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Trailing the Path to Preventive Oncology

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Abstract

Cancer is one of the communicable diseases killing the mankind and is likely to be a global pandemic by year 2050. Fifty percent of cancers are preventable because of the causal association with modifiable risk factors. Preventive oncology is any measure that is taken to prevent development or progression of malignant process. Around one third of cancer deaths are due to the 5 leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, alcohol use. History of the science dates back to as early as 1912 when tobacco was coined as a culprit for lung tumors. Preventive oncology is very important not only because of its health impact but also for huge impact on economy. The total economic impact of premature death and disability from cancer was $ 895bilion in 2008 which is 1.5% of world's Gross Domestic Product (GDP).

More than 30% of cancer deaths could be prevented by modifying or avoiding key risk factors like tobacco use, obesity, unhealthy diet with low fruit and vegetable intake, lack of physical activity, alcohol use, sexually transmitted HPV-infection, infection by HBV, ionizing and non-ionizing radiation, urban air and water pollution, adulteration of food with harmful chemicals and indoor smoke from household use of solid fuels. Non modifiable risk factors like Genetic and hereditary risk factors play a role in 10% of cancers where mutations in susceptible genes are found as a part of hereditary cancer syndromes.

There are various risk groups identified and risk models are available to target the population for the effective preventive measures in the community. Curtailing tobacco use, dietary and life style modification and avoiding chemical carcinogens as an occupational hazard are important aspects. Certain viruses are known to be carcinogenic. Prevention of transmission and vaccination for the same is important step forward towards prevention of diseases like hepatitis B/C and HCC, HPV and cervical and anal cancer. Screening for early detection of cancer is an important strategy for breast, cervical, lung, colorectal, prostate and skin cancers. There are chemo-preventive agents for risk reduction for certain risk groups like tamoxifen, raloxifen, aspirin, finasteride and vitamin D. Surgical risk reduction is recommended for certain genetic syndromes. Preventive oncology is the future of oncology as we come to know more and more about the etiological aspects, understand molecular epidemiology and molecular basis of the dreadful disease. This is the only way out to tackle the cancer which is slowly and silently becoming a pandemic.

Keywords: Prevention; Screening; Risk reduction; Cancer; Chemoprevention

Introduction

By definition, preventive oncology is any measure that is taken to prevent development or progression of malignant process.

Cancer is the most dreadful of all the illnesses. Etiology lies in a genetically predisposition modified with environmental exposure. Around one third of cancer deaths are due to the 5 leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco use, alcohol use. Tobacco use is the most important risk factor for cancer causing around 20% of global cancer deaths and around 70% of global lung cancer deaths. Cancer causing viral infections such as HBV/HCV and HPV are responsible for up to 20% of cancer deaths in low- and middle-income countries [1]. More than 60% of world's total new annual cases occur in Africa, Asia and Central and South America. These regions account for 70% of the world's cancer deaths [2]. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 within the next 2 decades [2]. Therefore, prevention is a better strategy. The art of it basically sits on understanding etiology, epidemiology, mechanism and the genetics, racial and geographic variability.

Cancer prevention occurs at 3 stages: Primary prevention: Before the development of disease by modifying or averting the risk factors; Secondary prevention: Before onset of the clinical symptoms or signs and tertiary prevention: After development of disease by decreasing complications and recurrence of the disease.

History

Michael Shimkin, M.D., of the University of California, San Diego, declared the new specialty, Preventive Oncology in 1975. Shimkin (Preventive Medicine, June 1975) coined the terminology of primary and secondary prevention explaining premalignant lesions and the efficacy of screening mammography. John Lee, M.D., of the University of Washington, Seattle, acclaimed progress against occupational carcinogens.

In 1898, medical students by the name of Hermann Rottmann in Würzburg proposed that tobacco dust-not smoke-might be causing the elevated incidence of lung tumors among German tobacco workers. In 1912, Adler proposed that smoking might be the factor for the growing incidence of pulmonary tumors [3]. Later, on January 11, 1964, Luther

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L. Terry, M.D., Surgeon General of the U.S. Public Health Service, released the first report of the Surgeon General's Advisory Committee on Smoking and Health based on 7,000 articles, relating to smoking and disease in the biomedical literature, the Advisory Committee concluded that cigarette smoking is the cause of lung cancer and laryngeal cancer in men, probable cause of lung cancer in women and the most important cause of chronic bronchitis [4].

Professor Harald zur Hausen discovered HPV as a causative factor for cervical cancer and was awarded the noble prize for medicine. Ian Hector Frazer, an immunologist and Jian Zhou, a virologist discovered HPV vaccine. There are various milestones or landmarks building the trail of the preventive oncology.

Why preventive oncology?

Apart from huge impact on the health of the individual and the family and the society, cancer impacts our economy negatively. The total economic impact of premature death and disability from cancer was $ 895bilion in 2008 which is 1.5% of world's Gross Domestic Product (GDP). This economic toll is 19% higher than the heart disease putting it behind, second in the rank. This burden is not evenly distributed among the nations. In U.S.A. it is 1.7% of its G.D.P. while in Hungary it is 3.05%. Twenty five nations are losing 2% of their G.D.P. for the cancer death and morbidity. Sixty percent of the deaths and more than 12.4 million cases diagnosed every year occur in developing countries where preventable cancers are taking a disproportionate toll. So, cancer is becoming a "silent pandemic" especially in low and middle income countries. It is predicted that tobacco will kill 7 million people in 2020 and 8 million in 2030, with more than 80% of the deaths occurring in low and middle income countries. More than one third of the deaths will be from cancer. Similarly, cervical cancer takes 274000 lives yearly out of which 241000 are from low and middle income countries though it is a preventable disease. Thus, cancer causes the highest economic loss than any of the ailments and has many preventable causes [5].

Domains of preventive oncology

For the prevention, we must know the etiology, know the risk groups and then apply the tools and strategy for risk reduction or prevention.

More than 30% of cancer deaths could be prevented by modifying or avoiding key risk factors like tobacco use, obesity, unhealthy diet with low fruit and vegetable intake, lack of physical activity, alcohol use, sexually transmitted HPV-infection, infection by HBV, ionizing and non-ionizing radiation, urban air and water pollution, adulteration of food with harmful chemicals and indoor smoke from household use of solid fuels. Tobacco use is the single most important risk factor for cancer causing about 20% of global cancer deaths and around 70% of global lung cancer deaths. In many low-income countries, up to 20% of cancer deaths are due to infection by HBV and HPV [6].

Risk assessment tools: Risk groups are identified for various types of cancers based on individual's medical illness, family history, race, ethnicity, gender, life style, age and occupation etc. Individuals are at increased risk because of modifiable or non-modifiable risk factors and are mainly targets for the preventive strategy.

Genetic and hereditary risk factors play a role in 10% of cancers where mutations in susceptible genes are found as a part of hereditary cancer syndromes. Gail model is to define the women at high risk of breast cancer [7]. The other models include Claus, [8] Tyrer-Cuzick, [9] and other models [10-12] BRCAPRO [13] and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) [14] are more commonly used to estimate the risk based of *BRCA* mutations.

There are various criteria designed for various genetic cancer syndromes like hereditary breast and/or ovary cancer syndrome include *BRCA1/2*, Li- Fraumani syndrome, Cowden syndrome, PTEN Hamartoma syndrome; Hereditary colorectal cancer syndromes like Lynch Syndrome, Classical Familial Adenomatous Polyposis (FAP), Peutz- Jeghers Syndrome, Juvenile polyposis syndrome etc. If the specified criteria are met, the individual is advised to undergo genetic counseling followed by genetic testing and risk reduction approach.

Modifiable risk factors: Tobacco use –cigarettes, bidis and shisha or smokeless forms (gutkha, quid, mava and snuff etc) leads to cancers and about one third of the cancer deaths in USA are attributed to tobacco. Smokeless tobacco leads to cancers of oral cavity and upper aero-digestive tract. To fight the mammoth, measures like de addiction, replacement with variety of pharmacological substances, ban of tobacco selling and related legislature are applied. Detailed discussion is beyond the scope of the article.

Exposure to UV rays is also directly related to melanoma and non-melanoma skin cancers [15]. Intense UV exposure is associated with melanoma while chronic sun exposure leads to squamous cell carcinoma [16,17]. Avoiding sun exposure and protective sun screens like oxybenzone, avobenzone, titanium dioxide, or zinc oxide must be used in a proper way. This protects against squamous cell carcinoma and has a doubtful role in melanoma and basal cell carcinoma [18]. Recent data [19,20] suggest the role of vitamin D in cancer prevention. Strong evidence indicates that intake or synthesis of vitamin D is associated with reduced incidence and death rates of colon, breast, prostate, and ovarian cancers [21]. Exposure to sunlight is the physiological mechanisms for synthesis of vitamin D in our body. Therefore, avoiding sun exposure is now perplexing.

Diet and exercise are 2 life style factors which can be modified to reduce the cancer risk. There are no direct evidences but pooled data suggest a 25% reduction in the incidence of distal (but not proximal) colon cancer in those who consumed more than 800 g of fruits and vegetables per day [22]. Sedentary lifestyle is responsible for approximately 5% of cancer death [23]. Higher levels of physical activity have been associated with decreases in the risks of colon and breast cancers, and possible decreased risks of endometrial, prostate, liver, pancreatic, stomach, and lung cancers have been described as well. Obesity is responsible for 10-40% of colorectal, endometrial, renal, esophageal, and postmenopausal breast cancers [24] and weight reduction decrease the risk by 60%.

The Women's Health Initiative trial [25] suggests that combination therapy with estrogen-progestin hormone replacement had a significantly increased risk, with a hazard ratio of 1.2.

Epidemiological studies have showed that people living in southern latitudes had low incidence of cancers as compared to northern latitudes which was correlated with sun exposure and vitamin D levels [21]. Experimental evidences also support the role of vitamin D as a preventive agent for breast, colorectal and prostate cancer. 1.25(OH) 2D3 has been shown to inhibit cancer cell growth, induce cancer cell maturation, induce apoptosis, and decrease angiogenesis. Vitamin D supplementation is a much needed, low cost, effective, and safe intervention strategy for breast cancer prevention that should be implemented. It has been shown that vitamin D levels are lower in ovarian cancer patients. Low 25(OH) D concentration associated with lower overall survival rate might suggest for the important role of

severe deficiency in more aggressive course of ovarian cancer. There are myriads of studies depicting supplementation and benefits for cancer prevention. However, USPSTF has assigned recommendation statement- I for such nutrient supplement [26].

Occupational exposures to chemicals such as coal-tar–based products, benzene, cadmium, uranium, asbestos, or nickel can significantly increase cancers like bladder cancer, lung cancer and mesothelioma. IARC defined two kinds of carcinogens depending on the causality [27]. This can be prevented with avoiding such agents by spreading public awareness, legislature against use of the substances and adopting sustainable industrial growth.

Infections with viruses

Approximately 17% of cancers occurring worldwide may be attributed to an infectious etiology [28].

Cervical and anogenital cancers are caused by Human Papillomavirus (HPV), Hepatocellular Carcinoma (HCC) by hepatitis B (HBV) and C (HCV), Kaposi sarcoma by Human Herpes Virus (HHV-8) and Adult T-cell Leukemia human T-cell lymphotropic virus -1 (HTLV-I)), Several types of non-Hodgkin lymphoma by Epstein-Barr virus and HHV-8). Infection with Human Immunodeficiency Virus (HIV) increases the risk of Kaposi sarcoma and non-Hodgkin lymphoma. Certain cancers may be Acquired Immunodeficiency Syndrome (AIDS)-defining malignancies.

These viruses spread via transfusion of blood or other such contamination. The estimated risk of hepatitis infection via blood transfusion is approximately 1 in 58,000 to 269,000 for HBV and 1 in 2 million for HCV. Risk of transmission of HTLV-1 by transfusion is 1 in 2 million, and that of HIV infection by transfusion is approximately 1 in 2 million [29]. Measures to prevent the infection are use of effective donor screening, sterilized needles and vaccination. Treatment of HIV infected individual with highly active antiretroviral therapy prevents development of NHLs. Cervical cancer can be prevented with HPV vaccination. Chronic infection with HBV has been estimated to increase the risk of HCC by up to 100-folds.

Prevention lies in 3 steps: Public health intervention, treatment of hepatitis B/C with anti retroviral therapy and early detection. Public health intervention involves Hepatitis B vaccination and has 85-95% efficacy preventing chronic HBV infection resulting into prevalence of less than 1% of chronic HBV infection in children in endemic areas. Although there have been no randomized trials of such screening, observational data suggest that serial ultra-sound examination and a-fetoprotein testing are useful or for identifying early cases of HCC that may be more amenable to successful treatment [30].

Screening for Cancer

Certain cancers can be prevented by using various screening modalities.

Breast cancer screening

The components of a breast screening evaluation include Breast awareness (i.e., patient familiarity with her breasts), Physical examination, Risk assessment, Screening mammography and screening breast Magnetic Resonance Imaging (MRI) in selected cases.

Self breast examination: Data from a large randomized trial of Breast Self-Examination (BSE) screening has shown that instruction in BSE has no effect on reducing breast cancer mortality. In this study, 266,064 women were randomly assigned to either receive instruction in BSE or not [31]. Compliance was encouraged through feedback and reinforcement sessions. After 10 to 11 years of follow-up, 135 breast cancer deaths in the instruction group and 131 in the control group were observed and the cumulative breast cancer mortality rate was not significantly different between the two arms(RR, 1.04; 95% CI, 0.82–1.33; P=.72).

Risk assessment: Women can be stratified into two basic categories for the purpose of screening recommendations: those at average risk and those at increased risk. Women with a lifetime risk of breast cancer less than 15 percent are considered to be at "average risk" and those with a lifetime risk greater than 20 to 25 percent are considered to be at "increased risk." The increased risk category consists of 6 groups:

(1) Women with a prior history of breast cancer

(2) Women 35 years or older with a 5-year risk of invasive breast carcinoma ≥ 1.7% by per Gail model

(3) Women with a lifetime risk of breast cancer > 20% based on models largely dependent on family history

(4) Women who have previously received therapeutic thoracic irradiation (e.g. mantle irradiation) between the ages of 10-30 years

(5) Women with Lobular Carcinoma *In Situ* (LCIS)

(6) Women with a pedigree suggestive of or with a known genetic predisposition.

Mamography: For women aged 40 years and older, the NCCN Panel recommends annual Clinical breast examination and screening mammography. The recommendation that women at normal risk begin annual mammographic screening at age 40 years is based on a consensus statement from the American Cancer Society (ACS) and National Cancer Institute in 1997 and is supported by the ACS guidelines for breast cancer screening published in 2003 [32], 15 as well as the results and meta-analyses of randomized clinical trials. The NCCN Panel believes that the benefits of yearly mammography outweigh the risks of the procedure as breast cancer mortality is lower with annual compared to biennial screening mammograms [33]. To reduce mortality from breast cancer, yearly screening is thought to be more beneficial. Additionally, mammograms can often detect a lesion 2 years before the lesion is discovered by CBE.

Women with a Lifetime Risk of Breast Cancer >20% based on model largely dependent on family history: According to the ACS guidelines for breast screening, MRI may be performed as an adjunct to mammography in a high risk woman if her lifetime risk of breast cancer is approximately 20% or greater based on models that rely mainly on family history. A cancer genetic professional should be involved in determining the lifetime risk of the individual based on models dependent on family history. For a woman aged 35 years or older with a 5-years risk ≥ 1.7%, the NCCN Panel encourages breast awareness and recommends CBE every 6 to 12 months and annual mammography. (Table 1 and 2) summarizes the risk- benefits and results of Meta analyses for mammography.

Risk models available for risk assessment: Women with a Lifetime Risk of Breast Cancer >20% based on model largely dependent on family history: In determining the lifetime risk of the individual based on models dependent on family history various models are available. These include Claus, [8] Tyrer-Cuzick [9] and other models [10-12]. BRCAPRO [13] and Breast and Ovarian Analysis of Disease Incidence

No	Varaible	Data source
	Benefits	
1	Mortality rate reduction	Primary end point in RCTs and meta analysis
2	Morbidity rate reduction	Secondary end point in RCTs and observational studies
3	Reassurance	No direct and indirect evidence
	Risks	
4	Radiation induced cancer	No direct evidence, indirect evidence from prospective and retrospective studies
5	False positive test and consequences	Prospective and retrospective cohort studies
6	Over diagnosis	Indirect evidence from time trend and cross sectional studies
7	False reassurance	No direct and indirect evidence
8	Pain and discomfort	Prospective cohort study

Table 1: Pros and cons of mammography.

Age	No. of included trials	RR for breast cancer mortality (95% CrI)	NNI to prevent I breast cancer death (95% CrI)
39-49	8 [34]	0.85 (0.75-0.96)	1,904 (929-6,378)
50-59	6 [35]	0.86 (0.75-0.99)	1,339 (322-7,455)
60-69	2 [36]	0.68 (0.54-0.87)	377 (230-1,050)
70-74	1 [39]	1.12 (0.73-1.72)	Not available

Table 2: Summary of meta-analyses of risk ratios for breast cancer mortality from mammography screening trials for all ages.

and Carrier Estimation Algorithm (BOADICEA) [14] are more commonly used to estimate the risk based on *BRCA* mutation.

Women aged 35 years or older with a 5-years risk of Invasive Breast Carcinoma Greater Than or Equal to 1.7%. The modified Gail model assesses the risk of invasive breast cancer as a function of age, menarche, age at first live birth or nulliparity, number of first-degree relatives with breast cancer, number of previous benign breast biopsies, atypical hyperplasia in a previous breast biopsy, and race.

The Gail model should not be used for women with a predisposing gene mutation, a strong family history of breast or ovarian cancer suggestive of a genetic predisposition, women with a prior history of thoracic radiation, or for those with LCIS.

Pitfalls of mammography:

- Health Insurance Plan of Greater New York (38), Canadian National Breast Screening Study-1 (39), Stockholm (37), Malmo (37), Swedish Two-County (2 trials) (37, 42), Gothenburg (41), Age (40).
- Canadian National Breast Screening Study-2 (43), Stockholm (37), Malmo (37), Swedish Two-County (two trials) (37, 42), Gothenburg (41).
- Malmo (37) and Swedish Two-County (Ostergotland) (37).
- Swedish Two-County trial (Ostergotland) (37).

Key points of the Meta analysis and trials that indicates:

- Breast cancer mortality benefit for all age groups between age 39 to 69
- Insufficient data for older women
- False positive results are common in all age groups and lead to additional imaging and biopsies.
- Women age 40 to 49 experiences the highest rate of additional imaging while their biopsy rate is lower than older women.

a. Although, meta- analyses provide positive evidence of effectiveness of screening in average risk women, it does not reflect the better effectiveness of contemporary treatment of cancer treatment. Therefore, screening must be based on individual's actual risk and shared decision making.

Breast magnetic resonance imaging: Guidelines published by the American Cancer Society recommend annual breast MRI (usually in addition to annual mammography) for the following patients:

1) Women who are carriers of mutations in the BRCA genes or other germ line mutation carriers with a known markedly increased risk of breast cancer

2) First-degree relatives of mutation carriers who have not been tested themselves

3) Women who have a history of radiation to the breast between the ages of 10 and 30 years

4) Women with a lifetime risk of breast cancer estimated at 20% or greater according to family history–based risk assessment models (e.g., BRCAPro, Myriad, Tyrer-Cusick).

Cervical Cancer Screening

The two main types of cervical cancer: are squamous cell carcinoma and adenocarcinoma, the first one being more prevalent. Screening can detect precursors and early-stage disease for both types. Treatment of precursors and early-stage disease can prevent the development of invasive cervical cancer.

Two tests are available: Pap (Papanicolaou) smear with conventional method or liquid based cytology and HPV testing.

Pap smear

Low-grade lesions and atypical squamous or glandular cells are better detected by the liquid-based technique and that the same specimen may be used for the Pap smear and for HPV testing [38-43]. Sensitivity and specificity of this test vary substantially: estimates of the sensitivity range from 30% to 87%, whereas specificity is reported as 86-100% [44]. In a meta-analysis of 12 case-control studies, cytology screening was associated with decreased risk of invasive cervical cancer (odds ratio 0.35, 95% CI 0.30-0.41 [45].

HPV testing

Out of various HPV genotypes infecting the genital tract mucosa, types 16 and 18 are responsible for about 70% of cervical cancer and 50% of cervical cancer precursor lesions. There is a high prevalence of HPV infection in sexually active women, particularly in younger women. Most young women will clear the HPV infection within 8 to 24 months. The prevalence of cervical HPV infection decreases after the age of 30, but the likelihood of persistent infection increases [46].

HPV testing, either alone or in combination with cervical cytology, is more sensitive than cervical cytology alone in detecting cervical histopathology, including adenocarcinoma. Randomized trials have demonstrated a decrease in the overall incidence of cancer with HPV testing, although a mortality benefit has not been demonstrated Strategies that include HPV testing increase the number of positive results and colposcopies performed and long-term outcomes are uncertain [47,48].

In co-testing, both Pap test and HPV testing are performed. Co-testing may detect earlier cervical abnormalities than Pap test alone,

but also leads to an increased rate of follow-up testing (colposcopy), and does not appear to affect mortality.

In primary HPV testing, the 2015 interim guidelines from the Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP) suggested primary HPV testing as an option for women starting at age 25 years [49].

Other US guidelines have not made recommendations regarding primary HPV testing. The Cobas HPV test has been approved by the FDA for primary HPV testing in women age ≥ 25 years.

Reflex (triage) HPV testing is done for equivocal cytology test results (atypical squamous cells of undetermined significance, ASC-US) It may be a useful tool as an alternative. HPV testing is approved for use in two contexts: (1) as a second (i.e., triage) test following an equivocal cytology result of ASCUS; and (2) for primary screening in conjunction with cervical cytology for women aged 30 years and older to conventional follow-up.

The USPSTF recommends (Table 3) screening women ages 21 to 65 years with cytology every 3 years or, for women ages 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 years. (Grade A)

The meta- analysis (Table 4) indicates that Given the available evidence we were not able to definitively answer the question regarding ages to initiate and discontinue cervical screening, however we were able to draw a few themes from the data Despite very high participation among younger women, the benefit of screening below age 30 is unclear. The evidence indicates exposure to cytology screening provides a substantial protective effect in women 30 years and older (for example, screened at ages 30 to 65 OR 0.40 (95% CI 0.34, 0.47); ages 40 to 59 OR 0.3 (95% CI 0.2, 0.4); ages 42 to 44 OR 0.37 (95% CI 0.29, 0.48); ages 52 to 54 OR 0.26 (95% CI 0.19, 0.36) [50].

Colorectal Cancer Screening

Most Colorectal Cancers (CRCs) arise from adenomas, many of which are polyps that progress from small to large (>1 cm) polyps, and then to dysplasia and cancer. The malignant transformation may result from acquired and or genetic syndromes. Some colon cancers arise from nonpolypoid adenomas that are flat or depressed and account for 22 to 36 percent of identified adenomas. Removal of adenomatous polyps prevents cancer. It is difficult for non polypoid adenoma. Risk factors include family history, age, geographic area, race, gender, dietary habits, and smoking. Currently, risk factors other than age and family history are not taken into account in most screening recommendations. There are High-risk genetic syndromes like Lynch syndrome (hereditary nonpolyposis colon cancer) and Familial adenomatous polyposis. There are basically 2 methods of testing: stool based detecting abnormality at earlier stage and radiological testing having an advantage of simultaneously removing the polyps.

Screening with gFOBT has been demonstrated to reduce mortality from colorectal cancer in randomized trials [51-53]. Other endoscopic and radiographic tests include Optical colonoscopy, Double-Contrast Barium Enema (DCBE), CT Colonography (CTC, formerly referred to as "virtual colonoscopy"). In the larger trial involving 170,432 participants between the ages of 55 and 64 years, one-time screening with sigmoidoscopy, compared with no screening, led to a 23 percent decrease in the incidence of CRC and a 31 percent decrease in CRC mortality after a median follow-up of 11.2 years [54].

Multi-Society Task Force guidelines, USPSTF guidelines, American College of Gastroenterology guidelines, National Comprehensive

Population	Women ages 21 to 65	Women ages 30 to 65	Women younger than age 21	Women older than age 65 who have had adequate prior screening and are not high risk	Women after hysterectomy with removal of the cervix and with no history of high grade precancer or cervical cancer	Women younger than age 30
Recommendation	Screen with cytology (Pap smear) every 3 years. Grade: A	Screen with cytology every 3 years or co-testing (cytology/HPV testing) every 5 years. Grade: A	Do not screen. Grade: D	Do not screen. Grade: D	Do not screen. Grade: D	Do not screen with HPV testing (alone or with cytology). Grade: D

Table 3: Clinical summary of U.S. preventive services task force recommendation.

Outcome	Assumed risk for no screening Number per million	Corresponding risk for screening Number per million (95% CI)	Relative effect (95% CI)	Number of participants (Number of studies)	GRADE quality of evidence
Cervical cancer mortality (invited to HPV test or cytology versus no screening) RCT; follow-up: 8 years	2,033	1,330 (964, 1834)	RR 0.65 (0.47, 0.90)	97,672	Moderate
Incidence of stage II+ cervical cancer (invited to HPV test or cytology versus no screening) RCT; follow-up: 8 years	2,604	1,466 (1,093, 1,966)	RR 0.56 (0.42, 0.75)	97,672	Moderate
Incidence of invasive cervical cancer (invited to HVP test or cytology versus no screening) RCT; follow-up: 8 years	3,747	4,216 (3,401, 5,226)	RR 1.12 (0.91, 1.39)	97,672	Moderate
Incidence of invasive cervical cancer (cytology versus no screening) cohort study; follow-up: 3 years	1,596	609 (368, 1,006)	RR0.38 (0.23, 0.63)	116,022	Low
Exposure to cytology screening (cases: diagnosed with invasive cervical cancer; controls: no cervical cancer); exposure: in previous 3 years to lifetime	4,781 cases and 17,916 controls		OR 0.35 (0.30, 0.41)	22,697	Very Low

Table 4: Summary of findings for effects of screening on cervical cancer mortality and incidence.

Cancer Network consensus guidelines and Council of the European Union all defer regarding the standard screening approach.

The USPSTF recommends three screening options for adult's age 50 to 75 years:

- Annual Fecal Occult Blood Testing (FOBT) with a sensitive test
- Flexible sigmoidoscopy every five years, with sensitive FOBT every three years
- Colonoscopy every 10 years
- Screening people at increased risk

For FAP, Screening of gene carriers or at-risk family members and if uninformative or negative, flexible sigmoidoscopy or colonoscopy every 12 months starting around age 10 to 12 years and continuing until age 35 to 40 years if negative. Colectomy near the time of initial diagnosis in patients with profuse polyposis, multiple large (>1 cm) adenomas, or adenomas with villous histology and/or high-grade dysplasia [55]. Patients with sparse, small (<5 mm) adenomas can usually be followed endoscopically. Recommendations for extra intestinal lesion in FAP have also been suggested:

Annual clinical examination of the thyroid and a baseline thyroid ultrasound in the adolescent age group is recommended for all patients with FAP. Other benign conditions like desmoids tumors, adrenal tumors and osteoma also need screening in appropriate way.

Individuals with Lynch syndrome should undergo screening for CRC and extracolonic cancers:

Annual colonoscopy starting between the ages of 20 and 25 years, or two to five years prior to the earliest age of CRC diagnosis in the family. Genetic testing for MSH6 or PMS2 mutations is done as indicated.

Annual screening for endometrial and ovarian cancer with pelvic examination, endometrial biopsy, transvaginal ultrasound beginning at age 30 to 35 years, or three to five years earlier than the earliest age of diagnosis of these cancers in the family.

Lung Cancer Screening

Lung cancer is the second most cancer killer in men. Following facts about lung cancer makes it an attractive disease for screening: The at risk population is known, the prevalence is high, morbidity and mortality is high, detection at early stage leads to better outcome.

PLCO Cancer Screening Trial, Mayo Lung Project, National Lung Screening Trial, NELSON trial and UKLC trial have evaluated various screening modalities in at risk and average risk population [56-59]. Individuals age 55 to 74 years with a 30 or more pack-year history of smoking tobacco who currently smoke or, if former smoker, have quit within 15 years (category 1). Individuals age 50 years or older with a 20 or more pack-year history of smoking tobacco and with one additional risk factor (category 2A). Additional risk factors are cancer history, lung disease history, family history of lung cancer, radon exposure, and occupational exposure to carcinogens (Table 5).

Risks and benefits of lung cancer screening

- Effective lung screening may prevent more than 12,000 premature lung cancer deaths per year.
- The NLST [55] results showed that annual LDCT decreased the RR of death from lung cancer by 20%.
- Quality of life improves and reduction in disease and treatment related morbidity is observed.
- The risks involved in screening are false-Positive Results, false-Negative Results, futile Detection of Small Aggressive Tumors or of Indolent Disease and Radiation Exposure with LDCT. Shared decision making may be recommended in view of all the harms [56-61].

Ovarian Cancer Screening

The US Preventive Services Task Force (USPSTF) recommends against screening for ovarian cancer, with their initial recommendation reaffirmed in 2008 for women in general.

For women at increased risk like those with possible inherited breast-ovarian cancer syndrome, genetic counseling and genetic testing for BRCA-1 and BRCA-2 and Lynch mutation is recommended**.** National Comprehensive Cancer Network (NCCN) recommend screening every six months with CA 125 and TVUS beginning between the ages of 30 and 35 years or 5 to 10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family.

Prostate and endometrial cancer is other diseases where issue of screening is taken up through various trials.

Prevention with vaccines and medicines

Fifty percent of cancer is preventable [62]. This is because of the modifiable risk factors involved in the process of carcinogenesis. Primary prevention i.e. reduction in the risk of cancer can be done with medications in high risk population. This is called chemoprevention. Breast cancer, prostate cancer, cervical cancer, colorectal cancer is the examples of such strategy.

The National Body	Guidelines
US Preventive Services Task Force [59]	Annual low-dose CT scan screening for high-risk individuals (ages 55 to 80 years with a 30 pack-year history of smoking and current smoker or quit within past 15 years). Discontinue when person has not smoked for 15 years or if limited life expectancy.
American Cancer Society [60]	Annual low-dose CT scan screening for high-risk individuals (age 55 to 74 years with 30 pack-year history of smoking and current smoker or quit within past 15 years). Informed individual decision making before testing.
American College of Chest Physicians/ American Society of Clinical Oncology	Annual low-dose CT scan screening for high-risk individuals (age 55 to 74 years with 30 pack-year history of smoking and current smoker or quit within past 15 years).
American Association of Thoracic Surgery (AATS)	Annual low-dose CT scan screening for high-risk individuals (age 55 to 74 years with 30 pack-year history of smoking and current smoker or quit within past 15 years) or age 50 with cumulative risk >5 percent over next five years
National Comprehensive [61] Cancer Network	Annual low-dose CT scan screening for high-risk individuals (age 55 to 74 years with 30 pack-year history of smoking or 20 pack-year history with an additional risk factor).
Canadian Task Force on the Periodic Health Examination	Advises against the use of chest x-ray in asymptomatic persons. Evidence is insufficient to recommend for or against screening with spiral CT in asymptomatic persons.

Table 5: Guidelines for Lung cancer screening.

Breast Cancer

Tamoxifen and Raloxifen are two SERMS approved for women with high risk of breast cancer defined as history of Lobular Carcinoma In Situ (LCIS), a five-year estimated risk for breast cancer of at least 1.66 percent as determined by the Gail model, [63] or family history of the disease. Tamoxifen was studied in various trials [64,65]. Use of Tamoxifen is associated with side effects like endometrial cancer and thromboembolic events. The greatest benefit is derived in premenopausal women (who are less likely to have thromboembolic sequelae and uterine cancer), women without a uterus, and women at higher breast cancer risk. A meta-analysis [66] concluded that use of tamoxifen reduced breast cancer risk by 38% and doubled the risk of endometrial cancer and thromboembolic events, but it did not affect overall mortality.

In STAR trial [67] both SERMS were directly compared where raloxifen had a fewer side effects .The US Food and Drug Administration (FDA) approved raloxifene for use for breast cancer chemoprevention in postmenopausal women. There are no reports on the use of raloxifene in **BRCA** mutation carriers.

The benefit of an AI as prevention was demonstrated in the International Breast cancer Intervention Study [68] where high risk was defined as high risk was defined as two or more blood relatives with breast cancer, mother or sister with breast cancer before 50 years, mother or sister with bilateral breast cancer, or high risk benign breast disease. There was a 50 percent reduction in the number of invasive breast cancer with anastrozole compared with placebo (32 [2 percent] versus 64 [3 percent], respectively, Hazard Ratio [HR] 0.47, 95% CI 0.32-0.68). Anastrazole led to more musculoskeletal side effects (64 versus 58 percent), hypertension (5 versus 3 percent), vaginal dryness (19 versus 16 percent,), and vasomotor symptoms (57 versus 49 percent). (USPSTF) and the American Society of Clinical Oncology (ASCO) support endocrine therapy in form of Selective Estrogen Receptor Modulators (SERMs) for women at high risk for breast cancer.Only ASCO considers the use of the Aromatase Inhibitor (AI) as a reasonable alternative in post menopausal women.

The cost of the AIs and long term side effects like osteopenia, hot flashes and cardio vascular ailments are the concerns for the long term usage.

Cervical Cancer

Gardasil (quadrivalent) and Cervarix (bivalent) are two vaccines recommended for prevention which act against HPV genotypes 6, 11, 16, and 18. The HPV-16 and HPV-18 genotypes cause almost two thirds of all cervical cancers and Cervical Intraepithelial Neoplasia (CIN) 2 and 3, whereas the the HPV-6 and HPV-11 genotypes are implicated in genital warts. Gardisal was studied in large randomized trials involving more than 17000 young girls (Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases.

Among HPV-naïve populations, the efficacy of 9-valent vaccine for preventing CIN2 or more severe disease, VIN2 or 3, and VaIN2 or 3 associated with HPV types 31, 33, 45, 52, and 58 was 97 percent.

In the overall population of study participants (with and without prior HPV infection), the rates of high-grade cervical, vaginal, and vulvar disease were the same among women who received the 9-valent vaccine and those who received the quadrivalent vaccine (14 cases/1000 person years in both groups).

Bivalent HPV vaccine was also studied in a trail giving the similar results (Efficacy of Human Papillomavirus (HPV)-16/18 AS04-adjuvanted vaccines against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women.

The United States Advisory Committee on Immunization Practices (ACIP) recommends the bivalent, quadrivalent, or 9-valent HPV vaccine for females aged 11 to 12 for the prevention of cervical, vaginal, and vulvar cancer and the related precursor lesions caused by the HPV types targeted by these vaccines.

(Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for persons aged 0 through 18 years and adults aged 19 years and older-United States, 201 Centers for Disease Control and Prevention (CDC).

World Health Organization (WHO) position paper suggests that girls within the age range of 9 through 13 years should be the primary target population for HPV immunization. Local public health programs should recommend vaccination of older females only if it is affordable and cost effective and does not divert resources from vaccinating the primary target population or screening for cervical cancer. Catch-up vaccination is also recommended for females aged 13 to 26 years who have not been previously vaccinated or who have not completed their vaccine series. Catch uo vaccine is not recommended by WHO or ACS.

The Advisory Committee on Immunization Practices (ACIP) recommends the routine use of quadrivalent or 9-valent HPV vaccine in males aged 11 or 12 years (Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for persons aged 0 through 18 years and adults aged 19 years and older-United States, 201 Centers for Disease Control and Prevention (CDC).

The quadrivalent vaccine (Gardasil) and 9-valent vaccine (Gardasil 9) are typically administered in three doses at time zero, and at two and six months of follow-up. The bivalent vaccine (Cervarix) is typically administered in three doses at time zero, and at one and six months of follow-up. HPV vaccine can be safely administered at the same time as other age-appropriate vaccines at a different anatomic site.

COST EFFECTIVENESS is studied for HPV vaccination. (Health and economic implications of HPV vaccination in the United States. Evaluating human papillomavirus vaccination programs. In various models, vaccinating both males and females is predicted to be more beneficial in reducing HPV infection and disease than by vaccinating only females, but at a higher cost than vaccinating females alone

Prostate Cancer

Prostate cancer is the second most common cancer in men worldwide, with an estimated 1,100,000 cases and 307,000 deaths in 2012. The long latency period between the initial evidence of prostate cancer and the development of overt or fatal disease, the androgen dependency of these tumors along with HG-PIN as an end point had made it a target for chemoprevention. Inhibition of 5-AR blocks production of the most potent androgen involved in prostate cancer pathogenesis.

Finasteride (Prostate Cancer Prevention Trial-PCPT) and Dutasteride (Reduction by DUtasteride of prostate Cancer Events-REDUCE) have been studied. Meta-analysis of 5-alpha reductase inhibitor studies indicates that these agents decrease the risk of prostate cancer by approximately 25% [16].

CPT the influence of finasteride on the development of prostate

cancer, Side effects of these agents include gynecomastia, decreased libido, erectile dysfunction, and decreased ejaculate volume. At the same time, these agents may decrease urinary tract symptoms due to benign prostatic hyperplasia. Incresde rate of high-grade prostate cancers have been observed in patients taking finasteride and dutasteride. US Food and Drug Administration (FDA) has not approved the use of these agents for prostate cancer prevention due to potential concerns about risks and long-term safety

Guidelines from the American Society of Clinical Oncology and the American Urologic Association recommend that men discuss the risks and benefits of chemoprevention with these medications with their physicians (Table 6).

Colorectal cancer (CRC)

The protective agents like aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are evaluated in various trials for CRC. Meta-analyses and systematic reviews suggest that Regular use of aspirin reduced the incidence of colonic adenomas in randomized controlled trials (relative risk [RR] 0.82, 95% CI 0.7-0.95), in case-control studies (RR 0.87, 95% CI 0.77-0.98), and in cohort studies (RR 0.72, 95% CI 0.61-0.85). The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med 2007; 146:365.) Consider risk versus benefit ratio when initiating aspirin for this indication.

Aspirin and other Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are associated with a 20 to 40 percent reduction in the risk of colonic adenomas and colorectal cancer in individuals at average risk. High doses of aspirin (600 mg/day) appear to provide a benefit for patients with hereditary nonpolyposis colorectal cancer (Table 7).

Surgical prevention

An individual with hereditary genetic predisposition, surgical removal of the risk organ is an alternate to chemoprevention. The examples of surgical management as a risk reduction strategy are prophylactic mastectomy in **BRCA** mutation carriers, prophylactic salpingo-oophorectomy in **BRCA** carriers and mismatch repair gene mutation carriers, and prophylactic colectomy in individuals with Familial Adenomatous Polyposis (FAP).

Study	Drug and Daily Dose	N=	Treatment Duration (years)	Entry Criteria	Overall outcome HR (95% CI)
PCPT	Finasteride 5 mg Placebo	18880	7	Age ≥ 55 y, PSA ≤ 3 ng/mL	0.70 (0.65-0.76)
REDUCE	Dutaseride 0.5 mg Placebo	6729	4	Age 50-75 y, PSA 2.5-10.0 ng/mL, core biopsies within 6 mos	RR = 0.77 (0.70-0.85)

Table 6: The prevention of prostate cancer.

Population	Drug (Dose), Duration	Phase	End points	Outcome
Familial adenomatous polyposis (FAP)	Sulindac (300400 mg/d, divided doses)	IIb	Polyp regression	Colorectal and duodenal polyps regressed in ~50%
Hereditary nonpolyposis colon cancer (Lynch syndrome)	Aspirin 600 mg/d, resistant starch	III	cancer	≥ 2 yr, hazard ratio (HR) colon cancer 0.41; 95% CI, 0.190.86; all cancers Incidence rate ratio 0.37; 95% CI, 0.180.78; no effect of starch

Table 7: Summary of clinical trials of nonsteroidal anti-inflammatory drugs as colorectal cancer risk-reducing agents in genetic conditions.

The majority of patients with hereditary breast and ovarian cancers have mutations in either the breast cancer type 1 or 2 susceptibility genes (**BRCA1** and **BRCA2;** referred in this topic as **BRCA**). Mutations in these genes are implicated in about 15 percent of women with familial breast cancer and a similar proportion of all women with incident ovarian cancers. Other hereditary conditions, such as Li-Fraumeni and Cowden syndromes, which are related to mutations in the **TP53** and **PTEN** genes, respectively

For women without a personal history of cancer in whom a **BRCA** mutation is identified, national guidelines recommend risk-reducing Bilateral Salpingo-Oophorectomy (BSO) between the ages of 35 and 40, and once childbearing is complete. Studies show that BSO significantly reduces the risk of ovarian cancer. The breast cancer risk reduction associated with bilateral prophylactic mastectomy is approximately 90%.

Despite the considerable risk reduction associated with this procedure, utilization of prophylactic mastectomy remains far less than that of prophylactic salpingo-oophorectomy. Possible reasons for the discrepancy between the rates of these prophylactic surgeries include lack of data proving survival benefit, concerns about appearance and sexuality following mastectomy, availability of medications that reduce breast cancer risk, and the options of screening modalities that can detect breast cancer at a premalignant or early stage.

The decision-making around which strategies to pursue for cancer risk-reduction (i.e., surveillance, risk-reducing surgery, and/or chemoprevention) involve a trade-off between life expectancy and quality of life.

Prophylactic salpingo-oophorectomy

For women with a **BRCA** mutation, risk-reducing Salpingo-Oophorectomy (BSO) is indicated by age 35 to 40 and when childbearing is completed. BSO is also indicated for carriers who are diagnosed with early-stage breast cancer. It is also appropriate for women with Lynch syndrome. This procedure provides premenopausal **BRCA** mutation carriers with protection from both ovarian cancer (90-95% risk reduction) and breast cancer (50% risk reduction); for postmenopausal carriers, it provides protection from ovarian cancer only. Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE. Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. Risk-reducing salpingo-oophorectomy in women with a **BRCA1** or **BRCA2** mutation.

Prophylactic hysterectomy at the time of oophorectomy remains a point of some debate. For women with Lynch syndrome, the risk of endometrial cancer is also increased, and it is appropriate to remove the uterus at the time of oophorectomy. Another issue of debate is the use of hormone replacement therapy after prophylactic oophorectomy, which remains controversial in this population due to the risks of breast cancer. At least one report has found that short-term use of hormone replacement to treat menopausal symptoms after oophorectomy in **BRCA** carriers did not increase the incidence of cancers. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in **BRCA1** and **BRCA2** mutation carriers: the PROSE Study Group.

It is a common practice to prescribe HRT from the time of BSO until about age 50, particularly for those undergoing risk-reducing mastectomy.

Colectomy

Individuals with the hereditary syndrome familial adenomatous polyposis are often afflicted with hundreds to thousands of colorectal polyps and have a virtual certainty of developing colorectal cancer in their lifetime if their disease is unchecked

A standard risk-reducing measure in this population is prophylactic colectomy, which is generally undertaken at the appearance of adenomas in known mutation carriers. Generally undertaken at the appearance of adenomas in known mutation carriers (Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer).

Status of cancer screening in India

The common sites for cancer in India are oral cavity, lungs, oesophagus and stomach in males and cervix, breast and oral cavity among females. Over 70% of the cases report for diagnostic and treatment services in advanced stages of the disease, resulting in poor survival and high mortality rates.

Screening for Breast Cancer: It has been suggested that given the socio-economic realities of a developing country such as India and the unsuitability of mammography, CBE may be an attractive screening procedure. Screening for Cervix Cancer the VIA-VILI combination test may be an acceptable simple technological tool for cervix cancer screening in resource poor countries like India**.** In India, it can always be debated whether introduction of cervical cancer screening programme at this juncture is at all practicable or we should straightaway settle for a HPV vaccine based primary prevention strategy.

Future of preventive oncology

With advances in molecular biology, we understand the stages of cancer development: initiation, promotion and progression. It involves multiple steps at genetic level and we can target it with molecules called chemo-preventive agents. Incresing use of technologies like I-robot and nanotechnology, the diagnosis may be in the earliest stages to make it amenable to therapeutic strategy. The important role played by new blood vessel growth in tumors, led to the development of antiangiogenic drugs now in clinical trials to treat cancer. Because angiogenesis begins early in cancer, such agents may also turn out to be useful in prevention. Regulation of certain oncogenes before conception has led the way to prevention of neonatal cancers. Perhaps some of the so-called congenital tumours- retinoblastoma and neuroblastoma - could be prevented.

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