Evidence Based Management of Cancers in India-2023

Prevention and Screening of Common Cancers

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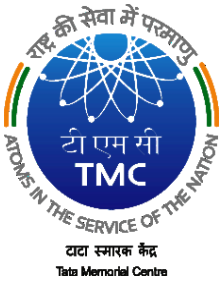

Tata Memorial Centre, Mumbai, India

PREVENTION AND SCREENING OF COMMON CANCERS

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Dedicated to
All our patients at
The Tata Memorial Hospital

Preface

Evidence-Based Management (EBM) is a scientific way that supports the organization progress towards the right decision at the right time with reduced risk. This practical approach accomplishes the cardinal principles, executes the SMART goals of the organization and achieves triumph. The Tata Memorial Hospital, Mumbai, India has established the reason for EBM in oncology across India and has been steering the annual meeting on EBM in common cancers for the past twenty years.

EBM 2023 is focusing on 'Prevention in Oncology' covering the emerging concept of 'Precision and Prevention', and secondly 'Prevention and early detection of common cancers.' This conference will focus on the role of prevention in breast, gynaecological, oral cavity, lung, prostate, colorectal and esophago-gastric cancers.

This year's e-book comprises - Incorporating lifestyle and genetic risk factors in cancer prevention and screening: A goal towards precision in prevention. This describes the implementation challenges faced for risk stratification. This is followed by guidelines for prevention and screening, early detection of above-mentioned cancers and providing recommendations for a way forward in India. Renowned faculty members have covered the above topics in a very focused and concise manner.

Each year we have concentrated on various features of cancer care; collated and published the best available evidence in the form of "EBM book" which is also easily accessible at our official website. This helps busy clinicians from all over the country and abroad to get updated on the best available evidence in cancer prevention, thereby translating into cancer control and patient care.

Prof. R. A. Badwe
Director,
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Content

Chapter 1

Incorporating life style and genetic risk factors in cancer prevention and screening: A goal towards precision Prevention.

Author:

Dikshit Rajesh

Incorporating life style and genetic risk factors in cancer prevention and screening: A goal towards precision Prevention.

Understanding etiology of a cancer is a complex process. Research on cancer causation has so far revealed that no single cause is necessary or sufficient in itself which could be attributed in development of cancer. Exposure to certain factors may put some individuals at more likelihood of developing cancer and these factors are known as risk factors. In absence of factors which are necessary or sufficient for development of cancer, causes of cancer are conceptualized in probabilistic sense that involves statistical terms and procedures. For example, tobacco chewers are more likely to develop oral cavity cancer than non-chewers, however most of the chewers will never develop oral cavity cancer while some non- chewers will do. This also implies that cancer has multifactorial etiology with various factors act together in common pathway and/or in different pathways to cause cancer. These factors may be related to life style, environment, infection and genetics. There is also a possibility that some of the causes of cancer are related to DNA replication errors known as intrinsic risk factors. These random errors in DNA replication can be recognized as non- modifiable risk factors and are of limited use in adopting strategies for community based cancer prevention.[1-3]

Implementing community-based cancer prevention programme is challenging logistically for populations like India. Therefore, such programme has to be launched with precision so as to maximize the benefits. Before launching these programmes at state/national level; evaluation of cancer burden, current trends of cancer to be screened, social determinant and priorities needs to be considered. Once the population and societies in needs are identified evaluation of behavior and genetic risk factors can be undertaken to achieve the goal of precision prevention

The lifestyle factors which are most commonly considered in planning primary prevention, early detection and cancer screening strategies are tabulated in Table 1:

Table 1: Important modifiable risk factors for cancer

Risk factors	Factor prevalent globally	Factor specific to India
Tobacco use	Cigarette smoking	Bidi smoking , various types of smokeless tobacco
Alcohol consumption	Beer, Wine	Country liquor, Taddi
Infection	HPV, HIV	HPV, H. Pylori, S. typhi
Reproductive and hormonal factors	Breast feeding, use of oral and hormonal contraceptives	More number of pregnancies, early age at marriage
Obesity	BMI	Abdominal obesity
Pollution	Air pollution	Indoor air pollution
Diet	High Fat, Processed meat	Spicy food?, Aflotoxin
Physical activity	Sedentary life style	Sedentary life style

Based on preventable risk factors recommendations guidelines are developed for primary prevention of cancer. There are strong evidences to suggest that tobacco control and smoking cessation reduces mortality for many cancer sites. Control of HPV and Hepatitis B infection is also shown to reduce incidence and mortality mainly from cervix and liver cancer. In order to assess the impact of adherence to guidelines on cancer control issued by American Cancer Society (ACS) a prospective cohort study on 566,401 individuals in age group of 50-71 years was conducted. The study was initiated in the year 1995-96 with a median follow-up of 10.5 years for cancer incidence, 12.5 years for cancer mortality and 13.6 years for overall mortality. The study concluded that adherence to ACS guidelines was associated with reduced risk of cancer incidence for all cancer sites combined, and in 14 of 25 cancer sites studied. The adherence to cancer control guidelines was also associated with reduction in cancer mortality and all-cause mortality.[4]These data strongly suggest importance of identification of risk factors in primary prevention of cancer with certain behavior changes. More Indian specific data are required to plan interventions specific to India. These life style factors may also be used in risk stratification of individuals in undertaking screening programmes.

The effect of these risk factors, however, is not the same on all individuals. These behavior factors affect some individuals severely while for other effect is moderate to weak. These differences can partly be explained by studying genetic susceptibility. There are differences in germline genome which alter the individual response in cancer development and progression. The research strategy has been to focus on common variants (with prevalence >10%) which provide small contribution to cancer development. This strategy is in contrast to study rare variants which have much higher risk in cancer development (for example mutation in BRCA1 and BRCA2). With the availability of hi-throughput technology it has been possible to study common genetic variants on thousands of individuals in the framework of Genome-Wide Association Studies (GWAS). Large scale GWAS has identified so far more than 700 cancer risk loci.[5-7]A single genetic variant confers only modest effect on given cancer type. However, a cumulative effect of these variants across the genome is substantial. The cumulative effect of variants are measured using Polygenic risk score (PRS). The PRS can be used to separate the individuals at high risk of developing cancer and also to determine screening intervals (frequency of screening). There are evidences to show the utility of PRS in improving existing screening programmes. The major challenge in using PRS in India is very limited availability of GWAS data for Indian Population.[8]

With the availability of lifestyle risk factors data on cancer site and PRS, a risk stratification model can be built to select individual for screening who are at high risk of developing cancer. In a risk stratified screening approach, targeted population is selected (based on cancer burden) and individuals are divided into groups with different level of risk of developing cancer over certain time. Depending upon logistics various protocols related to frequency of screening (frequent screening, only one-time screening or no screening) are selected.

Screening for lung cancer using low dose CT scan is one of the example for risk stratified screening. In a National Lung Cancer Screening Trial (NLST) conducted across 33 centres in USA, individuals were randomized if they had >30 pack years of smoking history.[9]There is consideration of HPV positive test results for cervical cancer screening programmes.[10]For breast cancer several risk stratification models have been developed. The most recent models uses both behavior risk factors and PRS. A risk prediction model based on PRS on 313

single nucleotide polymorphisms and other risk factors of breast cancer has predicted that life time risk of developing breast cancer in UK population varies from 2.8% for first percentile to 30.6% for 99th percentile suggesting that the model enable high level of risk stratification which can be useful to guide population-based screening.[11]

The screening approach based on risk stratification thus can be cost effective and logistically feasible. It also reduces the harm related to overdiagnosis particularly for individuals who are at lower risk of developing cancer. However, this approach will require identification of risk factors, development of PRS and then developing risk prediction model.

However, implementing the risk stratification strategies for community-based screening has following challenges:

1. No randomized trial evidence are available to implement risk stratified screening strategy.
2. Limited availability of India specific risk factors for most of the cancer type.
3. India specific GWAS data on cancer very limited. Because different ancestry can have different allelic frequencies it will be challenging to determine PRS for heterogeneous Indian population using GWAS data from European ancestry.
4. The screening strategies for individuals at moderate or low risk of cancer are not clear.

The next decade should see overcoming all these challenges and step towards precision prevention. The future guidelines for cancer screening could include integration of molecular knowledge and risk stratification to select individuals at highest risk of developing cancer. The risk stratification approach using risk factors and PRS will for sure eliminate the problem of overdiagnosis and overtreatment to greater extent. The future lies in screening individual by matching his genomic and environmental /behavior risk profile.

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Chapter 2

Breast Cancer

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Breast Cancer – Prevention and Early Detection

Current Scenario:

Breast cancer is the most common cancer in women worldwide with an estimate of 2.3 million new cases annually, contributing to almost 11.7% of all diagnosed cancer cases. 1 in 4 cancer cases and 1 in 6 cancer deaths among women are due to breast cancer. It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths.[1]Breast cancer is the most common cancer both in terms of new cases and deaths reported in India. It is responsible for 180,000 new cases accounting for 26.3% of all cancers among women and 90,000 deaths annually.[2]The Age Standardized Incidence rates in India are 25 to 33 per 100,000 in urban and 13 to 17 per 100,000 in rural India based on data from Population Based Cancer Registries.[3] Average annual increase in incidence is reported to be 8.6%.[4]

Risk Factors of Breast Cancer:

Countries with higher Human Development Index (HDI) are reporting rising incidence rates of breast cancers. Factors contributing to increase in prevailing risk of breast cancer are early puberty, late childbearing, decreasing fertility, late menopause, westernization culture of diet leading to obesity, hormone replacement therapy, use of oral contraceptives and lifestyle risk factors such as intake of alcohol, higher body weight, physical inactivity and also increased number of cases detected through organized or opportunistic mammographic screening.[5]Increased prevalence of breast cancer is being observed in Israel and in certain European sub-populations due to increasing mutation of high penetrance genes like breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2). These mutations are being reported to be exceptionally high among women of Ashkenazi Jewish heritage (range, 1%-2.5%).[6]

A. **Reproductive factors:** Studies from several countries show increasing incidence in estrogen receptor-positive cancers and decreasing rates for estrogen receptor-negative cancers reflecting effect of obesity epidemic and screening mammographs which preferably tend to ascertain slower growing estrogen receptor-positive cancers.[7-9] Dramatic changes in lifestyle, sociocultural behaviours, changes in environment due to growing economies led to an increase in the proportion of women working in the industrial workforce developing the risk of breast cancer by postponing the child birth,

conceiving less children, increased body weight and physical inactivity. These have caused a convergence toward the risk factor profile of western nations and a decrease of the global disparities in the morbidity of breast cancer.[1]

B. **Hereditary factors:** It is estimated that 5-10% of all breast cancers are hereditary. Inherited predisposition to breast cancer is suspected in cases with family history of cancer, breast cancer below 40 years, bilateral or multiple primary cancers or triple-negative breast cancer (TNBC) histology. These individuals need genetic counselling followed by germline multigene next generation sequencing (NGS) genetic testing. The lifetime risk of breast cancer is 60-80% in female carriers of a germline mutation in BRCA1, BRCA2 or TP53 genes and 30-60% risk in carriers of mutation in other genes like PALB2, STK11, PTEN, CHEK2, ATM etc.[10]Individuals found to have a mutation need to be counselled about its therapeutic implication, cancer screening, prevention and extended family testing. There are several ethical, legal or social issues that need to be addressed in genetic counselling.

Risk Prediction Models:

Literature suggests that a risk prediction model based on polygenic risk scores (PRS) and other lifestyle risk factors can be used to identify women at substantially different levels of absolute risk to develop breast cancer. [11, 12]In today's era of modern medicine there are several complementary risk assessment and calculation tools that aid the physician to decide regarding preventive therapy and individualize risks. The American Society of Clinical Oncology, the National Comprehensive Cancer Network (NCCN), the Canadian Task Force on Preventive Health Care and the US Preventive Services Task Force (USPSTF) recommend counselling high risk women, who are over 35 years about the available risk-reducing treatments and making a shared decision, taking into account both the agents' potential benefits and drawbacks (USPSTF B recommendation).[13-16] There are two popular risk assessment tools to establish eligibility: the modified Gail model and the Breast Cancer Risk Assessment tool.

Table 1: Development of risk prediction models have following requirements:

1.	Identification of risk factors for the population.
2.	Information on single nucleotide polymorphism (SNPs) for the population.
3.	Prevalence of identified risk factors in given population.
4.	Incidence rates of breast cancer in the population
5.	All-cause mortality data for the population.

Internationally, several studies have identified risk factors to develop risk prediction models like the [17] In India, there are relatively smaller number of large case control or cohort studies to identify risk factors of breast cancer in Indian population. A large case control study from Tata Memorial Centre, Mumbai has identified reproductive factors (increased number of full-term pregnancies, increased duration between menarche and first full-term pregnancy, induced abortion, current oral contraceptive use), obesity (Waist-to-hip ratio, BMI, waist circumference) and height as risk factors for breast cancer. In large scale Indian data, absence of breast feeding history was not associated with increased risk while waist to hip ratio and BMI was more strongly related to breast cancer risk.[18]

- **Polygenic risk score for breast cancer:**

The genome wide association studies (GWAS) have provided genetic predictors to pick up composite traits by calculating the effect magnitude at numerous loci. Every breast cancer locus separately seldom acts to influence breast cancer risk. However, their collective effect provides some risk determination in form of PRS that may be used to classify people into various disease risk groups. Women with breast cancer have been demonstrated to have higher PRS than seen with population controls.[11]

A study from US shows that model using PRS can recognize 16.1% of the population who can be advised to initiate screening from age 40 because they have an increased risk to develop breast cancer over the subsequent 10 years as compared to a woman of age 50. The model also could predict 32% of the population, whose risk at age 50 is 10 years lower than otherwise a woman at 40, demonstrating no added advantage of screening these women.[12] Study from India using 21 single nucleotide polymorphisms (SNPs) identified in GWAS conducted in Caucasian population, demonstrated the utility of PRS in identifying risk of developing breast cancer.[19] PRS improves the predictive ability of breast cancer and is useful for population-based screening using risk prediction model. In addition, PRS can identify women with risk of developing breast cancer with incomplete genetic test results.

1. PRIMARY PREVENTION

Primary prevention programmes for breast cancer are difficult to implement. Such programmes need to incorporate initiatives to promote awareness regarding breastfeeding, increase physical activity, and reduce alcohol intake and efforts to decrease excess body weight.

a. Chemoprevention of Breast Cancer:

There are emerging evidences of the probable role of cancer chemoprevention in preventing cancer by suppression or reversal of carcinogenesis (prior to invasion) through pharmacologically active drug interventions.[20, 21]This action could be at different stages of tumor initiation, promotion or progression. They are often termed as suppressing agents since they influence the promotion and progression of initiated cells. Clinical application of these agents can be at three tiers viz primary, secondary or tertiary.[21]

In breast cancers, two commonly used drugs classes are Selective estrogen receptor modulators (SERMS) (Raloxifene and Tamoxifen) and Aromatase Inhibitors (Anastrozole and Exemestane) which have proven clinical benefits in women with increased risk of the disease as evidenced from different RCTs. High risk women with a positive risk-benefit ratio are thereby benefited when these drugs are used for chemoprevention. Chemoprevention holds promise of reducing the risk of cancer in society.[20, 21, 22]The four major categories of cancer chemopreventive drugs are hormonal, medications, and diet related agents and vaccines. In breast cancer chemoprevention, hormonal agents are the predominant ones. These drugs are useful in steroid related cancers and can be further sub-classified as anti-estrogens and anti-androgens.[22, 23]

Anti-estrogens

i. Selective estrogen receptor modulators (SERMs): SERMs are designer drugs that exhibit a unique property of having both an estrogenic and an antiestrogenic action depending on the target tissue. This antagonistic or agonistic action is mediated via estrogen receptor (ER) activity. For example on breast tissue and endometrium SERMS have an antagonistic action and on skeletal tissue, vagina an agonistic effect. Tamoxifen offers a very long period of protection (at least 20 years) after treatment cessation. Considerable improvement has been demonstrated in the benefit-to-harm ratio for including tamoxifen for breast cancer prevention among high-risk women. Around 22 women need to

undertake treatment for 5 years in order to avert one breast cancer case in the subsequent 20 years. There have been good quality evidences showing role of SERMs, tamoxifen and raloxifene in decreasing risk of invasive breast cancer in both pre- and postmenopausal women. Both Tamoxifen and Raloxifene, lower the risk of vertebral fractures. Tamoxifen can increase the risk of uterine cancers to some extent. However, Raloxifene as compared to Tamoxifen leads to fewer thromboembolic events. [22, 23]

ii. Aromatase inhibitors (AIs): The mechanism of action of aromatase inhibitors is by inhibition of the enzyme aromatase, which catalyzes the aromatization procedure of androgens into estrogens. The data collected from recent studies show association of reduced breast cancer incidence among high risk women who have been on anastrozole and exemestane. These two drugs are well tolerated. However, larger clinical trials suggest some adverse effects such as joint pain and menopausal symptoms and hence require careful monitoring for such side-effects. Another choice could be use of AIs for high-risk postmenopausal women having medical comorbidities that contraindicate the use of SERM. [22-24]

Table 2: Evidence for the use of some of the Chemoprevention Agents

Agent	Evidence	Benefit	Duration of treatment
Tamoxifen	Breast Cancer Pt., NSABP P1	49% breast cancer risk reduction	5 years
Tamoxifen	International Breast Intervention Study	32% breast cancer risk reduction	5 years
Raloxifene	STAR trial	Equivalent to Tamoxifen in postmenopausal women with less risk	5 years

The international guidelines on chemoprevention for breast cancer have been updated to enhance the awareness and facilitate two-way dialogue between patients and their care givers. This includes discussion about evidence-based studies evaluating the risk-to-benefit ratio of preventive options for women at increased risk for breast cancer. Women who derive maximum benefit from primary prevention comprise high-risk individuals, less than 50 and demonstrating atypical hyperplasia. Despite increasing awareness and established benefits of preventive therapy, barriers from the care givers and patients themselves, limit the acceptance and compliance to preventive therapy. It is recommended to address these issues by

counselling the women at high risk, with good risk-to-benefit ratio of conventional chemoprevention methods to lessen their risk of developing breast cancer.

b. Surgical risk reduction options:

i. Risk reducing salpingo-oophorectomy (RRSO): It is recommended for BRCA mutation carriers. This is ideally carried out by 35-40 years of age or at the completion of childbirth or as per the age of incidence of Ovarian Cancer (OC) in family. RRSO offers a 50% reduction in Breast Cancer (BC) risk and 80-90% reduction in OC risk with improvement in disease-specific mortality.[25]

ii. Prophylactic Mastectomy: Bilateral prophylactic mastectomy (BPM) offers 90% protection from BC in BRCA mutation carriers.[26] Nipple sparing mastectomy (NSM) with immediate reconstruction is the gold standard ensuring a blend of optimal oncological protection and aesthetic outcome.[27] Attention must be paid to; flap thickness, under-surface of nipple-areola, peripheral footprint and axillary extension of breast; to avoid leaving behind microscopic mammary tissue. The procedure is associated with minimal morbidity, with 15-20% risk of complications.[28] Sequelae like loss of nipple-areola sensation and adjustment to a new body image and possible need of secondary procedures must be kept in mind when counselling women for prophylactic procedures.[29] Prophylactic surgical options must be individualized, in specialized breast centres with precise genetic and clinical counselling, emotional support, and thorough knowledge of all alternate risk management strategies, such as MRI surveillance.[30] BPM remains an option in the armamentarium. Additionally, for women with ipsilateral cancer, contralateral prophylactic mastectomy (CPM) helps in reducing the incidence of subsequent cancers, with no benefit in disease-specific or overall survival.[31]

2. SECONDARY PREVENTION

Breast cancer screening programmes are implemented at population level to decrease mortality due to breast cancers by promptly identifying women at early stage and providing effective and complete treatment.

a. Evidence of screening mammography (SM):

Mammography is so far, established as an ideal screening tool for early detection of breast cancer. Conventional mammography is being replaced by digital mammography, offering superior diagnostic quality and lesser radiation exposure, being well within limits approved by radiation safety boards' such as Atomic Energy Regulatory Board (AERB) and Food and Drug Administration (FDA). The benefit equates close to 40 to 75 lives saved for a death associated with radiation. Screening mammography protocols variably start after 40 years, and are variable repeated 1 to 3 yearly, based on country-specific recommendations (Table 3).[3]

- **Benefits of SM:**

The greatest benefit of SM is detection of breast cancer, causing reduction in mortality; close to 40% in women above 40 years of age; and its early detection causing reverse stage migration where treatment of non-metastatic cancers improves prognosis.[33] Also, low grade early-stage cancers can be cured with less intensive and aggressive therapies. A regular annual screening helps in superior detection of interval cancers in earlier stages.

- **Harms of SM:**

Relevance of screening pivots around the biology of breast cancer such that low grade ductal carcinoma in situ may stay dormant for decades may never evolve into invasive component and thus never manifest in the lifetime of a woman. SM when performed regularly helps in earlier detection of many such cancers, usually in the form of microcalcifications, thereby resulting in overdiagnosis, overtreatment, and morbidity associated with cancer therapy. At the other end of this spectrum, lies the detection of atypical benign microcalcifications and lesions warranting a biopsy confirmation, short-interval follow-up or recall; all related to unnecessarily increased anxiety and economic burden. Additionally, a negative (normal) mammogram may lead to false assurance, and possible ignorance of self-detection of the often-aggressive interval growing cancers. A Cochrane systematic review on SM that included seven randomized control trials (RCTs) on 600,000 women in age group of 39 to 74 years, compared results with and without SM. Pooled results of 3 high quality RCTs amongst the seven, demonstrated no reduction in breast cancer related and all-cause mortality after 13 years of follow up. (RR 0.90; 95% CI 0.79 to 1.02; RR 0.99; 95% CI 0.95 to 1.03).[34, 35]

- **Meta-analysis of Breast Cancer Screening by Mammography:**

While some individual mammography screening trials in breast cancer showed a benefit in mortality reduction, others had variable results with benefit only in women above 50 and not below 50. The designs of the studies also varied based on the methods employed for breast cancer screening. Meta-analysis of these screening trials helps in better understanding impact of implementing screening programmes for early detection of cancer before it becomes clinically evident.

USPSTF (2009) recommended selective screening for women 40 to 49 years and biennial mammography screening for women 50 to 74 years. As per the updates on screening modalities by using mammography, MRI and ultrasound (2016) on end-point as -breast cancer mortality, all-cause mortality and advanced breast cancer, no reduction was noted in all-cause mortality. However relative risk reduction was demonstrated for breast cancer mortality among women aged 39 to 49 by 8%, 50 to 59 by14%, 60 to 69 by 33% and 70 to 74 years by 20% respectively. There was decrease in the risk of advanced breast cancer by 2% among women aged 39 to 49 years and 38% among women aged 50 years or older.[36]

In real life situation the actual benefit of implementing screening may vary. A meta-analysis of quasi experimental studies comparing population with screening versus historical controls before screening showed significant reductions in breast cancer mortality of 13-17% in women in age group of 50-69 years.[37] Reduction in advanced cancer was demonstrated among women ≥ 50. No benefit was seen in women ≥ 70.

Finally, proper adherence to a population-based screening programme is important for observing a substantial reduction in incidence-based mortality from breast cancer.[38] In the UK breast cancer screening report from 9 RCTs, it was seen that adjustment for non-adherence and attenuation improved the absolute mortality benefit by 8% and the risk of overdiagnosis also increased by nearly 10%.[39]

The challenges of implementation of SM in developing countries are limited resources for mammographic equipment, scarcity of radiologists trained in breast imaging and the prohibitive cost of scanning regularly. This added to the relatively lesser incidence of breast cancer compared to the developed countries, does not justify the screening cost as a national policy. But opportunistic SM and screening for the high-risk population is recommended.

b. Breast self-examination (BSE)

BSE is commonly proposed as a method of early detection of breast cancer. However, two large, randomized trials, from Shanghai (n=289,392, 30-66 years old) and Russia [41] (n=120,310, 40-64 years old) each, showed no significant benefit in BC mortality (RR-1.05, 95% CI-0.90-1.24) of BSE as a population-based screening strategy.[40] Overall compliance to BSE was poor and was around 56% at 4 years in the St Petersburg cohort.[41, 42]The rate of breast biopsy doubled in the BSE arm (RR-1.88, 95% CI-1.77-1.99) with increased likelihood of benign lesion at biopsy. At present, BC screening by BSE cannot be recommended.[42] However, BC may be diagnosed early by increasing breast awareness.

c. Clinical Breast Examination (CBE)

Mammography does not appear as an ideal screening tool for early detection of breast cancers in Indian scenario because of logistics difficulties and younger age structure of the Indian population. One of the first RCTs, Health Insurance Plan (HIP) initiated in December 1963, that explored efficacy of breast cancer screening with mammography and CBE among women aged 40-64 years, showed that higher proportion of breast cancers were detected through CBE than through mammography especially among women under 50 years of age.[43] The results of Canadian National Breast Screening Study that was initiated in 1980, after 25 years of follow-up did not demonstrate any added advantage of annual mammography in reducing breast cancer mortality among women 40-59 as compared to physical examination or standard care.[44] The Philippines RCT that tried to evaluate CBE as a screening tool in 1995, had to be discontinued after the first screening round because of unacceptably low levels of adherence of screen positive women for referral (37%).[45] An overview of eleven systematic reviews on CBE published between 1993 and 2019 suggests that a well conducted CBE could bring the same effects as mammography regarding mortality and that greater effects were found among younger women and Asian women.[46]Two RCTs on CBE, both from India, have demonstrated downstaging of breast cancers in the intervention arm as compared to the control arm with use of CBE.[47, 48]However, Trivandrum RCT from India initiated in 2006, investigating effectiveness of triennial screening with CBE failed to demonstrate any mortality benefit after 14-years follow-up despite achieving stage shift and improved survival.[49]

Mumbai RCT initiated in 1998 demonstrated reduction of breast cancer mortality among women aged 50 years and above with biennial CBE screening, without issue of

overdiagnosis.[48]Probable reasons for no mortality benefit with CBE in Trivandrum study as compared to Mumbai study could be too long screening interval, lesser screening rounds, inadequate sample size, shorter follow-up interval after last screen and inappropriate target age group of women invited for screening.

Table 3: Screening mammography protocols based on country-specific recommendations

Organization	Age of onset	Age of discontinuing	Interval for screening	Level of recommendation
WHO	40-49	NR	NR	Strongly against in LRS
	50-69		Biennial	Conditional in LRS with strong health system
ACR	>=40	Based on each woman's health status and not age-based	Annual	
SBI	>=40	*When life expectancy is 5 to 7 years as per age or comorbidity *When abnormal results of screening would not be acted on because of age or comorbidity	Annual	
ACS	40-44	Up-to age beyond which life expectancy is 10 or more years	Annual	Optional
	45-54		Annual	Strong
	>55		Annual or biennial	Strong
USPSTF	40-49	Up-to 75 years	Biennial	Optional; Level C recommendation
	50-74		Biennial	Level B recommendation
CTFPHC	50-74	NR	Biennial to Triennial	Conditional recommendation
ECIBC	45-49	NR	Biennial or Triennial	Conditional recommendation
	50-69		Biennial over Triennial	Strong recommendation
	70-74		Triennial over Biennial	Conditional recommendation
Cancer, Australia	40-49	≥ 75 years: be eligible to receive free MAM, but do not receive an invitation to attend	NR	
	50-74		Biennial	
MOH, Singapore	40-49	≥70 years: individualized by considering benefits and risks of SM based on health status and estimated life expectancy	Annual	Grade C
	50-69		Biennial	Grade A
NCC, Japan	40-64	NR	SM with CBE	
	40-74	NR	SM without CBE	

Abbreviations: ACR: American College of Radiology; ACS: American Cancer Society; CBE: Clinical Breast Examination; CTFPHC: Canadian Task Force on Preventive Health Care; ECIBC: European Commission Initiative on Breast Cancer; LRS : Low resource setting; MOH: Ministry of Health; NCC: National Cancer Centre; NCCN: National Comprehensive Cancer Network; NR: No Recommendation; SBI : Society of Breast Imaging; SM : Screening Mammography; USPSTF: U.S. Preventive Services Task Force; WHO: World Health Organization; WHO: World Health Organization

3. FUTURE PERSPECTIVES:

Screening Recommendations

Many evidence-based, resource-stratified guidelines have been established by The Breast Health Global Initiative. The objective is to avert breast cancer mortality by 2.5% annually, thus reducing 2.5 million breast cancer deaths globally from, 2020-2040 by phased implementation in real world practice. It is based on three pillars namely; health promotion for early detection, timely breast diagnostics and comprehensive breast cancer management.[50, 51]

A high-quality RCT conducted in Mumbai[48] showed a significant and clinically relevant reduction in breast cancer mortality in women >/= 50 years of age once every 2 years by CBE conducted by trained healthcare workers. Therefore, CBE by trained health workers or other healthcare professionals is recommended once every 2 years in women older than 50 years up to the age of 70 years.

Breast cancer screening in genetically predisposed high-risk individuals needs to be started at a younger age (between 20 - 25 years), should be more intensive, and MRI with a dedicated breast coil is required for younger women with mammographically dense breasts. Chemoprevention and prophylactic surgery are other options that can also be discussed.

Future Directions

1. Emphasis on spreading awareness about lifestyle factors associated with breast cancer and stress on early detection.
2. Emphasis on weight loss as a means of primary prevention.
3. Development of risk scores combining genetic, hormonal and environmental factors to triage women for screening.
4. Screening for cancer is arguably one of the most complex public health interventions. Unless carefully conducted and monitored for quality control, the positive results of randomized trials may not be translated into the expected benefits when implemented as a public health policy at community level. The most important component of breast cancer screening is compliance which is critical at multiple levels. First, the target women must be sufficiently motivated to undergo screening. Unless breast cancer is perceived as a common and potentially life-threatening condition, women may not be motivated to undergo screening. Second, based on results of the Mumbai study, CBE

is deemed to be the most appropriate approach for India. However, unless CBE is performed properly, results of the Mumbai study may not be translated into the expected mortality reduction in the target population. Third is compliance to hospital referral. Many women are daily wage earners or have considerable family responsibilities; attending hospital for confirmation of diagnosis may mean financial loss or neglecting the dependent family. Four, compliance to completing the entire course of treatment which, in case of breast cancer, may take several months. Five, attendance to regular follow-up which is essential to the evaluation of mortality benefits at community level. Without proper follow-up it will never be known whether the screening programme has been worthwhile. It needs to be remembered that the Mumbai study was a success because it was a vertical programme which was closely monitored and centrally controlled with close watch on quality assurance. Although CBE itself is an inexpensive screening tool, the manpower costs required to undertake a successful population screening programme can be formidable. These issues require to be carefully considered if CBE were to be recommended as a national secondary prevention policy for controlling breast cancer.

CBE has now been incorporated in the operational guidelines of the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) in India.[52]However, success of CBE at population level will only be evident after several years of implementation as a public health programme.

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Chapter 3

Gynaecological Cancers

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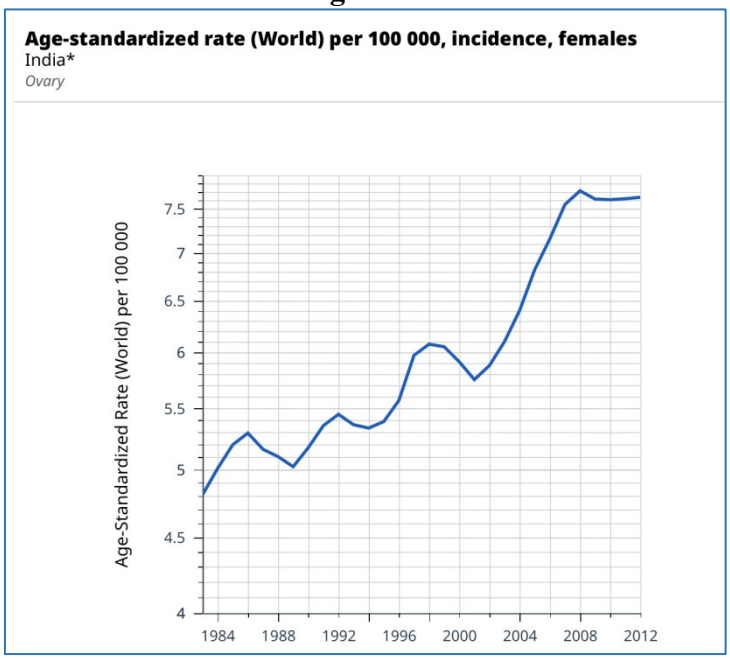
3.1 Ovarian Cancer

Guidelines for Prevention and Early Detection of Ovarian Cancer

Introduction:

Ovarian cancer is the third common cancer among women in India, currently constitutes 6.7% of new cancers in women. Lifetime risk of development of ovarian cancer in a woman with average risk of cancer lies between 1- 1.3%. [1,2] The incidence of ovarian cancer is on the rise (GLOBOCAN 2020), with over 45,000 new cases detected annually.[3]Ovarian cancer also shows a poor prognosis with age standardized mortality rate of 4.8%.

Figure 1:



1. RISK FACTORS AND PRIMARY PREVENTION:[4]

Risk factors associated with development of ovarian cancer can be divided into modifiable and non- modifiable factors. These factors along with the primary preventive strategies will be discussed in this chapter

A. Age: Ovarian cancer is a disease associated with older women with median age at diagnosis being 55 – 64 years.

B. Menstrual and obstetric factors: Higher the years of ovulation; higher is the risk of ovarian cancer; this stems from the incessant ovulation theory. Hence pregnancy, childbirth and breastfeeding are associated with reduced risk of ovarian cancer. Similarly, early menarche and late menopause are associated with increased risk.

C. Gynaecological factors:

- Endometriosis:
  It is known to be a risk factor for ovarian cancer – endometrioid and clear cell types with Relative Risk (RR) of 1.2-1.7.
- Ovarian cysts:
  They are associated with development of borderline and low grade ovarian cancers.
- Tubal ligation:
  Women who have had tubal ligation have decreased invasive serous cancer (19%), invasive mucinous cancer (32%), clear cell cancer (42%), and endometrioid cancer (52%).

  Recommendation: There is no strong evidence or recommendation for use tubal ligation for prevention of ovarian cancer. It is recommended only for contraceptive purposes.

D. Hormonal factors:

- Oral contraceptive pills:
  Intake of oral contraceptive pills (OCP) is associated with reduced risk of ovarian cancer. More than 10 years of OCP intake is associated with > 50 % reduction in risk of ovarian cancer. An inverse relationship has been shown between the use of OCP and development of ovarian cancer in BRCA 1 and BRCA 2 positive patients. The risk also appeared to decrease with longer duration of OCP use.

  Recommendation:

  i. Women with average risk: Despite the strong evidence related to OCP intake and reduction in ovarian cancer, there is insufficient data to recommend the use of OCP for the purpose of chemoprevention of ovarian cancer.[5] It is primarily to be used for contraceptive needs.

ii. Women with high risk: May consider chemoprevention with OCPs until risk reducing salpingo-oophorectomy (RRSO) is undertaken.[6]

- Hormone replacement therapy:
  There is conflicting evidence regarding the role of HRT in ovarian cancer.

  Recommendation: No strong evidence to avoid HRT in general population with average risk to prevent ovarian cancer.

- Infertility treatment:
  Irrespective of infertility treatment, infertility and nulliparity are risk factors for ovarian cancer. The scientific community and evidence are divided regarding the role of infertility treatment (clomifene citrate, gonadotropins, human chorionic gonadotrophin, and gonadotrophin releasing hormone) contributing to increased risk of ovarian cancer risk.

E. Genetic factors: Women with hereditary breast ovarian cancer syndrome and Lynch syndrome are at increased risk of ovarian cancer. There are various genes implicated in ovarian cancer with varying absolute risk.

Recommendation:

Testing criteria for these include [1, 7] :

a. Germline BRCA 1/ 2 testing:
   i. Women with personal history of non-mucinous epithelial ovarian cancer /fallopian tube / primary peritoneal cancer at any age.
   ii. Women with family history of cancer only and no personal history: An unaffected individual with a first- or second-degree blood relative with known mutation in any of the genes implicated in HBOC/ lynch syndrome

b. Somatic tumor testing for BRCA 1/ 2 genes: Women with epithelial ovarian cancer that do not carry a germline pathogenic or likely pathogenic BRCA1/2 variant.

c. Somatic tumor testing for mismatch repair deficiency (dMMR): Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer.

Table 1: Clinically relevant genes implicated in ovarian cancer development and risk reducing surgeries[1]

Gene implicated	Associated risk of ovarian cancer	Strength of evidence of association	Recommendation	Age of procedure
BRCA 1	39 – 58%	Very Strong	RRSO*	35 – 40yrs
BRCA 2	13 – 29%	Very Strong	RRSO	45 – 50yrs
BRIP 1	5-15%	Strong	RRSO	45 - 50yrs
PALB 2	3-5%	Strong	Consider RRSO	>45 yrs
RAD 51C	10-15%	Strong	RRSO	45 – 50yrs
RAD 51D	10-20%	Strong	RRSO	45 - 50yrs
MLH1	4 – 20%	Strong	RRSO+ Hysterectomy	Individualized
MSH2/EPCAM	8 – 38%	Strong	RRSO+ Hysterectomy	Individualized
MSH 6	1 – 13%	Strong	RRSO+ Hysterectomy	Individualized
PMS 2	1.3 – 3%	Strong	Insufficient evidence for RRSO	Avg. risk is similar to general population
ATM	2-3%	Strong	Evidence insufficient for RRSO; manage based on family history	

* Risk reducing salpingo-oophorectomy

Risk reducing salpingo-oophorectomy (RRSO): There is ample evidence supporting the use of RRSO in reducing ovarian / fallopian tube cancer in women with BRCA 1 / 2 mutations. The magnitude of reduction in risk of developing these cancers ranges between 80-90 %, with reduction in all-cause mortality for BRCA 1 carriers being 77%. However, a residual risk of 1 – 4.3 % of primary peritoneal cancer persists in these women.

Salpingectomy with delayed oophorectomy[8,9]: This is an area garnering momentum in the recent times with the theory of high grade serous carcinoma arising from the fimbrial end of fallopian tube. There is evidence regarding the safety and feasibility of the procedure, however, it's efficacy in reducing the risk of ovarian cancer is yet to be established. There are ongoing trials addressing this (NCT02321228, NCT01907789).

Recommendation: RRSOis strongly recommended in women carrying abnormal genes enumerated in the aforementioned table. There is insufficient evidence to

recommend risk reducing salpingectomy and delayed oophorectomy in this high risk population.

Opportunistic salpingectomy during hysterectomy for a benign gynaecological condition can be considered in women with average risk of ovarian cancer.

The fimbrial ends of fallopian tubes are recommended to be processed as per the SEE-FIM (Sectioning and Extensively Examining the FIMbriated end) protocol. In this protocol the fimbrial end of the fallopian tube is processed more rigorously with closer sections and Immunohistochemistry (IHCs).

F. Nutritional factors: There are reports suggestive of increase in ovarian cancer risk with consumption of cholesterol and saturated fats, and reduction in risk associated with intake of plant based food rich in phytoestrogens, B complex vitamins, beta carotene etc.

Recommendation: Healthy lifestyle, balanced diet and routine physical activity.

2. SECONDARY PREVENTION: SCREENING AND EARLY DETECTION

Early detection can be facilitated by awareness regarding the symptoms associated with ovarian cancer. Eight symptoms specific to ovarian cancer have been detailed in the MD Anderson symptom index – ovarian cancer. [10]

- Abdominal pain
- Feeling bloated
- Constipation
- Problems with paying attention or concentrating
- Urinary urgency
- Pain or burning with urination
- Back pain
- Leg cramps or leg muscle pain

Recommendation: In case of persistent of symptoms, it is recommended to visit a health care professional.

Screening of ovarian cancer can broadly be divided based on the individual's lifetime risk of developing ovarian cancer.[11]

a. Women with inherited risk due to known mutations (RR > 6 times general population)

1. BRCA 1 or 2 mutation
2. MMR protein deficiency
3. Other genes listed in Table 1.

Evidence: The United Kingdom Familial Ovarian Cancer Screening Study.[12]

This was a phase II study which was conducted in two parts – Part 1 between 2002 and 2008. More than 3500 patients who had an ovarian cancer risk of >/= 10% and who denied RRSO were included in the study. They had an annual CA 125 and TVS. Twenty seven of these women developed ovarian cancer 48% in early stage (1 or 2) and 52% in advanced stage (3 or 4). There were 10 women who developed ovarian cancer > 1 year of these tests, of these 90% were detected in stage 3 or 4 and 10% in stage 1 or 2.

This led the investigators onto part 2 of the study where > 4300 women were recruited between 2007 and 2012. This time around, screening was based on an algorithm (Risk of ovarian cancer algorithm-ROCA) – the timing of TVS depended on CA 125 testing, which were conducted 4 monthly. If an abnormal CA 125 was noted, these women would undergo a TVS earlier compared to the routine yearly scan. Thirteen women during screening were diagnosed with ovarian cancer 38% in early stage, 62% in stage 3 and nine in stage 4. Ninety two per cent had complete cytoreduction with one patient requiring NACT (neoadjuvant chemotherapy). They also noted that 18 women were diagnosed with ovarian cancer 1 year after their last screening and only 5 % was diagnosed in stage 1, 78% in stage 3 and 17% in stage 4. Complete cytoreduction was achieved only in 72% of these women and 44% needed neo adjuvant chemotherapy.

In study there was a definite stage shift demonstrated with higher rates of complete cytoreduction, but due to small number of events, impact on survival of these women was not demonstrable.

Recommendation: It is not clear that ovarian cancer screening impacts survival in women at inherited risk. This may be discussed with women carrying mutations in ovarian cancer susceptibility genes and they may be counselled to undergo ovarian cancer screening using a combination of transvaginal ultrasound and CA-125 testing. Women with mutations *in* BRCA1 *or the mismatch repair genes,* MLH1*,* MSH2, and MSH6, may begin screening between ages 30 and 35. For

women with mutations in *BRCA2,* ovarian cancer screening may be initiated between ages 35 and 40.[1]

b. Women with increased risk of ovarian cancer (3-6 times the risk compared to general population)

1. A first degree relative with ovarian cancer.
2. Personal history of breast cancer before 40 years.
3. Personal history of breast cancer before age 50 and one or more close relative with breast or ovarian cancer at any age.
4. Two or more close relatives diagnosed with breast cancer prior to age 50 or with ovarian cancer at any age.

Recommendation: There is no clear evidence to suggest that ovarian cancer screening will result in a survival advantage in women with these afore-mentioned risk factors for ovarian cancer. After careful consideration of risks and benefits, ovarian cancer screening with CA-125 and/or transvaginal ultrasound may be offered to these women within the framework of research studies.

c. Women with risk level near that of general population (RR < 3 times compared to that of general population)

1. Personal history of breast cancer diagnosed after 40 years and no family h/o breast or ovarian cancer.
2. History of Infertility and use of ART.
3. History of endometriosis.
4. History of HRT use.

Evidence:

- Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial.[2]

This was a RCT which recruited over 2, 02,000 women between 2001 and 2005. The women were divided in a 2:1:1 ratio between no-screening, multimodality screening (MMS) with CA 125 and TVS based on ROCA algorithm and annual TVS screening groups. At a median follow up of 16.3 years 2055 women were diagnosed with tubal or ovarian cancer: 522 (1·0%) of 50 625 in the MMS group, 517 (1·0%) of 50 623 in the USS group, and 1016 (1·0%) of 101 314 in the no screening group. Compared with no screening, there was a

47·2% increase in stage I and 24·5% decrease in stage IV disease incidence in the MMS group. However, this did not translate into survival benefit in either of the screening arms compared to the no screening group. Hence, they concluded that ovarian cancer screening cannot be recommended for general population.

- The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [13]

The PLCO cancer screening trial randomised over 77,000 women into no-screening group and screening group (annual CA 125 and TVS) between 1993 and 2001. At a median follow up of 14.7 years, Ovarian cancer specific survival was not significantly different across trial arms (p=0.16).

Recommendation: Ovarian cancer screening is not recommended in general population / women with risk level near that of general population.

3. FUTURE DIRECTIONS:

i. Emphasis on genetic testing for all non-mucinous epithelial ovarian cancers.

ii. Emphasis on risk reducing surgeries and other risk reducing strategies at appropriate time points.

iii. Generate evidence regarding bilateral salpingectomy followed by delayed oophorectomy as a risk reducing strategy which stalls the side effects of pre-mature menopause.

iv. Generate evidence for chemoprophylaxis as a means of primary prevention in women with high risk of developing ovarian cancer.

v. Look into newer radiological techniques (targeted contrast enhanced ultrasound, ultrasound molecular imaging using microbubbles targeted to kinase domain receptor, key factor in tumor angiogenesis) to detect tumor angiogenesis, component of early tumorigenesis as a method of screening.

vi. Other theoretical screening strategies which need further evaluation and consideration are: Hysteroscopic brushings from fimbrial end of fallopian tube; endometrial cytologic testing.

vii. Setting up of more organised dedicated genetic clinics.

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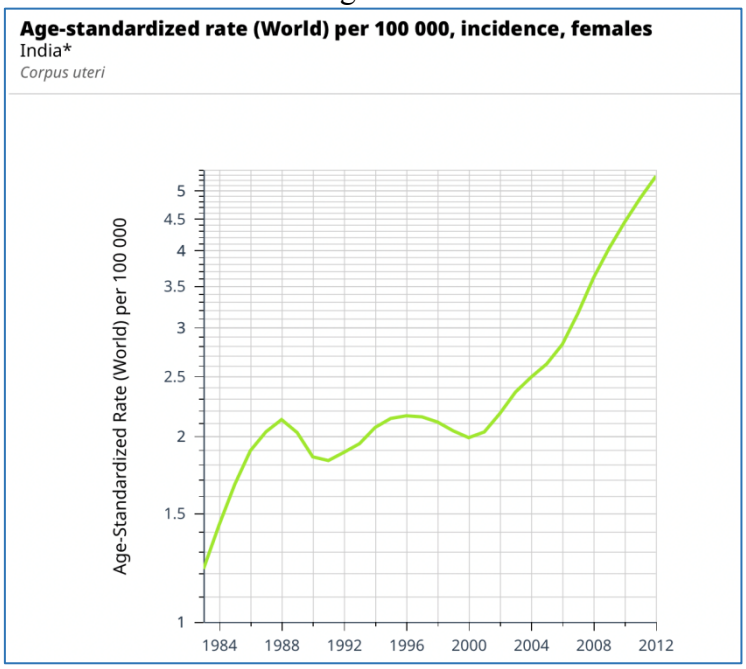
3.2 Endometrial Cancer

Guidelines for Prevention and Early Detection of Endometrial Cancer

Introduction:

Endometrial cancer is the third most common gynaecological cancer in India with 16,413 new cases detected annually. It is predominantly a disease of the affluent; however the incidence is on rise in LMIC (Low middle income countries) over the years, largely due to changing socio – demographic profile of the population.[1] Therefore, prevention and early detection of endometrial cancer is essential.

Figure 1:



1. <u>PRIMARY PREVENTION:</u>

Risk Factors:

A. <u>Obesity:</u> This is one of the strongest risk factor for endometrioid type of endometrial adenocarcinoma. Obesity associated hyperestrogenic state due to peripheral conversion of androgens to estrogen, hyperinsulinemia and chronic inflammatory state, contribute to carcinogenesis.[2]

Recommendation: To maintain ideal body weight by balanced diet, routine physical activity and healthy lifestyle.

B. <u>Hormonal factors:</u> Prolonged exposure to un-opposed estrogen (endogenous or exogenous) is associated with development of type-1 endometrial cancer.

i. Polycystic ovarian syndrome (PCOS): It is a metabolic disease affecting young women characterized by insulin resistance, anovulatory menstrual cycles and thus hyper-estrogenic state. Oligomenorrhoea or amenorrhoea in women with PCOS may predispose to endometrial hyperplasia and carcinoma. Women with PCOS have a relative risk (RR) of 3 for endometrial cancer.

Recommendation: Treatment of PCOS with progestogens to induce a withdrawal bleed at least every 3 to 4 months.

Transvaginal ultrasound should be considered in case of abnormal uterine bleeding or the absence of withdrawal bleeds.

In PCOS, an endometrial thickness of 7 mm or less is unlikely to be associated with hyperplasia. A thickened endometrium or an endometrial polyp should be investigated with endometrial biopsy and/or hysteroscopy.[3]

ii. Estrogen replacement therapy (ERT): Estrogen only hormone therapy without progesterone substitute carries a 2 -10 times RR of endometrial cancer.

Recommendation: Estrogen only Hormone replacement therapy (HRT) to be offered to women without uterus. Estrogen and progesterone is to be suggested as HRT to these women either in continuous, combined or cyclical form (12-14 days of progestogens per 28 days). However, progestogen in the form of levonorgestrel-releasing intrauterine system (LNG IUS) is preferred.[4]

iii. Tamoxifen: It is a selective estrogen receptor modulator (SERM) which is used in hormone sensitive breast cancer. It is also used for chemoprevention in women at increased risk for breast cancer. Tamoxifen has a complex mechanism of action with anti-estrogenic effect on the breast and estrogenic effect on the uterus. Tamoxifen use is associated with increased risk of endometrial polyps, hyperplasia and carcinoma, uterine sarcoma and carcinosarcoma. The ATLAS trial(Adjuvant Tamoxifen: Longer Against Shorter) for breast cancer which randomly allocated pre and post-menopausal patients to 5 or 10 years of

tamoxifen, showed a reduction in breast cancer recurrence at 10 years but increase in incidence of endometrial cancer. Absolute cumulative risk of endometrial cancer was 3.1 % in women who used tamoxifen for 10 years compared with 1.6 % in those who stopped it after 5 years, but mortality due to endometrial cancer was not increased.[5]The National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1), which compared tamoxifen with placebo in women at high risk of breast cancer, reported that the risk of endometrial cancer in tamoxifen users was not statistically significant in women aged 49 years or younger (risk ratio 1.42, 95% CI 0.55–3.81), but that there was a statistically significant increase in risk among women aged 50 years or older (risk ratio 5.33, 95% CI 2.47–13.17).[6]

Recommendation: Benefits of tamoxifen use in patients with hormone receptor positive breast cancer outweigh the risks of uterine pathologies.

Evaluation of pre-existing uterine pathology in women planned for tamoxifen therapy is recommended.[7]

iv. Oral contraceptive pills (OCPs): Five year use of OCPs is associated with a risk reduction of endometrial cancer by 30-40%.

Recommendation:

- Women with average risk: Despite the strong evidence related to OCP intake and reduction in endometrial cancer, there is insufficient data to recommend the use of OCP for the purpose of chemoprevention of endometrial cancer. It is primarily to be used for contraception.
- Women with high risk such as genetic risk: may consider chemoprevention with OCPs until risk reducing surgery is undertaken.[8]

C. **Age:** Endometrial cancer is primarily a disease of post-menopausal women with median age at diagnosis being 63 years.

D. **Menstrual and obstetric factors:** Early menarche, late menopause and nulliparity increase the lifetime risk of developing endometrial cancer; childbirth, multi-parity and breastfeeding reduce the risk.

E. Associated metabolic disorders:

- Diabetes mellitus: RR of endometrial cancer development with diabetes mellitus is around 2.
- Hypertension: Relative risk of developing endometrial cancer in hypertensive women is 1.5.

F. Genetic factors: Endometrial cancer is one of the common cancers associated with Lynch syndrome and Cowden's syndrome[9,10].

a. Lynch syndrome (LS): LS is an autosomal dominant inherited disorder characterized by mutation in one or more of the DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). Nearly 5 % of endometrial cancers are associated with LS.

Currently there are two general approaches to the diagnosis of LS:

- Molecular screening of tumor specimens for evidence of defective MMR function (MMR-D) or high levels of microsatellite instability (MSI-H) to identify patients with cancer who should undergo germline testing for the pathogenic MMR gene variants; or
- Direct germline testing performed on individuals whose personal and/or family histories of cancer are suspicious for LS.

Testing criteria:

i. Amsterdam Criteria. All of the following should be met:

- Three or more relatives with histologically verified LS associated cancers (colorectal, endometrial, small bowel, renal) - one of whom is a first degree relative.
- Involving at least two generations.
- One or more cancers were diagnosed before the age of 50 years

"3-2-1" rule: 3 affected members, 2 generations, 1 under age 50. Familial Adenomatosis Polyposis (FAP) must be excluded in colorectal cancer case(s) if any. The sensitivity and specificity of Amsterdam Criteria for a diagnosis of LS is 22% and 98% respectively.

ii. Universal testing of all colorectal and EC tissues for MMR protein IHC (or PCR based MSI analysis) is recommended. It has screening, prognostic and therapeutic implications.

Table1: Clinically relevant genes implicated in endometrial cancer development and risk reducing surgeries.

Gene implicated	Associated risk of endometrial cancer	Strength of evidence of association	Recommendation
MLH1	34-54%	Strong	RRH*+ BSO**
MSH2/EPCAM	21-57%	Strong	RRH + BSO
MSH 6	16-49%	Strong	RRH + BSO
PMS 2	13 – 26%	Strong	RRH
Cowden's syndrome (PTEN)	5 – 10%	Strong	RRH

*Risk reducing hysterectomy; ** Bilateral salpingo-oophorectomy

Recommendation:

Risk reducing hysterectomy (RRH) with bilateral salpingectomy with or without bilateral oophorectomy should be considered in women with Lynch / Cowden syndrome. However, it has not been shown to reduce endometrial cancer mortality, but can reduce the incidence of endometrial cancer.

The age of risk reducing surgery should be individualized - offered after completion of childbearing between 35 – 45 years.[9]The British Gynecological Cancer Society (BGCS) recommends risk reducing surgery after the age of 35 years in MLH1 and MSH2, and 40 years in MSH6 and after the age of 50 years in PMS2 pathogenic variant carriers.

Estrogen only hormone replacement therapy (ERT) is recommended in women who undergo hysterectomy with b/l(bilateral) salpingo-oophorectomy until at least the natural age of menopause due to its protective effect on colorectal cancer risk as well as beneficial impact on quality of life, urogenital, bone and cardiovascular health.[8]

2. SCREENING FOR ENDOMETRIAL CANCER:

1. Average risk population:

Recommendation: Routine screening is not recommended.

Women with:

- Post-menopausal bleeding,
- Pre- menopausal women in secretory phase /post-menopausal women with endometrial/ glandular cells on pap smear,
- Peri-menopausal irregular uterine bleeding,
- Thickened endometrium on sonography should be evaluated for endometrial pathology.

2. Women with increased risk due to:

    - Late menopause,
    - Nulliparity,
    - Infertility,
    - Anovulation,
    - Obesity,
    - Type 2 DM,
    - Hypertension should be taken into consideration during evaluation of women with abnormal uterine bleeding and postmenopausal women with bleeding.

    Recommendation: Routine endometrial cancer screening in asymptomatic women is not recommended. However, they should be informed about risks and symptoms of endometrial cancer and encouraged to report immediately.

3. High risk population:

    a. Women with genetic risk factors:

    Recommendation: Patient education, counselling and awareness with prompt early evaluation of abnormal uterine bleeding is recommended.

    Endometrial cancer screening does not have proven benefit in women with LS. However, endometrial biopsy is both highly sensitive and highly specific as a diagnostic procedure. Screening via endometrial biopsy every 1–2 years starting at age 30–35 years can be considered. Transvaginal ultrasound is not recommended as a screening tool in premenopausal women due to the wide range of endometrial stripe thickness throughout the normal menstrual cycle. Transvaginal ultrasound to screen for endometrial cancer in postmenopausal women has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion.[9]

    b. Women on tamoxifen:

    Recommendation: Women with intact uteri who are taking adjuvant tamoxifen for breast cancer should have prompt evaluation of any abnormal bleeding.

Trans-vaginal sonography, hysteroscopy and endometrial biopsy are recommended for AUB (Abnormal uterine bleeding).

TVS has a low positive predictive value and high false positive rate due to tamoxifen induced benign sub-epithelial stromal hypertrophy, therefore routine screening by transvaginal ultrasound is not recommended in asymptomatic women on tamoxifen.

Endometrial polyps are the most common type of endometrial pathology associated with tamoxifen use; they develop in more than 11% of postmenopausal patients on tamoxifen ≥4 years. For patients on tamoxifen, endometrial polyps should be resected rather than managed expectantly.[98]

3. FUTURE DIRECTIONS:

i. Emphasis on spreading awareness about lifestyle and environmental factors associated with endometrial cancer and stress on lifestyle modification.

ii. Emphasis on intentional weight loss (including bariatric surgeries) as a means of primary prevention of endometrial cancer.

iii. To incorporate Mismatch Repair Immunohistochemistry (MMR IHC) routinely on pathology specimens of all endometrial cancers, followed by genetic counselling and testing of patients with MMR deficiency.

iv. Development of risk scores combining genetic, hormonal and environmental factors to triage women for screening.

v. To study chemoprophylaxis as a means of primary prevention in women with high risk of developing endometrial cancer.

vi. Development of newer less invasive screening techniques.

vii. To consider and emphasise the use of LNG-IUS as a preferred intra uterine contraceptive device.

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3.3 Cervical Cancer

Guidelines for Prevention and Early Detection of Cervical Cancer

Cancer of the uterine cervix is the fourth most common cancer that occurs to women worldwide. Globally, the age-standardized incidence and mortality rates are 13.1 and 6.9 per 100,000 women respectively. In India, the age-standardized incidence rate is 14.7, and the age-standardized mortality rate is 9.2 per 100,000 women respectively. In 2020, 90% of the new cases and deaths worldwide were reported from low- and middle-income countries (LMIC).[1]

Risk factors for cervical cancers

Human papilloma viruses (HPV) are a very common sexually transmitted infection in young people. HPV is the primary etiologic infectious agent causing cervical cancer. Persistent infection with high-risk Human papilloma virus (hrHPV) types has been implicated as the major risk factor for cervical cancer. HPV genotypes types 16 and 18 together are responsible globally for 71% of cases of cervical cancer. HPV is mainly transmitted by sexual contact with majority of the individuals getting infected shortly after the onset of sexual activity. Nearly 80–90% of the HPV infections are asymptomatic and resolve spontaneously from periods ranging between 1–2 years.[2]

Younger age at first sexual intercourse or women who have had multiple lifetime sexual partners have reported to have two to three times increased risk of squamous cell carcinoma or adenocarcinoma of the cervix. Post HPV infection, several other additional risk factors have been associated with a higher risk of development of cervical cancer. Thus high parity, long-term use of oral contraceptive pills, tobacco consumption, co-infection with other sexually transmitted infections, immunosuppression, and diet low in nutrition have been reported and identified as the co-factors which are likely to increase the risk of HPV infection and its further progress to cervical cancer.[3, 4]

Decreasing Cervical Cancer Incidence Trends:

Two studies reporting for the periods ranging 1990 -2003 and an another linear regression model study for the period,1982-2003, evaluated trends in cervical cancer for cervix, showed decreasing trend in the age adjusted incidence rate for cervical cancer across all Population Based Cancer Registries (PBCRs) in India.[5, 6]Another recent study from the National Cancer

Registry Programme, (NCRP) - National Centre for Disease Informatics and Research (NCDIR) of Indian Council of Medical Research (ICMR), (ICMR-NCDIR-NCRP),using Age–Period–Cohort (APC) model from five Population Based Cancer Registries (PBCRs) in India, reported a significant decrease in cervical cancer for the period of 1985–2014. Among the PBCRs, Cervical Cancer incidence rates were decreasing in the absence of any organized screening programme and HPV vaccination programme in India.[7]

While the etiology and exact reasons for this decline are unclear it is likely to be due to a combination of factors like improved genital hygiene, improved living socio economic conditions, access to water supply, sanitation, better nutrition, changing reproductive patterns among others.[7]

1. PRIMARY PREVENTION MEASURES

Risk Reduction Measures for Cervical Cancers

A. Information, Education and Communications [IEC]

Awareness Messaging for prevention of Risk Factors of cervical cancers-

The following Communication and Education messages tailored to the target young age groups and suited to the cultural context should be developed for creating awareness about who is at risk of developing cervical cancers. Creating awareness about factors that increases the risk for cervical cancers such as initiating sexual activity at a younger age, multiple number of lifetime sexual partners , high parity, long duration use of oral contraceptives for more than 5-10 years, active and passive cigarette smoking, all associated with enhanced risk of cervical cancer in HPV infected women.[8-12]

Promoting the use of condoms for those engaged in sexual activity to provide the needed protection against HPV, which in addition also help protect against HIV and other sexually transmitted infections.

B. HPV Vaccines current status :

Introduction of HPV vaccination in national programmes should be based on an assessment of country specific relevant data and cervical cancer trends. It is important to consider the region and country-specific scale of the prevailing HPV-associated health cancers (cervical cancer, other HPV-associated cancers).[5-7]

HPV vaccination against HPV genotypes included in the vaccine, mainly HPV-16/HPV-18, has been effective in preventing HPV infection in HPV-naive individuals and is associated with a reduced incidence of cervical intraepithelial neoplasia [CIN 2/3] for two-dose and to a limited extent on single dose regimen.[13-16] The currently licensed bivalent, quadrivalent and nonavalent vaccines authorised against HPV offer comparable immunogenicity, efficacy and effectiveness for the prevention of CIN 2/3.[13]

However, the following factors enumerated need consideration before deciding on HPV vaccination for the country programme.

1. **Declining cervical cancer incidence**: Data from Indian population-based cancer registries shows that incidence of cervix cancer is declining in all parts of India, rural and urban, over past 20-30 years and the trend continues. This has happened without any organised cervical cancer screening programmes or HPV vaccination. The declining trend of cervical cancer incidence is likely to be due to a confluence of multiple factors such as better personal hygiene, access to sanitation, better nutrition, changing reproductive patterns, use of barrier contraception, use of intrauterine contraceptive devices and other as yet undefined factors.[17]

2. **No evidence for prevention of cervical cancer**: There is no evidence that HPV vaccination will prevent cervical cancer. This is because the clinical vaccine trials were designed to detect only surrogate outcomes of prevention of cervical precancerous lesions (CIN2 and CIN3). The vaccine trials were not designed to detect the outcome of prevention of cervical cancer since it takes decades to develop invasive cervical cancer. No evidence for long term protection of the immunity beyond 10-12 years' duration. There is lack of solid evidence that mass HPV vaccination reduces the incidence and mortality from cervical cancer, since the demonstrated proof of efficacy has been against persistent HPV infection and Cervical Intraepithelial Neoplasia [CIN] 1 & 2 + lesions.[18, 19] The actual impact of the effectiveness of the current HPV vaccines in reduction of cervical cancer will take extended duration until those women who have received the vaccine are older.[20]

3. **Limited duration of long term protection**: There is no data for sustained protection of immunity beyond 10-12 years old.[21]There has been no proof that the anamnestic response that will presumably launch immunological memory will itself be triggered in subsequent years by the route through which HPV infection is naturally acquired.

Long-term observation data is still needed to prove persistence of protection after vaccination against HPV 16 and 18.

4. **Cost-effectiveness analyses** for cervical cancer prevention and screening have demonstrated that cervical cancer screening is more cost-effective than either vaccination alone or vaccination with screening.[22]

WHO Position Paper Guidelines_2022: In the recent position paper published by the World Health Organisation (WHO) on HPV vaccines, WHO has updated its recommendations for the HPV vaccine. It has incorporated recent information regarding HPV vaccines and the evidence on vaccine immunogenicity and effectiveness with reduced dose schedules. The position paper states that a single-dose schedule should be able to provide a comparable efficacy and duration of protection as that of a two-dose regimen.

WHO therefore now recommends: One or two-dose schedule for girls aged 9-14 years and women aged 15-20 years and two doses with a 6-month interval for women older than 21 years. Immunocompromised individuals should receive at a minimum two doses and where possible three doses.[13]

2. SECONDARY PREVENTION

Declaration statement

Reproduced with amendments and with permissions from National Cancer Grid (NCG) guidelines of India[24]

Cervical Cancer Screening:

A. Choice of the screening test:

i. **Visual Inspection with Acetic Acid (VIA)-** Visual inspection with acetic acid (VIA) is simple, non- invasive and inexpensive visual test, has easy to learn approach, does not require laboratory involvement, is a real time test with results available immediately and even non- physicians can be trained to perform the procedure. The efficiency and cost-effectiveness of VIA has been evaluated in two randomized control trials (RCT) showing a significant mortality benefit following VIA screening [35% South India, 31% Mumbai]. The advantage of VIA are higher sensitivity than cytology, immediate availability of results allowing management decisions to be taken at the same visit, feasibility of the test

being performed by trained nurses of health workers and low cost. More recently, Sauvaget and colleagues, after pooling 26 studies from low- and middle income countries provided summary estimate of VIA accuracy for sensitivity of 80% (range, 79%–82%), specificity of 92% (range,91%–92%), PPV of 10% (range, 9%–10%), and NPV of 99%. Effects of factors such as region, capacity of screener (health worker, nurse, or physician), place of screening, study period, and size of study population had no effects on VIA accuracy demonstrating the overall reliability of VIA screening.

Recommendations:

VIA can be adopted as the screening modality of choice in settings where resources are not adequate to provide HPV testing.

ii. **High Risk HPV (hrHPV) testing as a primary screening test-** In the past 20 years, large cross-sectional studies designed to evaluate the performance of high-risk human papilloma virus (hrHPV) testing have demonstrated the sensitivity of hrHPV testing at 66–95%, with specificity between 76% and 95%. HPV test is the most sensitive among all the screening tests available till date. A large randomized study in India demonstrated that even a single round of HPV test followed by appropriate management of the screen positive women could reduce the cervical cancer mortality by 50%. The other advantages of the test are – the test is objective and highly reproducible, training needs are not very stringent, point of care tests are now available. The high negative predictive value of the test can allow prolongation of screening interval up to 10 years in the screen negative women.

Recommendations:

HPV DNA testing as primary screening test has been adopted in many national programmes globally in high and middle income resource settings. HPV testing can replace cytology as primary screening tool in setups which can afford HPV screening.

In women who test negative on an HPV test, rescreening should be done after a minimum interval of five years (annexure 1).

iii. **Cytology-** Organised cytology-based cervical screening in the Europe, North America and Australia led to a substantial reduction of the incidence of cervical cancer in these regions in the past five decades. Successes of the cytology based screening programmes

were mainly due to repeated testing at frequent interval, high population coverage, and quality-control procedures adopted in these regions.

The test has several limitations particularly for resource constrained settings–need for highly skilled cytotechnicians and pathologists, high infrastructural requirements, need for stringent quality control at each step.

Recommendations:

If resources permit, HPV testing should be the test of first choice (annexure 2).

Appropriate Age for Screening & Screening Frequency

Recommendations:

Twice in a life time Screening between Age of 30 and 49 can be highly protective and cost-effective which can be considered in Indian context where screening coverage is extremely low. Screening the population of women between 30-65 years at 3year interval is recommended. Though VIA as a screening test is not suitable for women above 50 years due to migration of SCJ into the endocervical canal but these women can be benefited by speculum examination and thus in down staging the disease if any.

B. MANAGEMENT&TREATMENTFORPRE-INVASIVEDISEASE

A screening programme will be effective only when there is mechanism to ensure high compliance of the screen positive women for further diagnosis and treatment.

1. Treatment for Pre-Invasive disease

Recommendations:

a. For all screen-and-treat recommendations, cryotherapy or thermo-coagulation is the first-choice treatment for women who have screened positive and are eligible for ablative treatment.
b. Cryotherapy or thermo-coagulation can be safely administered at the primary care facility, by trained staff.
c. When women have been assessed as not eligible for ablative therapy, they should be referred to appropriate centre for excisional procedures (LEETZ/CKC).

d. Hysterectomy is not the primary treatment for CIN and should only be reserved for the women with recurrent lesion in whom fertility preservation is not required. Even in these women invasive cancer should be carefully ruled out after colposcopy directed biopsies or LLETZ.

2. Adopting Single visit and Screen-Treat approaches.

WHO has recommended VIA / Point of care HPV based Screen and Treat programmes for better compliance to cervical pre-cancer treatment especially in regions with poor access to health care facilities.

Recommendations:

Primary screening by VIA gives immediate results, which when linked to cryotherapy/thermal ablation facilities to permit a single-visit Screen & Treat strategy. Pont of care HPV tests can also be used when available for screen and treat approaches (annexure 3 &4).

SUMMARY RECOMMENDATIONS

1. **Information, Education and Communications [IEC]:** Emphasis should be on IEC strategy for Target Populations and community-level efforts to improve knowledge about risk factors of cervical cancer, cervical screening programmes and enhancing community participation in the programme is critical for further reducing cancer incidence and mortality.

2. **Adolescent Health Programmes** to provide adequate knowledge about prevention of risk factors of cervical cancer, relevant to the age group.

3. **Cervical cancer screening**: Organised cervical cancer screening at the primary health care facilities and scale up the health system capacity to ensure efficient implementation and coverage for cervical cancer screening programme. Cervical cancer screening must continue to control cancer incidence over the upcoming decades.

4. Tata Memorial Centre has recently demonstrated a 30% reduction in cervical cancer mortality by implementation of a simple screening strategy using visual inspection of cervix using acetic acid (VIA) delivered by trained health workers in a large community based randomized controlled trial. This is being implemented throughout India at rural

and district levels. This strategy will result in immediate gains in terms of reduction in cervical cancer mortality and is likely to be cost-effective.

5. **Linking Screening to treatment**: Implementation of cost-effective screening with [VIA] based cervical cancer screening and linking screening to treatment programmes should be our first public health priority.

6. HPV vaccination programmes should be based on an assessment of locally relevant data and trends, including the scale of the prevailing HPV-associated public health problem (cervical cancer, other HPV-associated cancers).

TABLE 1: Summary of the Resource-Stratified Clinical Practice Guideline for Secondary Prevention of Cervical Cancer

Sr. No		ESSENTIAL/LIMITEDRESOURCE	OPTIMAL/ENHANCEDRESOURCE	OPTIONAL /HIGHRESOURCE
1	Primary Screening methods	-Visual inspection with acetic acid(VIA)	-Human papillomavirus(HPV) DNA(Self sampling/Clinician collected sample) -Cytology (quality assured) -Visual inspection with acetic acid(VIA)	-Human Papilloma virus (HPV)DNA((Self sampling/Clinician collected sample) -Cytology (quality assured)
2	By Whom	Trained Primary Care Workers Trained Nurse	Trained Nurse Physician	Trained Nurse Physician
3	Target Screening ages	30-65 years Primary target: 30-49 years	30-65 years Primary target: 30-49 years	30-65 years
4	Frequency of screening	-Every 3 years -atleast twice in a lifetime	-HPV DNA: 5-10years -Cytology / VIA : 3-5 years	-HPV DNA: 5years -Cytology: 3 years
5	Exiting Screening	65 years of age or older with consistently negative results overthepast15 years.	65 years of age or older with consistently negative results overthepast15 years.	65 years of age or older with consistently negative results over thepast15 years.
6	Use of triage and diagnostic steps	-VIA: Screen and Treat	-HPV DNA for cytology as primary screen -Cytology for HPV DNA as primary screen	-HPV16/18 Genotyping OR -Colposcopy and guided biopsy
7	After Triage		NEGATIVE: Follow-up in 12months with the same test ABNORMAL	NEGATIVE: Follow-up in 12monthsABNORMAL /POSITIVE:

Sr. No		ESSENTIAL/LIMITEDRESOURCE	OPTIMAL/ENHANCEDRESOURCE	OPTIONAL /HIGHRESOURCE
			/POSITIVE: Colposcopy if available	Colposcopy /directed Biopsy
			Visual assessment for treatment (VAT) if colposcopy is not available.	
8	Opportunity for implementing screen-and-treat approaches	Yes	Yes	NOT Recommended
9	Treatment of Women With Precursor Lesions	Ablative Procedures (Cryotherapy/ Thermal Ablation):Lesions suitable Lesions not suitable for ablation, refer to higher centre for Large Loop excision of Transformation Zone(LLETZ)/Cold knife conization (CKC)	Ablative Procedures (Cryotherapy/ Thermal Ablation):Lesions suitable Lesions not suitable for ablation: Large Loop excision of Transformation Zone(LLETZ)/ Cold knife conization (CKC)	Ablative Procedures (Cryotherapy/ Thermal Ablation/Laser):Lesions suitable Lesions not suitable for ablation: Large Loop excision of Transformation Zone(LLETZ)/ Cold knife conization (CKC)/Laser
10	Post treatment follow-up	Twelve-month post-treatment follow-up is recommended for all settings		
11	Special Population-Women who are HIV positive or immunosup-pressed for other reasons	-VIA: every 3 years	- HPV DNA: 3 – 5 years	-HPV DNA: 3-5 years

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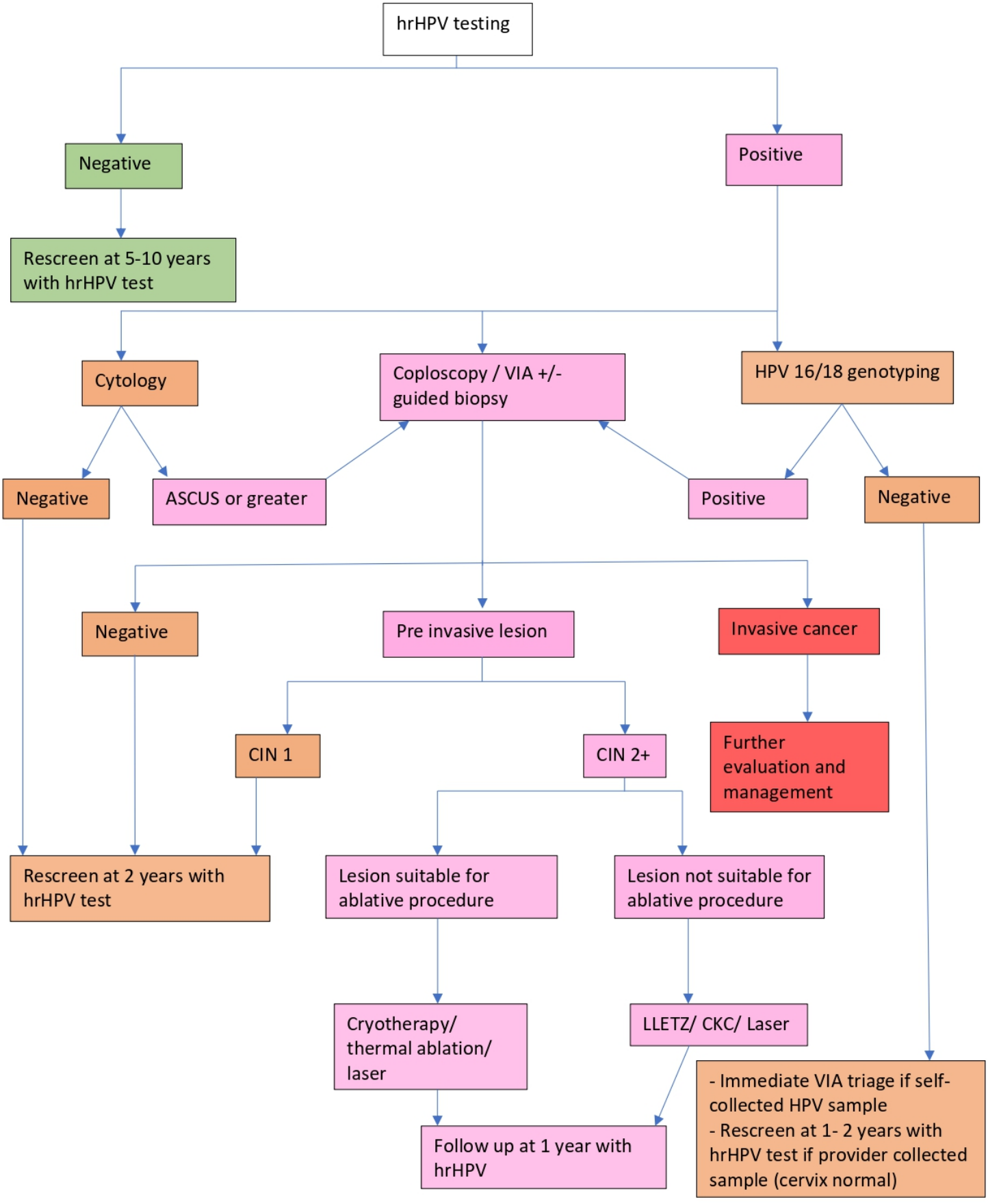
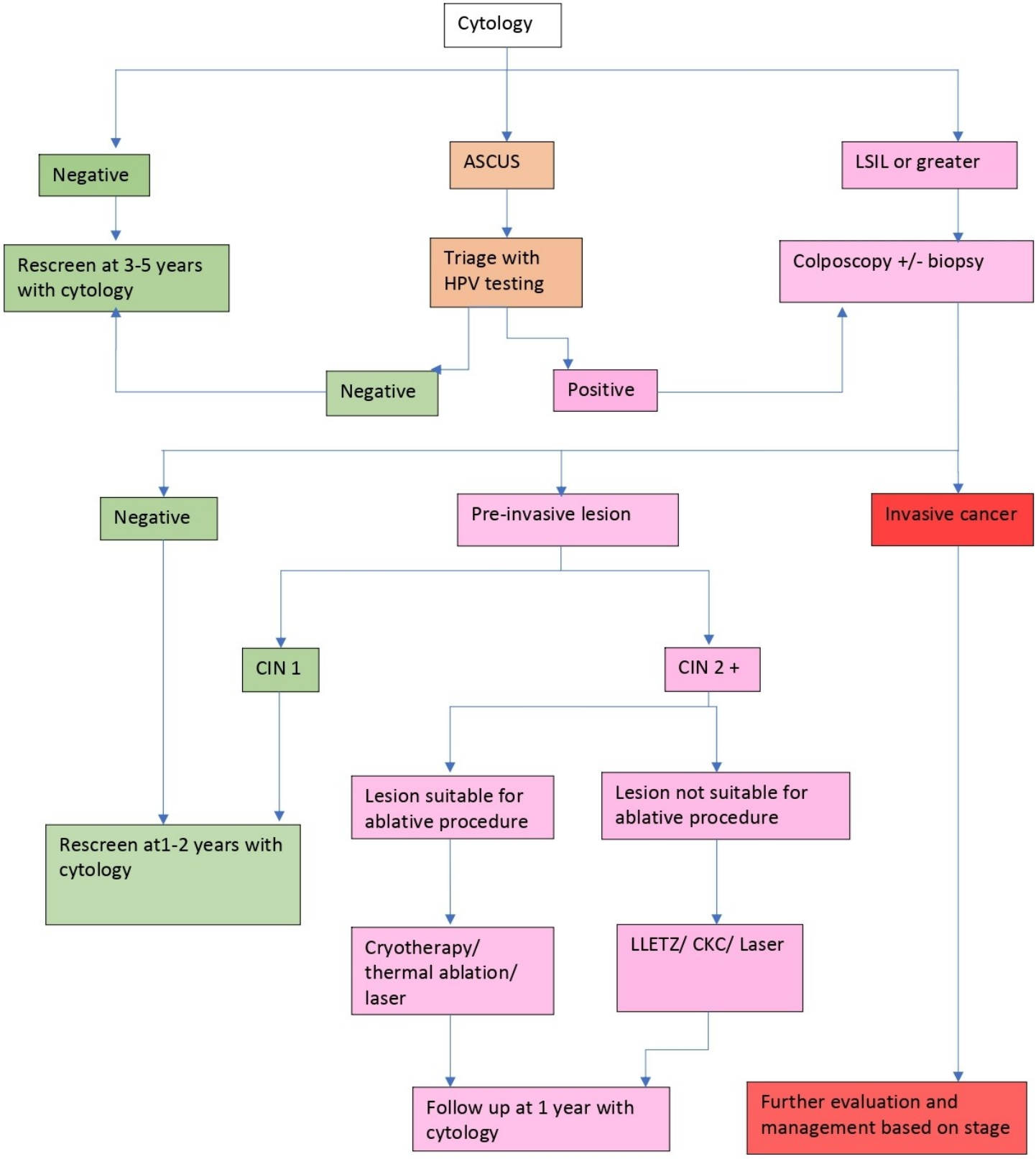
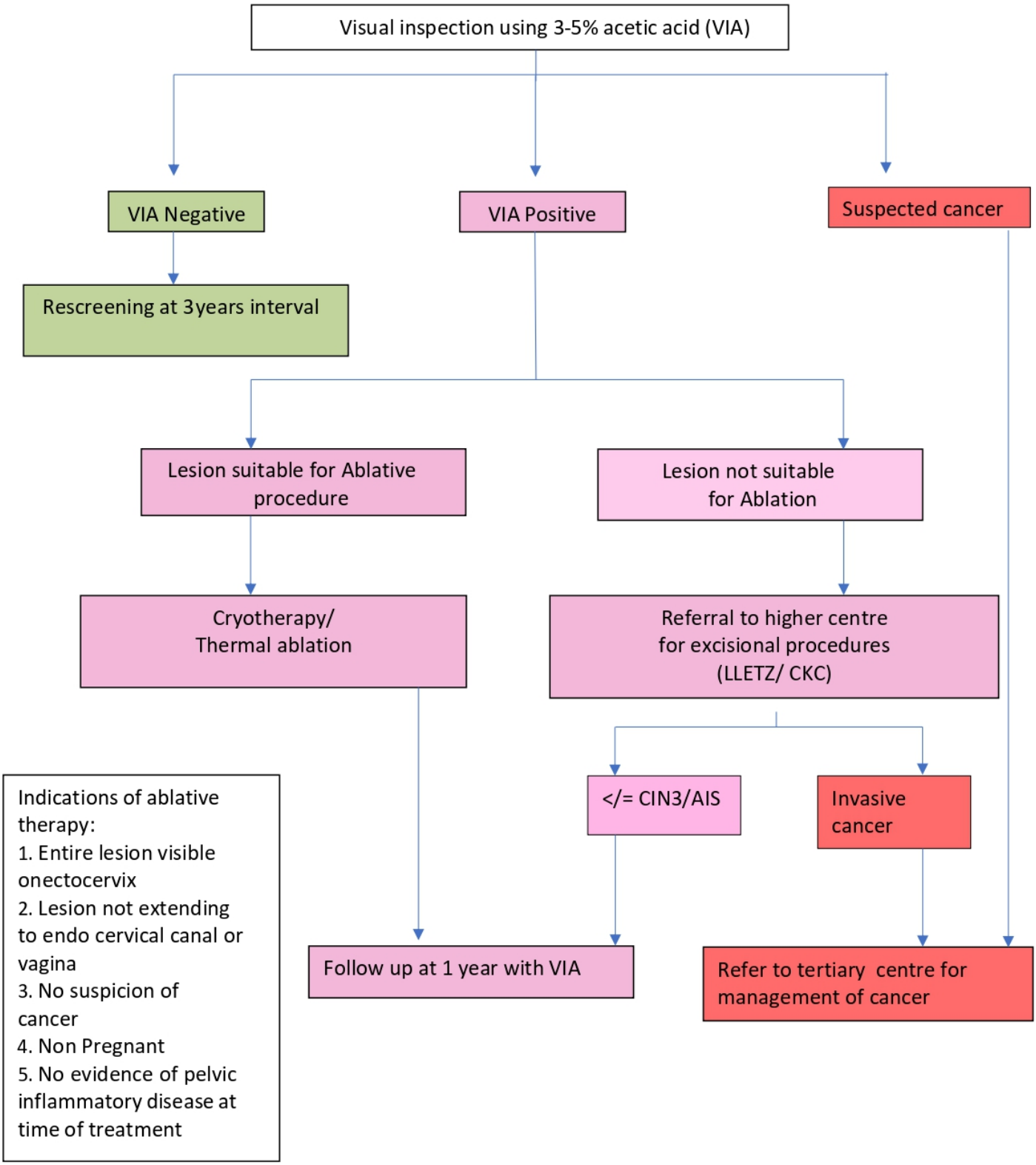
Annexure 1: Screen triage and treat: HPV testing as primary screening



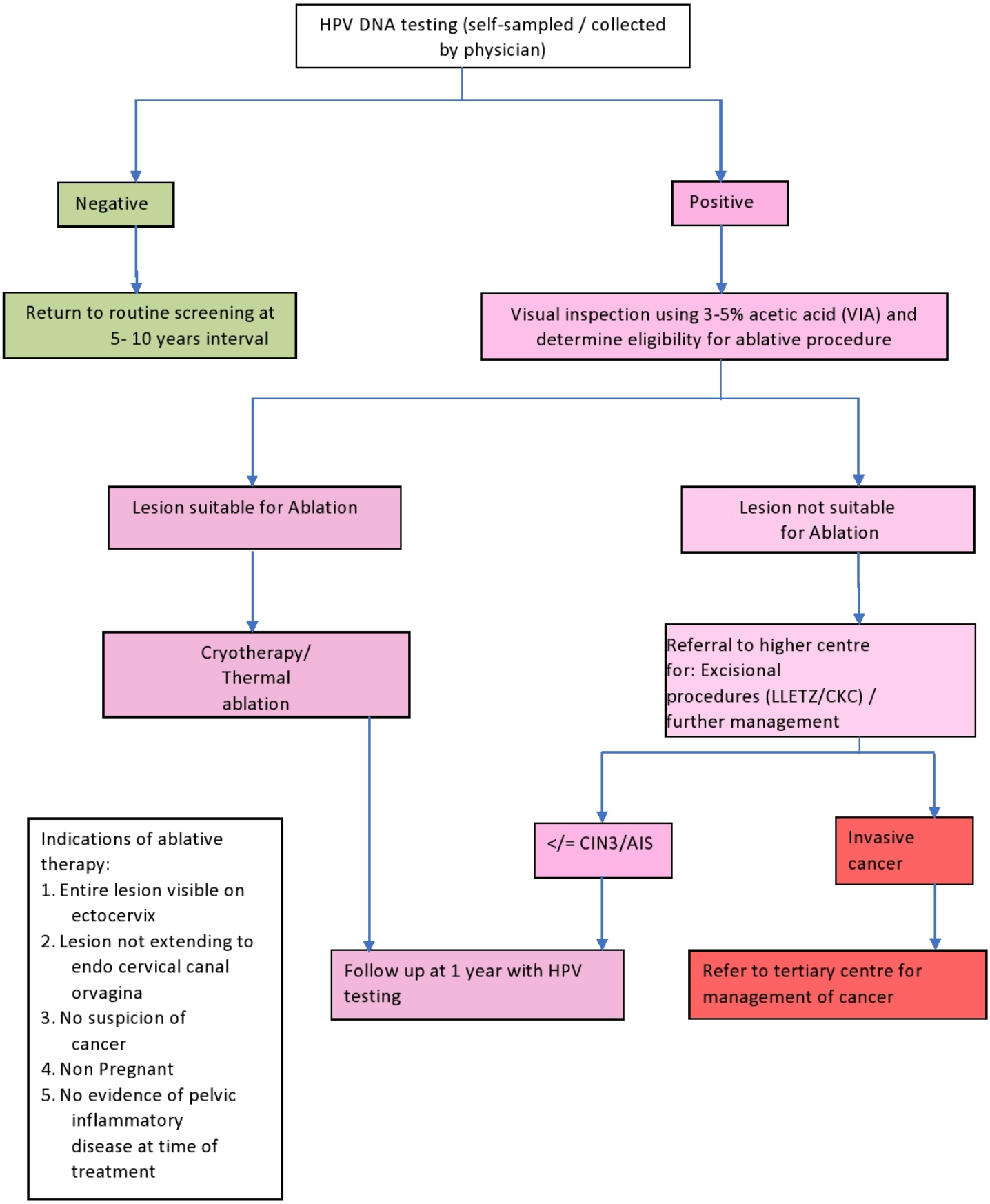
Annexure 2: Screen triage and treat: Cytology primary screen



Annexure 3: Screen and treat strategies: VIA screening



Annexure 4: Screen and treat strategies: HPV POC test screening



Chapter 4

Oral Cancer

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Evidence-Based Management of Oral Cancer

1. PRIMARY PREVENTION:

Lip and oral cavity (C00-C06) are one of the most common cancers among the lower Human Development Index (HDI) countries, probably due to the high consumption of etiologies.[1] Asia in particular contributes almost half of the burden with, India alone reporting 77,000 new cases and 52,000 deaths annually. India has the highest Age Standardized Rate (ASR) for incidence of 9.6 for both genders combined and 14.3 for men alone. Even among females, it is among the top five most common cancers in India.[2]These cancers seeming to affect younger individuals; the burden of disease can be truly astronomical.

Relevant exposures to oral cancer

Oral cancer is one of the preventable forms of cancer. The common risk factors of oral cancer are tobacco, used in both smoked and smokeless forms, areca nut and betel quid, and alcohol consumption.[3]There is a large geographic variation in India with respect to the form of tobacco usage, resulting in differing incidences of cancer across the country. A small proportion of oral cancer globally is caused by Human Papilloma Virus (HPV) and other viruses. Nutrition deficiency, poor oral and dental hygiene, trauma, as well as environmental and genetic factors also contribute to the risk factors of oral cancer.

Primary Prevention strategies

The aim of primary prevention in oral cancer is to reduce the incidence by cessation of exposure to risk factors especially tobacco and alcohol or increasing an individual's resistance to them.

A. Tobacco and Areca nut

Consistent evidence from several studies indicates that smoking tobacco in any form (cigarettes, bidis, cigars, chillum, etc.) increases the risk of oral cancer by 2 to 10-fold.[4]This risk is substantially increased with frequency and duration of use. The use of tobacco smoke along with alcohol and smokeless tobacco greatly increases the risk of oral cancer. The IARC working group has also published sufficient evidence in the form of meta-analysis, cohort and case-control studies that show quitting tobacco smoking

decreases the risk of oral cancer and oral potentially malignant lesions (OPMDs), and the risk decreases with increasing time since smoking cessation.[3]

Among the varied forms of smokeless tobacco being consumed, there are more than 28 compounds that contribute to its carcinogenicity. These can be divided into volatile N-nitrosamines, non-volatile alkaloid tobacco specific nitrosamines (TSNAs) and N-nitrosoamino acids.[5] Usage in any form such as khaini, mawa, mishri, betel quid, oral snuff and gutka increases the risk of developing OPMDs and cancer between 2 to 15-fold, respectively.[6] These are strong causative risk factors for precancerous conditions like oral submucous fibrosis (OSMF), leukoplakia, and erythroplakia, that place individuals at higher risk for oral cancer. More than half of oral cancers in India are attributable to smokeless tobacco products.[4]

Areca nut is regarded as a Type 1 Carcinogen by WHO-IARC. It contains approximately 11-26% tannins and 0.15-0.67% alkaloids, both of which are known cytotoxic and genotoxic agents.[7]These products are packaged together with tobacco and flavouring agents to be commonly sold as “guthka” and paan masala. They can also be consumed in a quid as “paan” which considerably adds to the carcinogenicity.[4]Its use is responsible for the high prevalence of oral submucous fibrosis (OSMF) in South-East Asia.

The working group of IARC conducted a meta-analysis that found former users of smokeless tobacco had a lower pooled risk of OPMDs, in particular leukoplakia, than current users.[3]There is sufficient evidence that behavioural interventions in adults like opportunistic counselling by physicians or social support by family or friends are effective in cessation of smokeless tobacco and areca nut use. Although limited, the evidence does suggest that behavioural interventions and/or pharmacological interventions like nicotine replacement therapy or antidepressants might also be an effective tool.[3]

B. Alcohol

Being an independent risk factor for oral cancer, epidemiological studies have shown that consumption of alcohol increases the risk of oral cancer by 2 to 6-fold, with proportional risk increasing with the quantity consumed. The combined use of alcohol and tobacco has been shown to have a multiplicative effect on the risk of developing oral cancer. In the systematic review and meta-analysis, it was found that risk of oral cancer increases by

two times in the population consuming alcohol.[8] According to the IARC working group, there is sufficient evidence that quitting the consumption of alcohol decreases the risk of oral cancer and oral premalignant disorders and the risk decreases with increasing time since quitting.[3]

C. Poor Nutrition

High consumption of vegetables and fruits is associated with a 40-50 % reduction in the risk of oral cancer. In high-income countries, a lack of vegetables and fruits in the diet may contribute to 15-20% of oral cancers. This is likely to be more in low- and middle-income countries (LMIC). Despite this, studies on chemoprevention have not been able to establish a preventive effect of carotenoid and retinoid dietary supplements on oral cancer prevention.[4]

D. Poor Oral Hygiene, Viruses, Chronic Trauma

Poor oral hygiene, viruses, and specific bacterial microflora in the oral cavity have been linked with the development of oral cancers.[9] Human Papilloma Virus (HPV) infection has been proven to be an independent risk factor for oropharyngeal cancer (OPC). A systematic review suggests that HPV vaccines can have a protective mechanism against oral vaccine–type HPV infection that includes high-risk HPV16 infection. This can result in a reduction in incidence of HPV-related oropharyngeal cancers.[10] In fact, a systematic review has reported a significant decrease in infection rates in study participants immunized with HPV vaccines across study design and heterogeneous populations.[11] A significant proportion develop IgG antibodies in the oral cavity post-vaccination, suggestive of successful vaccination.[3] Chronic trauma from decayed/broken teeth and ill-fitting dentures also contributes to the overall risk more so in presence of other risk factors.[4] Powerful public health campaigns to promote good oral hygiene and safe sexual practices would benefit in reducing oral cancer incidence. The promotion of a healthy lifestyle will influence knowledge, aptitude and hygiene at all levels of society. Health education is the most crucial component of oral health promotion.[9]

Table 1: Evidence for primary prevention in oral cancer (As adopted from IARC Perspective on Oral Cancer Prevention) [3]

Study design	Population	Evidence
Cessation of tobacco smoking		
Cohort study	NIH-AARP Diet and Health study in United States and included patients 50 – 71 years of both sexes	Former smokers had a lesser hazard of getting Head and Neck cancer compared to current smokers
Cohort study	Dutch Municipal Population Registry	Compared to current smokers' the risk of Head and Neck cancer was diminished for smokers who stopped smoking
Meta-analysis: 18 case-control studies	Milan, Aviano, France, Europe, Switzerland, America, New York, North Carolina, Tampa, Housa.	Cessation of smoking 1 to 4 years: OR 0.70 (95% CI 0.61–0.81) ≥ 20 years: OR 0.23 (95% CI 0.18-0.31)
Cessation of Smokeless tobacco use		
Betel quid (BQ) Systematic review and meta-analysis	Taiwan, China, and India	BQ cessation was associated with a 2.9% reduction in HNC after every year of cessation; however, even after 20 years of cessation. the risk did not reduce to the level of non-BQ chewers
Cohort study	India	A five-year cessation of chewing areca nut with tobacco had 49% and 81% reduction in the incidence of leucoplakia in males and females respectively.
Cessation of alcohol consumption		
Meta-analysis 13 Case-control studies	Milan, Aviano, France, Europe, Switzerland, America, New York, North Carolina, Tampa, Housa.	Benefits of cessation of alcohol after 20 years of quitting OR 0.60 (95% CI 0.40-0.89)
Seven Case-control Study	India	Risk of OPMDs were generally lower among former drinkers than current drinkers
Behavioural interventions		
Nine Studies (7 RCT; 2 Cohort studies)	Adults	All studies showed a positive effect on cessation. The relative risk in the control group was 1.28 at 6 months and 25.70 at 60 months compared to the intervention group
One RCT	United States Youth	Positive benefits following cessation of tobacco were observed. The relative risk in the control group was 1.70 (95% CI, 1.50 TO 1.86) at 12 months compared to the intervention

Study design	Population	Evidence
One RCT	United States Youth	Positive benefits effect in preventing the initiation of using smokeless tobacco following behavioural intervention was observed. Relative risk 0.58; 95% CI 0.35 to 0.99
Pharmacological interventions		
Four RCT	India & United States	Limited evidence was found for pharmacologic interventions with nicotine replacement therapy or antidepressants
Combined Behavioural and pharmacological evidence		
Sixteen RCT	15 studies – Smokeless tobacco One – Areca nut	Positive cessation rates were observed in 13 of 16 studies
Public Health Policies		
1 study	United States	Tobacco taxation reduced the prevalence of smokeless tobacco use in youth
4 studies	Bangladesh and India	The higher price would reduce the use of smokeless tobacco

Secondary Prevention and Screening

2. SECONDARY PREVENTION

Secondary prevention of oral cancer includes screening to detect oral potentially malignant disorders (OPMD) and oral cancer at an early stage. The key goals are to effectively detect and slow or stop disease progression at an early stage and to "down-stage" the disease. This should eventually translate into a reduction in mortality and morbidity. There are two broad scenarios where secondary prevention strategies can be implemented – in the clinic and in the field i.e. screening. All secondary prevention should start with education and self-examination, followed by a thorough examination by a trained healthcare worker/professional.

Evidence for oral cancer screening in India

Screening strategies in India have been either large scale involving the mass population or more targeted to a specific population that are at a higher risk to develop oral cancer.[12] The latter group typically should be part of a surveillance programme to monitor the natural progression of lesions. Screening can also be in multiple phasis where two or more screening tools are utilised either together or in succession, to increase the effectiveness.[12] Opportunistic form of screening is also very effective where individuals are screened for oral

lesions when they attend a clinic for other reasons.[12] The oral cavity, being easily accessible for examination, lends itself to be an ideal screening site that can be non-invasively assessed at all levels of screening. Moreover, majority of oral cancers have a premalignant phase which can be easily identified.

Oral cancer screening in India has been targeted for the high risk populations that often include tobacco and areca nut users. One of the early notable studies included tobacco users across three states, i.e. Ernakulum District in Kerala, Bhavnagar District in Gujarat and Srikakulam District in Andhra Pradesh.[13] Oral visual examination (OVE) was used along with intervention in the form of personal and mass media communication. They found an almost complete association between tobacco use, oral cancer and precancer. Tobacco habit cessation was associated with a decrease in the incidence of leukoplakia and palatal changes. Subsequently their 10-year follow up results showed similar results and also presented the possible benefit of training basic health workers to examine the mouth for early detection of lesions.[14] One of the only randomized trial in oral cancer screening was performed in Kerala by Sankaranarayanan et al.[15] They used conventional oral examination (COE) performed by trained non-medical university graduates as the screening method. The intervention was four rounds with a referral to a dentist for screen-positive lesions needing confirmatory diagnosis. The controls were subjects that did not receive any form of screening. Although not statistically significant, overall 12% reduction in oral cancer mortality was seen with the use of screening compared to the control arm. However, 24% reduction in mortality was reported among high-risk subjects that used tobacco and/or alcohol which was statistically significant. Of the 20% population that attended all four rounds of screening, a 79% reduction in oral cancer mortality was seen between the two arms. A smaller cohort study has been designed in industrial units in rural Maharashtra that included screening 104 workers over a one-year period.[16] Naked eye examination of the oral cavity was performed by a physician irrespective of the habit status at the start and end of the study period. Almost half the population was using tobacco at the beginning of the programme with 40% of them having oral precancerous lesions. With targeted interventions of workplace tobacco cessation, 80% of oral precancers regressed at the end of the year. A study performed across Mumbai city screened 21,015 subjects (4009 eligible) and was targeted at cancers among women.[17] The compliance for screening for the oral cavity was 88% with a screen positivity rate of 3.9%. They detected 27 oral precancers and one oral cavity cancer among the screened women, all of which complied with the treatment.

A Cochrane review in 2013 reported on the effectiveness of screening and early detection of oral cancer or OPMD in reducing oral cancer mortality.[18]Only one cluster randomised controlled trial by Sankaranarayanan et al., in India met the inclusion criteria. A recent review and meta-analysis has included another randomised trial by Chuang et al.,in Taiwan.[19]With screening high-risk population, the meta-analysis reported a 26% decrease in mortality and a 19% decrease in advanced cases. Both studies have reported a moderate to high risk of bias among the eligible studies suggesting inadequate evidence to support a national screening programme. Although there are no consistent results across the evidence available, opportunistic screening in a medical practice and selective screening of high-risk individuals may be very beneficial.

Current and emerging screening adjunct tools:

Oral visual examination (OVE) or conventional oral examination (COE), is described by a Cochrane review as "not surgically invasive, painless and socially acceptable", is one of the most common methods of oral cancer screening.[18] A meta-analysis of 18 studies found the sensitivity and specificity of using OVE for diagnosing dysplastic and/or malignant lesions of 71% and 85%, respectively.[20] The pooled diagnostic accuracy of identifying malignant lesions was 88% and 81% sensitivity and specificity, respectively.[20] Most of the screening tools used today are to augment OVE and improve its utility, both in field and in the clinic. Such adjuncts involve wide field evaluation of the oral cavity employing vital staining, oral rinses, light-based and optical technologies, and cytopathologic platforms to accurately detect and delineate abnormal mucosal "fields" that equate with oral carcinogenesis. Unfortunately, systematic reviews suggest that there is insufficient evidence of it efficiency when compared to OVE alone.[21]In fact, most of the tools are used to characterise already identified lesions rather than for screening. Moreover, a recent meta-analysis concluded that none of these methods can be recommended as a replacement for the currently used standard of a biopsy and histological assessment.[22]

A study compared the outcomes between using healthcare workers and technology (collected and sent images of lesions and normal mucosa), onsite specialist and remote specialist to screen 3,445 Indian industrial workers. Of the screen positives, 15.3% and 17.5% were deemed false positive and 0.03% and 0.2% false negative by the remote and onsite specialists, respectively.[23]This technology also has the potential to reach a larger geography more efficiently.

Table 2: Various diagnostic tests sued as adjuncts for oral cancer screening[11]

Technique	Example	Mechanism
Vital tissue staining	Toluidine blue, tolonium chloride	Stain nucleic acids that are abundant in precancer and cancer cells
Cytology	OralCDx	Collection of a trans-epithelial sample using a non- lacerational device and stained with a modified Papanicolau test. These were viewed as a histology section
Light based – Chemiluminescence	ViziLite plus, Orascoptic-DK	Due to the higher nucleus/ cytoplasmic ratio in dysplastic and malignant epithelium
Light based – Tissue fluorescence imaging	ViziLite, Microlux DL, VELscope, Identafi 3000	Cellular atypia changes the concentration and distribution of fluorophores, which will impact the tissue reaction to light
Light based – Tissue fluorescence spectroscopy		Spectrograph receives, records and analyses data eliminating any subjectivity
Biomarkers analysis		Saliva, blood, serum, urine studies based on genomics/epigenomics, proteomics, transcriptomics, metabolomics, and microbiomics
Imaging – Confocal microscopy	Vivascope	Imaging superficial soft tissues

Chemoprevention:

Chemoprevention has been an extensively used secondary prevention method for OPMDs and oral cancer. Many agents have been studied for chemoprevention of oral cancer such as vitamin A, retinoid, beta-carotene, vitamin E and other dietary agents. More recently, molecular targeted drugs such as cyclooxygenase-2 (COX-2) inhibitors, EGFR inhibitors and adenovirus vectors, have also been of interest for chemoprevention. A systematic review including 679 cancer cases found that the use of chemoprevention agents such as topical retinoids, bleomycin, adenovirus, COX inhibitors, photodynamic therapy and phytochemical-enriched products may be a viable adjuvant or substitute to traditional forms of treatment, with the advantage of reducing adverse effects and sparing important structures.[24] Unfortunately, the long-term effectiveness of chemoprevention agents could not be established through this review. Therefore, randomized trials with long follow-up periods and histologic confirmation might be necessary to fully understand the potential utility of topical chemoprevention agents.[24] Another systematic review and meta-analysis showed good clinical responses to chemopreventive agents such as beta-carotene, erlotinib, green tea

extract, isotretinoin, COX-2 inhibitors for oral premalignant lesions.[25] They concluded that no statistically significant differences were present between the current chemotherapeutic agents and placebo. Currently there is no definitive evidence that suggests the routine use of these agents in chemoprevention of OPMDs and oral cancer.

3. STRATEGY / WAY FORWARD FOR INDIA

An important issue for policy makers is to strengthen primary prevention. Based on the current evidence, primary prevention strategies for oral cancer should be based on the cessation of tobacco, alcohol and areca nut initiation and usage. More education and awareness activities focusing on the etiologies of oral cancer are needed, taking into account cultural barriers in the community. Focusing on high-risk populations and use of technology may reduce costs and increase efficiency. Effective implementation of the COTPA (Cigarettes and Other Tobacco Products Act 2003) and its subsequent amendments is needed as well as increasing taxes on all tobacco products.[26] There should be an incorporation of tobacco control in the school curriculum to reduce the age of initiation (eight to twelve years at present) of using tobacco products. Tobacco-containing food substances should also be banned under Food Safety and Standard Act of India, 2011. Policies to control the use of areca nut are relatively new, and there is no published data on its impact from India. Akin to tobacco (COTPA Act), the Government needs to implement and strengthen the national alcohol control policy to reduce the production, sale, consumption and advertisement of alcohol. Opportunistic counselling for cessation of tobacco, areca nut and alcohol as well as promotion of good oral hygiene by physicians must be done for high-risk subjects along with consistent powerful public health campaigns.

Screening for oral cancer has been researched and implemented across geographies using many models. It is important to tailor the model based on incidence of disease in the population, resource availability and the overall health system structure. Based on the current evidence, secondary prevention in the form of screening with oral visual examination by trained workers has shown significant benefit especially in the high risk population. Although screening studies performed this far in India do show potential benefit, cultural, logistic and reach has been major drawbacks of many programmes, with state run programmes face similar issues. The use of technology to improve screening reach and accuracy is very appealing, especially in the remote areas. Mobile phone applications have been developed and piloted among health workers for oral cancer screening in India.[23] This technology also

has the potential to reach a larger geography more efficiently. Artificial intelligence is also being used to train algorithms using large image databases to improve the accuracy of technology-based screening.[27]Although the evidence on the use of conventional adjunctive aids to screening have not been conclusive, researchers are now focusing on novel biomarker and imaging-based methods to improve accuracy.[20] A combination of multiple methods might be the most promising approach incorporated into future oral cancer screening research programmes.

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Chapter 5

Prostate Cancer

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Current and evolving strategies for prostate cancer screening

Introduction

Prostate cancer (PCa) screening is one topic that has the oncology community divided for about 2 decades. Being the second most common cancer worldwide and considering the growing proportion of elderly population, the absolute numbers of PCa over the coming years would be enormous. Given the current scenario of stage presentation, this would translate to a huge burden of advanced and metastatic disease. Screening aims to reduce this burden but comes at a trade-off of overdiagnosis and consequent overtreatment; which has been the main points of concern for those the idea of PCa screening.

In this chapter we summarize the probable strategies to avoid the development of PCa itself by primary prevention followed by a detailed discussion on screening for PCa. We round it off with our views regarding the current scenario in India and how we can offer effective screening strategies with an aim to reap its benefits and minimize overdiagnosis.

1. PRIMARY PREVENTION

Primary prevention is an intervention before health effects occur, through measures such as vaccinations, altering risky behaviours and banning substances known to be associated with a disease or health condition. PCa globally accounts for nearly 1.5 million new cases each year, with India accounting for nearly 36,000 new PCa cases yearly.[1] This offers a huge opportunity for use of primary prevention strategies and PCa is amongst the most extensively researched malignancies in this regard.

The role of diet in primary prevention

Diet plays an important role in the etiopathogenesis of many cancers. There is a definite biological rationale for the use of primary prevention strategies in PCa and preclinical studies appear promising. A Mediterranean diet, which is rich in nuts, fruits, vegetables, legumes, red wine, fish and olive oil is considered protective. These foods are rich in anti-oxidant and anti-inflammatory molecules such as omega-3 fatty acids, phenolic compounds, and oleic acid.[2]Leitzmann et al., conducted a prospective study among US health professionals that concluded that high consumption of fish was associated with a lower risk of PCa.[3] Higher levels of serum retinol are also associated with a lower risk of PCa.[4] Cruciferous vegetables are a rich source of isothiocyanates, particularly broccoli which is a rich source of

sulforaphane. It is postulated that isothiocyanates reduce PCa risk with the induction of glutathione S-transferases that are involved in the detoxification of carcinogens. In a case control study by Joseph et al., it was seen that increased consumption of cruciferous vegetables was associated with a reduced risk of PCa.[5] Soy products too have a proven association with protection against PCa. The soy isoflavones; genistein and daidzein, selectively accumulate in prostatic tissue. Soy isoflavones regulate androgen receptor expression and in turn block the expression of androgen dependent genes.[6] In mouse models, genistein has shown to upregulate tumor suppressor genes in PCa cells.[7] In epidemiological studies, total and unfermented soy food intake is associated with a reduced risk of developing PCa.[8] Saturated animal fats have shown to stimulate growth of PCa cells by increasing levels of circulating androgens.[9] Obesity and a high BMI lead to a more aggressive and advanced cancers at presentation. Though no association has been found between cigarette smoking and incidence of PCa, it is seen that mortality is higher in smokers than in non- smokers.[10]

Does chemoprevention have a role?

Chemoprevention has been extensively investigated in the prevention of PCa. 5α-reductase inhibitors prevent the conversion of testosterone to its more potent form- dihydrotestosterone. They were initially introduced in the 1990s to treat benign prostatic hyperplasia. The Prostate Cancer Prevention Trial (PCPT) randomized men to receive either placebo or 5 mg finasteride daily for the duration of 5 years. Participants underwent annual serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE). Prostate biopsy was done if PSA was more than 4 ng/ ml, for an abnormal DRE or at the end of trial if PCa had not been diagnosed earlier. Median prostate volume was higher in the placebo group. PCa was detected in 18% men in the finasteride group and 24% men in the placebo group. However, patients in the finasteride group had a greater proportion of patients with higher Gleason's score (7-10) on biopsy – 37% vs 22% in the placebo group. Sexual dysfunction was significantly higher in the finasteride group.[11] Long term results from the trial showed that there was no difference in overall survival or survival after the diagnosis of PCa.[12] A few years later, the Reduction by Dutasteride of Prostate Cancer Events (REDUCE trial) tested dutasteride as chemoprevention in patients at high risk of developing PCa. They included men between 50 to 75 years of age, with a PSA of 2.5-10 ng/ml and a negative prostatic biopsy at baseline. Dutasteride provided a relative risk reduction of 23% compared to placebo. Similar to the PCPT trial, a significantly higher number of participants with Gleason's 8-10 disease were seen at years 3-4 in the experimental arm.[13] A randomized,

double-blinded Phase IIB clinical trial by Price et al evaluated toremifene for the prevention of PCa in men with high-grade prostatic intraepithelial neoplasia. Patients receiving toremifene had significantly less incidence of PCa on biopsy at the end of one year (24.4% vs 31.2%). Gleason's scores were similar in both groups at the year-end biopsy, with excess toxicity not observed with toremifene. However, the trial did not explore outcomes beyond one year.[14]

In conclusion, dietary and pharmaceutical agents do seem to reduce the incidence of PCa. However, their impact on PCa-specific survival and overall survival remains unknown. Use of chemopreventive strategies have not found widespread acceptance due to the associated toxicities and likelihood of more aggressive disease at diagnosis. The use protective dietary agents should be encouraged as they would improve the overall health of older men, apart from their beneficial effect against PCa.

2. SECONDARY PREVENTION AND SCREENING

What is secondary prevention?

In contrast to primary prevention which focused on intervening before the disease occurs, secondary prevention aims to reduce the impact of a disease condition that has already occurred.[15] It emphasizes on early disease detection by 'screening', which is defined by the WHO as 'the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population by means of tests, examinations or other procedures that can be applied rapidly and easily to the target population'.[16] The target is healthy-appearing individuals with subclinical forms of the disease consisting of pathologic changes, but no overt symptoms that are diagnosable in a health visit.[17] For PCa, the PSA blood test presents an opportunity to screen these subclinical cases.

Impact of screening on PCa dynamics

Screening has the following two objectives:

1. Reduce the mortality associated with PCa.
2. Maintain quality of life (in other words, not hamper quality of life due to early detection and subsequent treatment).

Screening leads to an increase in the incidence of PCa with most patients being detected with early-stage disease and this should ideally lead to a decrease in the cancer-specific mortality. Why then, is there so much to debate about screening in PCa?

There is evidence that suggests, PCa often grows so slowly that men die of other causes before their PCa poses a threat to their life.[10,18] In men who died of other causes, autopsy findings have revealed indolent PCa in up to 60-70% of men in their eight decade.[19] Thus, screening results in detection of 'clinically insignificant' PCa - these are cancers that are so indolent that they do not pose a threat to life and thus do not deserve to be treated. PCa screening has been blamed to result in overdiagnosis and subsequent overtreatment resulting in treatment-related side effects.

While PCa related mortality has declined since the advent of widespread PSA screening, it is difficult to ascertain what proportion of the decrease is actually due to the screening. Also, the trend of a rising mortality immediately after the 2012 USPSTF recommendation raises a question to the direct causal relationship between PSA screening and PCa mortality.

The available evidence

Three large randomized controlled (RCT) trials have evaluated whether PSA based screening impacts PCa mortality. The age of men enrolled ranged from 40 to 80 years across the trials. The studies used varying PSA screening intervals and PSA cut-offs to proceed with further investigation. These studies are summarized in Table 1.

Table 1: Summary of the three largest trials evaluating PSA based prostate cancer screening

Study	Country, duration	Age group of enrolled men	n (Interval: Control)	Screening method & frequency	PSA threshold for biopsy	Prostate cancer specific mortality RR
CAP[20]	UK, 2001-2009	50-69	1,95,912: 2,19,445	PSA One time screening	≥3 ng/ml	0.96 [95% CI, 0.85 to 1.08]; $p = 0.50$
ERSPC[21]	9 European countries, 1993-2003	55-69	72,891: 89,352	PSA + DRE Every 2-4 years	≥3 ng/ml	0.80 [95% CI, 0.72-0.89]; $p<0.001$
PLCO[22]	US, 1993-2001	55-74	38,340: 38,343	PSA + DRE Every year	≥4 ng/ml	1.04 [95% CI, 0.87-1.24]; $p=0.67$

The European Randomised Study of Screening for Prostate Cancer (ERSPC)

study has been publishing updated data with the latest being at 16 year follow-up.[21] The percentage mortality reduction has remained unchanged since the publication of the first results in 2013. However, over the years, the number needed to screen and to treat have been decreasing are now below the number needed to screen observed in breast cancer screening studies.[23] (Table 2)

Table 2: Number needed to screen and treat to prevent one prostate cancer death, as per the ERSPC data

Years of follow-up	Number needed to screen	Number needed to treat
9	1410	48
11	979	35
13	781	27
16	570	18

Though the ERSPC data points towards reduced PCa mortality with screening; such consistent results have not been observed with the other trials. A meta-analysis of the above three and two additional smaller trials including a total of more than 7 lakh men reported that screening for PCa has no effect on all-cause mortality (moderate certainty) and may have no effect on PCa specific mortality (low certainty).[18]

The Prostate, Lung, Colorectal and Ovarian (PLCO) trial has been criticized for the high rate of contamination as 74% of the participants in the control arm were screened at least once. Thus, the PLCO trial actually compared population-based screening with 'opportunistic screening' (Opportunistic screening is discussed later). Apart from this; the above three major trials share some common limitations. None of them addressed the potential benefit of screening in high-risk individuals as only 5-7 % of the patients had a strong family history or were of African-American descent. Also, many individuals in these trials underwent sextant biopsies which are not the standard of care today. However, a recent attempt at eliminating the flipsides of the PLCO trial, using simulation models, showed that the impact of PSA screening in PCa mortality in the PLCO trial is quite close to the benefit seen in the ERSPC trial.[24]With regards to the CAP trial, the strategy of a single PSA test was deemed to be inadequate as the trial did not show any effect on PCa mortality and highlights the need for repeated testing if screening is considered.[20,25]

At the turn of the millennium, widespread PSA based screening in the USA led to a decrease in the PCa mortality.[26] In 2012, the US Preventive Services Task Force (USPSTF) issued a recommendation against (grade D recommendation) PSA based screening for PCa.[27] The next 5 years saw decrease in overdiagnosis; however, multiple papers reported a higher incidence of advanced PCa at diagnosis and a slow increase in the PCa related mortality.[28–31] In 2017, the USPSTF upgraded to a grade C recommendation for men in the age group of 55-69.[32] The task force acknowledged that the PLCO trial which was used for the grade D recommendation in 2012 had certain limitations and the change from grade D to grade C was based on a better understanding of the long-term follow up data from the randomized trials and also recognition of increased utilization of active surveillance for early cancers.[33] This allowed for PSA based screening in well informed individuals and 'shared decision-making' became the buzz word in uro-oncology.

The associated harms and their potential remedies

In all the above 5 trials, an elevated PSA prompted a transrectal prostate biopsy. All trials reported a higher detection of clinically insignificant PCa in the screening arms.[18] Also, a prostate biopsy is not without its own share of adverse effects which range from pain, hematuria and urinary tract infection to rarely sepsis. This presents us with two opportunities to mitigate the perceived downsides of screening:

1. Can we reduce the detection of clinically insignificant cancers while still continuing to not miss the clinically significant ones?
2. Even if clinically insignificant cancer is detected; how do we, best manage the patient's anxiety and reduce the risk of overtreatment and subsequent side effects.

In recent years, MRI of the prostate prior to a biopsy has shown to reduce the detection of clinically significant cancer and can also help avoid a biopsy in up to 25% patients if the MRI does not pick up any suspicious lesion.[34] This algorithm prompted trials to evaluate the role of MRI prior to biopsy in the screening population. Three trials have recently reported on this and have consistently shown a higher detection rate for clinically significant cancer, significantly lower detection of clinically insignificant cancer and a reduction in the number of men who undergo a prostate biopsy for a raised PSA.[35–37] If these trials do end up demonstrating lower PCa mortality over the next few years, then their MRI based algorithm would have circumvented the 'overdiagnosis' problem associated with PSA-alone screening.

Even with our best effort to reduce overdiagnosis of clinically insignificant cancer, we will end up having patients who get detected with such indolent disease. Here, the onus lies on the clinician in alleviating the patient's anxiety regarding the diagnosis of his 'cancer' and explaining the option of active surveillance to him wherein we 'observe' the cancer with serial PSA levels and imaging and intervene only when either the patient wants us to or when the cancer shows signs of becoming clinically significant.

Shared decision making

Currently there seems to be insufficient evidence to recommend generalized population-based screening as there seems to be, at best, a very marginal benefit in PCa mortality; and even this benefit has not been consistently demonstrated in various trials. However, there in increased interest in individualised early detection. All society guidelines recommend shared decision making with the patient prior to prescribing a PSA test.[32, 38] The clinician needs to inform the patient about the risk of overdiagnosis and possible overtreatment. A well-informed patient can then participate in a discussion and choose whether he wishes to undergo the test. The following points may be touched upon during the shared decision making:

1. PCa is one of the most common cancers diagnosed in men.
2. Screening for PCa may reduce risk of death from PCa. However, the absolute benefit is marginal.
3. Screening is done with a PSA test. The frequency of testing would depend on the personal risk of PCa and the first PSA level.
4. PSA can be falsely elevated. Additional tests like a prostate MRI may be performed if the PSA is elevated.
5. The decision to proceed with a prostate biopsy will depend on the PSA level and MRI findings.
6. Biopsies can rarely lead to serious infectious complications.
7. A negative biopsy does not rule out the presence of PCa.
8. The biopsy may detect a clinically insignificant cancer which can be observed. Currently it is not possible to determine which clinically insignificant cancers at diagnosis would eventually need active intervention.

Society recommendations

Table 3: Summarizes the recommendations by various guideline groups for prostate cancer screening. All societies recommend a shared decision making process and differ slightly in the details of the screening process.

Guideline group	Age to start screening	Frequency of screening	Age to stop screening	High risk groups
American Urological Association (AUA)	55	Every 2 years. Every 4 years for men >60 years with PSA <1 ng/ml	69 OR if life expectancy less than 10 years	Start screening at the age of 40 for African-American men and men with a strong family history
European Association of Urology (EAU)[38]	50	Every 2 years for those with PSA >1 at 40 years and PSA >2 at 60 years Every 8 years for those with PSA <1 at 40 years and <2 at 60 years	If life expectancy is < 15 years	Start at age 45 for men of African descent and those with a strong family history. Start at age 40 years for those with BRCA2 mutations.
US Preventive Services Task Force (USPSTF)	55	No recommendation	69	No recommendation
Canadian Urological Association (CUA)	50	PSA <1 → repeat every 4 years PSA 1-3 → repeat every 2 years	69 or if life expectance is less than 10 years	Start at age 45

3. STRATEGY FOR PROSTATE CANCER PREVENTION

Over the years, PCa has had a relatively lower incidence in India and has not been considered a public health problem as in the west. In the absence of any trials on screening conducted in India, it is difficult to make robust recommendations. The following opinion is based on Indian demography with its projected figures, evidence from the west and concerns about the existing stage at presentation.

Need for prostate cancer screening policy in India

The foremost requirement for considering screening of a cancer is it's age specific incidence rate which for PCa in India in 2020 was 5.5 per 1,00,000 males, compared to 72 in the United states where PSA based screening is routinely done.[1] A major reason for this stark difference in the incidence is the routine PSA based screening suggested by the USPSTF and an absence of any policy to test PSA in India. This also explains the >60% metastatic stage at presentation in our population compared to 5% in the Surveillance, Epidemiology, and End

Results (SEER)- Medicare data base.[39] The trend of PCa in India however suggests a rise in incidence.[40]

In major Indian cities like Delhi, Kolkata, Pune, and Thiruvananthapuram, PCa is the second most common cancer among men.[40] It is the third most common cancer in cities like Bangalore and Mumbai, and it is among the top ten most common cancers in the remaining population based cancer registries (PBRCs) of India. In all PBRCs, the incidence rates of this cancer are rising constantly and rapidly. It is difficult to ascertain what proportion of this rising incidence is attributable to random, unorganized PSA-testing being offered at various hospitals and laboratories in the country.

Age is the most important risk factor for PCa with majority of patients being diagnosed at ≥65 years. As per the projection of a recent UN report, between 2021 and 2050 the global share of people more than 65 years of age is likely to increase from less than 10% to around 17%.[41]In India, the proportion of the population aged 60 years and above was 7 % in 2009 and is projected to increase to 20 per cent by the year 2050. In absolute numbers, the elderly population is expected to increase from 88 million in 2009 to 315 million in 2050. Considering our high proportion of patients presenting with metastatic disease and our population denominators, in the absence of any screening programme, the absolute numbers of men with metastatic disease we will be seeing in the years to come is concerning. The implications of this concern are both in terms of higher morbidity and mortality of advanced disease at presentation and related to financial toxicity. According to the SEER database, the 5-year survival rate for localized and metastatic PCa is >99% and 31% respectively.[39]

The treatment options for early PCa include active surveillance, surgery, and radiation therapy along with hormonal therapy. While the options for advanced PCa about a decade ago were limited to androgen deprivation, most commonly achieved by bilateral orchidectomy which was inexpensive and highly effective, the basket of options for metastatic hormone sensitive and resistant disease today has hugely expanded. This zone has seen the highest number of level 1 evidences generated across all urologic cancers in the past decade with astounding survival benefits. The treatment spectrum now includes androgen-receptor pathway inhibitors like abiraterone and enzalutamide, cabazitaxel, docetaxel, sipuleucel-T vaccine, PARP inhibitors & theranostics like Radium-223 and LuPSMA therapy. Additionally, advanced disease needs supportive treatment like pain management, bone health agents, radiation therapy, and endourological procedures like clot evacuation and a channel transurethral resection of the prostate (TURP). A recent direct cost-comparison

conducted at Ghana estimated the cost of managing metastatic PCa to be four times (USD 1185) that for non-metastatic (USD 290) disease.[44]

The detection of indolent PCa with a Gleason grade of 3+3 in <=3 cores is considered as overdiagnosis; and in such patients, the oncological safety of active surveillance has been established. While such overdiagnosis with a PSA cut-off of 4 based screening is a common scenario in the western countries, the proportion of our men presenting with such disease is miniscule.[42,43]

Having discussed the need for a screening policy, the next obvious questions are how to screen, whom to screen, when to start screening and how often. These questions should be answered with the objective of detecting clinically significant PCa while avoiding the risk of overdiagnosis and overtreatment.

Strategies for screening – What have we learnt so far

Five large randomized controlled trials have been conducted in the west aiming to determine if PSA based screening helps reduce PCa mortality. While the largest trial did show a 27% reduction in PCa mortality, a recently conducted meta-analysis of more than 7 lakh men reported that screening for prostate cancer has no effect on all-cause mortality (moderate certainty) and may have no effect on prostate cancer specific mortality (low certainty). These trials also reported significant overdiagnosis due to detection of low grade early PCa and consequent overtreatment. MRI of the prostate has shown to reduce this risk of overdiagnosis by lesser detection of clinically insignificant cancer. In fact, it has been shown that quarter of patients with raised PSA can have the biopsy avoided if the MRI does not identify a suspicious lesion. This has led to a couple of on-going trials which have incorporated MRI in the algorithm of evaluating patients detected with a raised PSA on screening.[18]Currently the European association of Urology (EAU), NCCN and the US Preventive Services Task Force (USPSTF) recommend PSA based screening. They differ a little in the age at which to begin screening and the frequency of PSA testing. They all recommend ‘shared decision making’ with the patient prior to prescribing the PSA test to make sure that the patient understand the risks and benefits associated with screening.

DRE with its low reported sensitivity of 0.51 and specificity of 0.59 in hands of primary care clinicians is not considered an appropriate tool to screen for PCa.[45]

A recently concluded herculean effort led by our centre found breast self-examination to fair better than mammography in a large clustered randomized trial in terms of avoiding

overdiagnosis and consequent overtreatment; however, a similar comparison between DRE and PSA-based screening has not been done, possibly because of the stark difference in efficacy of the two methods.[46]

The two largest randomized controlled trials ERSPC and PLCO used a PSA cut-off of 3 and 4 ng/ml respectively to trigger the need for a biopsy and both trials had a significant rate of over diagnosis.[21,22]Population-based studies in India, have pointed towards a likely lower age-specific serum PSA range and mean total PSA than in the western population with a higher PSA density.[47–49]This would have a bearing on deciding the PSA cut-off if a trial is planned here.

A recently concluded trial in the NHS looked at multi parametric MRI-based screening with its potential advantage of picking only significant cancer however using a tool like that would certainly not be feasible in India even if it has proven its benefit over PSA-based screening due to issues with finances and logistics. Also, the same may be the case with expensive and inaccessible biomarkers like the 4K score and the prostate health index (PHI), amongst others.

While the criterion for men at high risk of developing PCa based on family history and racial ethnicity has been established in the west, the same information is missing for Indian men. Interim analysis from the international IMPACT study (Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls) showed that breast cancer gene 2 (BRCA2) mutation carriers had a higher incidence of PCa, were younger at diagnosis, and were more likely to have clinically significant tumors after three years of screening compared to non-carriers.[50] With the reported increasing incidence of breast cancer in India, more patients are likely to undergo testing for BRCA2 mutation. Should male family members of women with BRCA2 mutation be screened for PCa is another scenario that the clinicians would be encountering commonly.

It is also essential to realise the need to tailor the screening process in India to the socio-economic conditions prevalent here. The difficulties in incorporating MRI and other potential markers in the screening pathway in view of the financial and logistic issues have already been recognised. Recent reports have identified that the health literacy of a patient, has a bearing on the shared decision making process while discussing screening.[51] This shared decision making process would have to be personalised to continue to uphold the reason for which this process was recommended in the first place. It is important to prevent the clinician from being the sole decision maker here.

The way forward – Responsibility and opportunity

The changing age demographics and increasing incidence of PCa in the registries should trigger a thought about generating evidence about population-based screening by the policy makers in India. It took a couple of decades for the west to understand the harms of overdiagnosis and overtreatment of PSA-based screening with a cut-off of 4ng/ml and that is a path we should not be taking. On the other extreme, it took just a few years to realize that complete absence of any screening could lead to stage migration, a scenario we are already in. We in India are a PSA uncontaminated population with a stage distribution that the United States had three decades back. The quest is to find a middle path by generating our own evidence using a PSA value appropriate for our population. This should be done with the aim of reducing the burden of metastatic PCa at presentation and at the same time avoiding over diagnosis, possibly by incorporating an MRI into the prostate biopsy algorithm. Even with the most stringent criteria for screening, some degree of overdiagnosis is bound to happen and the onus lies on the clinicians to alleviate patient anxiety and use active surveillance optimally for the clinically insignificant cancers in a bid to avoid overtreatment.

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Chapter 6

Lung Cancer

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Thoracic Malignancies- prevention and screening

Introduction

Lung cancer is one of the most common cancers diagnosed worldwide. It is now the foremost contributor of cancer-related mortality, with a mortality rate of 18%.[1]

GLOBOCAN 2020 report estimated the incidence of lung cancer in India as 72,510 in all age groups and both sexes; with a crude incidence rate of 5.5 per 100,000 population. In terms of incidence rates, lung cancer ranked fourth overall among the various types of cancer (excluding non-melanoma skin cancer) after breast, oral cavity and cervical cancer. In males, it ranked second while in females it was seventh in terms of cancer incidence. The overall estimated lung cancer mortality in India in 2012 was 63,759, making it the third most common cause of cancer-related mortality in India after breast and cervical cancer. Among Indian males, lung cancer was the most common cause of cancer related mortality at 48,697 deaths; whereas among Indian females it was 15,062 (ranking seventh in terms of cancer-related deaths).[2]

1. PRIMARY PREVENTION

Risk Factors

Cigarette smoking is the primary risk factor for lung cancer. The risk increases with number of pack and years of smoking.[3] The incidence of lung cancer is increasing in never smokers pointing towards the effect of secondhand smoke as one of the important risk factors.[4] Other notable risk factors are strong family history, occupational carcinogens (asbestos, arsenic, chromium etc.) and history of chronic obstructive pulmonary disease (COPD).[5,6,7] Although asbestos is mainly linked with malignant pleural mesothelioma, 3-4% of lung cancers are associated with asbestos exposure especially in smokers.[8] The evidence of association of hormone replacement therapy (HRT) in postmenopausal women with lung cancer is not clear, however risk of death from lung cancer was shown to be increased in one large randomized control trial (RCT).[9]

Preventive measures

Prevention of lung cancer is divided under primary and secondary prevention. Primary prevention encompasses direct avoidance or reduction in exposure to known carcinogenic factors. Avoidance of tobacco consumption is of utmost importance as not only active smoker

but also reformed smokers and exposure to passive smoke are at increased risk than never smokers.[10]

Adolescent group needs special attention in smoking cessation, curiosity drives them to smoking and nicotine dependence shifts curiosity to addiction. Strategies for smoking cessation include behavioral changes and pharmacotherapy. Treating tobacco dependence is the most cost-effective intervention. Physicians should intervene and guide smokers to effective counselling.[11]Various behavioral tools have been identified to encourage smoking cessation. Evidence based five step strategy to guide clinicians (i.e. Ask, Advise, Assess, Assist, Arrange) is useful office based tool.[12] Behavioral therapy could be in the form of individual approach or group sessions. Newer modalities such as phone text or internet can also play a role although evidence is scarce regarding effectiveness.[13]

Most important reason why quit attempts fail is nicotine addictiveness and also nicotine withdrawal symptoms.[14] Pharmacotherapy helps in relieving nicotine withdrawal symptoms. Main categories of pharmacotherapy include nicotine replacement therapy (NRT), bupropion (an atypical antidepressant), and varenicline (a selective nicotine receptor partial agonist).[15]Various modes of delivery of NRT are patch, gum, combination NRT or others (tablets, inhalers, sprays and lozenges). Both NRT and bupropion have similar efficacy when compared with placebo with respect to quit cigarette smoking. Varenicline has been found to be more effective in helping people quit smoke as compared to NRT or bupropion when each compared to placebo. Combination of counselling and pharmacotherapy has been used with good effect.[16]

Legislative efforts for tobacco cessation-

- Banned smoking in public places and workplaces.
- Prohibited advertising tobacco products through mass media.
- Health warning labels on products.
- Sales restriction, ban on E-cigarettes.

2. SECONDARY PREVENTION- LUNG CANCER SCREENING

Lung cancer possesses all the features that make it a disease fit for screening [17]

1. It is a disease of public health importance.
2. Detectable pre-clinical phase.

3. A readily available test to detect it at an early stage.
4. Early treatment results in improved outcomes.

However, lung cancer screening comes with its own set of challenges. Lung cancer screening requires advanced imaging techniques like low-dose computed tomography (LDCT), high level of technical expertise in reviewing the imaging and high-end clinical infrastructure (Interventional Radiology, Expertise in minimally invasive thoracic surgery) to actually be effective in reducing mortality.[18] Apart from this there is significant morbidity associated with screening in the form of a high false-positive rate.[19]

Clinical Trial Data

Attempts at lung cancer screening have been going on for the past 75 years. In the 1950's and 60's several clinical trials were conducted (Philadelphia Lung Neoplasm Project, Erfurt Lung Study, Tokyo Government study etc.) to assess if serial chest x rays and sputum cytology could detect lung cancer earlier and result in mortality reduction.[18, 20] None of these trials were able to demonstrate a mortality reduction, in some cases there was an increase in mortality in the screened arm, due to unknown reasons.[21]

In the last few decades with the advent of the CT scan, low dose CT scan was seen to be a viable alternative to chest x-rays and various trials were started using the low dose CT scan(LDCT). LDCT uses lower radiation dose than conventional CT (1.4 mSv vs 7 mSv) thereby hypothetically reducing the harmful effects of radiation.[18, 21]

Earlier studies showed some promise with low dose CT screening, they demonstrated that LDCT could pick up cancers at an earlier stage, but were unable to demonstrate any mortality benefit. Most of the studies were underpowered, had design flaws or did not have a control arm.[18, 20–22]

a. National Lung Screening Trial (NLST)

Not until the publication of the NLST in 2011, did we have level I evidence for lung cancer screening. In this landmark trial, 53,454 patients were randomized to undergo screening with LDCT vs. screening with a routine chest x-ray. Trial was carried out at 33 sites in the United States of America (USA).[23]

Selection criteria:

1. 55-74 years of age.
2. Smoking history of >30 pack years.

3. Current smoker or those who quit less than 15 years ago.

All recruited individuals underwent three rounds of annual screening with Low Dose CT scan. LDCT decreased the relative risk of death from lung cancer by 20 %(95% CI 6.8- 26.7, p-0.004) compared to chest radiography. The number needed to screen to prevent one lung cancer death was 323 over 6.5 years of follow up. On extended follow up this figure reduced to 303. There was also a 6.7% reduction in all-cause mortality.

The false positive rate with LDCT at baseline was around 27%, but the rate of adverse events associated with diagnostic procedures was only 0.4%. The overdiagnosis rate was 18.5% at 6.5 years of follow up, which decreased to 3% at 11 years.

b. The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON)

This trial was carried out in The Netherlands and Belgium. 15,789 individuals were recruited to undergo screening with LDCT scan. The comparison arm underwent usual care with no screening.[19]

Selection Criteria

1. 55-74 years of age.
2. Current smoker, or former smoker who have quit less than 10 years ago.
3. Smoking history - >15 cigarettes a day for 25 years or >10 cigarettes a day for 30 years.

All recruited individuals in the LDCT arm underwent 4 rounds of screening with LDCT at baseline, After 1 year, 3 years and 5.5 years. Volumetric assessment of lung nodules was used instead of the Lung-RADS criteria used in NLST. Based on volume doubling time, lesions were considered positive, negative or indeterminate. After 10 years of follow up, a 26% reduction in mortality was seen in men and 39% in women. The number needed to screen was 130 over a 10 year follow up period.

Compared to the NLST and NELSON trial showed a reduced false positive rate at baseline (19.8%), due to the use of volumetric method to assess lung nodules, but this has been questioned in recent publications. The overdiagnosis rate was 19.7%, similar to NLST at 10-year follow up. The rate of adverse events was similar to NLST.

Various other trials from the West also demonstrated similar results, but none were shown to reduce mortality, except the MILD trial.[24]These trials have been summarized in Table 1.

c. Data from Asia and Rest of the World

As of today there is not enough data from the developing world to recommend LDCT screening in asymptomatic individuals.

However recent publication of the early results of the TALENT study (TALENT: Taiwan Lung Cancer Screening for Never Smoker Trial) from Taiwan has shown some promise.[25]This trial recruited 12011 patients between 2015 and 2019.

Selection criteria:

1. Never smoker
2. Age between 55-75 years
3. Having any one or more of the below listed risk factors-

- Positive family history (within 3rd degree relatives)
- Passive smoking exposure
- Past history of Tuberculosis/COPD
- Cooking index >110
- Not using ventilator during cooking

Early results showed that the T0 lung cancer detection rate was 2.6% which was much higher than the NLST (1.1%) or NELSON (0.9%). This data confirmed that LDCT was effective even in a never-smoker population, but longer follow up results are needed to see whether there is any reduction in mortality.

Korean Lung Cancer Screening Project (K-LUCAS) - Study conducted in South Korea, initial results are yet to be published. Study started recruiting in 2017. A total of 13692 participants have been recruited and are undergoing screening with LDCT. Preliminary radiological analysis showed a lung cancer detection rate of 0.6%. Long term survival reports and further analysis are awaited.[26]

Brazilian Lung Cancer Screening Trial (BRELT 1) - Pilot study to evaluate the feasibility of screening at major cancer centers in Brazil. 790 patients were recruited and underwent screening via LDCT. 12 participants (1.5%) were found to have early stage lung cancer. Further follow up studies are awaited.[27]

d. Data from India

1. Parang et al. - This pilot study from a private radiology centre in Mumbai, screened 350 smokers using LDCT. 93% were found to have lung nodules, out of which 2% were positive for lung cancer. The numbers from this study were too small to reach any solid conclusions.[28]
2. Singh N et al. - Pilot trial involving 250 participants at PGI, Chandigarh is currently recruiting and results are awaited. Anxiety questionnaires and cost-effectiveness are also being measured in this trial.[29]

Indian Perspective:

1. Lower incidence of smoking and lung cancer – When compared to western countries and also East Asian countries, most sites in India under the National Cancer Registry Programme NCRP report lung cancer incidence rates between 8-10 per 100,000 except Aizawl (Mizoram) which consistently reports incidence of >30 per 100,000.[3] Reported rates from US and China are respectively 74.5 and 94.5 per 100,000 population. [17]Screening is known to be more effective when the incidence is higher.
   - Data from TMH published by Noronha et al in 2012 showed that 52% of patients discussed in multidisciplinary joint clinics were non-smokers and only 6% were offered surgery.
2. Access to LDCT scan- The estimated number of CT scans available per million population in India is 3 (>14 in High Income countries) in 2008.[30] Even though this number is likely to have vastly improved in the previous decade, access is limited to major urban centres.
3. Overlap with Tuberculosis- Due to a higher incidence of Tuberculosis and significant overlap of clinico-radiological features of TB and Lung cancer. Any screening programme is likely to pick up more cases of tuberculosis than lung cancer.
   - In the K-LUCAS trial conducted in South Korea with 11,394 participants, 13% were detected to have post tubercular sequelae. On further statistical analysis it was seen that findings of tubercular sequelae reduced the specificity of the Lung CT Screening Reporting and Data System (Lung RADS) system by 5%, but sensitivity remained the same.[31]
   - In the BRELT 2 trial only 20 patients out of 3740 were found to have granulomatous diseases and this did not result in need for extra lung biopsies.

4. Availability of expertise- Even in the United States, less than 5% of eligible patients are been screened, due to lack of expertise and availability of LDCT.[32] Interpretation of LDCT requires experience and training. Further diagnostic tests and treatment require advanced interventional radiology and thoracic surgical services, which are not available even at tertiary care centres in India.

5. Cost-effectiveness- Computer aided modeling data from the United States show that it costs 49200 US dollars (41,00,000 INR) to the exchequer for every year of quality adjusted life year (QALY) gained via lung cancer screening.[33] The per capita expenditure for health care per person in India is around 65 US $(1800 INR). [34] The difference is astronomical and unlikely to change in the near future. In terms of health economics, screening at a national level supported by Government funds seems impossible in India.

3. CONCLUSIONS

Lung cancer screening with low dose CT scan (LDCT) has been conclusively proven to reduce mortality from lung cancer after publication of the NLST and NELSON trial. Guidelines from western countries have expanded the scope of lung cancer screening to include other high risk population groups (exposure to Radon, family history and lower smoking exposure).

But for widespread implementation of lung cancer screening various hurdles still exist in developing and developed countries. Cost-effectiveness even in developed countries with nationalized health systems are yet to be proven. Higher incidence of granulomatous diseases can affect results of LDCT screening.

At present, there seems to be a limited scope for lung cancer screening in India, as we have other more significant and pressing health related problems to tackle in the near future.
Accessibility, Affordability and Availability of expertise remain major challenges to be overcome in India, before widespread implementation of lung cancer screening.

Table 1: Landmark lung cancer screening trials

Abbreviated Name of Trial	Country of origin, date of publication	Number of participants in LDCT arm	% Reduction in mortality	Conclusions
NLST	USA, 2011, 2019	26722	20	LDCT is effective in reducing mortality
NELSON	Netherlands/Belgium 2020	7900	26	LDCT with volumetric analysis is effective in reducing mortality due to LC
DANTE	Italy, 2015	1264	0	Insufficient sample size
ITALUNG	Italy, 2017.	1613	30	LDCT is effective in reducing mortality
MILD	Italy, 2019.	2376	39	LDCT is effective in reducing mortality
LUSI	Germany, 2019.	2029	0	Underpowered study
DLCST	Denmark, 2016.	2052	0	Underpowered study

Abbreviation: NLST: National Lung Screening Trial.[23] NELSON: The Nederlands-Leuvens Longkanker Screenings Onderzoek.[19] DANTE: (Detection And screening of early lung cancer with Novel imaging Technology.[35] ITALUNG: Italian Lung Cancer Screening Trial.[36]MILD: The Multicentric Italian Lung Detection. [24]LUSI: The German Lung cancer Screening Intervention.[37] DLCST: Danish Lung Cancer Screening Trial.[38]

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Chapter 7

Colorectal Cancer

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Colorectal Cancer

Introduction

From a global perspective, colorectal cancer is the third most common cancer to be diagnosed but is second in terms of cancer related mortality.[1]As per the GLOBOCAN 2020 data, colorectal cancer is the fifth most common incident cancer in India with an overall age-standardized incidence rate of 4.8 per 100,000, with a slightly higher incidence for males (Males 6.0 / 100,000; Females 3.7/100,000).[2]Although this represents one of the lowest incidence rates in the world, the incidence has been steadily increasing, reflecting the changes in lifestyle and diet associated with socio-economic development.[3, 4]

Hereditary colorectal cancer including those associated with familial adenomatous polyposis (<1%), Hereditary non-polyposis colorectal cancer (2-5%), or MYH-gene associated polyposis (<1%) represent just 5% colorectal cancer cases.[5]A further 20-25% cases have strong familial association without a well-established genetic component.[6]As nearly 70-80% of colorectal cancer is sporadic, the role of environmental, diet and lifestyle factors perhaps play an important role in its etiology, forming the rationale towards primary prevention.

1. PRIMARY PREVENTION IN COLORECTAL CANCER

Primary prevention aims at reducing cancer risk through modifying environmental, and lifestyle risk factors as well as reducing risk through the use of chemopreventive drugs. Established risk factors for Colorectal Cancer (CRC) include cigarette smoking, obesity, excessive alcohol consumption and consumption of large amounts of red and processed meats.[7-10]Whereas physical activity, aspirin, hormone replacement therapy consumption of dairy products and whole grains, may have some protective influence on CRC risk.[10, 11-14]These risk factors are not only associated with CRC but with a number of other disease processes. Primary prevention for CRC therefore holds the potential for significant public health impact. Evidence for risk factors for CRC is largely from retrospective, case-control and cohort studies. While these studies help in quantifying cancer risk it is the results of intervention trials that validate primary prevention measures. In this section we will attempt to summarize the evidence of the various risk factors for colorectal cancer and subsequently briefly present the evidence from major published intervention trials.

Risk Factors for Colorectal Cancer

Non-modifiable risk factors for CRC include age, sex, family history and genetic predisposition. As primary prevention aims at reducing cancer risk by altering modifiable risk factors, only these will be considered in this section. The World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) Continuous Update Project Report; probably represents the most comprehensive source of scientific research on cancer risk associated with physical activity, body weight and dietary factors. There is convincing evidence that risk of CRC is significantly increased with the consumption of processed meats and alcohol, and increased body fatness, while physical activity reduces CRC risk. Evidence for the role of dietary fibres, wholegrains, dairy products, calcium supplements and red meat is strong but less convincing. The role of vitamin C, vitamin D, fish consumption, multivitamin supplements and the consumption of fruits, non-starchy vegetables and foods containing haem iron is still unclear as the evidence is limited.[15-17]Table 1 summarizes the findings of the WCRF/AICR 2018 revised report on colorectal cancer.

Table 1: Relative risks for risk factors for colorectal cancer – WCRF CUP 2018 revised report[15]

Factor	No. of Studies	No. of Cases	Indicators of risk	Relative risk (95% CI)
Risk Factors				
Red meat	8	6662	Per 100gm/day	1.12 (1.00-1.25)
Processed meat	10	10738	Per 50gm/day	1.16 (1.08-1.26)
Foods containing haem iron	6	6070	Per 1mg/day increment	1.04 (0.98 – 1.10)
Alcohol	16	15896	per 10gm ethanol/day	1.07 (1.05-1.08)
Body fatness	38	71089	Per 5kg/m^2	1.05 (1.03-1.07)
Adult height attained	13	65880	Per 5cm increase	1.05 (1.02-1.07)
Protective factors				
Whole grains	6	8320	Per 90gm/day	0.83 (0.78-0.89)
Foods containing dietary fibres	21	16,562	Per 10gm/day	0.93 (0.87-1.00)
Non-starchy vegetables	11	14,136	Per 100g/day	0.98 (0.96-0.99)
Fruits	13	16,355	Per 100gm/day	0.96 (0.93 – 1.00)
Foods containing vitamin C (Colon cancer)	6	4391	Per 40mg/day	0.94 (0.89-0.99)
Fish	11	10356	Per 100gm/day	0.89 (0.80-0.99)
Dairy Products – Milk	9	10738	Per 200gm/day	0.94 (0.92-0.96)
Cheese	7	6462	Per 50gm/day	0.94 (0.87-1.02)
Dietary Calcium	13	11519	Per 200mg/day	0.94 (0.93-0.96)
Calcium supplements	1 RCT	36,282	1000mg Calcium 400IU vitamin D Vs placebo	0.81 (0.58-1.13)* (16)
Foods containing Vitamin D	10	5171	Per 100IU / day	0.95 (0.93-0.98)
Vitamin D Supplements	2	415	Per 100IU/day	0.93 (0.88-0.98)
Multivitamin Supplements	1 RCT	210	Vitamin E (400IU) + Vitamin C (500mg) + beta-carotene (50mg) Vs placebo	0.89 (0.68-1.17) (17)
Total Physical activity (colon cancer)	12	8396	Highest Vs Lowest	0.80 (0.72-0.88)
Recreational physical activity	20	10258	Highest Vs Lowest	0.84 (0.78-0.91)

* Excluding women using supplements at baseline; RCT – Randomized Controlled Trial

Metabolic Syndrome and Colorectal Cancer

Metabolic syndrome comprises of a combination of a number of metabolic disorders including obesity, hypertension, hyperglycemia and hyperlipidemia.[18, 19] Although this syndrome is associated with a number of disorders like Type 2 diabetes, cardiovascular disease and coronary artery disease, a number of recent systematic reviews and meta-analyses have demonstrated an increased risk of CRC associated with the metabolic syndrome.[20-22] The

prevalence of metabolic syndrome among adult Indians is 30% with a higher incidence in the urban areas compared to the rural population.[23] Metabolic syndrome has also been shown to be associated with an increased incidence of early onset CRC (i.e. before 50yrs).[24] The more the number of metabolic disorders in the syndrome, the higher the CRC risk.[20, 21, 24-26] Outcomes in terms of cancer specific mortality and all-cause mortality are also negatively influenced by the metabolic syndrome. Identifying the metabolic syndrome and initiating measures through lifestyle modification and medication to control it would therefore serve as an important aspect of primary prevention for CRC.[22, 26]

Smoking and Colorectal cancer

Cigarette smoking has been known to be associated with an increased risk of a number of cancers including lung, cancers of the upper aero-digestive tract, bladder, kidney, cervix and pancreas. However, the causative association of tobacco smoking and CRC was only established in 2009 by the International Agency for Research on Cancer (IARC).[27]In a comprehensive meta-analysis of 188 case-control and cohort studies with a total of 3,83,154 CRC cases, Botteri et al., clearly defined the pooled relative risk (RR) of tobacco smoking in CRC (Table 2). The authors also demonstrated a linear increase in CRC risk with the intensity of smoking. With 20 cigarettes/ day the RR was 1.14 (95% CI 1.06–1.23), increasing to 1.31 (95% CI 1.12–1.52) with 40 cigarettes/day. The duration of smoking also demonstrated a similar linear pattern of increased risk [20 years - RR 1.09 (95% CI 1.04–1.15); 40 years - RR 1.20 (95% CI 1.09–1.32)]. The duration and intensity of smoking represented by pack-years expectedly also showed a linear increase in RR [20 pack years – RR 1.10 (95% CI 1.05–1.14); 40 pack years - RR 1.20 (95% CI 1.05–1.31). The causal association of smoking and colorectal cancer was demonstrated by the fact that cessation of smoking decreased CRC risk, but this was only seen 10 years after stopping smoking. At 26 years of stopping smoking the risk in former smokers was less than current smokers.[7]

Table 2: Pooled relative risk tobacco smoking in CRC[7]

Comparison	Pooled Relative Risk (95% CI)
Colorectal cancer	
Current Vs Never smokers	1.14 (1.10-1.18)
Former Vs Never smokers	1.17 (1.15-1.20)
Ever Vs Never smokers	1.18 (1.15-1.22)
Colon cancer	
Current Vs Never smokers	1.05 (0.99-1.10)
Former Vs Never smokers	1.15 (1.11-1.19)
Ever Vs Never smokers	1.11 (1.07-1.15)
Rectal cancer	
Current Vs Never smokers	1.16 (1.09-1.23)
Former Vs Never smokers	1.17 (1.12-1.22)
Ever Vs Never smokers	1.15 (1.10-1.22)

Aspirin and Colorectal Cancer

Amongst all chemopreventive agents for CRC, aspirin (acetylsalicylic acid) is probably supported by the most robust data. It is an irreversible blocker of cyclooxygenase (COX) 1 and COX 2.[28]Aspirin exerts its chemopreventive action by inhibiting a number of pathways including prostaglandin synthesis, platelet activation, Wnt signaling and inflammation. The first reported association of aspirin with decreased CRC risk was in 1988, where the incidence of CRC was lower in individuals taking aspirin containing medications.[29]Since then, there have been a number of large trials evaluating the chemopreventive action of aspirin in different patient risk groups, with different end points. Table 3, summarises the randomized controlled trials (RCT) for aspirin in CRC. A major concern with long term aspirin use has been that of gastrointestinal bleeding, which may be increased by as much as 58% and the risk of intracranial haemorrhage which may be as high as 27%.[30-32] This has prevented its universal recommendation as a chemopreventive agent in CRC. In 2016, the United States Preventive Services Task Force (USPSTF) "recommended low dose aspirin for the primary prevention of cardiovascular disease and colorectal cancer in persons who are 50-59yrs of age, have a 10% or greater 10-year cardiovascular risk, who are not at an increased risk of bleeding, have a life expectancy of at least 10 years and are willing to take daily low-dose aspirin for at least 10 years".[33]This was a Grade B recommendation indicating that the net benefit was moderate. The task force estimated the benefit of aspirin to be less in the 60-69 year age group, and suggested that the decision for aspirin to be made on an individual basis in this patient group. These recommendations were based on two systematic reviews on primary prevention trials on aspirin commissioned by the USPSTF. The systematic review by

Guirguis-Blake et al., showed that the risk of non-fatal myocardial infarction and non-fatal stroke was reduced by 22% and 14% respectively, while Chubak et al., showed that the mortality of CRC was reduced by 33% at 20years and the incidence of CRC by 40%, beginning 10-19years after aspirin initiation.[34, 35]

Table 3: RCT for Aspirin in CRC prevention

Study	Recruitment	Participants	Study details	Results
End point – CRC incidence				
British Doctors Aspirin Trial[36]	1978-1979	5139 Male UK Doctors born on or after 1900	500mg Aspirin daily, No placebo, Randomized 2:1	Significant decrease in the incidence of CRC HR 0.70 (0.51-0.97)
UK- TIA Trial[36]	1979-1985	2449 >40yrs, TIA or minor ischemic stroke within 3 months	300mg / 1200mg / Placebo	No decrease in CRC incidence HR 0.82 (0.49-1.38)
Physicians Health Study[37, 38]	1982-1988	22071 U.S Male physicians	325mg alternate day Vs Placebo Study terminated after 5 year follow up	No decrease in CRC or polyp risk CRC RR 1.15 (0.80-1.65) Polyp RR 0.86 (0.68-1.10) No decreased risk after 12 years follow up
SALT[39]	1984-1989	1360 1-4 months after TIA/minor ischemic stroke	75mg daily Vs placebo	No decrease in CRC incidence OR 0.71 (0.27-1.86)
Thrombosis prevention trial[39]	1989-1992	5085 45-69yr, men at increased risk of vascular events	75mg daily Vs Placebo	Significant decrease in CRC incidence OR 0.61 (0.40-0.94)
Women's Health Study[40, 41]	1992-2004	39876 Women ≥ 45yrs	100mg alternate day Vs placebo	During the trial – no decrease in CRC risk RR 0.97 (0.77-1.24). After 10 years follow up – significant decrease in CRC incidence HR 0.58 (0.42-0.80)
CAPP 2[42-44]	1999-2007	861 Lynch syndrome ≥ 25yrs	2x2 factorial Aspirin 600mg/day Resistant starch 30gm/day	Initial post-trial analysis – no difference in Adenoma/CRC risk RR 1.0 (0.7-1.4) 55.7 month follow up (in participants completing 2 years of aspirin) reduced CRC incidence HR 0.41 (0.19-0.86) 10 year follow up – ITT analysis showed a significant decreased CRC risk HR 0.65 (0.43-0.97)

Study	Recruitment	Participants	Study details	Results
ASPREE[45]	2010-201	19114 ≥ 70 yrs (≥ 65yrs for Hispanics/blacks)	100mg/day Vs Placebo	Increased risk of CRC in aspirin users. HR 1.77 (1.02-3.06)
End point – Adenoma incidence				
CALGB[46]	1993-2000	517 30-80yr, CRC with curative resection	325mg/day Vs Placebo	Aspirin decreased adenoma risk RR 0.65 (0.46-0.91). The time to the detection of a first adenoma was longer in the aspirin group than in the placebo group HR 0.64 (0.43-0.94)
CAPP1[47]	1993 -2003	133 10-21 yrs, FAP with no prior colectomy	2x2 factorial design Aspirin 600mg/day Resistant starch 30gm/day	Aspirin did not significantly reduce polyp count [RR 0.81 (0.54-1.10)]
APACC[48, 49]	1996-2001	238 (1year), 185 4 years), 18-75yr with history of prior colonic adenoma	160 or 300mg/day	After 1 year aspirin users had lower incidence of having ≥ 3 adenomas [RR 0.30 (0.10-0.89)] and decreased risk of having adenoma > 5mm [RR 0.44 (0.24-0.82)] No decreased adenoma risk at 4 years.
UKCAP[50]	1997-2005	853 <75yrs, history of adenoma ≥ 0.5cm removed in prior 6 months	Aspirin 300mg/day	Aspirin reduced the risk of recurrent and advanced adenoma Recurrent adenoma [RR 0.79 (0.63-0.99)] Advanced adenoma [RR 0.63 (0.43-0.91)]
J-CAPP[51]	2007-2009	311 40-60yr, prior endoscopically removed adenoma / CRC	100mg/day	Aspirin reduced adenoma and CRC risk [OR 0.6 (0.36-0.98)] Risk was reduced in non-smokers [OR 0.37 (0.21-0.68)] Increased risk in smokers [OR 3.45 (1.12-10.64)]

J-CAPP – Japanese Colorectal Aspirin Polyps Prevention, ASPREE - Aspirin in Reducing Events in the Elderly

CALGB – Cancer and leukemia group B, TIA – Transient Ischemic attack. SALT – Swedish Aspirin Low Dose Trial

CAPP 2 – Colorectal Adenoma/Carcinoma prevention programme 2, APACC - Association pour la Pre´vention par l'Aspirine du Cancer Colorectal

Role of Non-aspirin Non-Steroidal Anti-inflammatory Drugs (NSAIDS)

Non-aspirin NSAIDS act in a similar way to aspirin by inhibiting COX1 and COX2, however unlike aspirin they exert their action via reversible competitive inhibition. A number of early case-control studies offered some evidence of the efficacy of non-aspirin NSAIDS in

reducing CRC and adenoma risk.[52-54]The role of Sulindac in familial adenomatous polyposis has been evaluated in a RCT. This double-blind, placebo-controlled, trial randomised 41 patients with genotypically confirmed FAP (but phenotypically unaffected), to receive either 75mg or 150mg sulindac orally twice a day for 4 years. The number and size of polyps were evaluated every four months. At the end of 4 years, even with the rate of compliance in the sunlidac group exceeding 76%, there was no difference in the number and size of polyps between the groups.[55]The role of selective COX2 inhibitors have also been evaluated in a number of randomized controlled trials. Both celecoxib and rofecoxib have been shown to be effective in significantly decreasing adenoma risk.[56-59] However, on account of the associated cardiovascular side effects they cannot be recommended as chemopreventive agents.

Conclusion – Primary prevention

There is convincing evidence that physical activity protects against CRC whereas processed meat, alcohol, and obesity increases the risk for CRC. The role of dietary fibers, wholegrains, dairy products, calcium supplements and red meat as protective factors against CRC is strong but less convincing. There is limited evidence for the role of Vitamin D, Vitamin C, multivitamin supplements, and consumption of fish, non-starchy vegetables, fruits and haem-iron containing foods. Due to the increased risk of CRC associated with the metabolic syndrome, measure to control hyperglycemia, hypertension and hyperlipidemia may decrease CRC risk. Aspirin is recommended for chemoprevention for CRC in a very select patient population.

2. SCREENING AND SURVEILLANCE FOR COLORECTAL CANCER-STRATEGIES FOR SECONDARY PREVENTION

Each year, over 1.4 million new cases of CRC are diagnosed and it is the third most common type of cancer in males and second in females.[60]While CRC has been predominantly seen in Western countries, India shows an increasing trend in the incidence of CRC with an over 20% rise in a decade between 2004 -2014.[61] Rectum is the predominant location for CRC in India.[62]CRC is a "screenable" cancer and screening has accounted for reduction in incidence and mortality related to CRC since 1985 in the United States.[63]Since most CRCs develop via"adenoma-carcinoma" sequence, removing precursor lesions can help prevent cancer while also identifying cancer in its earliest, curable stages. About 70% of all sporadic CRCs arise from adenomatous polyps, while about 30% from sessile serrated lesions (SSLs).[64]Since patients with these conditions are usually asymptomatic at their initial stages, screening is

carried out to identify these lesions before they progress to develop CRC and develop symptoms. The goal of screening is also to reduce cancer-specific morbidity and mortality by removal of adenomatous polyps at an early stage.

Risk factors for colorectal cancer

Non modifiable risk factors are estimated to be seen in 30 % of the patients with CRC which include family or personal history of advanced adenoma or colorectal cancer, history of inflammatory bowel disease, and history of hereditary polyposis syndromes. On the other hand, obesity, inactivity, smoking, and binge drinking are all modifiable risk factors .[65]Based on these risk factors, patients are stratified into 3 groups according to the risk of developing colorectal cancer into average risk, increase risk, and high-risk categories (Table 4).

A. **Age:** As age progresses, so does incidence of CRC, with exponential rise after age of 50 years.[66]Hence guidelines for average risk screening recommend starting after age 50.[67]

B. **Family History:** About 20% of patients with CRC have a positive family history.[68]The relative risk of CRC was found to be 2.3 with an afflicted first-degree relative, 3.9 if the relative was diagnosed before age 45, and 4.2 if more than one relative was affected.[69]In patients with family members having advanced adenomas, there is an increased likelihood of developing CRC before age 60.[70]

C. **Diet:** CRC development has also been attributed to diets that are poor in fibres and rich in red meat and fat.

D. **Drugs:** NSAIDs like Aspirin, Calcium and Hormone replacement therapy is known to reduce risk of CRC.[69, 70]Hence the United States Preventive Services Task Force (USPSTF) recommends (Grade B) initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased bleeding risk, have at least a 10-year life expectancy, and are committed to taking low-dose aspirin daily for at least 10 years.[67]

Table 4: Risk stratification for screening

Persons at Average risk for CRC	**Individuals ≥ 50 years of age with:** - No family history of colorectal neoplasia (adenoma, cancer) - No personal history of adenoma or CRC - No personal history of IBD
Persons at Increased Risk for CRC	Personal history of CRC Personal history of adenoma Family history of sporadic CRC Family history of sporadic adenoma
Persons at high risk for CRC	HNPCC/ Lynch syndrome Polyposis syndromes: - Familial adenomatous polyposis (FAP) - Attenuated FAP - MYH-associated polyposis - Peutz-Jeghers syndrome - Turcot's syndrome - Muir-Torre syndrome - Juvenile polyposis syndrome - Hyperplastic polyposis syndrome - IBD (UC, Crohn's disease)

Screening strategies and approach

Detection of disease in its early stages with early management has been the key focus of screening in colorectal cancer, which is a step towards secondary prevention. Identifying the patient's level of risk for CRC is critical as screening and follow up is based on the same. Availability of resources and Patient & Provider preferences often govern choice of tests for screening. Fecal tests have been standard diagnostic tests for early cancer detection. These tests are simple to carry out, repeatable with high compliance at regular intervals, and capable of being further verified when colonoscopy resources are available to explore positive results. Fecal tests often need confirmation with colonoscopy, whose quality often affects outcomes of screening. Adenomatous polyps with advanced stages can be found with several screening techniques, including colonoscopy, sigmoidoscopy, CT colonography, and to a lesser degree stool-based testing, but colonoscopy is the best method for finding SSLs. The majority of recommendations concur that CRC screening is advised for those with average risk starting at

age 45 and should be a part of a systematic framework that guarantees that tests are performed at specified intervals and those positive tests are promptly followed up (Table 5& 6).

Table 5: Recommendations from different societies for average risk individuals

Organization	Screening test and interval	Patient's age
U.S. Preventive Services Task Force (2021)[67]	High-sensitivity guaiac fecal occult blood test (HSgFOBT) or fecal immunochemical test (FIT) every year Stool DNA-FIT every 1 to 3 years Computed tomography colonography every 5 years Flexible sigmoidoscopy every 5 years Flexible sigmoidoscopy every 10 years + annual FIT Colonoscopy screening every 10 years Selectively screen adults aged 76 to 85 years :- Discuss together with patients the decision to screen, taking into consideration the patient's overall health status (life expectancy, comorbid conditions), prior screening history, and preferences.	Start at 50 years; individualize after 75 years Suggests 45-49 years
American College of Gastroenterology (2021) [71]	Preferred Colonoscopy every 10 years' Fecal immunochemical test annually (if colonoscopy is declined) Alternative, prevention Multitarget stool DNA test every 3 years, Flexible sigmoidoscopy every 5 to 10 years, Computed tomography colonography or colon capsule every 5 years. Alternative, cancer detection High-sensitivity FOBT annually Stool DNA test every	Recommended 50 and 75 years Suggested 45-49 years Beyond 75 years to be individualized

Organization	Screening test and interval	Patient's age
	3 years	
American Cancer Society (2019)[72]	Flexible sigmoidoscopy every 5 years Colonoscopy every 10 years Computed tomography colonography every 5 years Tests that primarily detect cancer Highly sensitive fecal immunochemical test (FIT) every year Highly sensitive guaiac-based fecal occult blood test (gFOBT) every year Multi-targeted stool DNA test (mt-sDNA) every 3 years	Start at 45 years of Age People who are in good health and with a life expectancy of more than 10 years should continue regular colorectal cancer screening through the age of 75. For people ages 76 through 85, the decision to be screened should be based on a person's preferences, life expectancy, overall health, and prior screening history. People over 85 years should no longer be screened.
U.S. Multi-Society Task Force (2017)[73]	**Tier 1** Colonoscopy every 10 years Annual faecal immunochemical test **Tier 2** CT colonography every 5 years FIT-fecal DNA every 3 years' Flexible sigmoidoscopy every 10 years (or every 5 years) **Tier 3** Capsule colonoscopy every 5 years. Available tests not currently recommended Septin 9	Start at 45 years of Age

Table 6: Screening for high risk individual

Persons at Increased Risk	Recommendation	Patient's age
CRC or adenomatous polyps in a first-degree relative ≥ 60 years or in two second-degree relatives with CRC	Intervals as per average-risk screening recommendations	Age 40 years
CRC or adenomatous polyps in a first-degree relative before 60 years or in two or more first-degree relatives at any age	Colonoscopy every 5 years	Age 40 years, or 10 years before the youngest case in the family
Personal history of resected CRC	High-quality perioperative clearing, followed by colonoscopy 1 year after resection. If negative, repeat in 3 years. If 3-year examination is negative, repeat in 5 years and at 5-year intervals thereafter. Local surveillance can be considered for rectal cancer resected without total mesorectal excision.	
One or two small tubular adenomas	Colonoscopy after 5–10 years	
Three to ten adenomas or one adenoma ≥ 1 cm or any adenoma with villous features or high-grade dysplasia	Colonoscopy after 3 years.	
More than 10 adenomas	Colonoscopy after < 3 years	
Piecemeal resection of sessile adenoma	Colonoscopy after 2–6 months.	

Patients at High Risk	Recommendation	Patient's Age
FAP	Annual sigmoidoscopy and counselling to consider genetic testing for APC mutations. Colectomy should be considered if FAP is confirmed by genetic testing.	10–12 years
Lynch Syndrome	Colonoscopy every 1–2 years. Genetic counselling to consider testing for MMR mutations. Screening for extracolonic cancers	Age 20 to 25 years or 10 years before the youngest case in the immediate family
Chronic ulcerative colitis or Crohn's colitis	Colonoscopy every 1–2 years. Screening for dysplasia using chromoendoscopy with targeted biopsies, or random biopsies.	8 years after the onset of pancolitis or 12–15 years after the onset of left-sided colitis

Screening methods

1. FOBT (Fecal occult blood test)

These are easy to perform card tests impregnated with alpha-guaiaconic acid. Addition of a hydrogen peroxide developing solution is done for FOBT.[74]The presence of heme in a stool sample turns the card bluish-green signifying a positive result. Since the amount of heme in stool often dictates sensitivity, three different samples are often tested. Follow up with yearly testing is advised. FOBTs have shown benefit in detecting cancer at an earlier stage and also helping reduce mortality by 15-33%when positive tests are followed up with colonoscopy for confirmation.[75]Issue commonly faced with FOBT is that of false positive tests especially with various food products and also medications.

2. FIT (Fecal immunochemical test)

Unlike FOBT, FIT is based on globin present in stool and not heme. Tagged antibodies on a card are used in the faecal immunochemical test (FIT), which binds exclusively to human haemoglobin. Because globin (instead of heme) is metabolized in the small intestine, FIT performance is unaffected by erosions or stomach ulcerations brought on by prolonged NSAID or aspirin usage. FITs are generally quantitative, but depending on a predetermined cut off, they can be created to signal a positive test. The specificity of FIT was 95% in one study at a threshold of 20 Hg/g faeces.[76, 77]Considering the absence of any dietary precautions, unlike FOBT, FIT is associated with higher compliance. FIT also shown a high sensitivity for CRC (>80%). [78]However, because SSPs tend to be less vascular than ordinary adenomas and are less prone to haemorrhage, the sensitivity of FIT for advanced adenomas (23.8%) is lower than it is for CRC.[74, 79]

3. Fecal DNA

Fecal DNA (fDNA) is used for CRC screening based on the fact that patients with CRC excrete tumor cells and DNA in their stools.[80]fDNA test is intended to identify anomalies in various loci of chromosomal instability (k-ras, APC, and p53), BAT-26 (a measure of MSI), and DIA (DNA Integrity Assay), which are marker for defective apoptosis. Sensitivity for CRC detection is only modest (51.6%). However, addition of the hypermethylated vimentin gene and techniques to counteract the impact of bacterial enzymes increases its sensitivity further.[81]In a study, almost 10,000 individuals who underwent a full screening colonoscopy

(n = 9989) were compared to the fDNA test and the FIT. The fDNA test has a greater sensitivity for CRC than the FIT (92.3% vs. 73.8%).[79]

4. Sigmoidoscopy

Given its cost-effectiveness and reduced risk of complications than colonoscopy, sigmoidoscopy is a desirable alternative for preventing distal CRC. The effectiveness of sigmoidoscopy for CRC screening is now confirmed by RCT that demonstrates appreciable levels of CRC protection. A single sigmoidoscopy check can reduce the risk of CRC death for more than 10 years.[82]However; indirect comparisons of findings from observational studies suggest that there is a 40% to 60% lower risk of CRC incidence and mortality after screening colonoscopy, even though risk reduction was statistically significant for deaths from cancer of the proximal colon only. No RCTs comparing colonoscopy with sigmoidoscopy have been performed. No guidelines recommend sigmoidoscopy as primary screening strategy over colonoscopy.

5. Colonoscopy

Colonoscopy represents a single stop solution where in polyps can be screened for and removed and cancer can be sampled during screening. Considering that colonoscopy is often less frequently required with better acceptance and tolerability of contemporary sedation procedures, patient compliance tends to be better. Patients with average risk who have negative screening colonoscopy findings experience a decreased incidence of CRC over long-term follow-up that lasts more than 10 years.[83]

6. Computed Tomography Colonography (CTC)

Using computed tomography (CT), CTC creates two- or three-dimensional pictures of the large bowel which is evaluated by a radiologist for the detection of polyps that appear as protruding lesions into the colonic lumen. Similar to a traditional colonoscopy, the procedure entails the patient using a purgative to clear their large intestine. In order to identify feces the bowel routine also requires ingesting a tagging solution that contains barium sulphate. After that, the patient goes through a procedure akin to a CT scan in which a tube put into the rectum is used to insufflate the large bowel with air or CO2. This is similar to the double contrast barium enema. However, any abnormalities found on CTC require confirmation using colonoscopy. The absence of anesthesia requirements and the effective detection of large lesions (> 1 cm) are two potential benefits of CTC. A previous study with over 2500

participants showed high sensitivity of 90% for the detection of polyps larger than 1 cm. Another study approximately 80 % sensitivity for the detection of polyps ≥6 mm in size.[84, 85]A low complication rate of 0.03% and lesser apprehension with lower invasiveness of the procedure as compared to standard colonoscopy are the reasons for compliance towards CTC. However, the creation of a noncathartic preparation regimen may further increase compliance towards CTC.

Surveillance

Surveillance intervals should be established based on evidence that interval examinations lower cancer-related mortality and prevent metachronous CRC. The onset of metachronous cancer is now heralded by advanced adenomas as a stand-in marker. The key tenets of the current recommendation include the idea that the baseline colonoscopy is of high quality, with good bowel preparation, and is able to risk stratify as per the findings. According to the USMSTF recommendations there are two main risk categories for adenomas: low-risk adenomas (1-2 tubular adenomas of size < 10 mm) and high-risk adenomas (adenomas with villous histology and high-grade dysplasia of size > 10 mm, or 3 or more adenomas).[86] As opposed to this, the British Society of Gastroenterology divides patients into three risk categories: low risk (1-2 adenomas of 10 mm size), intermediate risk (3-4 small adenomas or one adenoma of > 10 mm in size), and high risk (≥ 5 small adenomas or ≥ 3 adenoma with at least one ≥ 10 mm in size).[87] They also recommended high-risk group to undergo surveillance at 1 year due to concerns about missed lesions at baseline (Table 7). Patients with resected CRC are at a higher risk and need a more aggressive treatment plan. The USMSTF has released new guidelines that advise monitoring after one year, followed by colonoscopies at three and five-year intervals, in addition to high-quality perioperative clearing colonoscopy.[86]

Table 7: Surveillance intervals based on findings

Colonoscopy Finding	Recommended surveillance interval in Average risk individual
No polyps	10 Years
Small rectal or sigmoid hyperplastic polyps	10 Years
1–2 small tubular adenomas	5- 10 Years
3–10 tubular adenomas	3 Years
> 10 adenomas	<3 Years
Villous adenoma or adenoma with high-grade dysplasia	3 Years
Small SSP without dysplasia	5 Years
SSP ≥ 10 mm, or SSP with dysplasia, or TSA	3 Years
Serrated polyposis syndrome	1 Years

Medications used for secondary prevention

Aspirin and other NSAIDs are known to be protective against development of polyps. In the setting of secondary prevention, Aspirin is known to be protective with better CRC specific survival rates and also overall survival.[88]However there is lack of data from randomised control trials in this setting. Data on other medical therapies for secondary prevention is limited with no drugs showing any promise.

Conclusion

Screening and surveillance are strategies of secondary and tertiary prevention respectively which remain integral to reducing mortality associated with CRC. While there is debate on whether screening is indicated in the Indian population, high risk candidates deserve evaluation for CRC with a cafeteria choice (both invasive and non-invasive) of investigations available to individuals at their disposal.

3. SCREENING IN COLORECTAL CANCER- FEASIBILITY AND IMPLEMENTATION IN INDIA

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the world and is also one of the few cancers for which most guidelines endorse a population-based screening programme. Guidelines recommending screening for colorectal cancer find widespread acceptance since most colorectal malignancies progress over a long latent period, of at least 10 years, from adenomatous polyps to malignancy. India does not recommend for population-based screening for CRC as most published guidelines are largely meant for a western population, in whom both the incidence and presentation of colorectal cancers are vastly different than in the Indian population. As per the GLOBOCAN 2020 data, the Age-standardized incidence rate of CRC in India is 5.5 per 100,000 as opposed to >25 in Europe and North America.[1]While CRC does not appear to be a major health problem in India at first glance, the incidence of CRC in India appears to be rising, as opposed to the rates in western countries which have shown a steady decline in both incidence and mortality of CRC over the past 5 decades.[89, 90]This is despite the problem of underreporting in India, where the population registries cover less than 8% of the population as opposed to worldwide registries that cover more than 20% of the population.[91] The presentation of CRC is different in India with a much larger percentage of advanced and metastatic cases at presentation and with poorer oncological outcomes as compared to the West.[62]

Healthcare allocation has never been perceived as a an important area for budgetary allocation with government healthcare expenditure in India being 3% of the GDP, the 13th lowest in the world, as opposed to an average of 18% in most high-income countries and around half of the total health expenditure in India is out-of-pocket-expenditure .[92, 93]Further, the distribution of healthcare facilities is mostly concentrated in larger towns and cities with rural areas having poor access to healthcare. Costly screening tests, need for follow up tests and frequent screening intervals are not practical in India.

Unfortunately, all noninvasive CRC tests require confirmation by colonoscopy, something that simply is not practical in India. All available screening modalities are resource intensive and require trained personnel to perform. The cost-benefit ratio of a CRC screening programme was never felt to be favorable enough to justify large-scale screening in India, which not only has a lower incidence of CRC, and a broad-based population pyramid with

>90% of the population being younger than 50 years, in whom a screening test is likely to have little benefit. However, guidelines for screening in India and opportunistic screening are the need of the day to stem the rising incidence of CRC in India.

Currently available screening modalities

Table 8: Summary of available tests

Test	Availability	Key points
Stool based tests		1. Noninvasive and less cumbersome, leading to better patient adherence. 2. No bowel preparation or dietary/medication restriction needed 3. Less sensitive and specific than imaging/colonoscopy. 4. Positive test needs confirmation by colonoscopy.
• Fecal Imunochemical testing (FIT)[94]	Available in India. Can be sent through mail for mass screening	1. Detects human Hb in stool. 2. Test requires single stool sample 3. Covered by all guidelines. 4. Reducing cut off from FDA recommended 20 µg/g to 10 µg/g increased sensitivity to>90% but decreases specificity to 90%. 5. Recommended frequency- i. Annually by US/Korean/Japanese guidelines ii. Biennial by European/Taiwanese guidelines.
• Multitarget stool DNA testing (FIT-DNA)	Not available in India	1. Detects methylated DNA markers+ feacal Hb. 2. Complex stool sample collection procedure. 3. Higher sensitivity than FIT but lower specificity 4. Approved for use only within the US.
• Guaiac based fecal occult blood (gFOBT)	Widely available, cheap	1. Requires 3 stool samples. 2. Based on non-specific peroxide reaction→ high number of false positives due to

Test	Availability	Key points
		diet/medications. 3. Largely replaced by FIT in most guidelines due to poor specificity.
Blood based tests	Not available in India	1. Not recommended by any major guidelines. 2. Most newer tests based on circulating and cell free DNA. 3. mSEPT9 a tumor suppressor gene mutated in CRC is only blood based test approved by the FDA
Direct visualization tests	• Widely available • Requires experienced personnel to perform	1. Invasive tests require prior bowel preparation and dietary modification. 2. Significant patient discomfort may require anesthesia/sedation. 3. Gold standard test for CRC, allows for tissue diagnosis and even removal of polyps. 4. Advanced endoscopic techniques (NBI/Chromoendoscopy) enhance sensitivity. 5. Recommended screening modality in high risk populations
• Colonoscopy	Widely available but resource intensive	1. Adherence is low due to financial and psychosocial barriers→most guidelines recommend colonoscopy as part of a two-stage screening cascade except in the US where it is the most commonly used modality of screening.[95] 2. Definite evidence of cancer mortality reduction-29-68% derived from multiple cohort studies and RCTs. [96-100] 3. NordICC study[101]- Largest and only pragmatic RCT highlights i. poor patient compliance of 42% ii. benefit may be overestimated- relative risk reduction 18% 4. Recommended frequency- every 10 years(in average risk

Test	Availability	Key points
		population)
• Flexible sigmoidoscopy	Widely available, less resource intensive	1. Complete bowel preparation not needed, can be done without sedation/ anesthesia. 2. RCTs show mortality benefit of one-time sigmoidoscopy of 22-33%[82, 102] 3. Lack of visualization of proximal bowel is the major drawback, not recommended a standalone modality by any guideline.
• Capsule colonoscopy	Available in select centres in India	1. Wireless swallowed camera that gets activated in terminal ileum, taking pictures of colonic mucosa. 2. Outperforms CT colonoscopy in average risk screening with 88% sensitivity and 82% specificity.[103, 104] 3. Less reliable for detection of sessile serrated polyps. 4. Requires more extensive bowel preparation than colonoscopy, may needs prokinetic agents. 5. Difficult to swallow, delayed transit time can cause incomplete examination due to limited battery life of capsule. 6. Only recommended by American guidelines – every 5 years
• CT colonoscopy	Available in many centres across India	1. Less invasive, no need for sedation, fewer complications but requires same degree of bowel preparation as video colonoscopy. 2. Disadvantages i. Radiation exposure ii. Incidental findings in up-to 66% of patients, often leading to additional procedures.[105] iii. Requires trained radiologist to interpret. 3. Only recommended by American guidelines- every 5 years.

Table 9: Sensitivity and specificity of available screening modalities for CRC[106]

	Colonoscopy (10 yearly)	**FIT** (yearly)	**CT Colonoscopy** (5 yearly)	**Sigmoidoscopy** (5 yearly)	**gFOBT** (yearly)	**FIT-DNA** (yearly)
Sensitivity (Adenoma>10mm)	95%	23.8%	84%	Similar to colonoscopy for segment of colon visualized.	23.9%	42.4%
Sensitivity CRC	95%	73.8%	84%		70%	92.3%
Specificity	86%	96.4%	88%	87%	92.5%	89.8%
CRC deaths averted per 1000*	22-24	20-23	16-24	16-21	20-23	21-24

*Assumes screening from ages 50 to 75 years, including 100% adherence, complete follow-up without delay, and appropriate surveillance

Novel CRC tests under development

Test	Marker	Ongoing trial/considerations
Stool/blood based	Various stool/serum biomarkers	NCT00843375- currently recruiting, estimated completion- March 2023
Blood based **1. Freenome** **2. Guardant** **3. CancerSEEK** **4. GRAIL**[#]	**cfDNA+ AI** ctDNA ctDNA for 8 common cancers multicancer detection test	**PREEMPT trial ongoing** ECLIPSE trial ongoing NCT04213326 ongoing PATHFINDER ongoing
Image based **1. MR colonography** **2. CT capsule**	Like CT colonoscopy, no radiation x-ray imaging capsule, combination of capsule and CT colonoscopy	Requires bowel distention +preparation No bowel preparation needed

The Indian scenario

Lack of awareness of cancer, poor access to healthcare services and lack of government funding makes the implementation of a population-based screening programme challenging in a country like India. While the rates of colorectal cancer are declining in most of the Western world, India has seen an increase in the incidence of CRC by over 20% in the past 15 years, with a larger proportion of advanced and metastatic disease as compared to the West.[62, 107] Also, there appear to be a few problems unique to India, where the population demographic is young, the median age of CRC presentation is almost a decade younger than in the West, with a higher incidence of left sided cancers.[62, 108]The lack of a low cost

screening modality is the main barrier to the implementation to widespread screening in India. While stool based tests have the advantage of remote testing by transporting stool samples to test centre, they are limited by the need for a confirmatory colonoscopy, and a two-stage screening programme is not likely to be successfully implemented. The social and financial implications of screening also need to be considered in a country where a 69% of the population struggles with financial insecurity, convincing otherwise healthy people to spend money on costly, invasive tests to prevent a cancer years' in the future is not going to be met with success.[109]

Screening for CRC is not feasible at a national level, and is unlikely to be funded by any National programme, with policy makers arguing that public funds may be better spent than on a population based screening for what is perceived to be a low incidence disease. However, opportunistic screening offered to patients visiting healthcare centres or even education regarding the existence of screening modalities may go a long way in reducing the mortality of CRC in India. This will only be possible if national recommendations are instated to define a population that should be screened. Most patient who visit local health care practitioners for rectal bleeding or with altered bowel habits are diagnosed to have benign conditions without being adequately worked up leading to a significant delay in treatment of an underlying CRC. Capturing this population demographic for opportunistic screening is likely to be the most cost effective intervention that can be implemented in India. Further the higher incidence of left sided CRC in India, makes sigmoidoscopy particularly attractive, as it is not only faster to perform, but it does not require formal bowel preparation or sedation and can be performed on the same day that the patient presents to the clinic. Sigmoidoscopy also allows for tissue diagnosis, removal of polyps, and has been shown to have a benefit in terms of mortality reduction.[82, 102]

While colonoscopy is impractical as a CRC screening modality due to the cost, need for expertise to perform, significant patient discomfort and need for bowel preparation, sigmoidoscopy can be a good alternative. The possibility of serious complications such as rectal perforation precludes training healthcare workers from providing this service, however training primary care physicians and general surgeons to perform this test as a strategy for CRC mitigation will help in expanding the availability of this test across the country.

In a hospital based registry, early cancers were fewer than 4%, and the overwhelming majority constituted advanced rectal cancers [62] Thus, the primary aim in India cannot be the reduction in incidence by detection and removal of polyps, but rather early detection of malignant disease, with the aim to improve treatment outcomes and reduce morbidity. Unlike the western demographic for screening where the incidence of polyps is close to 30%, it is much lower in India. It is unlikely that asymptomatic people will consider paying for screening in our country, with the economic and social barriers being simply too strong to overcome. Opportunistic screening targeted towards targeted towards high risk populations, such as those presenting with rectal bleeding, family history or previous history of rectal polyps would be far more feasible given the financial and manpower limitations faced. National awareness programmes similar to the widespread tobacco awareness campaigns will go a long way as most patients suffer significant delays in seeking oncological treatment due to misdiagnosis of rectal bleeding as haemorrhoids or other benign disorders.[108]

Conclusion

CRC treatment often leads to catastrophic health expenditure with the current healthcare infrastructure unable to meet even half of the patients' need. Efforts are needed to stem the rising incidence of a largely preventable disease associated with significant morbidity and healthcare costs. More research is needed to establish the role of screening in high risk individuals or symptomatic patients.

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Chapter 8

Esophageal Cancer

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Esophageal Cancer

Introduction

Esophageal carcinoma (EC) has two predominant types, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Each has distinct epidemiology, etiology & pathology. EAC is the more common subtype globally, while in India, ESCC predominates.[1]However, with the increasing trend of obesity and associated reflux; in India too, the incidence of EAC is on the rise.[2]

Present scenario

Carcinoma esophagus is the 8th most common cancer (3.1% of all solid tumors) and accounts for 5.5% of all cancer related deaths according to GLOBOCAN 2020.[3]Experts predict a 58.4% increase in the incidence and 61.8% increase in the mortality by 2040, given the current trends. Though the survival for ESCC and EAC have increased in the high development index countries over the past 20 years, with EAC faring better, the long-term survival continues to be dismal in specific subsets like older patients, ESCC & sub-Saharan region.[4]

India experienced 47,606 cases of carcinoma esophagus in 2016 with East Kasi hills in Meghalaya having the highest age adjusted incidence of 75.4/100,000 population. A 13.2% increase in incidence of esophageal cancers is expected by 2025.[5]

Prevention of Esophageal Cancer

ESCC and EAC have distinct risk factors, affected populations and clinical patterns.[6,7]Identifying and eradicating etiological factors and early detection of precancerous lesions is the key to preventing esophageal cancer. The effective strategy should include primary, secondary and tertiary prevention.

Primary prevention is to identify risk factors and to try to eliminate them. The different etiological factors of esophageal cancer and primary preventive strategies are discussed here.

Etiological factors

ESCC	EAC
1. Smoked and smokeless tobacco	1. Cigarette smoking
2. Alcohol consumption	2. Gastroesophageal reflux disease
3.Low intake of fruits and vegetables; deficient micronutrients	3. Low intake of fruits and vegetables, deficient micronutrients
4. Processed, salted and pickled vegetables	4. Abdominal obesity
5. Hot beverages	5. Alcohol consumption- inconsistent
6. HPV 16 and 18 – inconsistent association	6. Genetic susceptibility
7. Genetic susceptibility	
8. Low BMI, low socioeconomic status	

1. PRIMARY PREVENTION

A. Smoking cessation

Cigarette smoking is more strongly associated with ESCC than EAC. There is a three to seven-fold increased risk of ESCC in smokers. The causal association with EAC is lesser, but well established. Many studies have shown a two-fold increased risk of EAC.[7, 8]A dose-response relationship exists between pack-years of smoking and adenocarcinoma outcome.[9]Other forms of tobacco use like betel quid use, common in South and South-East Asia, can also cause ESCC.[7]Though limited, there is data suggesting association of other form of tobacco with ESCC.

Smoking cessation is an effective strategy to reduce the incidence of esophageal cancer.[9]More prolonged smoking cessation is associated with decreased risk of EAC and gastroesophageal junction adenocarcinomas.

B. Reduced alcohol consumption

Alcohol use is associated with an increased risk of ESCC. In excessive amounts (three or more drinks per day), alcohol increases ESCC risk by three to five times. But the evidence for an association between alcohol drinking and EAC is limited. [7, 8]ESCC and EAC are more prevalent among men – 3 to 8-fold higher. This is probably attributed to the increased prevalence of smoking and alcohol consumption among men. Alcohol and smoking work synergistically in the etiology of EC. Avoidance of excessive alcohol consumption is recommended for the prevention of EC (especially ESCC).

C. Dietary intervention

Low antioxidant nutritional status may make the esophageal tissue more prone to inflammation and increases the risk of EC. Low intake of fruits and vegetables, high meat intake, deficiency of micronutrients, vitamins (vitamins A, C, E, riboflavin, and carotenoids), and trace elements are associated with an increased risk of esophageal cancer.[10]

Salted and pickled vegetables contain carcinogens. Ecological studies showed high consumption of pickled vegetables to be associated with higher risk of EC. Compounds like N-nitrosamines, Roussin red methyl ester, and mycotoxins released by fungi and yeast growing in pickled vegetables are the likely carcinogens. IARC has considered picked vegetables as a possible carcinogenic for EC, though there is a lack of a consistent association in literature.[11]

A higher concentration of nitrates and nitrites in drinking and cooking water as well as conversion to nitrosamines in the acidic pH of the stomach is carcinogenic. The protective role against ESCC carcinogens is by inhibition of nitrosation reaction which is done by polyphenols and ascorbic acid content in fruits and vegetables. Thermal damage due to the consumption of hot beverages has increased the risk of EC.

Nutritional intervention trials have shown that dietary supplementation of vitamins and minerals are associated with reduced cancer rates. This association is significant among those receiving supplementation with beta carotene, vitamin E, and selenium. The reduction in risk begins about 1-2 years after supplementation. Supplementation with retinol and zinc, riboflavin and niacin, or vitamin C and molybdenum was not associated with significant effects on mortality. The beneficial effects of selenium, vitamin E, and beta-carotene on mortality were evident even up to 10 years after the stopping the supplementation and the benefit was found to be greater in younger participants (EC decreased by 17 % among participants younger than 55 years). Supplementation is effective at a younger age before the onset of precancerous lesions.[12]

Selenium deficiency has been shown to be a risk factor for esophageal and gastric cancer. Evidence suggests that higher selenium levels are associated with reduced risk of esophageal and gastric cancers in selenium deficient populations. Studies have shown a significant dose-response relationship between lower levels of zinc and increased risk of EC.

D. HPV and H pylori treatment

The role of HPV in EC is controversial. This possible causal association has been studied extensively and some results have shown an association while others deny it.[7, 13]

Infection with Helicobacter Pylori, particularly Cag A+ strains, is inversely associated with EAC risk.[14]Hence there is no role of H pylori treatment in EC, unlike gastric cancer. Meta analyses of H pylori with ESCC found no overall association.

E. Gastroesophageal reflux management

The gastric refluxate contains bile acid and intestinal enzymes, which irritate esophageal mucosa and lead to columnar transformation in Barrett's esophagus (BE), which is the premalignant precursor of EAC. Medications that relax the lower esophageal sphincter, like nitro-glycerine, calcium channel blockers, benzodiazepine and morphine, increase reflux.[15]
Both medical and surgical anti reflux therapies are effective at reducing symptoms of gastroesophageal reflux. Role of either in EC prevention is unclear. While some studies have shown that there is no definitive evidence that either therapy reduces EC, others have shown decreased risk in EAC and BE with high dysplasia with the use of proton pump inhibitors (PPIs).[16]The role of anti-reflux surgery in protection against EAC is debatable. Anti-reflux surgery may be more beneficial than medical therapy for prevention of EAC in patients with Barrett's esophagus.[17]

F. Increased physical activity

Obesity is a risk factor for EAC. The risk of EAC increases 3-fold in individuals with BMI >30.[18]The presence of abdominal/intra- abdominal and central obesity rather than BMI is a risk factor for Barrett esophagus and EAC.

Physical activity is movements produced by skeletal muscles that result in energy expenditure. The protective role of physical activity has been observed against EAC and ESCC.[19]Possible mechanisms include decreased inflammatory cytokines, increased anti-inflammatory adipocytokines, levels of IGF and leptin, and increased insulin sensitivity.

G. Chemoprevention

Non-steroidal anti-inflammatory drugs (NSAIDs) and non-aspirin COX- inhibitors confer a significant protective effect against EAC.[20]The longer duration and higher frequency of usage

may increase the degree of protection. There is strong evidence for the association between aspirin and a reduced risk of ESCC.[21]In the recently published umbrella review, aspirin use is associated with a significant 50% reduction in the incidence of ESCC, though the role in adenocarcinoma is supported by weak evidence.

AspECT study showed that aspirin and high-dose PPI chemoprevention therapy (especially combination) safely and significantly improved outcomes in patients with BE.[22]Statins also show a reduction in the risk of neoplastic progression though further studies are required for definitive recommendations.[23]

H. Investigational avenues

Functional variants in alcohol dehydrogenase and aldehyde dehydrogenase enzymes, along with alcohol consumption and smoking, enhance EC risk synergistically. Frequently mutated genes like TP53, Notch 1, CDKN2A, PIK3CA, RB1, TPCH1, SUFU, FBXW7, and NFE2L2 have been implied in EC causation.[6]In the future this genetic information could be used in the prevention, early detection, and personalized treatment of EC.

2. SECONDARY PREVENTION

Secondary prevention involves screening individuals or population with high risk of developing EC to diagnose the premalignant lesion or the cancer in early stage thereby improving survival.

Squamous carcinoma esophagus

Squamous dysplasia is thought to be a precursor lesion of ESCC but very few studies have confirmed this association and none of them are prospective. There appears to be a significant time lag in progression of dysplasia to an invasive lesion, which could potentially be used for screening.

ESCC screening has been studied in high prevalence areas, the so-called central Asian esophageal cancer belt and in high-risk individuals (Caustic acid ingestion, achalasia, Tylosis and previous head & neck SCC).

Population based screening:

China, given its high incidence of ESCC, had started population-based screening since the 1960s. The government has invested in various population studies such as the “Taihang

Project", the "Central Government Transfer the Payment for Local Cancer Prevention and Control Programme" and the "Huai River Basin Cancer Early Diagnosis and Treatment Project".[24, 25]

These studies have resulted in more than 2 million people undergoing screening upper gastrointestinal endoscopy by 2018. These community-based studies have shown higher detection of severe dysplasia or early ESCC resulting in timely treatment and improved survival in this subset. Various strategies like single shot screening at 50 years to a total of 6 screening endoscopies from 40 to 70 years have been studies with regard to negative predictive value and cost effectiveness. The best results have been seen with 3 endoscopies, once every 10 years in these high-risk regions.[26]

Currently, one RCT is underway in China comparing Lugol's Iodine chromo endoscopy with no screening. More than 32,000 patients have been randomized till date, with 70% of the lesions detected being in early stage. Results regarding ESCC specific and all-cause mortality benefit at 10 years are awaited.[27]

Screening in high-risk individuals:

The American Gastroenterologist Association recommends screening only in specific precursor conditions. These include tylosis, caustic ingestion, achalasia, previous head and neck SCC and Fanconi anemia.[28]

Table 1: Screening in High risk Individuals

Condition	Screening strategy	Duration	Level of Evidence
Tylosis	4 quadrant biopsies in upper, middle and lower esophagus beginning at 30 years	Until 70 years/ expectancy less than 5 years	III-IV
Head & Neck SCC	Chromoendoscopy/NBI every 6 months to 1 year after completion of primary treatment	10 years	II-III
Achalasia	Annual OGD 10 years after onset of disease	Not specified	III
Caustic ingestion	OGD every 2-3 years beginning 10 years after exposure	Not specified	IV

Adenocarcinoma of esophagus:

The incidence of EAC is closely associated with presence of long-standing gastro esophageal reflux disease (GERD) & Barrett's esophagus (BE). The risk of EAC increases with the frequency of GERD symptoms reaching a 7-fold risk in those with daily symptoms. BE is an intestinal metaplasia of the distal esophagus with columnar epithelium due to chronic acid exposure. BE is a pre malignant lesion for EAC. The risk of developing EAC increases with the grade of associated dysplasia: annual incidence of 0.2-0.5% in those with low grade dysplasia and upto7% in people with high grade dysplasia.[29]Given the slow progression of BE to EAC, it is the potential condition for implementing screening and prevention strategies.

Large observational and population-based studies from the Netherlands and Ireland have shown endoscopic screening and surveillance in BE to improve the detection EAC in early stage.[30, 31]This results in improved survival compared to those not undergoing surveillance. However, the magnitude of this benefit gets blunted while adjusting for bias. The selection of patients for BE screening in most of the clinical guidelines is based on presence of GERD symptoms, age, sex and smoking. The Michigan Barrett's Esophagus pREdiction Tool, is a robust tool that has been externally validated for BE screening. It incorporates age, waist-to-hip ratio, GERD symptoms, and pack-years of cigarette use to predict risk of malignancy. [32]Models incorporating biomarkers, genetic information, lifestyle and clinical information are also under study and yet to find wide-spread application.

Table 2: Clinical society recommendations for BE screening

Society	Year	Guideline for endoscopic screening
British Society of Gastroenterology	2014	GERD with any 3 of the following risk factors: >50 y, Caucasian, male gender, obesity or family history
American College of Gastroenterology	2016	Men >50 y with GERD, or Weekly reflux symptoms with 2 of the following risk factors: >50 y, central obesity (waist circumference >102 cm or waist-to-hip ratio >0.9), Caucasian, smoking, first-degree relative with BE or EAC
American Society for Gastrointestinal Endoscopy	2019	Family history of EAC or BE (high risk) OR GERD with 1 of the following risk factors (moderate risk): >50 y, male gender, Caucasian, smoking, obesity

Screening techniques:

High-definition endoscopy remains the gold standard in screening for esophageal cancers. Chromoendoscopy with Lugol's Iodine has been shown to improve the accuracy of diagnosis. Various other adjuncts available are Narrow band imaging, Optical coherence tomography, micro endoscopy, Autofluorescence, spectroscopy and transnasal, software-based post processing imaging and endocystoscopy, each having its own merits and demerits.[24]

Non-endoscopic methods include mechanical balloon, Inflatable balloon, sponge and various breath markers. These are still investigational.

Research gap:

There is a clear paucity of Indian data with respect to screening in ESCC and EAC given the need for high resource and expertise for endoscopy based screening. However, given the rising incidence of these cancers and expected incidence in future based on prediction models it is time to generate high quality evidence, especially in high risk areas.

Recommendations:

- ESCC continues to be a major cause of concern in focal population pockets in India due to local practices.
- Primary prevention in form of tobacco cessation, moderation of alcohol consumption and identifying dietary and food storage factors might help in altering the trend.
- Currently, there is insufficient evidence to support population-based screening for esophageal cancer
- Government sponsored pilot programmes of endoscopic screening can be attempted in areas with high prevalence (eg, north-east India) to generate prospective high-quality evidence that caters to our specific situation.
- Epidemiological studies from apex institutes are needed to understand the prevalence and trend of Barret's esophagus and esophageal adenocarcinoma in the country.

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Chapter 9

Gastric Cancer

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Gastric Cancer

Introduction

Gastric cancer is the 6th most common cancer worldwide.[1] Compared to the rest of the world, India is relatively a low- incidence region with gastric cancer being the 5th most common cancer among men, and the 6th most common cancer among women.[2,3] Gastric cancer in India is associated with a very high cancer related mortality, ranking as the 2nd most common cause of cancer related deaths.[4] Although India is at par with the global stage in terms of offering standard-of-care treatment to patients diagnosed with gastric cancer, the predominant reason for high mortality rate is advanced stage of disease at presentation. Clearly, gastric cancer is a significant health-burden to the nation, with an urgent need for creating facilities for early detection and strategies to reduce the ensuing mortality. The high-incidence Asian countries like Japan, South Korea, and Taiwan have implemented comprehensive national- level screening programmes for gastric cancer, and have succeeded in reducing the gastric cancer related mortality over a period of time.[5,6] A successful implementation of similar programme in India, is a difficult task with numerous challenges.

This chapter will focus on understanding the epidemiology of gastric cancer in India, the risk factors, as well as its. The evidence for primary and secondary prevention of gastric cancer with a perspective on implementation of preventive strategies in Indian population has also been discussed.

Epidemiology of Gastric Cancer

Highest incidence rates are observed in the Republic of Korea with almost 60 per 100,000 new cases annually for males[7]. India, on the other hand, has annual age- adjusted incidence rate of 6.2/100,000 for males and 2.9/100,000 for females. On the global stage, the stomach cancer incidence rate has been gradually declining over the past 50 years. Successful eradication drive for Helicobacter pylori (H. pylori) infection (responsible for 90% of all non-cardia gastric cancers), along with changes in food and meat preservation practices and a greater availability of fresh produce are main reasons behind this decline.[8] Although H. pylori eradication has brought about the greatest decline in gastric cancer incidence, there has been a 7- fold increase in cardia- subtype gastric cancers during the same period.[8,9] Such a shift towards cardia-subtype cancers, however, has not been observed in India, which continues to have a low incidence of gastric cancer despite a high prevalence of H. pylori infection,

indicating a complex interaction between H. pylori infection, dietary and lifestyle habits, and genetic predisposition; a relationship we are yet to fully understand.[10]

There is a marked geographical variation in the incidence of gastric cancer within India as well. The highest incidence has been recorded from Aizawl district in the state of Mizoram with an annual incidence of 64.2/100,000, followed by Tamil Nadu, with an annual incidence of 12.2/100,000. The lowest incidence rate has been reported from the state of Gujarat of 1.1/100,000 for men and 0.5/100,000 for women.[10-12]

The latest analysis of trends of cancer incidence from the National Cancer Registry Programme (NCRP) report 2020 shows a 0.5% annual increase in the incidence of gastric cancer in the country, with a projected annual incidence of 56,733 new cases of gastric cancer by the year 2025.[11]

1. RISK FACTORS AND PRIMARY PREVENTION OF GASTRIC CANCER

The various known risk factors for gastric cancer include smoking, H.pylori infection, and N-nitroso compounds in smoked foods. The modifiable risk factors with pertinent strategies for primary prevention have been elucidated below.

A. Diet

Dietary habits have a complex relationship with gastric cancer, with some foods such as alcohol, coffee, and meat consumption increasing the risk, with others such as fresh fruits and vegetables having a protective effect.

i. **Salt:** A high salt intake is linked with an increased incidence of intestinal metaplasia (IM) and atrophic gastritis, both of which are precancerous conditions associated with a high risk of gastric cancer. A meta-analysis reported an odds ratio (OR) of 1.68 for the association between salted/ salty meat and IM.[13]A high salt intake alone was reported to be associated with IM with atrophic gastritis with an odds ratio of 2.87.[14] An increased salt intake is reportedly associated with raised risk of dysplasia and cancer in patients with H. pylori infection.[15]

ii. **Alcohol:** A meta-analysis of 22 studies showed that light-to- moderate alcohol consumption was not associated with an increased risk of gastric cancer, however, heavy alcohol consumption was associated with a higher risk of gastric cancer compared to non- drinkers (Relative Risk-RR 1.13), even after adjusting for country, sex, BMI, physical activity, and education.[16]

iii. **Meat:** Red meat and processed meats are associated with a higher risk of gastric cancer. This association shown in a meta-analysis of 43 studies wherein the consumption of red meat (RR 1.41) and processed meat (RR 1.57) were both associated with a higher risk of gastric cancer. The RR of gastric cancer was 1.26 for every 100g/day increment in red meat consumption, and 1.72 for every 50g/day increment in processed meat consumption. White meat consumption, however was associated with a reduced risk of gastric cancer with an RR of 0.86 for every 100g/day increment in white meat consumption.[17]

iv. **Fresh fruits and vegetables:** Consumption of fresh fruits and vegetables exert a protective effect on gastric cancer risk, primarily by the production of anti-oxidants. Large, prospective studies have proven this association time and again. The Japan Public Health Centre (JPHC) cohort study was a large study of 39,993 people which commenced in 1990. A 10 year follow- up analysis showed a reduced gastric cancer risk with consumption of vegetables (RR 0.64) and fruits (RR 0.7) on one or more days of the week.[18] The European Prospective Investigation into Cancer and Nutrition (EPIC) study showed a protective effect of citrus fruits on gastric cancer risk (OR 0.8).[19] The EPIC study also reported that the Mediterranean diet, based on a high consumption of fish, fruits, vegetables, nuts with a low consumption of red, processed meat and dairy products was associated with a significant reduction in gastric cancer risk (HR 0.67).

B. <u>Lifestyle</u>

i. **Smoking and Tobacco:** There is abundant evidence that links smoking to gastric cancer. A meta-analysis of 42 studies showed a RR of 1.62 in males and 1.2 in females for smokers. A dose- response relationship was also demonstrated between smoking and gastric cancer risk. Smoking increased the risk for cardia as well as non- cardia cancers.[20]

ii. **Physical activity:** Physical activity has been shown to exert a protective effect on gastric cancer risk. A prospective cohort study from the UK Biobank of 3, 59,033 individuals with an 8 year follow- up period showed that moderate levels of physical activity were associated with a significantly reduced risk (Hazard Ratio (HR) 0.58) of non- cardia gastric

cancers.[21] Interestingly, very high levels of physical activity was shown to be associated with a higher risk of gastric cancer than moderate levels of activity, due to the association of gastro-esophageal reflux with intense physical activity. A meta-analysis of 7 prospective cohorts and 4 case-control studies showed a modest protective effect (RR 0.81) of regular physical exercise on gastric cancer risk.[22]

C. H.pylori

International Agency for Research on Cancer (IARC) identifies Helicobacter pylori infection as a class I carcinogen.[23] A retrospective cohort study from USA consisting 3,70,000 cases with H.pylori infection showed cumulative incidence for developing cancer of 0.37%, 0.5%, and 0.65%, at 5, 10, and 20 years after detection of infection respectively. This was significantly higher in smokers.[24]The study also showed that successful eradication of H. pylori infection decreased risk of gastric cancer (HR 0.24). Fuccio et al., reported a 35% reduction in the risk of gastric cancer after H.pylori eradication in their meta-analysis. Indeed, this evidence is mirrored in the Maastricht V/ Florence consensus guidelines wherein H. pylori eradication is recommended as the best strategy for primary prevention of gastric cancer.[25]

- **Helicobacter pylori mass eradication**

The Cag A gene (Cytotoxic-associated gene A) of H. Pylori is the chief virulent factor leading to gastric adenocarcinoma. Hence, detecting and eliminating H. pylori is important as a potential means of reduction of gastric adenocarcinoma.

Persistent H. pylori infection was found to be significantly associated with gastric cancer patients in a non- randomised study. 3 years follow-up period showed cancer in 4.3% patients with persistent infection as compared to control group with H. pylori eradication (1.5%).[26] Similarly, lower risk for gastric cancer was reported in patients treated with anti-H.Pylori medication in a meta-analysis of 6695 participants, comprised of 7 randomised control trials (RCT) (RR:0.65 95% CI, 0.43–0.98). It concluded that H. pylori eradication treatment could reduce gastric cancer risk.[27]

Mass eradication of H. pylori has been proposed as an alternative to mass screening in reducing the incidence of gastric cancer. H. pylori eradication after initiation of cancer may prove unsuccessful, so medication should be administered prior to carcinogenesis. However,

treating H. pylori even after cancer diagnosis may reduce the risk of metachronous cancer up to 50%.

- **Pylori: Indian Enigma**

Misra et al., alluded to the phenomenon of high prevalence of H. pylori and low gastric cancer incidence as the "Indian enigma" of H. pylori [28]. Studies show mixed results with a definite association in roughly 50% of patients, and a negative association in the rest.[28,29] Genomic studies of H. pylori strains in India have shown them to have European origins, which are innocuous or mildly pathogenic, unlike their East Asian counterparts.[30]

The primary manifestation of H. pylori in an Indian population is in the form of duodenal ulcers, with a rarity of gastric ulcers. This phenomenon of a corpus- sparing gastritis and rarity of gastric atrophy is well documented. The "Indian enigma" of low gastric cancer incidence, despite a high H. pylori infection prevalence has thus been attributed to varying dietary and environmental factors, as well as differing host genetics.[31-33] Thus, there is a prevalent argument against the eradication of H. pylori in India owing to the low gastric cancer incidence.[34] However, a discussion regarding H. pylori eradication must cover all consequences of H. pylori infection, and not solely gastric cancer. H.pylori is known to cause peptic ulcers and iron deficiency anaemia in adults and children respectively. These constitute major health care problems in India. Approximately 10% of North Americans experienced peptic ulcers in the H. Pylori era and 25% suffered from life-threatening complications leading to health care burden. Hence, the argument against the eradication of H. pylori rather, is one of efficacy and feasibility, than that of its necessity.[34]

D. Drugs

Several drugs have been shown to have a protective effect on gastric cancer incidence, namely, non- steroidal anti-inflammatory drugs (NSAIDs), statins, and metformin. A meta-analysis has shown an inverse relationship between NSAIDs and both, cardia and non- cardia gastric cancers.[35] Another meta-analysis showed low- dose aspirin to have a higher efficacy in reducing gastric cancer risk than NSAIDs (RR 0.7). Statins have been shown a 15- 20% reduction in gastric cancer risk.[36] Metformin has also shown a reduction in gastric cancer risk in type 2 diabetics (HR 0.76).[37]

E. Others:

Pathogenic agents such as Epstein Barr virus (EBV) and Human papilloma virus (HPV) have also been shown to be associated with gastric cancer. Several studies have noted causal relationship between EBV and Gastric cancer and EBV-positive gastric cancer is considered a unique molecular subtype of gastric cancer associated with good prognosis in patient.[38] HPV infection is also considered to be a potential carcinogenic factor for gastric cancer but its causal relationship is debated.[39, 40] Environmental factors and genetic predisposition as well as polymorphisms have also been described as risk factors for gastric cancer.

Table 1: Risk factors for gastric cancer

Sr. no	Risk factor category	Risk factors
1	Diet	Salt and salty diets Spicy foods Meat (red, smoked, processed, salted) Dairy foods Fish (salted/smoked/fermented with salt) Hot tea Mouldy and leftover bread Vitamin C deficiency Inadequate intake of fresh fruits and vegetables Rich foods Refined grains Pickled vegetables and foods Fried foods Irregular food habits Starchy foods and sweets Hot foods Lack of access to safe drinking water N-nitroso compounds Fat and oil Fermented foods
2	Lifestyle	Smoking Alcohol Physical inactivity Over-eating and fasting Opium Anxiety

		Hookah High calorie diet Depression
3	**Family history**	Family history of cancer Family history of gastric cancer
4	**Medical history and drugs**	History of gastrectomy/ gastric surgery History of esophageal cancer Blood type History of gastric polyp/ gastric ulcer Menstrual and reproductive factors Chronic atrophic gastritis Intestinal metaplasia Gastro-esophageal reflux
5	**Infections**	Helicobacter pylori Ebstein Barr Virus Human papilloma virus
6	**Demographic**	Age Level of education Race/ ethnicity Economic status and income level Sex Place of residence
7	**Occupational exposure**	Cement Mineral dust Chromium compounds
8	**Ionizing radiation**	
9	**Genetic polymorphisms**	

Table 2: Genetic syndromes associated with an increased lifetime risk of gastric cancer

Sr. No.	Syndrome	Lifetime risk of developing gastric cancer
1.	Hereditary Diffuse Gastric Cancer	By age 80- Men: 67% Women: 83%
2.	Lynch Syndrome	1 to 13%
3.	Juvenile Polyposis syndrome	21%
4.	Peutz Jeghers Syndrome	29%

5.	Familial Adenomatous Polyposis	1 to 2%

2. SECONDARY PREVENTION

The goal of secondary prevention is to lessen the impact of already existing disease.

Goals of secondary prevention

1. Medical goals

- Reduce mortality
- Reduce morbidity
- Mitigate symptoms

2. Psychological goals

- Relieve anxiety- patient and family
- Improve QOL

3. Social goals

- Resume work
- Achieve independence

4. Health service goals

- Reduce medical cost
- Reduce admissions/readmissions
- Early discharge

This consists of early detection and management of disease encouraging personalised treatment for prevention of recurrence. It also includes implementation of programmes for early return to original health and function, thus preventing long-term problems.

A. Early detection through screening activities

Two approaches for screening gastric cancer may be adopted; mass screening or opportunistic screening (for high-risk population). The need of population screening remains debated however, it has been incorporated in few countries with a high incidence of gastric cancer.

The consensus statement by Asia Pacific Gastric Cancer group recommended population-based screening and treatment of H. pylori infection in areas where annual incidence was more than 20 per 100,000population.[41]National population screening programmes have currently been implemented in Japan and South Korea recommending radiographic examination screening or gastroscopy for individuals above 50 or 40 years of age

respectively.[42, 43] The highest age-standardized incidence rates of gastric cancer in the world have been reported from Korea, but gastric cancer–related mortality to incidence ratio is much lower than that in other countries. This is likely due to effective screening and early initiation of treatment.[43]Cost-benefit analysis has shown that screening significantly lowers medical expenses with improved prognosis than the non-screening group. Other Asian countries with a strategy for screening for high-risk individuals include China, Taiwan and Singapore.

However, population-based screening for gastric cancer in Western societies is not adapted with studies questioning its cost effectiveness. In a study reviewing the cost-effectiveness of screening the general population for upper GI cancers by combining an upper GI endoscopy (UGIE) at the time of screening colonoscopy, Gupta et al., found that it was not cost-effective to do UGIE with colonoscopy unless it involved subsequent surveillance for Barrett's oesophagus. The results suggest that UGIE for gastric cancer screening alone would not be cost-effective.[44] Areia et al., conducted a cost-utility analysis comparing 3 screening strategies versus no screening in the general Portuguese population between ages 50 and 75 years.[45] One method was serum pepsinogen screening, and two different endoscopic strategies were included. In first method, every individual was screened with UGIE every 5 years while in the other method individuals with a positive faecal occult blood test (FOBT) underwent UGIE at the time of diagnostic colonoscopy which allowed for significant cost reduction. It was found that this was the only cost-effective strategy compared to no screening. Independent upper endoscopy and serum pepsinogen testing were not cost-effective.

When to screen?

Gastric cancer incidence increases with advancing age. It is more common in people older than 40 years than the young. Hence, a cut-off age for gastric cancer screening, similar to colorectal cancer screening is proposed. Most Asian working groups recommend the optimum age for screening to be 40–45 years. However, this cut-off age may vary with individual countries pertaining to regional incidence of gastric cancer.

Whom to screen?

High-risk populations based on ethnicity, family history, patients with premalignant lesions and those with suspected genetic syndromes should be offered to screen. Genetic syndromes

associated with an increased lifetime risk of gastric cancer have been detailed in table number 2.

How to screen?

i. Endoscopic mapping with biopsies: UGIE is the current gold standard for diagnosis. UGIE is widely utilised for gastric cancer screening in Japan, Korea, and other high incidence areas owing to its high detection rate. However, being an invasive procedure, it has inherent albeit a small risk of complications mainly haemorrhage and perforation with a reported mortality of 0.43%.[46] Endoscopic evaluation is highly operator dependent and its success largely depends on the skills of the endoscopist and the ability to detect subtle mucosal changes.

   The advent of advanced endoscopic imaging modalities has increased accuracy for the diagnosis of gastric neoplasia as compared to standard "white light" endoscopy. The use of chromoendoscopy (CE), using mucosal dyes and stains (such as indigo carmine or methylene blue) and narrow-band imaging, a filter-based enhancement technology, allows to highlight subtle mucosal irregularities and guiding endoscopic resections. A meta-analysis evaluating 902 lesions from 10 different studies revealed higher overall accuracy of CE when compared to White Light endoscopy (WLE) (86.6% versus 54.9%) for diagnosing early gastric cancer. The accuracy to identify the preneoplastic lesions was found to be 98.4% and 81.0%, respectively.[47] However; these procedures are time-consuming requiring additional resources. Also, the endoscopists experience affects the outcomes.

   Narrow band imaging has been investigated to overcome this drawback. Higher sensitivity and accuracy of narrow band imaging (NBI) for diagnosis of intestinal metaplasia (IM) compared with WLE has been demonstrated in a prospective multicentric study.[48]The major limiting factor for these techniques is its limited availability and the expertise needed for interpretation. Further research is required for determination of the optimal modality.

ii. Serum pepsinogen: Progression model of carcinogenesis shows that intestinal-type gastric cancer develops in staged manner viz. intestinal metaplasia, dysplasia, first low grade and then high grade (equivalent to “carcinoma in situ”), followed by invasive carcinoma. Two distinct types of pepsinogens are noted immunologically: serum pepsinogen I (PGI) and

serum pepsinogen II (PGII). Atrophic gastritis leads to reduced production of PGI, while the levels of PGII largely remain the same. The ratio of serum levels of PGI and PG II could be used as an indicator for identification of development of gastric cancer.

iii. Gastrin 17: Gastrin-17 (G-17) is a peptide that is synthesized in the G cells of the gastric antral region. It stimulates the secretion of gastric acid. It is proposed that gastric atrophy; a precursor of cancer can be identified based on the levels of G-17. With predominant gastric corpus atrophy, the antrum is usually spared. Lower acid levels produced in the gastric body leads to feedback stimulation and raised levels of G-17. However, when atrophy is seen in both the antrum and the body, G-17 levels may be normal or low. Hence gastric atrophy can result in lower, normal, or higher levels of G-17. This makes routine use of G-17 unreliable.

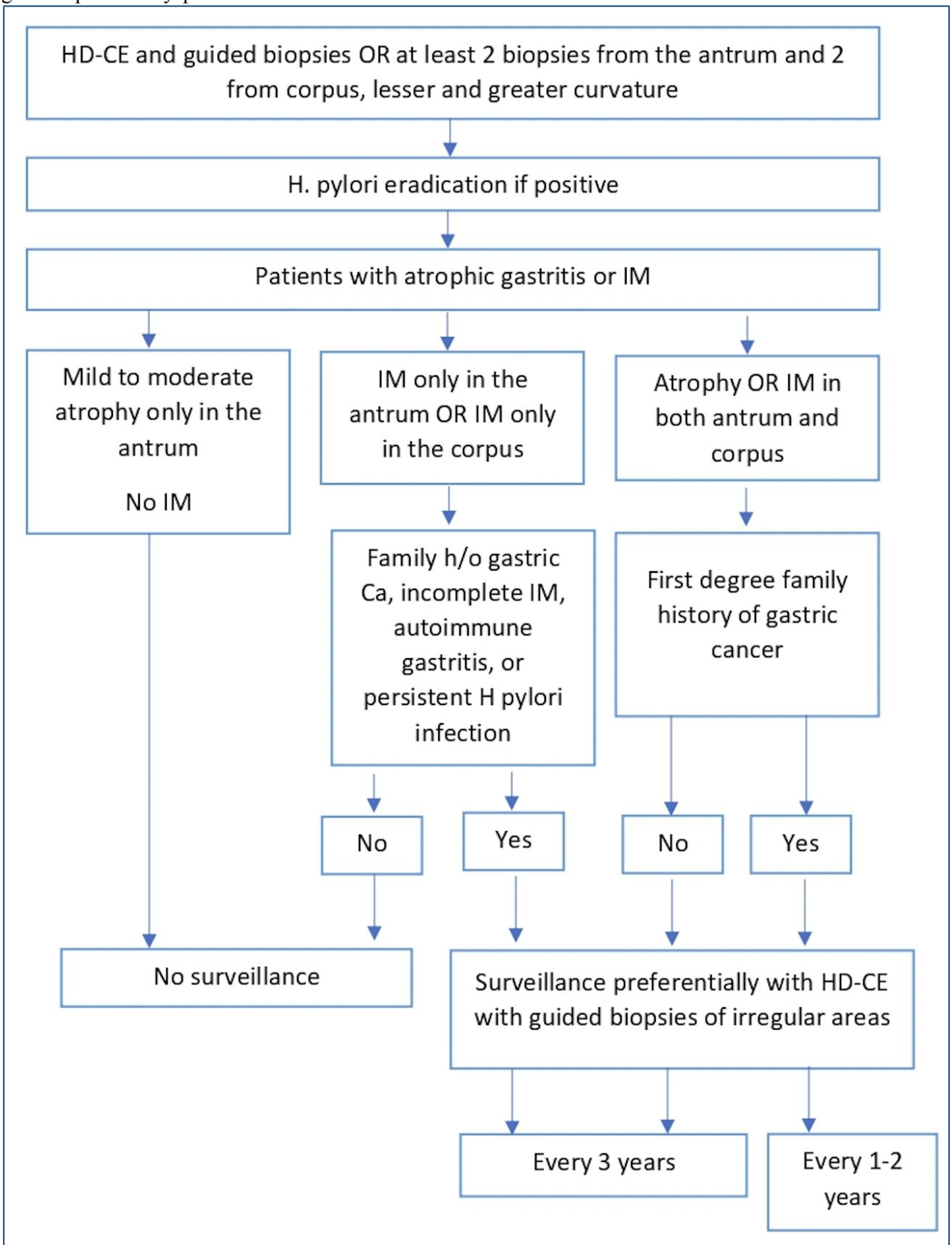
Other methods:

1. Photofluorography
2. Antigastric parietal cell antibodies
3. miRNAs

B. Surveillance of premalignant lesions

Chronic atrophic gastritis and IM are considered pre-malignant conditions as they are associated with increased risk for the development of gastric cancer and form the background in which dysplasia and adenocarcinoma may occur. This highlights the importance of diagnosis and risk stratification for these conditions.[49] Screening and surveillance of at-risk population helps in decreasing cancer related mortality by means of early detection and treatment. The cancer is also detected in early stages which may be amenable to endoscopic treatment rather than surgery. Two scoring systems for streamlining and standardizing the detection of gastric cancer were proposed by Management of Epithelial Precancerous conditions and Lesions in the Stomach guidelines (MAPS I). The Operative Link on Gastritis Assessment (OLGA), and Operative Link on Gastritis Assessment based on Intestinal Metaplasia (OLGIM) systems were proposed for staging and stratification of Gastric atrophy and IM. [50]Proposed management for patients with atrophic gastritis, gastric intestinal metaplasia, or gastric epithelial dysplasia has been depicted in figure 1. (Adapted from the MAPS II guideline update 2019.[5]

Figure1: Proposed management for patients with atrophic gastritis, gastric intestinal metaplasia, or gastric epithelial dysplasia



2. GASTRIC CANCER PREVENTION IN INDIA: WAY FORWARD

India has lower incidence of gastric cancer as compared to other countries, however, the overall survival is lower in comparison owing to a high mortality due to late stage at presentation. Though, the treatment protocols and level of care is standardized in most tertiary care centres of India, at par with international standards, uniform application of these protocols outside these tertiary care centres remains a challenge. Availability of all modalities of diagnosis and treatment is another problem in many parts of the country. The Indian conundrum of having majority of gastric cancer patients living in rural areas and most of the specialist and tertiary care centres being available in urban centres further contributes to suboptimal outcomes. Unlike some of east Asian countries, India does not have any national screening programme and application of preventive strategies to whole population remains a distant pipedream with lot of challenges.

Implementation of preventive strategies that aim to reduce the risk factors and promote protective ones as well as strategies for secondary prevention promoting early diagnosis by identifying patients with precancerous conditions should remain our prime policy at present to decrease the incidence and mortality of gastric cancer in India.

Primary Prevention

Majority of Indian population is vegetarian and India has very little red meat consumption which reflects in lower incidence. However, malnutrition stemming from deficient intake of essential nutrients and vitamins in lower socioeconomic strata on the country as well as skewed excess intake of processed carbohydrates amongst the urban population leads to increased risk of gastric cancer. A sound dietary strategy catering for both these strata of society for primary prevention of gastric cancer including nutritional supplementation and education and awareness about dietary modification would help reducing the incidence of gastric cancer.

Tobacco control is another important strategy. Around 30% of the Indian population aged 15 years or older consumes tobacco in some form, which translates to almost 195 million people tobacco users across the country.[51] In India, tobacco is used in various forms such as snuff or smoke. Various methods of smoking like hukka, cigarettes, beedi and taibur and maizol have been practiced for ages in different part of the country. The practice of smoking local cigarettes like Maizol and Taibur (tobacco smoke infused water) in Mizoram has been

attributed for the higher incidence of gastric cancer. A massive, large- scale, national level effort to decrease tobacco consumption in India is the need of the hour, and stands to make the largest impact on several cancers apart from just gastric cancer.

H. pylori eradication, although have been found useful worldwide, the scenario in India is different. Firstly, the task for eradication is enormous considering India's population. Also, antimicrobial resistance to H. pylori strains is widespread in India and displays marked regional variation. Hence, a single nationwide blanket regimen is unlikely to be effective for eradication and regimens would need to be tailored to individual susceptibility. The third problem is of durability of eradication. Recurrent infections with H. pylori, can pose a considerable challenge in achieving eradication at a large scale. Several authors have reported recurrence rates of 2 – 63%, with reinfections being detected from 3 months to 3 years after successful eradication.[52, 53]The conundrum of H. pylori eradication is complex when one considers it's all facets and the implications of attempting to execute such a plan on a national scale. Hence, at present, a mass H. pylori eradication strategy cannot be recommended. However, the eradication of H. pylori at an individual level must be attempted.

Secondary prevention

Endoscopic screening may be cost-effective in high-incidence areas, but in average-risk populations, including India, there is no evidence that endoscopic screening is effective. To establish a nationwide screening system for gastric cancer, it would require significant financial and human resources to be employed and is unlikely to be cost effective. From the Indian perspective, targeted surveillance with screening programmes established in high-incidence sectors (such as Mizoram and Tamil Nadu) would be a promising approach. Also, improving the awareness in general population along with enhanced primary provider education regarding early detection of signs and symptoms will be the most simple and effective step towards improving the outcomes of gastric cancer.

Summary

The incidence of gastric cancer continues to rise and poses a significant public health burden, with a majority of cases presenting at an advanced stage. Despite being a low-incidence country on a global platform, India exhibits marked regional variability in gastric cancer with distinct high and low incidence regions. Prevention by H. pylori eradication and/or nationwide endoscopic screening as a part of secondary prevention, remain challenging issues

with questionable cost effectiveness and cannot be recommended at present. Readily implementable strategies for primary prevention on a population scale should remain our prime policy which include tobacco cessation, dietary & lifestyle modifications, and increasing awareness and education for early detection.

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