Cancer In Women: Risk Factors and Prevention

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Abstract
Breast, lung, colon, endometrial, cervical and ovarian cancers are the most common cancers in women. Breast cancer incidence is increasing; but mortality caused by this cancer is decreasing. If breast cancer occurs early in age, the risk of contra lateral breast cancer, local and distant recurrence, and subsequent mortality are increased. The development of breast cancer depends on complex interactions between genetic, hormonal, behavioral, and environmental factors play. Hereditary breast and ovarian cancer syndrome (HBOC) is related to germline abnormal variants in BRCA1 and BRCA2 which are inherited in an autosomal dominant way.

Both hereditary and environmental factors contribute to the development of colorectal cancer (CRC). The colorectal cancer risk is related to height, body mass index (BMI), smoking, alcohol intake, physical activity, parity and menopausal hormone therapy use. Inflammatory bowel diseases are strong risk factors for CRC. In the etiopathogenesis of cervical cancer HPV infection is a very important risk factor suggesting the role of viral infections in the pathogenesis of cancers. Smoking is a major risk factor for lung cancer worldwide (attributable to 80% of lung cancers in men and about 50% of lung cancers in women). Smoking is not only a major risk factor for lung cancer, but it is also related to increased risk of other cancers.

Obesity, predominance of high-fat foods in nutrition together with physical inactivity increases the risk of developing cancer. Healthy lifestyle can prevent a significant proportion of all cancers (between 30–40%) and exercise is associated with lower relapse rates and better survival.

Despite frequent and official recommendations to eat more fruits and vegetables several times a day, we have to think about their quality regarding the level of metals, pesticides and other toxic pollutants that can be found in most fruits and vegetables today.

The Most Common Cancers in Women
Breast cancer is the most common invasive cancer among women. About 52% of new breast cancer cases and 62% of deaths occur in the developing countries nowadays, contrary to the opinion that it is mainly a cancer of Western women. The bad news is that breast cancer incidence rates are increasing: in 2012, there were 1.67 million new cancer cases diagnosed (25% of all cancers). However, the good news is that mortality caused by breast cancer is decreasing [1].

As in other cancers, breast cancer risk factors may be divided into adjustable and non-adjustable factors. Physical inactivity, alcohol consumption, obesity, smoking and use of hormone replacement therapies are adjustable risk factors for breast cancer disease, while age, genetics, family history, increased breast density, precancerous breast lesions and prior chest wall radiation belong to non-adjustable factors. Besides the above, there is a group of potentially adjustable factors which include early onset of menarche, null parity, first live birth after the age of 30 and late menopause [2,3]. Average risk (12% lifetime risk) for developing breast cancer includes women without positive family history and without prior precancerous breast lesions. Women with a first-degree relative diagnosed with breast cancer before the age of 50 years, prior atypical ductal or lobular hyper plasia, or history of lobular carcinoma in situ, increased mammographic breast density, and prior chest radiation are at high risk for developing breast cancer. Women with a strong hereditary predisposition or known BRCA1 or BRCA2 mutation carriers are at very high risk for breast cancer disease [4].

Lung cancer is the second most common cancer among women and the main cause of cancer mortality. In the US, 80–90% of lung cancers are connected to smoking. Smoking is the number one risk factor for lung cancer. The risk increases along with the number of cigarettes smoked daily and the number of years of smoking. In addition, the use of cigars and pipes as well a sex posture to secondhand smoke adversely affects and significantly increases the risk for lung cancer. Smoke is a mixture of a large amount (more than 7,000) of chemicals and carcinogens. In tobacco smoke, we can find nicotine, cyanide, benzene, acetylene, formaldehyde and toxic gases (carbon monoxide and nitrogen oxide) [5]. Besides, arsenic, chromium, nitrosamines, cadmium are also present, and all of these compounds can be deadly, not only causing cancer, but also heart and lung diseases. There are also small amounts of radioactive material in smoke which particles over time make an appreciable radiation dose to the lungs [6].

Exposure to asbestos, chromium and nickel which usually occurs as workplace exposure can also increase the risk of developing lung cancer; particularly if a person is a smoker. Persons who have first-degree relatives diagnosed with lung cancer have also an increased risk of the disease. While family history cannot be changed, cessation of smoking and work exposure to harmful materials can decrease the risk of developing lung cancer [7].

Radon is considered to be a second leading cause of lung cancer producing about 20,000 deaths in the US each year. Although radon gas usually exists at very low levels outdoors, in areas with no sufficient ventilation (mines) radon is a risk factor for lung cancer. Due to their closeness to the ground, radon levels are higher in basements and first floors [7,8]. Previous radiation therapy to the chest (cancer survivors) also increases the risk of developing lung cancer [7,9].

With 614,000 cases, (9.2% of all cancers), colorectal cancer (CRC) is the third most common cancer in women worldwide. Mostly, CRC occurs over the age of 50. The incidence rate is similar in both genders and in rectal cancer a slight male predominance is observed. In Central and Eastern Europe, there is a higher mortality rate (20.3 per 100,000 for men, 11.7 per 100,000 for women), while in Western Africa (3.5 and 3.0, respectively) the rate is at its lowest. CRC is formed after various histological and molecular changes in a complex interdependence between genetic susceptibility and external influences. Risk factors may be genetic...
(hereditary polyposis syndromes - FAP, Gardner, Turcot and Peutz-Jeghers syndrome, juvenile polyposis), family-based (hereditary nonpolyposis colorectal cancer syndrome-HNPCC, information on CRC in the family), underlying diseases (inflammatory bowel diseases, previous CRC, radiotherapy in the pelvic region, colorectal polyps), external factors (diet rich in meat and animal fat, physical inactivity, smoking) and other factors (age over 40 years, being overweight, eating a diet composed mostly of high-fat foods especially from animal sources, smoking, and being inactive can make a person more likely to develop this cancer). About a quarter of patients with CRC have a positive family history [10,11].

Cervical, ovarian, uterine, vaginal and vulvar cancer form a group of five main gynecological cancers. Currently, screening programs for cervical cancer are performed. Cervical cancer with an estimated 528,000 new cases in 2012 is the fourth most common cancer in women. Middle Africa is a region with high risk (over 30 cases per 100,000 women) for cervical cancer: Smoking is doubling the risk to get cervical cancer. Ovarian cancer has an increasing incidence in parallel with age and develops after menopause. Pregnancy with labor at term in early years (<26 years) decreases the risk for ovarian cancer. In contrast, first full-term pregnancy after the age of 35 increases the risk for ovarian cancer [12].

**Risk Factors**

**Reproductive Factors and Hormone Status**

In the development of breast cancer, reproductive factors have a huge impact which varies according to subtypes. Breast feeding lowers the risk for both luminal subtypes of breast cancer. Here we also have another dilemma: the International Agency for Research on Cancer (IARC) concluded that estrogen-progestin oral contraceptives (OCs) were carcinogenic to humans due to circulating levels of endogenous estrogens and androgens associated with a higher risk of breast cancer in younger women (<50 years). At the same time, the working group also concluded that OCs use can be protective against other types of cancer, including endometrial and ovarian cancer. When used for five and more years, OCs decrease the risk of developing ovarian cancer for a 50% compared to women who have never used OCs. On the other hand, there is evidence that long-term OCs use increases the cervical cancer risk and the risk decrease after the OCs are stopped. It seems that 10 years after cessation of OCs, the risk returns to normal rates [13]. Therefore, women should have to discuss the potential risks and benefits of OCs with their clinician. Breast feeding reduces the risk of endometrial cancer by 33%. Pregnancy and breastfeeding are also related to a reduced risk of ovarian cancer due to less frequent ovulations when pregnant or breastfeeding. Multiple pregnancies or having first full-term pregnancy before the age of 26 decreases the risk of ovarian cancer [14]. If estrogen increases more than relative to progesterone, there are more chances to develop endometrial cancer. Some recent studies suggest that women who use estrogens alone (without progesterone) on a long term after menopause (more than 5–10 years) have more chance to get ovarian cancer [15].

**Genetic Factors**

There are more than 90 common risk loci for breast cancer which have been identified and about 16% of the familial risk of breast cancer can be linked to those variants. Hereditary breast and ovarian cancer syndrome (HBOC) is related to germline abnormal variants in *BRCA1* and *BRCA2* which are inherited in a dominant way. Patients with these abnormalities have an increased risk for breast, ovarian and pancreatic cancer with the lifetime risk of 40–80% for breast and 11–40% for ovarian cancer [4,16].

The most important gene changes for colorectal carcinoma (CRC) are: APC mutations (adenomatous polyposis coli) gene, which is characteristic for persons with familial adenomatous polyposis (FAP), mutations of K-ras gene, deletion of DCC (deleted in colon cancer) tumor suppressor genes, and mutations of p53 tumor suppressor gene. The two most common family syndromes are familial adenomatous polyposis syndromes (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). In families with HNPCC, carcinomas of the endometrium and ovaries in female members are common. Molecular diagnosis of hereditary mutations in these genes contributes to the detection of pre-symptomatic carriers of hereditary mutations and their inclusion in the program of monitoring and treatment [17].

**Obesity and Diabetes Mellitus**

Obesity is found to be a risk factor in many cancers. Breast and endometrial cancers are also associated with that risk factor with clear correlation between the degree of obesity and increased cancer risk. Compared to normal-weight women, women with obesity run 2.4 to 4.5 times higher risk of developing endometrial cancers. It seems that increases in circulating estrogens in postmenopausal women are crucial for the disease development. However, both genetic and epigenetic alterations are needed for neoplastic transformation. In obesity setting, we can find a normal/dysfunctional angiogenesis, and also chronic inflammation with interaction of pro-inflammatory cytokines that all provide an adipose tissue microenvironment which is very appropriate for (in association with systemic endocrine modifications) promotion of tumor initiation, primary growth, invasion, and finally metastatic progression [18,19].

Diabetes and cancer are linked much more than it would be expected in overall population. This can be explained by common risk factors for both diseases (overweight or obesity, inappropriate nutrition with dietary errors, physical inactivity), together with biological changes and the impact of some anti-diabetic treatments or hormone therapy. The incidence of breast and endometrial cancer for women with diabetes has significantly increased. Type II diabetes is related to hyper insulinemia that results in increased free estrogen level, over expression of the insulin-like growth factor (IGF) system, which plays a significant role in promoting malignant behavior. Besides that, high levels of insulin signaling promote tumor angiogenesis (creating blood vessels network). Individuals with high circulating insulin level have an increased risk for breast cancer recurrence and if they are obese and inulin-resistant, they also have an elevated risk of cancer mortality [20,21].

What can we do? Women can decrease a risk of breast cancer by increasing their physical activity, but this is not true for women who used hormone replacement therapy. Besides that, women with breast cancer who get at least 30 minutes of moderate physical activity per day regularly may improve their survival, and this is independent of their activity level before diagnosis. The use of estrogen and sequential combination therapy increases the risk of endometrial cancer but if the progestin in sequential combination therapy is used for at least 10 days, increased risk of endometrial cancer is cancelled.

**Viral Infections**

It is well known that viral and bacterial infections are involved in the development of human cancers. In 88% of anal carcinoma there is a relation with human papilloma virus (HPV). HPV is linked to approximately70% of vaginal cancers, about 50% of penile cancers and 45% of vulvar cancers. Oropharyngeal cancers are primarily caused by HPV-16 and followed by HPV-18 type of virus, and all together they are related to HPV in a very large range of 13% to...
almost 56% of cancers. Women with persistent infection with high-risk types of HPV usually develop cervical cancer: The incidence of anal HPV in women ranges from 14–56. 3/100 person a year with mostly HPV-16 and 52 infecting types [12,22,23].

For breast cancer the prevalence of HPV is higher, i.e. 21.5% vs. 5.1% in controls as shown in different studies in a wide range of countries. HPV infections may precede the development of breast and other cancers for a long time (years, decades). Although we can confirm that HPV infection is implicated in the etiopathogenesis of the cancer, we also must conclude that this infection alone is not enough to start malignant transformation of cells. Mostly, HPV infections regress spontaneously, and persistent infections which lead (but only eventually) to malignancy (cervical cancers) are detected in a small proportion of women. Therefore, we can conclude that for efficient carcinogenesis, HPV infection together with other cofactors is needed (including differential susceptibility of an individual to the malignancy) [22,24].

Higher risk for cervical cancers was also demonstrated in the individuals infected with C. Trachomatis especially in women with human papilloma virus infections. Both screening and treatment of women for C. trachomatis infection would lower the risk for malignant disease [24,25].

**Occupational Risk Factors**

So, called “modifiable” risk factors for many cancers are occupational risk factors. We say so-called because it is not always possible to change the work place and it depends upon many factors on which individuals can hardly have an influence. In a number of studies, association of textile industry and lung cancer, bladder cancer, colorectal and breast cancer was found.

What are the most common occupational risk factors? Ionizing together with non-ionizing radiation exposure, exposure to pesticides and polycyclic aromatic hydrocarbons also as metals increase the risk for breast cancer. Interestingly, there is evidence that night-shift work increases the risk for breast cancer. To date, there is no clear evidence how occupational factors lead to breast cancer disease. There is an observation for a positive association between the number of years working on rotating night shifts and a higher incidence of breast cancer: A high risk of developing breast cancer is observed among women who worked more than 20 years in night shifts. The explanation for that could be suppression of melatonin by direct exposure to light at night (7).

Lung cancer risk is increased in presence of asbestos, arsenic, diesel exhaust, silica and chromium. The risk for developing lung cancer is even higher for smokers. As already mentioned, radon is the second causing factor of lung cancer. Radon has quick degradation, producing very tiny radioactive particles which after inhalation can lead to damage of lung cells in such a manner to increase the lung cancer risk. It is suggested to measure short and long-term levels of radon in homes/work places. The tests are easy and inexpensive and if the radon level is above four picocuries per liter of air, the action has to be taken. In the US, it has been shown that by lowering radon levels in homes, lung cancer deaths could be smaller for about 5,000 yearly (2–4%) [26,27].

Inhalation of all type of asbestos fibers leads to an increased risk of lung cancer; the greater and longer the contact with asbestos, the higher the risk for the disease, and mostly, lung cancer occurs in asbestos workers after 15 years of exposure. If the persons are smokers, this period can be shorter, and the risk for lung cancer is much higher [28].

**Other Risk Factors**

Mammographic density is a very strong factor for increased risk of breast cancer. It seems that in women with BRCA1/BRCA2 mutation, mammographic density also increases the risk for disease. The risk for women with mammographic density greater than 75% is 4.64 times greater than for women with mammographic density lower than 5% [14].

Some data suggested that the administration of aspirin or NSAIDs can lower the incidence of endometrial cancer; the data are more clearly seen with obese women. Also, there is a possibility that aspirin use in women with breast cancer can reduce the recurrence rate and improve survival [29]. There are studies in progress to confirm or decline such data, and more evidences are needed. A huge proportion of breast cancer patients have also a lower level of vitamin D. Low 25(0H) D level increases the risk of breast cancer. Dietary intake of vitamin D is connected with a lower breast cancer risk. Although there are some controversial data about coffee use, there is evidence that the more coffee women consume, the risk of endometrial cancer is lower [15].

There is evidence that there is a minimally higher ovarian carcinoma risk in women who had habit to use tak on the genitals. Compared to fertile women, infertile ones are at a higher risk for developing ovarian cancer: It is partly connected with the fact that infertile women have not carried a pregnancy to term [30,31].

For colorectal cancer (CRC), inflammatory bowel diseases are among the strongest risk factors, which is most pronounced in ulcerative colitis based on the principle that if the disease develops earlier and lasts longer, the risk of CRC is higher. Patients who have already had CRC, there is a three times greater risk of new tumors [17]. The risk of developing the disease is increased with a dietary habit of using more meat and animal fat (> 40% of daily calorie intake), physical inactivity and excessive use of tobacco and alcohol, while according to the results of clinical and epidemiological studies, vitamin D reduces the risk of CRC by 33% [31]. Studies, which were conducted in order to demonstrate that the risk for CRC can be reduced by the use of foods high in fiber, calcium, antioxidants, non-steroidal anti-inflammatory drugs have not yielded conclusive results [15]. Aspirin showed a preventive effect on the development of polyps. The population of high risk for the disease (family history of hereditary polyposis syndromes and non-polyps) is colorectal cancer, family history of polyps and colon cancer, and patients suffering from inflammatory bowel disease, people with already surgically removed intestine polyps and treated CRC and those with previous radiotherapy of pelvic region) must carry out regular examinations and the best method is colonoscopy, even before 50 years of age [32,33].

The most preventable cause of cancer is smoking cessation. It is very clear nowadays how smoking is related to cancer. Smoking is linked to nearly 50% of all cancer cases and by giving up smoking, many of deaths are preventable. Smoking increases the risk of lung cancer and other cancers (head and neck cancers, gastrointestinal cancers, kidney, gynecologic cancers, and some types of leukemia). The risk for breast cancer is also higher in smokers, especially in women who start smoking before they have their first child (those who started smoking 10 or more years before having a first child, had a 45% higher risk compared to nonsmokers). Changes in DNA which could lead to a malignant transformation of cell happen after every 15 cigarettes smoked. Therefore, it is crucial to give up smoking as soon as possible [34,35].

Based on reviews of a huge amount of research studies, alcohol (ethanol or ethyl alcohol) is declared to be a human carcinogen. The more alcohol a person drinks regularly over time, the higher the person’s risk of developing an alcohol-associated cancer. Alcohol consumption is related to the development of head and neck cancer,
esophageal cancer, and with a modestly increased risk of colorectal and breast cancer. Furthermore, in primary liver cancer alcohol is an independent risk factor. For persons who use both alcohol and tobacco, the risk for cancer can be multiplicative (as in head & neck cancers) [35,36].

Healthy lifestyle (low alcohol and red meat consumption, increased consumption of fruits and vegetables, no tobacco use, no refined sugars use, regular physical activity) alone can prevent a significant proportion of all cancers (between 30–40%). Obesity, consumption of inappropriate ingredients such as concentrated sugars, flour products, preserved food with additives; low fiber intake; high consumption of red meat, and imbalance of omega 3/omega 6 fats all contribute to a higher cancer risk. Although not completely confirmed, the use of selenium, folic acid, vitamin B-12, vitamin D, and antioxidants could be protective elements in cancer prevention. Today, nutrition research presents a diet with fruits and vegetables as protectable as regards cancer, ischemic heart disease and diabetes with conclusion that when a diet is adjusted according to such recommendations, the incidence of breast and colorectal cancers may be expected to be reduced by 60–70%, and of lung and other cancers by 40–50% [3,36]. Despite the frequent recommendations to eat more fruits and vegetables, nowadays we have to take into consideration their quality regarding the proportion of metals, pesticides and other toxic pollutants that can be found today in most fruits and vegetables.

References


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