspondence:
E-mail: senay.yildirimkahriman@demiroglu.bilim.edu.tr; syildirim7@yahoo.com
Abbreviations used: CT – computed tomography; ELF – extremely low frequency; IARC – International Agency for Research on Cancer; IL – interleukin; HPV – human papilloma virus; RF – radio frequency; UVR – ultraviolet radiation; WHO – World Health Organization.

EXOGENOUS FACTORS

Tobacco and cancer

Tobacco use, which is considered to be the most preventable factor in cancer disease, is held responsible for one third of cancer deaths each year [5]. The most common use of tobacco is smoking, but it is also consumed in the form of pipes, cigars or hookahs. Smoking is the single most important risk factor in the development of lung cancer. The diagnosis of lung cancer is rare in a non-smoker. Cancer of the larynx, mouth, pharynx, esophagus, pancreas, urinary bladder and kidney, besides lung cancer, are known to be associated with smoking. In addition, stomach, liver, cervix, nasal cavity and myeloid leukemias are also associated with smoking. Avoiding smoking means preventing 15 different cancers [6].

Cigarette has a highly complex chemical content of over 8700 identified ingredients [7]. It contains carcinogenic substances that belong to different chemical groups such as non-polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines, aldehydes, volatile organic hydrocarbons and metals. Most carcinogens in cigarettes are transformed in the cell by the catalysis of the cytochrome P-450 enzyme, thus being able to bind to DNA and creating new DNA adducts. These events are called metabolic activation processes. This process in the cell competes with the metabolic detoxification process. In metabolic detoxification, carcinogens in cigarettes are converted to harmless metabolites by the catalysis of glutathione-S-transferase, uridine-5-diphosphate glucuronacyltransferase, apoxide hydrolase and sulfa-

tases. The balance between metabolic activation and metabolic detoxification varies between individuals, and this balance is likely to play a role in the development of cancer susceptibility. People with higher activation and lower detoxification capacity are more likely to develop a cigarette related cancer disease. These findings are supported by molecular epidemiological studies investigating enzyme polymorphism [8]. Some carcinogens in cigarettes can directly form DNA adducts without metabolic activation process. There are also repair mechanisms in the cells that eliminate these DNA adducts and maintain the normal DNA structure. However, if repair mechanisms are not working properly, somatic mutations are likely to occur and this can lead to cancer development. Persistent DNA adducts can cause false coding during DNA replication. Such mutations are observed in lung cancer, especially *KRAS* oncogene, and in some other types of cancer, *TP53* gene. Gene mutations can lead to loss of normal functions that control cell growth, resulting in increased cell proliferation and cancer [9].

Smoking cessation is the only proven strategy to prevent the pathogenic process of cancer development.

Dietary factors that contribute to cancer

Dietary habits play a key role in increasing or decreasing the risk of cancer. The possible role of the diet in the etiology of cancer emerged in the 1970s, with the understanding that the rates of colorectal, breast and prostate cancer were high in western countries that consume more animal products, oil and sugar. In contrast, developing countries that consume low animal food, fat and sugar have a low incidence of these cancers. These observations partially explain the different rates of cancer seen in populations with different diets. For example, the incidence of colorectal cancer is lower in the African population that consumes high fiber in their diets [10]. Stomach cancer is more common in East Asia, where salty foods are consumed more [11].

Obesity and cancer. Epidemiological studies show that overweight and obesity, a growing epidemic in many countries, are associated with an increased risk of cancer. There are studies showing a worse prognosis and higher mortality rate in obese cancer patients [12]. Postmenopausal breast cancer, endometrial cancer, ovarian, prostate, colorectal, renal, pancreas, liver, gallbladder cancers and esophageal adenocarcinoma are cancers associated with obesity [13].

While obesity is an important factor leading to cancer, reduced food consumption has a protective effect against cancer. Energy restriction has been shown to reduce the occurrence of spontaneous tumors in laboratory mice [14]. Energy limitation inhibited the emergence of induced breast tumor in mice and suppressed the growth of implanted tumors [15, 16]. Breast cancer incidence decreased by 23% in hospitalized women due to anorexia nervosa [17].

Although the metabolic disorder caused by obesity is considered as a risk factor for cancer, the underlying biological mechanism has not yet been fully understood. Epidemiological, clinical and preclinical studies suggest that the proinflammatory microenvironment associated with obesity interacts with adipose tissue (adipocytes, macrophages and other cells in adipose tissue), and cancer-prone cells may be formed by the effect of obesity-related hormones, cytokines and other mediators. *In vitro* and *in vivo* preclinical studies show that some factors such as originating from adipose tissue some cytokines (interleukin (IL)-6), IL-8), monocyte chemotactic protein 1, tumor necrosis factor-α and macrophages can affect cell metabolism and advance cancer. Inflammatory adipose tissue significantly increases the risk of cancer and can stimulate cell transformation, cell survival and proliferation, invasion, angiogenesis and metastasis [18].

Alcohol and cancer. Alcohol was previously considered a cancer-leading factor that did not cause cancer. However, more recent *in vivo* studies have shown that ethanol given to animals such as mice and rats develops tumors, and therefore alcohol is a direct carcinogen [19]. IARC has identified alcohol as a Group 1 carcinogen since 1988 [20]. Moderate or excessive alcohol consumption increases the risk of oral cavity, pharynx, esophagus, stomach, larynx, colorectum, central nervous system, pancreas, breast and prostate cancer [21]. The mechanism of alcohol causing cancer has not been fully explained, but there are some defined mechanisms on the subject. These mechanisms involved are the genotoxic effects of acetaldehyde (the metabolic product of alcohol), alcohol's revealing types of reactive oxygen, disrupting retinoid metabolism, raising the level of estrogen hormone and genetic polymorphisms [22].

Nutrients and cancer

Refined sugar. While examining the relationship of refined sugar and refined white flour products with cancer, glycemic index or Hemoglobin A1C levels are among the criteria that can be evaluated. High glycemic index has been found to be associated with upper respiratory tract, endometrium, stomach, ovarian and colorectal cancers. Similarly, high Hemoglobin A1C is associated with colorectal cancer. There are also some studies showing that there is a relationship between diabetes and colorectal cancer, endometrial cancer and pancreatic cancer [23, 24]. Sugar is thought to increase the risk of cancer by causing excess weight and obesity, and it does not have a direct oncogenic effect.

Low dietary fiber. Low dietary fiber is considered a risk factor for colorectal cancer [25, 26]. Dietary fiber is thought to have a protective effect against colorectal cancer by diluting fecal carcinogens, reducing colon transition time and turning into anticarcinogenic short-chain fatty acids [10].

Red meat. In 2015, IARC examined more than 800 epidemiological studies and classified red meat as "possible carcinogen" and processed red meat as

"carcinogen" [27]. Meta-analysis studies have shown that excessive consumption of red meat and processed meat increases the risk of colorectal, lung, esophageal and gastric cancer and there is no relationship between consuming white meat and cancer risk [28]. In some processes, such as cooking, smoking or subjecting the meat to a high temperature, it is known that carcinogenic substances such as N-nitrous compounds, polycyclic aromatic amines and heterocyclic amines are formed in the meat. Possible mechanisms of red meat or processed meat in increasing the risk of cancer can be listed as (1) increased oxidative load forming DNA adducts and causing lipid peroxidation in the intestinal epithelium (2) proliferative stimulation of the intestinal epithelium through hem or epithelial transformation caused by nutrient metabolites (3) an increased inflammatory response that may trigger malignant change [29, 30].

Omega-6/omega-3 ratio and cancer. The high omega-6/omega-3 ratio in the body plays a role in the pathogenesis of some diseases such as cancer. The precursor of omega-3 fatty acid, alpha linoleic acid, is a molecule associated with the anti-inflammatory response. Linoleic acid, the precursor of omega-6 fatty acid, is associated with the pro-inflammatory response. It is thought that the rate of omega-3/omega-6 in the body is more important than the individual intake of omega 3 and omega 6 in cancer development. High omega-6 intake in western countries seems to be associated with many cancers. Omega-3 and omega-6 fatty acids compete with each other at the level of activity of enzymes that promote the formation of factors that cause cancer. In addition, if the membranes of cancer cells are richer in unsaturated fatty acids and poorer in saturated fatty acids, omega-3 fatty acids make cancer cells sensitive to free radicals. This makes the cell membrane less stiff and more vulnerable. While omega-6 increases the survival by preventing the death of tumor cells, omega-3 fatty acids provide self-destruction of tumor cells. Omega-3 fatty acids suppress the production of prostaglandin E2, which is responsible for inflammatory response, cell growth, apoptosis, angiogenesis and metastasis. There are *in vitro* and *in vivo* studies showing that omega-3 fatty acids make tumor cells more sensitive to anticancer drugs [31]. It can be thought that omega-3 fatty acids have anticancer effects by affecting multiple targets at different stages of cancer development such as cell proliferation and survival [32].

Salt consumption. There are epidemiological studies showing that high salt consumption is a risk factor for stomach cancer [33]. Some experimental studies show that salt increases the risk of stomach cancer by synergistic effect with *Helicobacter pylori* infection. High salt consumption facilitates the colonization of *Helicobacter pylori* in the gastric mucosa, promoting proliferation of mucosa cells where bacteria are colonized and reduces mucin secreted from the mucous gland cells that act against the infection caused by the bacteria [34, 35]. Salt has also been shown to have independent effects that increase endogenous mutations and cell proliferation in the gastric mucosa [36, 37].

Radiation and cancer

Ionizing radiation and cancer. Ionizing radiation can cause cancer in any tissue or organ, but red bone marrow, breast and thyroid are among the most sensitive tissues. The occurrence of cancer can occur 40 years after exposure to radiation, and exposure to radiation at a young age increases the risk [3]. Information on the carcinogenic effects of ionizing radiation is based on tracking atom bomb and nuclear accident survivors, epidemiological studies on those exposed to radiation from medical or environmental sources, experimental animal studies, and *in vitro* studies. Radon gas is the most important radiation exposure from environmental sources. It is formed as a result of the decaying Uranium into Radium. Radium is found in large quantities in soil, rocks and indirectly in some building materials. It is known that radon gas from radium causes a high rate of radioactive pollution in buildings. Radon gas accumulates in respiratory system organs and is considered to be an important factor causing lung cancer [38]. Ionizing radiation directly or indirectly damages the DNA molecule. Some of these damages lead to cell death while others make non-fatal modifications. Non-fatal modifications cannot be repaired or can be repaired incorrectly causing malignant changes [39].

Non-ionizing radiation and cancer. Non-ionizing radiation (ultraviolet radiation (UVR), visible light, infrared, microwave, radio frequency (RF), and extremely low frequency (ELF)) does not have the energy to break chemical bonds and ionize. UVR is accepted as the main factor leading to skin cancers (cutaneous malignant melanoma, basal-cell carcinoma, and squamous-cell carcinoma). Skin cancers are the most common types of cancer in light-skinned populations in the world. IARC classifies devices that emit UVR and UVR from sun (e.g. sunbeds) as Group 1 carcinogens [39, 40]. This classification is based on experimental and epidemiological studies. UVR can lead to pre-mutagenic lesions in DNA by direct absorption of light photon by DNA or by excitation of cellular chromophores that will affect DNA sequentially. Induction of DNA damage can also occur by absorption of UVR by endogenous (melanin, porphyrin, flavin groups) or exogenous (e.g. azathioprine, an immunosuppressive drug) photosensitizers. Photosensitizers lead to the generation of reactive oxygen species that lead to pre-mutagenic DNA lesions. In addition, UVR can cause damage to DNA by creating reactive nitrogen species, creating double strand breaks in DNA and inducing epigenetic changes [41]. These damages lead to the development of some responses (such as cell death, chromosome aberrations, mutations, genetic instability, cell transformation) that contribute to carcinogenesis sequentially.

Common sources of non-ionizing radiation include microwave ovens, computers, wireless networks, cell phones and power lines. RF and ELF radiation emitted from these sources have been included in the "possible carcinogen (Group 2B)" by IARC [42]. Epidemiological studies showing the risk of developing brain cancers in long-term mobile phone users are the main evidence for the identification of RF radiation as a possible carcinogen. In subsequent *in vivo* studies, it has been shown that long-term exposure to mobile phone radiation increases the risk of brain tumors [43, 44]. Children and adolescents may be more sensitive to RF radiation than adults [45]. There is evidence that RF radiation causes cancer development by mechanisms such as generating reactive oxygen species, inducing an inflammatory response, and inhibiting DNA repair and creating chromosome aberrations [46–48]. Although the WHO still has not defined it as a carcinogen, there are studies showing that RF and ELF radiation-induced electromagnetic fields contribute to the increase in brain cancers especially in children and adolescents, decrease in fertility rates in men, and increase of Alzheimer's disease worldwide [49, 50].

Medical irradiation and risk of cancer. Exposure of individuals to radiation for medical diagnosis and treatment is a risk factor in cancer. Epidemiological studies show that children are more sensitive to radiation than adults. A single dose of radiation used for diagnostic purposes does not pose a great danger, but it is possible that the radiation exposed as a result of the widespread and frequent use of X-rays increases the risk of cancer [51]. Computed tomography (CT), which is accepted as the gold standard in the diagnosis of many diseases, has started to be used frequently in pediatric medicine. However, direct epidemiological evidence suggests that the radiation doses used in CT contribute to malignant neoplasms [52]. There are studies showing that head, neck and thorax CT scans increase the incidence of thyroid cancers [53, 54]. There is an increasing number of studies showing that medical imaging techniques (e.g. CT scans and fluoroscopic procedures) used for diagnostic purposes in pediatric patients reveal the risk of cancer in the future [52, 55].

Radiotherapy treatment can also lead to the development of secondary cancers as it affects healthy tissue. Ishida *et al*. [56] showed that patients who received cranial radiotherapy had a 6-fold higher risk of developing secondary cancers than those who did not. Radiotherapy for childhood leukemia or lymphoma treatments has a risk of developing secondary malignancies such as thyroid, skin and breast cancer [57–59]. Similarly, radiotherapy used in breast cancer treatment has led to the development of angiosarcomas [60].

Occupational carcinogens

Chemicals and cancer. Due to occupational exposure, the routine penetration of some chemicals through the skin (e.g. coal tar) or the routine inhalation of some chemicals (e.g. asbestos) cause mutagenic effects and these substances are considered a risk factor for cancer [61, 62]. The Table shows the main occupational chemical carcinogens that are carcinogenic to humans.

Analyzes made based on current literature information showed that 2–8% of total cancers are associated with occupational exposures [70]. The most common cancer caused by occupational carcinogens is asbestos-induced lung cancer. [71]. A total of 23 different types of cancer, including lung, skin, bone, hematopoietic and lymphoid tissues, Hodgkin and Non-Hodgkin's lymphoma, urinary bladder, nasal cavity, thyroid, breast, kidney, larynx, liver, nasopharynx, biliary tract, brain, colon, oesophagus, eye, malignant melanoma, mesothelioma, ovary, salivary gland and stomach were associated with occupational carcinogens [61]. Some cancers are associated with more than one agent, while some agents are risk factors for more than one type of cancer. For example, agents such as asbestos, silica, arsenic, cadmium or nickel exposed in coal and related industries cause lung cancer. However, asbestos causes especially lung cancer and mesothelioma, but also causes cancer of the larynx and ovary [61, 65]. Cancers commonly associated with chemicals and chemical mixtures include lymphohematopoietic system tumors (25%), bladder (20%), lung (15%) and skin (15%) cancers [61]. Coal tar, which causes skin cancer, can be given as an example of chemical mixtures that are occupational carcinogens [67].

Ionizing radiation, radionuclides and cancer. Besides chemicals, ionizing radiation and radionuclides are associated with a wide variety of cancer types such as larynx, lung, skin, brain and central nervous system, liver, breast, leukemia, thyroid, bone, colon, kidney, stomach and bladder. Radon gas inhaled by underground miners causes lung cancer. Radium isotopes ingested by dial painters tend to accumulate in bones and teeth and are associated with bone tissue cancer. UV radiation produced in welding is associated with eye cancer [72].

Table. Main occupational chemical carcinogens

Agents	Main cancer cite	Main Industry/use	References
Aflotoxin	Liver	Agro-food industry	[63]
Aminobiphenyl	Bladder	Rubber manufacture	[64]
Arsenic	Lung, skin	Glass, metals, pesticides	[65]
All types of asbestos	Lung, mesothelioma	Insulation, filter material, textiles	[65]
Benzene	Leukemia, lymphoma	Solvent, fuel	[66]
Beryllium	Lung	Aerospace industry/metals	[65]
Coal tar	Skin	Aluminum production, steel and iron foundries, tar refineries	[67]
Naphtylamine	Bladder	Dye/pigmet manufacture	[68]
Nickel compounds	Respiratory tract cancer	Production of batteries, jewelry, various alloys, nickel plating, and stainless steel	[69]
Vinyl chloride	Lung	Plastic industry	[65]

Environmental pollution and cancer

***Pollutants in drinking water and cancer risk*.** Bladder, skin and lung cancer risk has been determined in areas with high arsenic pollution groundwater [73]. Disinfection with chloramination, ozonation and chlorine dioxide cause the formation of nitrosamines in drinking water. The types and levels of these nitrosamines formed in drinking water systems are affected by many factors such as weather events (e.g. temperature), source water (e.g. organic precursors), water treatment processes (e.g. disinfectant types) and distribution system materials. As a result, the formation of nitrosamines in drinking water systems changes spatially and temporally [74]. Exposure to drinking water nitrosamines can pose a carcinogenic risk to human health, especially for children [75].

Pollutants in soil and cancer risk. Lead, which passes into the soil from chemical fertilizers used for agricultural purposes, is absorbed by plants and enters the daily diet. Lead entering the body cannot be metabolized or destroyed and is particularly associated with renal cancers [76]. Due to its widespread use, pesticides accumulating in air, water and soil cause pollution of agricultural resources. Pesticides that enter the body from agricultural sources are another risk factor associated with cancer [77]. In places where coal use is intense, polycyclic aromatic hydrocarbons create a serious accumulation in agricultural soils and emerge as a potential risk for cancer [78]. In addition, it has been determined that chronic exposure to arsenic and chromium accumulating in agricultural soils is a potential risk factor in cancer development. It has been shown that those living in areas where gold mining is carried out are exposed to systemic arsenic absorption and arsenic accumulated in the soil may be associated with cancers in the local population [79].

ENDOGENOUS FACTORS

***Infections and cancer*.** Infectious agents are one of the major risk factors in cancer disease, which have been identified after smoking. According to 2012 data of epidemiological studies, 2.2 million of 14 million new cancer cases are associated with infections [80]. Infection agents defined by the IARC as carcinogens; *Helicobacter pylori* (*H. pylori*), hepatitis B virus, hepatitis C virus human immunodeficiency virus type 1, human papilloma virus (HPV), Epstein — Barr virus, human herpesvirus type 8 (also known as Kaposi's sarcoma herpesvirus), human T-cell lymphotropic virus type 1, *Opisthorchis viverrini*, *Clonorchissinensis*, and *Schistosoma haematobium* [81, 82].

Infectious agents can cause cancer to occur in different ways. For example, some infectious agents (e.g. hepatitis B virus, HPV, and Epstein — Barr virus) can directly contribute to the emergence of cancer by disrupting cellular barriers such as cellular regulation of telomerase, apoptosis, cellular adhesion or cell cycle control points, or mechanisms that reduce the rate of cell proliferation [83]. Some infectious agents such as hepatitis C virus, *H. pylori* create a long-term inflammatory response, which can indirectly contribute to the emergence of cancer by increasing proliferative signals and mutations [84]. Some infectious agents, such as human immunodeficiency virus type 1, also suppress the immune system that protects the organism against cancer development [85, 86].

Vaccines, safe injections, screening of donated blood and blood products with approved quality, antimicrobial treatments, eating habits avoided from consumption of raw or undercooked fish, safe sexual intercourse will have a significant effect in reducing cancer-related infections [81, 85].

Hormonal factors and cancer. It is controversial that female sex hormones (estrogen and progesterone) are an initiating factor in breast, endometrium, ovarian cancers, androgens in prostate cancers. However, it can be said that these hormones act as stimulating factors in tumor growth and progression [87].

Factors that lead to higher exposure to estrogen over the course of life, such as early menarche, late menopause, late first pregnancy and not giving birth, increase the risk of breast cancer. It is possible that female sex hormones increase the risk of developing these cancers through mechanisms such as increasing cell proliferation, decreasing apoptosis and causing DNA damage [88]. Factors that reduce exposure to endogenous estrogen, such as pregnancy and breastfeeding, reduce the risk of breast cancer. Some studies show that pregnancy and breastfeeding are a protective factor in breast cancer because of the differentiation of breast cells to produce milk. Cells that undergo this differentiation are less likely to turn into cancer cells [89]. Similarly, menopausal hormone therapy (estrogen + progesterone) can increase the risk of breast cancer. Since estrogen therapy alone in menopausal hormone therapy may increase the risk of endometrial cancer, it can only be applied to people with hysterectomy [90]. Oral contraceptives containing female sex hormones are considered as risk factors for breast cancer and cervical cancer. The possible mechanism underlying female sex hormones as a risk factor in cervical cancer is that these hormones increase the expression of E6 and E7 oncogenes, which degrade the p53 tumor suppressor gene in HPV virus (the main risk factor in cervical cancer) [91, 92]. On the other hand, the use of oral contraceptives is a risk-reducing factor in endometrial and ovarian cancers. Possible underlying reasons for this situation are female sex hormones suppressing endometrial cell proliferation and reducing the number of ovulations [93, 94].

The acceptance of androgens as a risk factor in the progression of prostate cancer is based on experimental studies. However, there are no clear clinical results showing that endogenous androgens cause the progression of prostate cancer [95]. It is not known exactly how androgens increase the risk of prostate cancer. However, it has been shown that there is a significant relationship between the single nucleotide polymorphism in genes encoding enzymes associated with the synthesis of these hormones and the risk of prostate cancer [96].

CONCLUSION

Prevention is the most effective strategy in combating cancer. With the knowledge of current risk factors, it seems possible to prevent cancer significantly and therefore the primary prevention is an issue that should be prioritized. In order to make progress in understanding the risk factors in cancer, the biological knowledge that explains the causes of cancer needs to be advanced. As the studies on risk factors increase, it will be possible to develop new strategies for cancer prevention.

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ЗОВНІШНІ ФАКТОРИ РИЗИКУ РОЗВИТКУ ЗЛОЯКІСНИХ НОВОУТВОРЕНЬ

С. Ілдирім-Кахріман*

Університет Деміроглу Білім, Стамбул 34394, Туреччина

Обсяг наших знань про етіологію раку постійно збільшується. Значна частина досліджень вказує на те, що основними факторами ризику виникнення раку є зовнішні чинники, пов'язані з довкіллям або способом життя. З іншого боку, є й внутрішні причини розвитку раку, пов'язані з помилками реплікації ДНК. Цим факторам важко запобігти. Але оскільки внесок саме зовнішніх факторів у виникнення злоякісних захворювань є найбільшим, розвиток раку в цих випадках можна відвернути. Мета даного огляду — проаналізувати відомі зовнішні фактори розвитку злоякісних новоутворень у світлі останніх досліджень.

Ключові слова: рак, зовнішні фактори ризику, профілактика раку.