Acting for Prevention
Tobacco Control

Summary

➢ The main benefit from quitting smoking arises from avoiding the more pronounced increase in risk that would result from continuing to smoke.

➢ Quitting smoking before middle age avoids much of the lifetime risk incurred by continuing to smoke, conferring substantially lower lung cancer risk compared with continuing smokers.

➢ The WHO Framework Convention on Tobacco Control (WHO FCTC) is the first-ever public health treaty with widespread support worldwide, encompassing a series of stipulations designed to control tobacco use and supply.

➢ Comprehensive smoke-free and tobacco-pricing policies, two of the WHO FCTC- endorsed policies, have been effective in reducing exposure to secondhand smoke, diminishing cigarette consumption and increasing quitting smoking.

➢ There are pharmacologic and non-pharmacologic tobacco dependence treatments options, varying in effectiveness, available to aid those who want to quit smoking.

Risk reduction

For smoking-induced morbidity and mortality to disappear, smoking initiation in the young must cease. Ironically, it would take many decades for morbidity and mortality trends to reflect the effects of such intervention, mainly due to the long latency of increased health consequences in prevalent smokers who will continue to do so. However, if current smokers quit, the risk of developing or dying from cancer as compared to continuing counterparts would diminish even if stopping after decades of smoking. An assessment of changes in cancer risk and of other diseases caused by smoking with cessation was conducted by an International Work Group of experts convened at IARC in Lyon on March 13-19, 2006 [1,2]. The assessment addressed three questions:

► Is the risk of developing cancer, for each of the 13 tobacco-associated cancer sites considered, lower in former smokers than in otherwise similar current smokers?

► Are otherwise similar former smokers, the risk of disease lower with more prolonged abstinence?

► Does the risk return to that of never smokers after a long period of abstinence?

Conclusions from the Working Group on the effects of smoking cessation on the risk of developing and dying from lung, laryngeal and oral cancers are shown in Tables 4.1.1 and 4.1.2, indicating a lower risk of cancer at these sites in those who quit as compared to those who continue to smoke [2].

Tobacco control interventions

To arrest the global tobacco epidemic, initiatives are needed to slow tobacco use and supply. The body of policies stipulated in the treaty became binding international law on 27 February 2005. Of the 38 articles, articles 6 to 14 cover policy interventions directed at preventing tobacco use, decreasing consumption, reducing toxicity, protecting non-smokers and diminishing tobacco use in public places. Articles 15 through 17 relate to measures controlling the availability of tobacco [Table 4.1.3] [3]. The concerted adherence of countries to the treaty around the world will make it a global response to the tobacco epidemic. An assessment of the policy interventions included in the WHO FCTC will depend on how effectively countries formulate and implement these policies. As of November 2005, 160 countries have subscribed to the treaty [Figure 4.1.1] [4]. IARC convened a group of international tobacco control policy experts in March 2007 to propose a framework for guiding the evaluation of tobacco control policies expected to be formulated worldwide in response to WHO FCTC. This framework and its scientific and policy bases will aid tobacco control policy authorities to assess if intended targets are fulfilled [4].

Comprehensive tobacco control programs are more likely to be successful in reducing tobacco use than programs relying in few interventions. Jassans and Raw [5] have proposed a scale to quantify the implementation of tobacco control interventions at country level. Their work is based on a baseline survey conducted in 2005 in 30 European countries. Tobacco control policies taken into account in the scale included price of cigarettes and other tobacco products, smoke-free work and other public places on July 1, 2005, spending on public information campaigns in 2004, comprehensive bans on advertising and promotion on July 1, 2005, large health warning labels, on 1 July 2005, and cessation services in place. Tobacco control performance varied greatly within Europe, from countries accruing 270 points (Lithuania, Ireland, Norway and Iceland) to countries accumulating <30, with results by type of intervention indicating areas where future efforts could be concentrated.

Protection from exposure to SHS Countries enacting laws banning smoking in public places have shown high compliance and significant decrease in SHS exposure. The banning of smoking in pubs and restaurants in Scotland started in 26 March 2006, with pre-ban concentration levels of particulate matter (PM 2.5) aver-aged from Reversal of Risk After Quitting Smoking [2]

Table 4.1.1 Benefits of quitting smoking on risk of developing and/or dying from lung cancer

Adapted from Reversal of Risk After Quitting Smoking [2]
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regulation of tobacco product disclosures
price and tax measures to reduce demand
regulation of the contents of tobacco products
tobacco advertising, promotion and sponsorship
protection from exposure to tobacco smoke

One year after the Scottish ban a significant 16% drop in cotinine concentration was, however, not statistically significant. Nonetheless, non-smokers living with smokers experienced a 16% drop in cotinine concentration (56%). Nonetheless, non-smokers living with smokers experienced a 16% drop in cotinine concentration that was, however, not statistically significant. The findings from the evaluation assessing exposure in primary school students found significant reductions in exposure, as revealed by salivary cotinine concentrations, only in children living in households with no smokers (a 51% drop) or in those where the only father smoked [445]. [5]. These results from the Scotland evaluation pinpoint the importance of the household (and car) as a source of exposure to SHS.

Price and tax measures to reduce demand

Policies prohibiting smoking in public places are intended to protect the health of all but in particular that of non-smokers. Tax policies on tobacco products also affect a substantial portion of the population and are intended to discourage tobacco use in established and in potential users, in addition to generating revenues. The WHO FCTC contemplates the use of taxes on tobacco products as an effective approach to control tobacco use by increasing prices and impacting product demand. Chaloupka and colleagues have extensively documented the role of fiscal policies in reducing tobacco consumption and increasing cessation in users and sustaining abstinence in non-smokers [13]. Studies from high-resource countries show that a 10% increase in the price of cigarettes, following elevations of tax, produce a decline in use that varies between 2.5% and 5%, affecting both the prevalence of smoking and the amount consumed [10]. Gallus and colleagues have also studied the effect of price on smoking prevalence in Europe reporting for each 10% increase in the price of cigarettes a drop in consumption of 5–7% [12].

The impact of similar price increases (10%) on tobacco use in low-/medium-resource countries approaches, depending on the population studied and the income level referred to (3.4–6.6% in China; 13.3% and 5.2% in lower and higher income groups, respectively in Bulgaria) [11]. Long-term reduction in tobacco use or in net tobacco revenue tend to be higher than shorter term effects, reflecting the progressive overcoming of addiction among those who are successful in quitting or in reducing consumption (up to 2% and 8% reduction in consumption in the short and long term respectively in Brazil) [11]. Income is also a significant variable explaining tobacco demand (i.e. increments in income leading to greater consumption). Changes in smoking behaviour in response to increments in tobacco prices tend to be more pronounced in the young and in less affluent groups in the population.

Table 4.1.3 WHO FCTC annex 6: addressing any interventions to reduce tobacco supplied and sold (Adapted from World Health Organization, 2003[2])

Table 4.1.4 Status of the WHO Framework Convention on Tobacco Control (WHO FCTC) 168 Contracting Parties

Fig. 4.1.3 Status of the WHO FCTC 168 Contracting Parties

Non-policy interventions

The majority of smokers desire to quit smoking, but the path from intention to actual cessation is long and in many cases complex. There are pharmacologic (i.e. nicotine replacement therapy, NRT, Table 4.1.4) and non-pharmacologic strategies (i.e. counselling, Table 4.1.5) available to aid smokers quit their dependence on nicotine, the addictive component of tobacco. The availability of these treatments is often constrained by cost and resistance. Since approximately 70% of smokers want to stop smoking, it is imperative that smokers become aware of the existence of these pharmacologic approaches and that healthcare providers use every opportunity possible to assess patient’s desire to quit, provide information on quitting aids, advise additional support of non-pharmacologic interventions for the treatment of tobacco dependence, and consider whether it would be possible for a patient to access a referral to a cessation program or consider referring the patient to an appropriate program. In many countries, these programs are provided and funded by government agencies, and are widely available to those who desire to quit smoking. The duration of the vaccine immunity is, however, unknown at present. Dosing and administration schemes are being formulated in order to treat patients on Phase II clinical trials that will reveal vaccine efficacy. The potential use of this secondary prevention approach is very promising given the number of smokers who wish to quit and the number of former smokers who desire to remain abstinent.

Discussion

Two WHO FCTC-endorsed policies with impact at the population level and several approaches to tobacco dependence treatment are covered in this chapter. The success of these policies in achieving reductions in tobacco use and protection in non-smokers will depend on a more complex array of factors than those included in this chapter, such as total or partial ban of smoking restrictions in work and public places, enforcement of restrictions, tax avoidance, smuggling of tobacco products and/or proliferation of grey markets to name few. Still, these policies are those that have been shown to decrease the use of tobacco products and that are receiving global attention in response to the activation of the WHO FCTC legislative clock. These are not the only policy interventions effective in curtailing tobacco use. Suppression of tobacco advertising, promotion and sponsorship, education and communication campaigns to raise awareness and product labelling, for example, have been shown to moderate tobacco use in adolescents and adults.

Long-term cancer risks are influenced by smoking initiation and also by smoking cessation in the population. At present, there are many countries showing increasing trends in lung cancer mortality in younger age groups where there are no evident antismoking policies in place. The increase in lung cancer mortality is, however, unknown at present. Dosing and administration schemes are being formulated in order to treat patients on Phase II clinical trials that will reveal vaccine efficacy. The potential use of this secondary prevention approach is very promising given the number of smokers who wish to quit and the number of former smokers who desire to remain abstinent.

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Increasing smoking cessation. If these smoking trends remain unaltered, projected lung cancer incidence and mortality will grow rather than decrease. Policies leading to smoking cessation and preventing smoking initiation must be fostered and maintained. Also important, smokers and former smokers can and should be assisted in their attempts to quit and remain abstinent by receiving pharmacologic and non-pharmacologic intervention treatments within the healthcare system or as advised by the principal healthcare provider. However, smokers tend to avoid clinic-based smoking cessation programmes but on the other hand respond to environmental prescriptions such as smoking bans. Hence the importance of policy-based interventions designed to deter tobacco use and eventually leading to the denormalisation of this behaviour.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration of treatment</th>
<th>Contraindications</th>
<th>Adverse effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine replacement therapy</td>
<td>Dose is adjusted to level of nicotine dependence and is decreased progressively over treatment period</td>
<td>8–12 weeks, can be longer (up to 1 year) for the prevention of relapse</td>
<td>Patch: allergy to constituent of nicotine patch</td>
<td>Patch: skin irritation, sleep disturbance</td>
</tr>
<tr>
<td></td>
<td>Patch: 21–42 mg/d orally</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gums: 8–10 pieces (2 or 4 mg each) per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhaler: 4–8 puffs per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lozenge: 1–2 lozenges per day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion, sustained release</td>
<td>150 mg/d for first 3 days, then 300 mg/d</td>
<td>8 weeks, can be longer (up to 1 year) for the prevention of relapse</td>
<td>Seizure, central nervous system tumour, bipolar disorder, alcohol withdrawal, benzodiazepine withdrawal, use of monoamine oxidase inhibitors, anorexia, bulimia, liver disease</td>
<td>Insomnia, seizure, gastrointestinal disturbance, ph infections</td>
</tr>
<tr>
<td>(Zyban)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg/d for first 3 days, then 300 mg/d</td>
<td>8 weeks, can be longer (up to 1 year) for the prevention of relapse</td>
<td>Seizure, central nervous system tumour, bipolar disorder, alcohol withdrawal, benzodiazepine withdrawal, use of monoamine oxidase inhibitors, anorexia, bulimia, liver disease</td>
<td>Insomnia, seizure, gastrointestinal disturbance, ph infections</td>
</tr>
<tr>
<td>Varenicline (Champix)</td>
<td>0.5 mg/d for first 3 days, then 0.5 mg twice daily for the next 4 days and 1 mg twice daily thereafter</td>
<td>12 weeks, can be longer (up to 24 weeks) for the prevention of relapse</td>
<td>None</td>
<td>Nausea, vomiting, constipation, flu syndrome, heart rate abnormality, abdominal symptoms, sleep disturbance</td>
</tr>
</tbody>
</table>

**Table 4.1.4** Pharmacologic treatment of tobacco dependence. Adapted from Le Foll and George, 2007[14]

**Table 4.1.5** Nonpharmacologic interventions for the treatment of tobacco dependence and their estimated efficacy. Adapted from Le Foll and George, 2007[14] Note: CI = confidence interval

**Table 4.1.6** Nonpharmacologic interventions for the treatment of tobacco dependence and their estimated efficacy. Adapted from Le Foll and George, 2007[14] Note: CI = confidence interval


REFERENCES

The French-speaking Regional Centre for Training in Gynaecologic Cancer Prevention (known by its French acronym CERFFO), located in Conakry, Guinea, provides information, training and technical assistance based on practical solutions that insure the implementation and continuation of gynaecologic cancer prevention strategies fitted to social, cultural and environmental settings of our region.

The centre has three missions: Training, Research and Services Management.

At the centre, reproductive health providers may further new assessment approaches for screening and treating major gynaecologic cancers, improve healthcare systems in diagnosis and health management, and contribute to the implementation of gynaecologic cancer prevention programs with respect to national policies and programs for fighting against cancer.
Over the past 50 years, the number of occupa-
tionally-induced cancers has likely decreased in high-resource countries [1]. This is due to a num-
er of different trends. The decline in blue-
collar heavy industry and the corresponding growth of white-collar knowledge indus-
ties has served to decrease the number of workers in particularly ‘dirty’ occupations. At the same time, many industries have insti-
tuted procedures and processes that provide much cleaner work sites than in the past [2]. The motivations for this are complex and multi-
dimensional. In part, this is a by-product of epidemiologic research carried out in the past [3,4]. In many countries the identification and characterisation of occupational carcinogens triggers regulatory actions intended to reduce the permissible exposure levels. Such actions may range from substitution of one substance in an industrial process for another, modified procedures, such as intermediate control, or the use of protective equipment by workers. But the real benefits of such regulations may be quite non-
specific. That is, while regulations concerning a particular carcinogen may serve to reduce the risk of cancer in relation to that carcino-
gen, cleaning up an industrial process induces reduction in exposure to many substances, some of which may be in the hidden part of the iceberg of occupational carcinogens.

It is impossible to estimate how many occupa-
tional cancer cases have been prevented; it is cer-
tainly a partial success story. In addi-
tion, there has been a growing realisation on the part of many industries that good industrial hygiene makes good business sense. The cau-
tory tale of companies that have suffered from regulatory or legal opprobrium, as well as compensation costs, as a result of being identified as a ‘cancer-causing company’ might have served as an incentive for other companies to clean up.

Setting standards for regulatory purposes is a difficult task that relies on epidemiologic, toxicologic and other data [5,6]. Historically, these standards have usually been based on considerations of acute toxicity, increasing, however, cancer has become a key endpoint. The main problem with setting standards aimed at reducing carcinogen exposure is the lack of reliable epidemiologic data on dose-response relationships. For the most part, the regulators must rely on animal data, with complex math-
ematical models used to translate the animal experiences into terms that are relevant for human risk assessment.

One approach, which can only be imple-
mented if a known carcinogen has not yet been introduced into industrial practice, is to ban its introduction. On occasions when an agent has been used and shown to be carcinogenic in one country that information can then be used by other countries. For example, following reports from the United States on the increased bladder cancer risk among workers exposed to 4-aminobiphenyl, its introduction was banned in the United Kingdom [7]. Substitution of prod-
ucts known to be carcinogenic has been used successfully, as in the example of asbestos and man-made mineral fibers. More common have been attempts to reduce exposure levels to known or suspect carcinogens. Successful examples include the virtual elimination of radon-related cancer risk among nuclear

4.2.2 International occupational exposure limits and guidelines for butadiene (which is classed by IARC as an established human carcinogen, Group 1)

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Butadiene concentration (mg/m3)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1991</td>
<td>22</td>
<td>(Probable human carcinogen)</td>
</tr>
<tr>
<td>Belgium</td>
<td>1991</td>
<td>22</td>
<td>(Probable human carcinogen)</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>1991</td>
<td>20</td>
<td>TWA (time-weighted average)</td>
</tr>
<tr>
<td>Denmark</td>
<td>1993</td>
<td>22</td>
<td>(Potential occupational carcinogen)</td>
</tr>
<tr>
<td>Finland</td>
<td>1998</td>
<td>2.2</td>
<td>TWA (time-weighted average)</td>
</tr>
<tr>
<td>France</td>
<td>1993</td>
<td>36</td>
<td>TWA (time-weighted average)</td>
</tr>
<tr>
<td>Germany</td>
<td>1998</td>
<td>34</td>
<td>(Human carcinogen) Technical exposure limit</td>
</tr>
<tr>
<td>Hungary</td>
<td>1993</td>
<td>10</td>
<td>(Potential occupational carcinogen)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1996</td>
<td>46</td>
<td>Short-term exposure limit</td>
</tr>
<tr>
<td>The Philippines</td>
<td>1993</td>
<td>2200</td>
<td>TWA (time-weighted average)</td>
</tr>
<tr>
<td>Poland</td>
<td>1998</td>
<td>100</td>
<td>TWA (time-weighted average)</td>
</tr>
<tr>
<td>Russia</td>
<td>1991</td>
<td>100</td>
<td>Short-term exposure limit</td>
</tr>
<tr>
<td>Sweden</td>
<td>1991</td>
<td>20</td>
<td>(Suspected of having a carcinogenic potential) TWA (time-weighted average)</td>
</tr>
<tr>
<td>Turkey</td>
<td>1993</td>
<td>2200</td>
<td>TWA (time-weighted average)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>1991</td>
<td>22</td>
<td>TWA (time-weighted average)</td>
</tr>
<tr>
<td>United States:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACGIH (Threshold Limit Value)</td>
<td>1997</td>
<td>4.4</td>
<td>(Suspected human carcinogen)</td>
</tr>
<tr>
<td>NIOSH (Recommended Exposure Limit)</td>
<td>1997</td>
<td>(Potential occupational carcinogen: low/feasible concentration) TWA (time-weighted average)</td>
<td></td>
</tr>
<tr>
<td>OSHA (Permissible Exposure Limit)</td>
<td>1996</td>
<td>2.2</td>
<td>TWA (time-weighted average)</td>
</tr>
</tbody>
</table>

Limits and guidelines from International Labour Office (1991), United States Occupational Safety and Health Administration (OSHA, 1996); American Conference of Governmental Industrial Hygienists (ACGIH, 1997), United States National Library of Medicine (1997); Deutsche Forschungsgemeinschaft (1998); Ministry of Social Affairs and Health (1998). * Countries that follow the ACGIH recommendations for threshold limit values include Bulgaria, Columbia, Jordan, Republic of Korea, New Zealand, Singapore and Viet Nam.

Table 4.2.3 Decrease in occupational exposure and guidelines for butadiene (which is classed by IARC as an established human carcinogen, Group 1).

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon monoxide (CO)</td>
<td>37%</td>
</tr>
<tr>
<td>Lead</td>
<td>78%</td>
</tr>
<tr>
<td>Nitrogen dioxide (NO2)</td>
<td>14%</td>
</tr>
<tr>
<td>Ozone</td>
<td>6%</td>
</tr>
<tr>
<td>Particles of ≤10 μm diameter (PM-10)</td>
<td>22%</td>
</tr>
<tr>
<td>Sulfur dioxide (SO2)</td>
<td>37%</td>
</tr>
</tbody>
</table>

Table 4.2.3 Percent decrease in air concentrations of six key pollutants, USA (1980-1990)
There has been significant improvement in occupational hygiene conditions in large industries in high-resource countries [2]. The challenge is to extend this improvement to smaller enterprises and to medium- and low-resource countries, where there remains significant exposure to such agents as asbestos, crystalline silica and pesticides [14].

### Operative measure

**Examples**

**Preventing exposure**

- Use of gloves and face mask
- Pharmacists handling cytotoxic drugs

**Full respirator**

- Specified emergency procedure for spillage of hazardous material

**Controlling exposure**

**Environmental monitoring**

- Measurement of asbestos fibre level in breathing zone
- Film badge to assess radiation exposure

**Assessing uptake and excretion**

- Urinary measurement of metabolite, e.g. dimethylphosphate in workers exposed to dichlorvos
- Urine analysis for haematuria

**Determining of protein adducts and screening for preneoplastic lesions in MOCA (4,4’-methylenebis(2-chloroaniline))-exposed workers**

**Determining of DNA adducts in coke oven workers exposed to polycyclic aromatic hydrocarbons**

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**Table 4.2.3** Means to either prevent or determine the level of exposure to occupational carcinogens

<table>
<thead>
<tr>
<th>Compound</th>
<th>Average ambient air concentration [mg/m³]</th>
<th>Cancer associated</th>
<th>IARC classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde</td>
<td>3</td>
<td>Nasal tumours in rats</td>
<td>2B</td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>0.01 – 10</td>
<td>Long cancer in workers</td>
<td>2A</td>
</tr>
<tr>
<td>Arsenic</td>
<td>(1 – 30) x 10⁻⁵</td>
<td>Long cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Benzo(a)pyrene</td>
<td>No data</td>
<td>Long cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Bis[chloromethyl]ether</td>
<td>No data</td>
<td>Epitheliomas in rats</td>
<td>1</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>0.5–10</td>
<td>Kidney tumours in rats</td>
<td>2B</td>
</tr>
<tr>
<td>Chromium VI</td>
<td>(5 – 200) x 10⁻⁵</td>
<td>Long cancer in workers</td>
<td>1</td>
</tr>
<tr>
<td>1,2-Dibromoethane</td>
<td>0.07 – 4</td>
<td>Urinary excretion in rodents</td>
<td>2B</td>
</tr>
<tr>
<td>Diesel exhaust</td>
<td>1.0 – 10</td>
<td>Long cancer</td>
<td>1</td>
</tr>
<tr>
<td>Nickel</td>
<td>1 – 180</td>
<td>Long cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>Polychlorinated hydrocarbons (benzo[a]pyrene)</td>
<td>(1 – 10) x 10⁻⁵</td>
<td>Long cancer in humans</td>
<td>1</td>
</tr>
<tr>
<td>1,1,2,2-Tetrachloroethane</td>
<td>0.1 – 0.7</td>
<td>Hepatocellular carcinoma in mice</td>
<td>3</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>1 – 10</td>
<td>Cell tumours in tissues of rats</td>
<td>2A</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>0.1 – 10</td>
<td>Haemangiosarcoma in workers</td>
<td>1</td>
</tr>
</tbody>
</table>

---

**Table 4.2.4** WHO guidelines (1998) for air pollutants with carcinogenic health endpoints. These substances have been classified by IARC as either human carcinogens (Group 1), probable human carcinogens (Group 2A) or possible human carcinogens (Group 2B).

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**REFERENCES**

The most important implication of our understanding of the prevention of chronic hepatitis and hepatocellular carcinoma is the possibility of preventing the onset of these cancers through vaccination. The hepatitis B virus (HBV) vaccination program has been highly successful in preventing chronic hepatitis and hepatocellular carcinoma.

Vaccination

**Summary**

- Hepatitis B virus (HBV) vaccine has proven to be highly effective in preventing chronic hepatitis and hepatocellular carcinoma.
- Twenty-five years after having been licensed, HBV vaccination programs are now carried out in at least 158 countries. However, they have yet to achieve high coverage in many high-risk areas, such as in sub-Saharan Africa.
- Two human papillomavirus (HPV) vaccines were licensed in 2007 and show high efficacy in the prevention of precancerous lesions of the cervix uteri in young women who have not already been infected by the HPV types included in the vaccine.
- The duration of the efficacy of the HBV vaccine and the need for a booster are not yet known, and the vaccine price is currently unaffordable in medium- and low-income countries.
- The development of vaccines against infections other than HBV and HPV has been very difficult. A more realistic goal to prevent certain cancers is greatly encouraged.
- An epidemic of jaundice due to HBV infection in children was reported in the year 1880 and was an adverse effect of a smallpox vaccine campaign in Germany (see [2] for a review) that started in 1880. The etiology of what was formerly called "serum hepatitis" was identified in the 1950s and became better understood in the two subsequent decades following the development of laboratory markers of exposure (antibodies against hepatitis A core antigen, anti-HBc) and chronic infection (hepatitis B surface antigen, HBsAg).
- HBV infections are among the most common causes of death worldwide, with over 1 million deaths per year. The majority of these deaths are due to liver cancer and cirrhosis.

**HBV vaccine**

An epidemiological database due to HBV infection was reported for the first time in 1983 and was an adverse effect of a smallpox vaccine campaign in Germany (see [2] for a review). The etiology of what was formerly called "serum hepatitis" was identified in the 1950s and became better understood in the two subsequent decades following the development of laboratory markers of exposure (antibodies against hepatitis A core antigen, anti-HBc) and chronic infection (hepatitis B surface antigen, HBsAg).

HBsAg seroprevalence has marked geographic diversity of these agents. With respect to the role of immunity in Hp infection. The state-of-the-art in developing vaccines against HIV, the etiology of what was formerly called "serum hepatitis" was identified in the 1950s and became better understood in the two subsequent decades following the development of laboratory markers of exposure (antibodies against hepatitis A core antigen, anti-HBc) and chronic infection (hepatitis B surface antigen, HBsAg).

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include HPV vaccination in infant immunisation schedules (Fig. 4.3.1) and to improve coverage in countries that have already opted to do so (Fig. 4.3.2). The drop in the price of the HBV vaccine and the efforts of vaccine-denouncing organisations should help to make these targets possible. In addition, as policies of selective immunisation of high-risk individuals are seldom effective, routine HPV vaccination is now also advocated in low-endemicity countries on the grounds that whenever a potentially devastating disease like hepatocellular carcinoma is easily preventable, steps should be taken to achieve this outcome.

HPV vaccine

HPVs are DNA viruses that infect epithelial (skin or mucosal) cells. There are more than 100 known mucosal HPV types, and at least 13 of them, called high-risk types, can cause cancer of the cervix [8]. HPV16 and 18 are found in over 70% of cervical cancer world-wide and also predominate in cancer sites other than the cervix (i.e. anus, vulva, vagina, penis, and a small fraction of cancers of the head and neck). The discovery that cervical cancer was associated with sexual contact paved the way to an understanding of the role of HPV infection, which is predominantly sexually transmitted [8].

The two currently available HPV vaccines [9,10] include HPV16 and 18 and are based on L1 virus-like particles (VLPs), i.e. empty viral capsids that are able to induce an immune response. The HPV16/18 vaccines were at least 90% effective in preventing high-grade cervical lesions (CIN2 and 3) in women aged 16–26 years who had been infected with HPV16 and 18 before vaccination, or CIN2 and 3 caused by other HPV types in clinical trials [9]. Therefore, in the analyses by intention to treat, the efficacy diminished from 99% to 89% (95% confidence interval: 79–99%) when all CIN2 and 3 lesions were considered [Table 4.3.1]. This efficacy profile obliges us to: 1) concentrate on the vaccination of girls before they become sexually active; 2) try to increase the number of high-risk HPV types present in the vaccine; and 3) make every possible effort to match immunisation with high-quality organised screening programs [11]. Although data on all high-risk HPV types present in CIN2 and 3 have not yet become available, some cross-protection against persistent infection from high-risk types other than HPV16 and 18 has been reported (Table 4.3.2) [10].

Table 4.3.2 Efficacy of quadrivalent vaccine against human papillomavirus (HPV) 16/18

<table>
<thead>
<tr>
<th>Vaccine / Control</th>
<th>HPV16/18</th>
<th>CIN2 or more severe</th>
<th>2 / 21</th>
<th>90 (53–99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN3 or more severe</td>
<td>3 / 28</td>
<td>89 (59–99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent infections (12 months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV16/18</td>
<td>11 / 86</td>
<td>76 (49–90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other high-risk types</td>
<td>100 / 137</td>
<td>72 (5.5–47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All high-risk types</td>
<td>112 / 180</td>
<td>38 (18–54)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Available vaccines did not, however, prevent development of CIN2 and 3 in women who had been infected by HPV16 and 18 before immunisation, or CIN2 and 3 caused by other HPV types in clinical trials [9]. Therefore, in the analyses by intention to treat, the efficacy diminished from 90% to 89% (95% confidence interval: 79–99%) when all CIN2 and 3 lesions were considered [Table 4.3.1]. This efficacy profile obliges us to: 1) concentrate on the vaccination of girls before they become sexually active; 2) try to increase the number of high-risk HPV types present in the vaccine; and 3) make every possible effort to match immunisation with high-quality organised screening programs [11]. Although data on all high-risk HPV types present in CIN2 and 3 have not yet become available, some cross-protection against persistent infection from high-risk types other than HPV16 and 18 has been reported (Table 4.3.2) [10].

However, successful prevention of cervical cancer through immunisation presents enormous challenges. The greatest of these are the lack of information on the duration of vaccine efficacy, which at this point has been evaluated for no more than five years, and by the vaccine price that is unaffordable in many medium- and low-income countries. In addition, reaching girls before puberty or in their early teens may be more difficult than delivering vaccines to newborns and infants, especially in low-resource countries. Cultural barriers and misinformation may also burden HPV vaccine acceptance.

For the moment, no plan exists to expand the use of HPV vaccine to boys, as 1) efficacy of the vaccine in the prevention of HPV infection in men is not yet proven, and 2) if good coverage is achieved, a sexually transmitted infection like HPV should be greatly reduced even by vaccinating one gender only.

Vaccines against other cancer-causing chronic infections

Research into new prophylactic and therapeutic vaccines is also ongoing for at least three additional infections that are responsible for a large portion of the cancer burden worldwide: HCV, HIV and HPV. Although the first two agents are RNA viruses and the third is a bacterium, they all have in common some characteristics that have greatly permitted past efforts to produce effective vaccines: 1) they display high genetic and antigenic diversity and mutate very rapidly; in the host, 2) they induce, after natural infection, strong humoral and cellular responses that seem, however, unable to eliminate the infection or prevent reinfection; and 3) no small animal model or cell culture systems were available until recently to help vaccine developments.

Several candidate vaccines (e.g. virus-like particles, recombinant proteins, DNA vaccines) against HCV, an increasingly important cause of liver cancer, were tested in chimpanzees [12], and induced a strong cellular immune response. Vaccination did not, however, prevent the chimpanzees from becoming infected, but the course of the infection was apparently attenuated.

Fig. 4.3.3 Evolution of chronic gastritis, peptic ulcer disease and liver cirrhosis. Panel A shows the hypothetical course of infection in unvaccinated persons. A T-cell vaccine might decrease the burst of viremia and shortening the time that viral loads are controlled (blue). From Johnston and Fauci, 2007.
A unique feature of HIV is that a pool of latently infected lymphocytes (resting CD4+ T cells) is established very early during primary infection (Figure 4.3.3). Thus, the window of opportunity for a prophylactic vaccine to clear HIV and prevent chronic infection is very small. On a positive note, HIV has some highly conserved epitopes. Initially, vaccine developers focused on recombinant forms of the viral envelope, which is the target of the virus, but later their attention moved to vaccines that enhance T-cell immunity. However, T-cell mediated control of infection may not prove to be complete. Deciding whether the level and durability of modulated protection observed in clinical trials are sufficient to seek or grant vaccine licensing will challenge whether the level and durability of protective antibodies is sufficient, as are most classic preventive vaccines. Instead, they would need to be delivered in the context of global preventative measures. As a result, Figure 4.3.4, will be the case for HPV vaccines and cervical cancer screening (17).

finally, it is worth bearing in mind that the private pharmaceutical sector has less incentive to invest in research and development of vaccines against cancer than anti-cancer medications (18). The development of new cancer preventive vaccines, as well as their accessibility to low-resource countries, is therefore crucially dependent upon the support of public and private donors such as the Bill & Melinda Gates Foundation, and those included in the Global Alliance for Vaccines and Immunisation. Combined public and private research expenditures will therefore be necessary to develop important new vaccines.
Cancer Chemoprevention

Summary

- In healthy subjects living in well-nourished communities, current evidence does not support recommendation for any agent for chemoprevention of cancer.
- There is evidence that use of some antioxidant supplements may increase mortality.
- Folic acid supplements are suspected to increase the risk of colorectal cancer.
- In women at high risk for breast cancer, tamoxifen and raloxifene may be considered for reducing the risk of developing breast cancer.
- Randomised trials using ordinary doses of vitamin D (i.e. 400–600 IU per day) have shown no influence on cancer risk, although these ordinary doses seem to reduce mortality.

Chemoprevention is the reduction of cancer risk through the use of pharmaceuticals or other agents such as micronutrients. Chemoprevention is an appealing low-cost and easy cancer control method, mainly for subject having an inherited predisposition to certain cancers.

Laboratory data and observational studies have also suggested that several commonly used pharmaceuticals could have anti-cancer activity, and could be candidates for chemoprevention in cancer of the digestive tract, such as the anti-inflammatory drugs.

Chemopreventive agents are to be considered as pharmacological compounds, that is, substances that will interact with several biological receptors which may reduce cancer risk, and also cause other effects due to impact on other physiological activities. This notion also applies to apparently “natural” substances that can be found in usual foodstuffs, as chemoprevention will generally use doses (much) higher than those in typical dietary intakes. Also, a putative chemopreventive compound may be selected, while the average diet represents a composite mixture of hundreds of compounds.

Therefore, a number of randomised trials have been mounted to verify the reality of anti-cancer activity suggested by basic research and observational studies.

Many trials tested composite intervention, mixing vitamins and other elements, which renders it difficult, if not impossible, to disentangle the effects of individual compounds. In the remainder of the text, we have selected results from trials that provide information on effects specific to each supplement.

Anti-Oxidants

Vitamin A and retinoids

Compounds related to vitamin A comprise preformed vitamin A compounds, essentially retinol and retinyl esters. These compounds were initially shown to modulate differentiation in many experimental systems. No significant effects on mortality rates were observed for supplementation with combination of retinol and zinc [12], beta-carotene and vitamin A [5]. One large randomised trial of a vitamin A analogue, letermovir, showed no impact on occurrence of secondary breast cancer in breast cancer survivors [13]. Vitamin A and retinoids may antagonise the physiological action of vitamin D, mainly on bone. Two studies have reported doubling of hip fracture rates among women with high retinol intakes from food or supplements (>1.5 mg per day) [14,15]. In 1998, a systematic review by an IRCP Expert Group concluded that there was evidence suggesting lack of anti-cancer activity of preformed vitamin A compounds, and thus also of vitamin A [Table 4.4.1] [10].

Retinoids are a class of compounds structurally related to vitamin A. In 1999, a systematic review by an IRCP Expert Group concluded that there was inadequate or limited evidence for anti-cancer activity of nine different retinoid acid compounds, and some were teratogenic in humans or in animals [Table 4.4.1] [11].

Vitamin C

Vitamin C is deemed to be a free-radical scavenger, and high intakes of foodstuffs rich in vitamin C (e.g. citrus fruit) could play a role in decreasing gastric cancer incidence. Double-blind randomised trials of supplementation with ascorbic acid, vitamin C (combined with other anti-oxidants usually vitamin E, selenium, beta-carotene) of populations at high risk for gastric cancer in China and Venezuela did not result in higher rates of regression of dysplastic lesions in the stomach [16,17].

Vitamin E

Vitamin E exists in eight different isomers, and alpha-tocopherol is the most biologically active. Vitamin E has anti-oxidant properties that were deemed to play a role in control of cellular oxidative damage. In the ATBC study [6], the group receiving a vitamin E supplement (50 IU per day) had no reduction in lung cancer incidence but a 34% reduction in prostate cancer incidence. However, deaths from cerebrovascular accidents doubled. A randomised placebo-controlled trial within the Women’s Health Initiative Study found no effect of 600 IU per day of vitamin E on cancer risk [18].

A meta-analysis of vitamin E supplementation including 16 randomised trials suggests that high doses all vitamin E supplementation were associated with increased risk of breast cancer.

Table 4.4.1 Evidence of cancer preventive activities from the IARC Handbooks of Cancer Prevention series.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Humans</th>
<th>Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Limited</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Limited</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Inadequate</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Indometacin</td>
<td>Inadequate</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Carotenoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-carotene (high dose supplements)</td>
<td>Lack of activity</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Beta-carotene (usual dietary levels)</td>
<td>Inadequate</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Alpha-Tocopherol</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Folic acid</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>N-Ethylretinamide</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>9-cis- retinoic acid</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Fenretinide (4-PRP)</td>
<td>Inadequate</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Ethylamide</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>N-Ethylretinamide</td>
<td>Inadequate</td>
<td>Lack of activity</td>
</tr>
<tr>
<td>Targretin</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>LGD 1550</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
</tbody>
</table>
against oxidative stress through the selenium-mediated reduction in COX-2 cyclooxygenases: COX-1 is constitutively expressed and regulates the homeostasis of various leukocytes. Selenium at high doses is known to be toxic, and therefore, its use in cancer chemoprevention is limited. However, supplementation with selenium has been shown to increase cancer risk in high-risk subjects, and thus, it should be used with caution. Another important aspect is the role of aspirin, sulindac, piroxicam, and indomethacin, which are known to be effective in reducing the incidence of colorectal cancer. The cyclooxygenase pathway is a major target for prevention by non-steroidal anti-inflammatory drugs (NSAIDs) due to its role in inflammation, apoptosis, and angiogenesis, and it is suggested that ordinary doses of vitamin D supplements would have more beneficial effects than ordinary doses, on cancer risk, in the risk of other non-cancerous diseases, and on mortality. The associations between high intakes of vitamin D supplements and a wide range of cancer types have been conflicting, but recent studies have suggested that vitamin D supplementation may be associated with a reduction in colorectal cancer risk.

**Multivitamin preparations**

A systematic review conducted using the articles from the NCI/NIH (National Cancer Institute/NIH) database of over 300,000 subjects showed that there was no significant reduction in the incidence of colorectal cancer associated with multivitamin use. However, a recent meta-analysis of randomized trials on colorectal cancer prevention found that multivitamins, including vitamin D supplements, may be associated with a reduction in colorectal cancer risk. The question remains whether higher doses of vitamin D supplements would have more beneficial effects on ordinary doses, on cancer risk, in the risk of other non-cancerous diseases, and on mortality. The associations between high intakes of vitamin D supplements and a wide range of cancer types have been conflicting, but recent studies have suggested that vitamin D supplementation may be associated with a reduction in colorectal cancer risk.

**Micronutrients in subjects with poor nutritional conditions**

One large trial tested a combination of beta-carotene, vitamin E, selenium, and trace elements (e.g., iron and zinc) in a poorly nourished Chinese population. After 5 years, the group treated with the combination experienced a significantly reduced risk of all-cause mortality, primarily as a result of a statistically significant 21% lower stomach cancer mortality rate. There was a significant reduction in oesophageal cancer, the primary endpoint of the study. Indirect evidence that beta-carotene may protect from stomach cancer in high-risk subjects comes from the randomized, double-blind controlled interventional trial in subjects with gastric dysplasia in the area with a very high gastric cancer incidence in Colombia. Gastric biopsies taken at baseline were compared with those taken after 72 months, daily use of 30 mg beta-carotene (combined with vitamin C) resulted in a statistically significant increase in the frequency of regression of premalignant lesions of the stomach [25].

**Methyl donation: Folic acid**

Folic acid plays an important role in DNA repair, synthesis and methylation reactions. Two randomised trials of multivitamin trials showed that folic acid supplements may help reduce the risk of colorectal and prostate cancer, and of adenomatous polyposis [26,27]. Other micronutrients

Lycopene (from tomato), flavonoids and green tea extracts are substances for which anti-cancer activity is suggested by observational studies. No recommendation about the value of these substances in cancer prevention can be issued before publication of randomised trials testing their efficacy.

**Vitamin D**

Vitamin D is to be considered more as a hormone than as a vitamin. Furthermore, Vitamin D is not strictly speaking a vitamin, as its synthesis takes place in skin exposed to ultraviolet B radiation. Ecological studies have suggested that cancer burden is increased with increasing altitude. Increasing altitude has been associated with a decrease in vitamin D status because of reduced exposure to sunlight, and this decrease has been linked to increased cancer risk. The question remains whether higher doses of vitamin D supplements would have more beneficial effects on ordinary doses, on cancer risk, in the risk of other non-cancerous diseases, and on mortality. The associations between high intakes of vitamin D supplements and a wide range of cancer types have been conflicting, but recent studies have suggested that vitamin D supplementation may be associated with a reduction in colorectal cancer risk.
cyclooxygenase (COX)-2 inhibitor celecoxib effectively inhibit the growth of familial adenomatous polyposis polyps [44, 45]. However, randomised trials in patients with sporadic adenomatous polyps reduced the possibility of using this class of drug for cancer prevention because of significant cardiovasuclar toxicity despite effectiveness in preventing sporadic polyposis [43, 44]. Administration of aspirin did not result in regression of adenomas [46] or high doses required to achieve the protective effect may cause toxicity, which outweigh benefits of treatment [47].

Results of a large-scale, placebo-controlled long-term trial organised within the Women’s Health Initiative suggested that alternate-day use of low-dose aspirin (100mg) for an average 10 years of treatment did not lower risk of total, breast, colorectal or other site-specific cancers [48].

**Estrogen receptor modulators**

Since 1990, tamoxifen has become widely used for breast cancer treatment. Tamoxifen use has been rapidly known to increase thromboembolic events and cancer of the corpus uteri. In spite of these side effects, tamoxifen being classified as an IARC Group 1 carcinogenic agent [49], it has been tested for preventing contralateral breast cancer in women with a first breast cancer. Trials started in women without a uterus, and there is conclusive evidence that tamoxifen reduces the risk for contralateral breast cancer by 38% in women with a previous diagnosis of breast cancer [50]. There was no effect for breast cancer negatives for over 10 years treatment (ER-negative), but BR-positive cancers were decreased by 48% (95% CI 36-58%). Rates of endometrial cancer were increased in all tamoxifen prevention trials.

Raloxifene is a non-steroidal selective estrogen receptor modulator (SERM). One trial (the MORE trial) on treatment of osteoporosis found a reduction 72% in the incidence of breast cancer among women who use raloxifene [51]. A further trial (the RUTH trial) with breast cancer as a primary endpoint found a 44% decrease in breast cancer incidence among raloxifene users, but also a 49% increase of stroke and 44% increase of venous thromboembolism [52]. The preventive effect of raloxifene was confined to ER-positive breast tumours.

In order to better evaluate the respective properties of tamoxifen and raloxifene, a randomised trial was mounted in the USA by the National Surgical Adjutant Breast and Bowel Project [53]. This trial showed that raloxifene and tamoxifen had a similar ability to reduce breast cancer incidence. Raloxifene induced fewer thromboembolic events, but seemed to increase the incidence of in situ breast cancer. Death rates among women taking tamoxifen or raloxifene were similar.

**Omega-3 fatty acids**

Omega-3 fatty acids are mainly found in oily fish, and were deemed to protect against oxidative reactions involved in cancer and cardiovascular diseases. Systematic reviews of prospective cohort studies and of randomised trials found no evidence for a protective effect of these fatty acids on either cancer (including colorectal and breast cancer) or cardiovascular diseases [54, 55].

**Dietary fibre (see also chapter on diet and cancer)**

A systematic review of 13 prospective cohort studies found no effect of dietary fibre intakes on colorectal cancer incidence [56].

In five randomised trials, dietary supplementation with wheat bran or other types of fibre did not affect the rate of recurrence of colorectal adenomas [57-59]. The randomised trial by Bonithon-Kopp et al. [58] found that subject assigned in the intervention arm (10ppg/halka 3.5g per day) had in fact a significant increased risk of adenoma recurrence.

**Calcium**

One double-blind, placebo-controlled randomised trial [60] found that calcium supplement Administration (1g elementary calcium per day) reduced by 15% the risk of recurrence of adenomatous polyps of the large bowel. The effect of calcium was independent of intial dietary fat and calcium intake. The same trial also found that calcium supplement seemed more likely to decrease the risk for more advanced polyps, suggesting that such supplements could decrease the incidence of colorectal cancer [63].

Another double-blind, placebo-controlled randomised trial concluded that a moderate reduction of adenomatous colonic polyps with calcium supplements 1.2 g elementary calcium per day was only seen in subjects with above average serum 25-hydroxyvitamin D levels [64]. The randomised trial of Bonithon-Kopp et al. [58] found a decrease of colorectal polyp recurrence in subjects assigned to calcium 2g per day, but the difference with the placebo group was statistically non-significant.

Calcium supplements (1g elementary calcium per day) were associated with a 17% decrease in kidney stone formation in the WHI trial [54].

**Conclusions**

Most of these trials testing chemopreventive properties of many compounds found to possibly have anti-cancer properties in observational studies turned out to be negative or to show serious adverse events. Therefore no recommendation for use of a compound (even “natural substances” found in the diet) for cancer chemoprevention should be made before a large randomised trial (preferably double-blind and placebo-controlled) has evaluated both the efficacy as well as adverse effects of ingestion of the compound.

In healthy subjects living in well-nourished communities, current evidence does not support recommendation for any agent for chemoprevention of cancer, and there is evidence that use of antioxidant supplements may increase mortality (beta-carotene, vitamin E), or increase mortality in subject with high baseline serum levels of the compound (selenium), or may increase the risk of fracture (Vitamin A). Folic acid supplements are suspected to increase the risk of colorectal cancer. In communities with sub-optimal nutritional status, supplements with anti-oxidants may reduce mortality and stomach cancer risk.

In women at high risk for breast cancer, tamoxifen and raloxifene may be considered for reducing the risk of developing a second breast cancer (e.g. contralateral other breast). In subjects with familial adenomatous polyposis, the non steroidal anti-inflammatory drug sulindac may eventually be considered for prevention of adenoma recurrence although gastrointestinal and cardiovascular toxicity may be limiting. In the future, low-dose combinations of effective agents may serve to mitigate toxicity.

Randomised trials conducted so far using ordinary doses of vitamin D (i.e. 400-600 IU per day) have shown no influence of vitamin D supplements on colorectal cancer risk. However, these doses seem to reduce all-cause mortality. The effects of intakes of high doses of vitamin D (1500 IU per day) over the long term are unknown, and such schedule should be tried with a placebo-controlled randomised study [32].
REFERENCES


Screening for Cervical Cancer

Summary

In most developed countries, cytological screening (Pap test) has led to a significant reduction in the incidence of and mortality from cervical cancer, particularly in coun-
tries that have implemented population-
based screening programmes. In coun-
tries with lower participation compliance and a less developed healthcare system, screening has been much less effective in reducing mortality.

In developing countries, the cost of infrastructure and initial investments for organised cytological screening may be prohibitive. Alternative methods such as visual inspection with acetic acid (VIA) or with Lugol’s iodine solution (VILI) are effective in preventing cervical cancer in low-resource countries.

HPV testing is an alternative but currently expensive method for screening and preventing cervical cancer. There is a need to develop simple, affordable and accurate methods of HPV testing with comprehensive guidelines for its use in screening programmes.

Screening should be implemented in the context of an organised programme following comprehensive quality assurance guidelines, with adequate attention paid to training and planning, resources for management of detected lesions, and coordination, monitoring and evaluation of performance and effectiveness.

Invasive cervical cancer is prevented for several years by asymptomatic and slowly progressing precancerous lesions such as high-grade cer-
vical intraepithelial lesions (CIN grade 2 and 3) or adenocarcinomas in situ. The early detection of CIN by screening and their effective

treatment leads to prevention of invasive cer-
vical cancer. Following the introduction of cervi-
cal screening programmes in many developed
countries a decline in incidence and mortal-
ity from cervical cancer has been observed in
the past 5 decades (Figure 4.5.1).

Persistent infection with one or more of the oncogenic types of human papillomaviruses (HPV) is the cause for cervical neoplasia [1]. and cervical cancer is a rare long-term outcome of a common viral infection of the cervical epithelium. This knowledge has opened up new avenues of prevention such as HPV vaccination and HPV testing for cervical screening. While HPV vaccination is an excit-
ing and emerging preventive option in the long run, currently screening remains the principal strategy to prevent cervical cancer globally. CIN 2–3 lesions represent a ‘preclinical’ stage of cervical squamous-cell carcinoma that has high prevalence and is detectable in the course of population-based screening. On the other hand, screening is often not effective in detect-
ing the pre-invasive glandular lesions of the cer-
vical canal. Cervix screening has instead aimed in preventing adenocarcinomas of the cervix.

Conventional cervical cytology (Pap smear, Figure 4.5.2), the most commonly and widely used cervical screening test, has been largely responsible for the early detection of cervical precancerous lesions and subsequent decline of invasive cervical cancer incidence and mor-
tality in many developed regions of the world where successful screening programmes have been implemented. However, certain limitations of the Pap smear, in terms of the subjective nature of the test, resources required and low sensitivity in most routine settings, have led to the development and evaluation of alternative screening tests such as liquid-based cytology, HPV testing and visual screening tests.

The efficacy of Pap smear screening

Cytology screening involves collection of cer-
vical cells from the cervical epithelium using a wooden spatula or a brush, preparation and

fixation of the smear by a doctor or a nurse follow-

by staining and reading and reporting of the results by a cytotechnician and a
cytopathologist. Cytology requires a labora-
tory infrastructure, with internal and external quality control measures to process slides and
microscopy, and a system to communicate the results to the women. High-quality training,
continuing education and proficiency testing of
personnel are essential to ensure reliable and
efficient testing. Population-based Pap smear
screening programmes were initiated in British
Columbia in 1949 and in regions of Norway in
1959 and Scotland in 1964. Since then, large-scale population-based cytology screen-
ning programmes have resulted in a marked reduction in the incidence of and mortality from cervical cancer in the past 5 decades in the developed countries of Europe, North America, Japan, Australia and New Zealand. Organised screening with systematic cell recall, follow-up and surveillance systems have shown the greatest effect (e.g. Finland, Iceland), while using fewer resources than the less organ-
ised programmes (e.g. USA, France). In the UK,
Alternatives to the Pap smear

Liquid-based cytology

Liquid-based cytology (LBC) relies on a uniform thin-layer of cervical cells (Figure 4.5.4) without debris prepared from processing a fluid medium containing the cervical cells, leading to improved sample adequacy and microscopic readability of the smear. It is a more expensive test than conventional cytology, and requires additional instrumentation to prepare the smears. Although HPV testing is the most objective and reproducible of all currently available cervical screening tests. In several cross-sectional studies the sensitivity of HPV testing in detecting CIN 2 and 3 lesions varied from 66–100% and the specificity varied from 62–90% [4,11,12]. The sensitivity of HPV testing reported by studies in developing countries has been somewhat lower than that reported by studies in developed countries.

Fig. 4.5.4 Liquid-based cytology smear showing A. normal cervical cytology B. high-grade squamous intraepithelial lesion (HSIL)

Earlier reviews claimed improved sensitivity to detect high-grade CIN [3,8], results from a recent review [9] and a randomised trial [10] do not support claims of better performance by LBC.

HPV testing

The fact that cervical neoplasia are caused by persistent infection with oncogenic types of HPV has led to the evaluation of HPV testing as a primary screening test for cervical neoplasia.

In summary, compared to cytology, HPV testing seems to be a viable screening option, and potentially provides for use in under-resourced areas or for women who are reluctant to participate in screening programmes, further definitive research is needed to provide a solid evidence base to inform the use of self-sampling for HPV DNA testing for the purpose of increasing screening rates, especially in women who are never or seldom screened [16].

Although self-sampling for HPV DNA testing seems to be a viable screening option, and potentially provides for use in under-resourced areas or for women who are reluctant to participate in screening programmes, further definitive research is needed to provide a solid evidence base to inform the use of self-sampling for HPV DNA testing for the purpose of increasing screening rates, especially in women who are never or seldom screened [16].

In low-resource settings, where repeated screening of women is not feasible, HPV testing may provide an objective method of identifying and investing the limited resources on women at risk for disease [4]. However, it is currently more expensive (US$20–30) than other screening tests and requires sophisticated laboratory infrastructure including testing equipment, storage facilities, and trained technicians. Further developments in terms of less expensive testing and less sophisticated infrastructure and equipment requirements are essential to make HPV testing feasible in low-resource settings.

Efforts are now under way to develop simple, affordable, rapid and accurate HPV testing methods for use in low- and medium-resource settings.

In summary, compared to cytology, HPV testing is substantially more sensitive for prevalent CIN 2 or worse lesions, but significantly less specific. Whether this gain represents overdiagnosis or protection against future high-grade CIN or cervical cancer is not clear. Reduced incidence cervical cancer incidence rates started declining after coverage for screening was improved (Figure 4.5.3). Cervical cancer incidence has been reduced by as much as 80% where the cytology screening quality, coverage and follow-up of women are high. The highest reduction in cervical cancer incidence was in the 30–49 age group, where the focus of screening was the most intense.

Pap smear screening has been very sparsely implemented in most developing countries. Establishing quality-assured cytology screening programmes with national coverage is a challenging task in many developing countries, in view of the infrastructure for testing, trained personnel for reading, quality assurance and the resources and organisation required. Cytology screening programmes in Latin American countries such as Cuba, Brazil, Mexico, Peru and Colombia, among others, have not resulted in a significant reduction in the cervical cancer burden in these countries [5]. Possible reasons for the lack of success in these countries include a combination of sub-optimal cytology testing, lack of quality assurance, poor coverage of women at risk and inadequate follow-up of screen-positive women with diagnosis and treatment.

A critical appraisal of reasons for the sub-optimal performance of cytology screening in low- and medium-resourced countries has promoted the reorganisation of programmes in many Latin American countries and the evaluation of alternative screening tests, such as HPV DNA testing, visual screening with 3–5% acetic acid or Lugol’s iodine, and paradigms that require one or two visits to complete the screening and diagnosis/treatment processes [4,6]. Following the reorganisation of the Pap smear programme in Chile, incidence and mortality started to decline [7].

Table 4.5.1 Cervical cancer incidence and mortality in the cluster randomized controlled trial in Tamil Nadu, India. R. Sankaranarayanan et al. (2007) [24]

<table>
<thead>
<tr>
<th>Control group</th>
<th>Intervention group (VIA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible individuals</td>
<td>30,958</td>
</tr>
<tr>
<td>Cervical cancer incidence</td>
<td></td>
</tr>
<tr>
<td>Cancer cases</td>
<td>158</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.99 (0.58–1.66)</td>
</tr>
<tr>
<td>Overall</td>
<td>30–39 years</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.75 (0.59–0.95)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>0.62 (0.49–0.94)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>0.62 (0.51–1.24)</td>
</tr>
<tr>
<td>Cervical cancer mortality</td>
<td></td>
</tr>
<tr>
<td>Cancer deaths</td>
<td>92</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td>Overall</td>
<td>30–39 years</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.55 (0.31–1.00)</td>
</tr>
</tbody>
</table>

Fig. 4.5.2 Age-standardised incidence of invasive cervical cancer and cervical cancer mortality rate England. HPSC (2002) [17]. Quinn et al. (1999) [29]. B.J. Willoughby et al. (2006) [30]. Cancer Research UK (http://info.cancerresearchuk.org/)

Fig. 4.5.3 Cervical cancer incidence and mortality as the cluster randomised controlled trial in Tamil Nadu, India. R. Sankaranarayanan et al. (2007) [24]

HPV DNA testing is the most objective and reproducible of all currently available cervical screening tests. In several cross-sectional studies the sensitivity of HPV testing in detecting CIN 2 and 3 lesions varied from 66–100% and the specificity varied from 62–90% [4,11,12].
of or mortality from invasive cervical cancer among HPV-screened subjects compared with cytologically-screened subjects has not yet been demonstrated; this is an ongoing issue being addressed in a randomised trial in India [17].

Intermediate results from this trial show similar detection rates of CIN 2 and 3 lesions per 1000 screened women among those screened by cytology, HPV testing or visual screening with 4% acetic acid. HPV testing reportedly does not add significant psychological distress when combined with cytology in routine primary cervical screening [18].

**Visual inspection**

Visual screening is carried out after application of dilute acetic acid or Lugol’s iodine solution. Visual inspection with acetic acid (VIA) involves naked-eye inspection of the cervix using a bright torch light or a halogen focus lamp, 1–2 minutes after the application of 3–5% acetic acid using a cotton swab or a spray. A positive test is characterised by well-defined acetowhite areas close to the squamo-columnar junction (SCJ), to the external os, on the entire cervix or a cervical growth turning acetowhite (Figure 4.4.5) [19]. Immediate results following VIA allow diagnostic investigations and/or treatment in the same session as screening. However, VIA is a subjective test that suffers from high false-positive rates and low to moderate specificity and reproducibility. Quality assurance procedures for VIA are yet to be standardised and ensuring consistent high performance can be challenging under field conditions, requiring constant monitoring and frequent re-training of test providers.

The sensitivity of VIA to detect CIN 2 and 3 lesions and invasive cervical cancer varied from 37–95% and the specificity varied from 49–97% in several cross-sectional studies in developing countries [4]. The wide range in the accuracy of VIA underscores the subjective nature of the test, the varying competency of test providers, and the varying quality of reference standards used to establish the true positive disease. When Pap smear was concurrently evaluated, the sensitivity of VIA was found to be higher than or similar to that of Pap smear, but had lower specificity. It appears that a good quality VIA has an average sensitivity of around 50% and specificity of around 85% to detect high-grade CIN in experimental study settings.

The immediate availability of test results following visual testing has opened up the option of “screen and treat” or “single-visit” approach to ensure high compliance to the treatment of screen-positive women, in which those women, with no clinical evidence of invasive cancer and satisfying the criteria for ablative therapy, are immediately treated with cryotherapy, without confirmatory investigations such as colposcopy or histology. The safety, acceptability and feasibility of combining VIA and cryotherapy in a single-visit approach have been demonstrated in rural Thailand [20], Ghana [21], Guatemala [22] and South Africa [23]. In a randomised controlled trial in South Africa, VIA followed by cryotherapy resulted in 37% and 46% lower prevalences of CIN 2–3 lesions at 6 and 12 months follow-up compared with a control group [23]. Cryotherapy for HPV test-positive women resulted in much higher declines in the prevalence of CIN 2–3 at 6 and 12 months (77% and 74% respectively) in this study.

Currently, the efficacy and effectiveness of VIA screening in reducing cervical cancer incidence and mortality are being addressed in randomised controlled trials in India [17,24]. A 25% reduction in cervical cancer incidence and a 33% reduction in mortality have been observed 7 years from the beginning of VIA screening in one of the trials (Table 1)[24].

**Visual inspection with Lugol’s iodine**

Visual inspection with Lugol’s iodine (VILI) involves naked-eye examination of the cervix to identify mustard-yellow lesions in the transformation zone after application of Lugol’s iodine (Figure 4.5.6) [19]. The sensitivity of VILI varied from 44–92% and specificity from 75–85% in cross-sectional studies [25–27].
Conclusions

Cervical cancer affects striving global health inequities, resulting in deaths of women in their most productive years, resulting in devastating effects on the society at large. It is the largest single cause of years lost to life in cancer developing the world. The major barrier to prevention of cervical cancer is failure to be screened at all.

Organised screening is generally considered to be substantially more effective and efficient than opportunistic screening. The long natural history of cervical cancer presents several opportunities in terms of prevention, screening, early detection and treatment of CIN to prevent invasive cancer. Both screening and vaccination have the potential to save many lives. At the public health level, health care infrastructure, affordability and capacity to initiate and sustain vaccination and screening programmes are critical factors in cervical cancer control. Substantial evidence now exists on implementation of screening programmes based on cytology, visual screening tests or HPV testing, and such action has the potential for profound public health benefit, if appropriate screening policies are implemented in earnest. It is time to focus attention on provision of adequate resources for putting in place the important programmatic components of coordination, education, and quality assurance of participation, testing, diagnosis, treatment, follow-up care and evaluation.

To screen successfully in low-resource settings the following requirements must be met:

- Adequate and timely investments to assure sufficient infrastructure for screening, diagnosis and treatment and to train screening staff;
- Screening, diagnosis and treatment provided onsite in clinics that are accessible to the majority of eligible, target women;
- An affordable, low-cost/low-technology screening test that can lead to immediate treatment of abnormalities;
- High coverage of at-risk women;
- Appropriate educational efforts directed towards health workers and women to ensure correct implementation and high participation, and
- A built-in mechanism for monitoring and evaluation of the program and appropriate coordination and quality assurance.

Delays in investing in screening in low-resource countries means that many women will continue to miss opportunities for preventing cervical cancer for several decades to come. While HPV vaccination provides the hope for the future, screening provides the means for the present.

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Screening for Breast Cancer

Summary

Breast cancer is the most frequent cancer in women and accounts for over one in five new cancer cases in women worldwide. Due to an overall aging of the world population, the number of cases is expected to increase in the coming years.

The large randomised trials performed from 1976–1990 have shown that an invitation to breast cancer screening based on mammography can reduce mortality from breast cancer by averaging 23% in women aged 50–69 years. More recently, analysis of population-based screening programmes in women aged 40–69 years has demonstrated that regular mammography screening attendance can provide 40–45% reduction in breast cancer mortality.

There is only indirect evidence that screening by clinical breast examination will reduce the number of breast cancer deaths.

Screening should be implemented in the context of an organised, population-based programme following comprehensive quality assurance guidelines. Adequate attention should be paid to planning and training, identification and invitation of the target population, multidisciplinary management of screen-detected lesions, as well as to coordination, monitoring and evaluation.

Cancer of the breast is the most common cancer in women worldwide, and in many regions it is the most common cause of death from cancer in women. Breast cancer is characterised by a preclinical detectable phase lasting from 1–7 years, depending on the specific disease subtype. Mammography (X-ray examination of the breasts) can detect preclinical cancer, that is, detect the tumour before it is palpable and before it causes symptoms. Tumours detected and treated at an early stage are associated with a better survival rate than those detected symptomatically. Early diagnosis may permit breast-conserving surgery (Stage I disease), reduce the need for adjuvant therapy and decrease complications related to intensive treatment and recurrence [1-3].

The impact of screening

The incidence of breast cancer worldwide has been on the rise for at least the past half century. Factors such as diminished and delayed childbearing are partly responsible for this increase. Improved diagnostic methods are also generally considered to influence the increase. However, the introduction of screening mammography occurred several decades after the documented increase in incidence and can account for only a minor part of the increase. On the other hand, the marked increase in the incidence of in situ breast carcinoma appears to be directly related to the availability of mammography, as this form of breast cancer is difficult to detect by clinical methods [4-6].

In many developed countries mortality rates have been rather stable despite the steady increase in incidence. No clear overall decline in mortality was observed in any place before the late 1980s, when a gradual downturn in mortality was observed in any place before the late 1980s, when a gradual downturn in mortality was observed in many places around the world. In many countries, mortality rates have been on the rise for at least the past half century. Factors such as diminished and delayed childbearing are partly responsible for this increase. Improved diagnostic methods are also generally considered to influence the increase. However, the introduction of screening mammography occurred several decades after the documented increase in incidence and can account for only a minor part of the increase. On the other hand, the marked increase in the incidence of in situ breast carcinoma appears to be directly related to the availability of mammography, as this form of breast cancer is difficult to detect by clinical methods [4-6].

Mammography screening is performed on large numbers of predominantly asymptomatic women. The potential harm caused by mammography includes the creation of unnecessary anxiety and morbidity, inappropriate economic cost and use of ionizing radiation. The strongest possible emphasis on quality assurance occurred in Europe, North America and Australia. These decreases in breast cancer mortality have been attributed to a combination of earlier detection and improved treatment, but the relative contribution of each has not been determined [3,4,7,8].

Protocols for screening

Breast cancer screening is delivered in a variety of ways, including organised programmes and "opportunistic" activities which result in referral to mammography facilities by clinicians and self-referral by women themselves. Organised programmes are recommended because they include an administrative structure responsible for implementation, quality assurance and evaluation. The screening process begins with information and invitation of the eligible women to attend screening and extends from performance of the screening test to most cases mammography to the diagnostic assessment of women with suspicious test results and, if necessary, treatment of women with screen-detected lesions. Overall screening outcome and quality depend on the performance at each step in the screening process. Population-based programmes generally require a high degree of organisation in order to identify and personally invite each woman in the eligible target population. The population-based approach to programme implementation is recommended because it provides an organisational framework conducive to effective management and continuous improvement of the screening process, such as through linkage with population and cancer registries for optimisation of invitation to screening and for evaluation of screening performance and impact.

By the mid-1990s at least 22 countries had established national, sub-national or pilot population breast cancer screening programmes [9]. Currently, most of the 27 member states of the European Union are running or establishing population-based breast cancer screening programmes based on mammography [10]. Many programmes target the age group 50–69 years for mammography screening. The youngest age targeted for screening is generally 40 years. Some opportunistic programmes do not set an upper age limit for eligibility, whereas some population-based screening programmes target women up to age 74 or, in at least one case (The Netherlands) age 75. The upper age limit for three-yearly population-based invitation to attend the NHS Breast Screening Programme in the United Kingdom is 70 years. Older women can also request to attend screening. Most screening programmes have adopted a two-year screening interval; shorter intervals of 12 or 18 months have been adopted by programmes targeting women under age 50 which is consistent with the shorter mean sojourn time of breast tumours in younger women [11].

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Evaluation of screening

Screening by mammography began to be widely adopted in the late 1980s following the demonstration of its effectiveness in two major randomised trials [20,21].

Inconclusive results were found in two trials in Canada in which annual mammography and breast physical examination were compared with single breast physical examination and subsequent care in 40-49-year-old women [22], and with annual breast physical examination in women aged 50-59 years [23]. Additional randomised controlled trials have also demonstrated a significant decrease in breast cancer mortality in the invited populations compared to the non-invited control populations. The principal factors influencing the magnitude of this decrease include the participation rates of the invited women, the performance of mammography in the control population, and the diagnostic accuracy of mammography in each particular trial [19].

Most of the existing randomised controlled trials have been criticized for putative methodological weaknesses by critics who also argued that breast cancer mortality is not a valid end-point for screening trials [24,25]. These criticisms dismissed of all the positive randomised trials is generally considered to be inappropriate because, essentially, it is based on a mechanical evaluation of historical rates that are of questionable relevance to the results [26].

A re-appraisal of the randomised controlled trials, conducted by a working group of experts convened by the International Agency for Research on Cancer, concluded that the exclusion of the positive randomised controlled trials was unjustified and that there is sufficient evidence for the efficacy of screening women aged 50-69 years by mammography as the sole screening modality in reducing mortality from breast cancer. Women who were invited to be screened showed a reduction in breast cancer mortality amounting to 25% with the degree of benefit depending on the particular trial. Since not all women accepted the invitation, the reduction among those who chose to participate in screening is somewhat higher, being estimated at 33% [19].

None of the population screening trials had sufficient statistical power to evaluate the results by 10-year age cohorts, and attempts to determine the efficacy of mammography screening in the 40–49-year age cohort have yielded less promising results [19]. The lower incidence of breast cancer, and a somewhat greater radiopacity of the premammographic breast at mammography, combined with a more rapid progression of breast cancer in premammographic women may be contributing factors, but the current evidence is far from complete [1,27].

The effect of up to seven years of annual mammographic screening is under investigation in a randomised controlled trial in the UK which recruited women 39–41 years of age at study entry. The recently reported results at 10-year follow-up are not statistically significant but are consistent with other findings showing a significant but lesser impact of screening in women aged 40–49 years than in older women. The authors pointed out that the non-significant effect was much larger (i.e. 37% mortality reduction) in the women actually exposed to screening (participants) than in the entire group of women invited to attend screening (cohort). Due to the study protocol, sensitivity was reduced after the initial screening examination, which may have reduced the observed effect of screening [26].

Organized service mammography screening has been evaluated in Sweden by combin- ing individual breast cancer patient data with screening invitation data to document the impact upon the individual women of actually receiving the screening mammography exami- nation. In this large study involving women in the age range 40–69 years in nearly half of the country, data were collected on 342,187 women in the pre-screening era and 556,423 women in the screening era. Approximately two thirds of the study population was from regions with invitation to screening in the age-
In an average follow-up period of 13 years, the but the analysis was restricted to women <70. In some counties also offered screening to women in the age range 70-74, age range 50-69. Some counties also offered screening to women in the age range 40-69 and approximately one third was (Figure 4.6.5). For effective quality management, screening should be implemented in the context of an organized, population-based programme following comprehensive quality assurance guidelines. Adequate attention should be paid to planning and training, identification and invi-
tation of the target population, multidisciplinary management of detected lesions as well as coordination, monitoring and evaluation. Due to the favourable prognosis of breast cancer in high-resource countries, long-term follow-up is required to assess the full impact of service screening programmes [29,30].

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POD’s Mammography Programme: http://www.cancer.gov/cancertopics/screening


IARC Screening Quality Control Group (ECN): en_publication_details&CATNBR=ND7306954ENC

IARC Screening Quality Control Group (ECN): http://bookshop.eu.int/eGetRecords?Template=Test_EUB/

European Guidelines for Quality Assurance in Breast Cancer Screening, Diagnosis and Treatment: http://www.fda.gov/CDRH/mammography/mqsa-rev.html

FDA’s Mammography Programme: http://www.fda.gov/CDRH/mammography/


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Chapter 4.7: Screening for Colorectal Cancer

**Screening for Colorectal Cancer**

**Summary**

- Early detection of colorectal cancer increases the likelihood of cure and can lower mortality.
- Different screening modalities exist, including the fecal occult blood test (FOBT), flexible sigmoidoscopy, colonoscopy, and virtual colonoscopy.
- Population-based FOBT screening may reduce CRC mortality by 16%, but cannot much reduce CRC incidence.
- The use of rehydrated FOBT in one trial did decrease CRC incidence by about 20% after 10 years, but the high rate of false positives induced by the low specificity of rehydrated FOBT limits its use.
- Observational non-randomised studies suggest that endoscopic methods would decrease both CRC incidence and mortality, with much larger gains in mortality than FOBT.
- Offering FOBT screening to a population must take into consideration the logistics of screening and the burden CRC screening will represent in terms of colonoscopy.

In 2002, the worldwide burden of colorectal cancer (CRC) was estimated as 550,000 new cases and 278,000 deaths for men and 472,000 new cases and 200,000 deaths for women (1). Colorectal cancer is most frequent in North America, Australia, New Zealand and Western Europe, and occurs much less often in Asia, Africa, and parts of Europe. Benign or malignant neoplasms of the colon and rectum are the third most common malignancies in 2002, with 278,000 new cases and 278,000 deaths for men and 200,000 new cases and 100,000 deaths for women. (2).

**Colorectal Cancer**

Colorectal cancer is a total endoscopic evaluation of the colon, up to the caecum. This procedure also allows removal of polyps. The chance of cure during the 5 years following a negative colonoscopy is very small (19). Colonoscopy is less adapted to a mass screening programme, as the detection rate is high and the possibility of complications (e.g. intestinal perforation) is present. There is indirect evidence from non-randomised studies that colonoscopy and polyectomy may reduce CRC incidence and mortality. In the prospective National Polyps Study, rescreening after 10 years required further colorectal resection for removal of significant polyps eventually detected. Several software packages are commercially available or have been developed by academic researchers, and detailed evaluation of their effectiveness merits is still needed. A recent multicenter trial in the USA of 2600 asymptomatic men and women aged 60 years or older confirmed the sensitivity of CT to be equivalent to colonoscopy.

**Flexible sigmoidoscopy**

Rigid rectosigmoidoscopy is now abandoned in screening protocols, while flexible sigmoidoscopy is often proposed because FOBT is used. FOBT screening does not lower CRC incidence because this test rarely detects the presence of adenomatous polyps.

**Flexible sigmoidoscopy**

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**Screening for colorectal cancer**

- Early detection of colorectal cancer increases the likelihood of cure and can lower mortality.
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- Offering FOBT screening to a population must take into consideration the logistics of screening and the burden CRC screening will represent in terms of colonoscopy.

**REFERENCES**

Screening for Oral Cancer

Summary

- Oral cancer and its precancerous lesions can be readily detected by visual inspection of the oral cavity by health care providers.
- Oral cancer screening leads to the diagnosis of an increased proportion of early stage oral cancers and improves 5-year survival.
- A statistically significant 33% reduction in oral cancer mortality following oral visual screening has been demonstrated in a large-population-based randomised controlled trial.
- The assessment of the oral cavity during routine health care interactions and improved awareness among health care providers and seekers provide excellent opportunities for implementing oral cancer screening.

Oral cancer is a major health problem worldwide, accounting for 274 000 new cases and 143 000 deaths annually, of which two thirds occur in developing countries. [1] Oral cancer is often preceded by precancerous lesions such as leukoplakia, erythroplakia, lichen planus and submucous fibrosis. Oral leukoplakia refers to the presence of flat, predominantly white lesions in the lining of the mouth that cannot be characterised as any other disease. White lesions in a uniform smooth, coarsely granular or wrinkled surface are referred to as homogenous leukoplakia and are more likely to be malignant. Oral erythroplakia refers to the presence of flat, nodular, white or red exophytic and white or red lesions characterised as any other disease. Erythroplakia refers to velvety red, non-removable lesions in the oral mucosa (Figure 4.8.3) and they often harbour early invasive cancers. Oral submucous fibrosis (Figure 4.8.4) is characterised by recurrent inflammation and stiffness of the oral mucosa with progressive limitation in opening the mouth and protrusion of the tongue.

The natural history of oral precancerous lesions is not as extensively documented as that of the precursors to cervical cancer. Thus, for example, it is not known whether the different types of leukoplakia and erythroplakia constitute a continuum similar to the different stages evident during the development of cervical intraepithelial neoplasia. Although only a small fraction of subjects with these lesions may progress to invasive cancer, around 30-80% of invasive cancers are associated with pre-existing oral precancerous lesions (Figure 4.8.5). In hospital-based studies, a malignant transformation rate of 4.4-17.5% for leukoplakias, and in population-based studies transformation rates of 0.13-2.2% over several years have been reported [2]. The risk of malignant transformation varies with size (higher in women), type and location of leukoplakia (higher with non-homogeneous types and those located on the tongue or the floor of the mouth), presence of candida albicans and presence of epithelial dysplasia. The proportion of leukoplakias which regress has been reported to vary between 5 and 20% per year. It is difficult to determine to what extent the above findings are due to variations in case selection or are a true reflection of the natural history.

Early detection of oral cancer

Early oral cancers clinically present as small indurated ulcers, surface thickening, nodules (Figure 4.8.6), reddish velvety areas (Figure 4.8.7) or ulceroproliferative growths (Figure 4.8.8), often with no symptoms. Pain is usually absent with these early lesions. Careful assessment of oral precancerous lesions for any suspicious areas, and directed biopsies, is important in the early detection of underlying invasive oral cancers. Both oral precancerous and early suspicious carcinomas can be readily detected by trained clinicians, nurses and auxiliary health workers, by a systematic visual oral inspection and by palpation [3]. A high level of awareness among health care providers can lead to a high degree of clinical suspicion and appropriate diagnostic follow-up (such as referral), directed biopsies and histopathological examination. It is possible to diagnose such lesions in subjects during routine health care interactions, particularly at the primary healthcare level. Although other methods of early detection such as mouth self-examination, adjunctive tests like toluidine blue application, oral cytology and fluorescence imaging exist, systematic naked-eye visual inspection of the oral cavity and neck coupled with palpation of oral mucosa and neck are the most useful and readily applicable early detection procedures.

Oral visual inspection

The evidence supporting the routine use of oral visual inspection in the early detection of oral cancer is based on the performance characteristics of the test in cross-sectional studies, evaluation of routine screening programmes in health services and from a randomised controlled trial.

Oral visual inspection has been shown to be a sensitive and specific test to detect oral precancerous lesions and early asymptomatic oral cancers in several studies; the sensitivity of visual examination for detecting oral lesions varied from 58 to 94% and the specificity from 70 to 92%.[3-10] The frequency of positive screening tests ranged between 1.3 and 7.3% of screened subjects and the frequency of adherence to referral among screen-positive subjects was sub-optimal, ranging from 54% to 72%.

An oral cancer screening programme in Cuba, initiated 1984, involved annual oral examination of subjects aged 15 and above by dentists. Although the proportion of stage I cancers increased from 24% in 1983 to 49% in 1988, no reduction in oral cancer mortality has been observed since the introduction of screening, due to sub-optimal coverage of target populations both for participation and treatment. [1] A case-control study in the context of the programme revealed a 33% reduction (odds ratio 0.67 [95% CI: 0.46-0.95]) in the risk of advanced oral cancer [12]. The programme has been recognised to cover subjects aged 30 years and above with oral visual inspection once in 3 years and with an improved referral pathway for diagnosis and treatment. In a community-based cluster randomised controlled oral cancer screening intervention trial involving three rounds of oral visual inspection at 3-year intervals provided by trained health workers during 1995–2004 in Trivandrum, South India, a shift towards early stage at diagnosis (41% vs. 23%) and a higher 5-year survival frequency (50% vs. 34%) were observed.
Objectives

The primary objective of the study was to evaluate the feasibility of mouth self-examination in India, especially in high-risk populations. The secondary objective was to ascertain the level of awareness to prompt subjects at high risk to avail themselves of early detection services.

Methods

The evaluation was conducted in the context of a large cluster-randomized controlled trial in Kerala, India, which involved 21,000 subjects. The study included four stages: (1) Oral cancer screening using basic health workers in an area of high oral cancer mortality rate; (2) Training of health workers in the early detection of oral cancer and precancer cases; (3) Implementation of mouth self-examination in the control of oral cancer; and (4) Evaluation of mouth self-examination in the early detection of oral neoplasia.

Results

The study showed that mouth self-examination is a simple, effective, and feasible method for identifying oral cancer and precancer cases in high-risk populations. The sensitivity and specificity of mouth self-examination were 86.5% and 95.3%, respectively.

Conclusions

Mouth self-examination is a promising method for early detection of oral cancer and precancer cases in high-risk populations. Further research is needed to validate the results in larger studies and to assess the impact of mouth self-examination on cancer mortality and morbidity.

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Table 4.8.1 Oral cancer cases according to stage (and percentage distribution), detected during an Indian screening trial (1997-1999), compared with an unscreened control population.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (≤ 2 cm)</td>
<td>51 (23%)</td>
<td>20 (13%)</td>
<td>2.46 (1.39 - 4.34)</td>
</tr>
<tr>
<td>II (2.1-4 cm)</td>
<td>34 (17%)</td>
<td>17 (11%)</td>
<td>2.06 (1.14 - 3.72)</td>
</tr>
<tr>
<td>III (≥ 4 cm)</td>
<td>37 (18%)</td>
<td>35 (22%)</td>
<td>0.57 (0.35 - 0.92)</td>
</tr>
<tr>
<td>IV (adjacent structures involved)</td>
<td>67 (33%)</td>
<td>70 (44%)</td>
<td>0.97 (0.63 - 1.52)</td>
</tr>
<tr>
<td>Not known</td>
<td>16 (14%)</td>
<td>16 (10%)</td>
<td>1.56 (0.65 - 3.78)</td>
</tr>
<tr>
<td>Total</td>
<td>205 (100%)</td>
<td>158 (100%)</td>
<td>-</td>
</tr>
</tbody>
</table>


In the screened population (Table 4.8.1) [8], a 21% reduction in oral cancer mortality was observed in the intervention group compared to the control group 9-years from the initiation of screening in this study, which did not reach statistical significance. However, a statistically significant 34% reduction in mortality was observed among tobacco and/or alcohol users as compared to similar control subjects (Table 4.8.2). In summary, evidence from the Indian study shows that oral visual screening can reduce mortality in high-risk individuals. The cost-effectiveness of oral visual inspection is currently being addressed in the context of this trial.

Visual inspection after toluidine blue staining

Toluidine blue dye has been predominantly used as an adjunct for early detection of oral cancer in subjects with precancerous lesions, in order to provide better demonstration of possible malignant and dysplastic changes so as to help select sites for biopsies [13]. This test has been evaluated only in a few specified clinical settings where the reported false negative and false positive rates ranged from 20–30%. The value of visual examination after toluidine blue application as a primary screening test in the early detection of oral cancer is not known.

Mouth self examination

There is very little information on self-screening for oral cancer or on health education to promote mouth self-examination, especially in high-risk populations. In a study to evaluate the feasibility of mouth self-examination in India, 36% of 22,000 subjects who were taught mouth self-examination reportedly practiced the test and in the 247 subjects visiting the clinic within two weeks of a promotion campaign, 89 pre-cancers and 7 oral cancers were detected [14]. There is no information available on long-term feasibility and frequency rates of oral cancer with self-screening.

Oral cytology

Screening by oral cytology has never achieved the same recognition or efficacy as cervical cytology screening, and its role as a primary oral screening test is not yet clear. Keratinization of the oral epithelium poses a major challenge in collecting an adequate number of cells and oral lesions need to be visible before a sample can be collected. Inadequate cellular smears and the subjective nature of interpretation leads to high false negative rates for oral lesions [6,15]. New collection techniques using brush biopsy have reportedly improved the sensitivity (92.2%) and specificity (94.3%) for detection of oral cancer or dysplasia when tested on visually identified lesions [16,17]. Recently, liquid-based oral cytology has also been investigated [18].

Fluorescence spectroscopy or imaging

Fluorescence spectroscopy evaluates the physical and chemical properties of tissue by analyzing the intensity and character of light emitted in the form of fluorescence. Autofluorescence, and 5-aminolevulinic acid (5-ALA) induced protoporphyrin IX (PpIX) fluorescence can be recorded using a target integrating colour CCD camera [19]. Their usefulness as screening tools remains to be established.

Saliva-based tests

The value of using genetic targets in saliva as a early detection approach for oral cancer is currently being investigated [20].
Screening for Stomach Cancer

**Summary**

> Stomach cancer screening has been practiced in certain high-risk areas such as Japan and the Republic of Korea.

> The efficacy and effectiveness of such screening has not been shown in a randomized trial.

Stomach cancer screening has been practiced in Japan since 1963 and has been public health policy in the Republic of Korea since 1996. Screening is based on early detection of stomach cancer, with surgical resection of the stomach if a tumour is detected. The two techniques used for detection are X-ray examination, after the patient swallows a barium contrast medium, and endoscopic examination, with biopsies taken to confirm the presence of cancer. Gastric cancer screening is rare in less-developed countries, although pilot schemes based on the Japanese model have been conducted in Venezuela, Chile and Costa Rica.

It is difficult to judge the efficacy of stomach cancer screening in reducing mortality from stomach cancer. No randomized trial of stomach cancer screening has ever been conducted, though case–control studies with mortality from stomach cancer as an endpoint have been carried out. However, these studies were subject to several sources of bias that reduce the quality of the evidence they provide on screening efficacy. Recently, some prospective studies have shown important reductions in mortality from gastric cancer among participants in screening programmes in Japan and Costa Rica [1–3]. These studies are not subject to the recall bias that affects case–control studies. However, since these are observational studies, they still have the problem of self-selection: individuals who choose to participate in the screening programme may have a cancer risk that differs from that of non-participants. Therefore these studies cannot substitute for randomized trials.

**Fig. 4.9.1 Endoscopic views of gastric cancer (A,C) and corresponding images with dye enhancement (B,D).**

A. Depressed early gastric cancer. B. D Deep ulcer scar surrounded by superficial early gastric cancer excluding the mucous and submucous.

**REFERENCES**


Screening for Prostate Cancer

Summary
- Prostate cancer is now the leading in situ form of cancer in men in many countries.
- Evidence shows harms of screening, but no evidence from randomised trials shows efficacy of prostate cancer screening with PSA (or any other modalities).
- Population screening for prostate cancer cannot be recommended at present.
- Testing for PSA and integrated programmes of expert multidisciplinary diagnosis and treatment are effective at reducing mortality from prostate cancer.
- The availability of a cheap and safe test such as PSA has thrown up new issues and challenges for epidemiology.

Among several methods that have been proposed to screen for prostate cancer, case-control studies have found conflicting results for digital rectal examination. Prostatic Specific Antigen (PSA) measurement, obtained from a testing for pSa and integrated form of cancer in men in many countries, so whether to recommend screening depends on whether any moderate reduction in mortality is offset by a decreased quality of life for the men treated [8]. In a randomised trial of the effect of a 10-year incidence of low-grade prostate cancer has declined, 13% of men with a PSA of 2.5 ng/L or more had prostate cancer during the past decade, which resulted in an apparent improvement in clinical outcome. In a cohort of over half a million men aged 70 to 79 living in 16 cancer registries in the United States, Veterans Affairs Hospital in San Antonio. After surgery, 72% of men had a change of medical regimen, 61% had a change of drug treatment and 29% received a new medical diagnosis. Walsh and Thompson proposed that changes in diagnostic protocols could affect survival outcomes of men recently diagnosed with prostate cancer [12]. Since the introduction of PSA testing, the reported incidence of low-grade prostate cancer has declined, with 13% of men with a PSA of 2.5 ng/L or more having prostate cancer during the past decade, which resulted in an apparent improvement in clinical outcome.
The real impact and tragedy of widespread prostate cancer testing is the doubling of the lifetime risk of a diagnosis of prostate cancer without any effect on the risk of dying from this disease. In 1985, an American man had an 8.7% lifetime risk of being diagnosed with prostate cancer and a 2.5% risk of dying from prostate cancer [16]. Twenty years later, in 2005, an American man had a 17% lifetime risk of being diagnosed with prostate cancer and a 3% risk of dying from prostate cancer [17]. Despite this, the increase in PSA testing will be impossible to stop.

Trial results for and against testing have always been contentious among supporters and opponents of screening. In the case of breast cancer, even with data available from nine randomized trials with reasonable methods, claims have been made that there is no evidence to support mammographic screening. With fewer trials available for evaluating prostate cancer screening and with contamination rates in the control group likely to be very high, questions will undoubtedly be posed about the reliability of the findings.

REFERENCES

Ovarian cancer is the fourth most common cancer in females, with annual incidence rates ranging between 8.5 and 21.5 per 100 000 in female populations of European countries. The International Agency for Research on Cancer estimated that in 2002 there were 204 499 ovarian cancer cases and 124 860 ovarian cancer deaths worldwide [1]. Ovarian cancer is a heterogeneous group of malignancies that can remain asymptomatic despite being at an advanced stage, or cause non-specific symptoms. In about 70% of patients, ovarian cancer is diagnosed at an advanced stage, leading to a poor prognosis: in Europe, the average 5-year survival of ovarian cancer patients is around 40% [2].

The ability to non-invasively distinguish between non-cancerous and ovarian cancerous processes has been investigated, including transvaginal sonography (TVS), Doppler ultrasonography, measurement of serum CA 125, computer tomography scan (CT), magnetic resonance imaging (MRI), fluorodeoxyglucose (FDG) and positron emission tomography (PET) scan (the FDG-PET scan) and radioimmunoscintigraphy [3-7]. However, for a number of reasons, from lack of sensitivity or specificity to cost issues, TVS remains the major detection tool. The use of the Risk of Malignancy Index (RMI), which incorporates menopausal status, CA 125 and TVS, has also been proposed. The RMI version developed by Jacob and co-workers has a pooled sensitivity of 78% (95% CI 72–84%) and pooled specificity of 90% (95% CI 81–95%), with an inverse correlation between sensitivity and specificity [8-9]. Other computerised expert systems and a variety of scoring systems based on the combination of ultrasound image characteristics, serum CA 125 level and various other clinical and patient-related parameters have also been tried, but have proven to be less effective than TVS performed by expert ultrasonographers [10].

Various serum biomarkers have been proposed, like the CA 125, or some blood protein profiles that would represent biological signatures of ovarian cancer; but none of these biomarkers has shown superiority to echography, and furthermore their large-scale application leads to many false positive results and unnecessary laparotomy procedures [11].

On-going trials in the USA [12] and in the UK [8] are at assessing the value of ultrasound and biomarker-based tests. Their results will not be available for several years. In the meantime, currently available methods prove quite unable to detect ovarian cancer early [13], and new technologies are eagerly awaited.

REFERENCES

**Screening for Lung Cancer**

**Summary**

- Lung cancer is a good candidate for screening, but early attempts based on X-rays and cytology did not prove to be effective.
- The search for serological biomarkers for early detection of lung cancer is an active area of research.
- Pulmonary spiral CT-scan results in the identification of early lesions with good prognosis, but the possibility of lead-time bias and over-diagnosis cannot yet be ruled out.
- Currently, no methods can be recommended for population-based screening of lung cancer.

Lung cancer has one of the poorest survival rates of all cancers, mainly due to the lack, in the majority of patients, of symptoms and signs during the early phases of neoplastic growth. This fact, together with the high risk in specific groups of the population, namely smokers (the cumulative risk at age 75 reaches 15% or more in continuous smokers) [3], workers exposed to occupational carcinogens, and women exposed to high level of indoor air pollution, make lung cancer a good candidate for targeted pre-clinical detection.

Efforts to identify an effective approach to screen pre-clinical cases of lung cancer concentrated on X-ray examinations, search of abnormally elevated cotinine levels, and the combination of the two (see [2] for a review). Unfortunately, although screen-detected cases had a longer survival than clinically detected cases, the difference was accounted for by lead-time bias, that is, the fact that an earlier detection of a cancer would generate a longer survival even if the natural history of the disease is not altered (i.e. mortality is not affected), and by over-diagnosis, that is, the fact that the screening detected slow-growing lesions that by their nature have a long survival [2].

In the past decade, two new approaches have been proposed for screening lung cancer in high-risk populations. First, efforts are being made to identify disease biomarkers, typically in sputum, using novel molecular techniques, notably proteomics (i.e. the systematic analysis of proteins and protein fragments). Although promising, this approach has not yet led to the identification of a valid biomarker [3].

The second approach relies on CT-based, low-energy X-rays, notably the so-called spiral CT-scan, which generates a high-resolution, threedimensional image of the lungs. Non-randomised trials of indoor air pollution, make lung cancer a good candidate for targeted pre-clinical detection.

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The second approach relies on CT-based, low-energy X-rays, notably the so-called spiral CT-scan, which generates a high-resolution, threedimensional image of the lungs. Non-randomised studies of spiral CT scan in high-risk populations have resulted in the identification of a relatively large number of nodules in the lungs, which can be removed surgically, and in the majority of cases are shown to be early forms of lung cancer [4]. The survival of the patients whose early cancers are removed is excellent, but two issues remain to be elucidated before one can conclude that spiral CT scan should be implemented in population-based screening [5]. First, the occurrence of spiral CT scan-detected nodules is higher than that of clinically diagnosed cancers in a comparable population, suggesting that a proportion of the nodules are false positives, i.e. represent slow-growing neoplastic lesions that would not have become clinically relevant (so-called over-diagnosis). Second, a reduction in mortality in a screening population has not yet been demonstrated (i.e. the possibility of lead-time bias has not been excluded). These two possible biases are illustrated in Figure 4.12.1.

Randomised trials ongoing in the United States and Europe should provide the final evidence on the effectiveness of spiral CT scan as screening method for lung cancer. In the meantime, national and international authorities generally recommend against the implementation of population-based screening programs for lung cancer [6].

REFERENCES


**Panel A: Absence of screening**

**Panel B: Implementation of screening**

![Figure 4.12.1](image-url)
Screening for Cutaneous Melanoma

Summary

- There is at present no established method for detection of cutaneous melanoma.
- Methods proposed to date are poorly cost-effective and result in identification of expensive treatment of melanoma.
- Screening for rare cancer is known to be poorly cost-effective; hence, it is likely never have become life-threatening.

The goal of screening is to prevent deaths from cutaneous melanoma through detection of the cancer at an early, curable stage. The commonest methods for early detection of melanoma are whole-body skin examination (WBSE) and skin self-examination (SSE)

Cutaneous melanoma has two characteristics: (1) rapid growth and (2) potential for metastasis. In Queensland, Australia, where the incidence of cutaneous melanoma is the highest in the world, a randomised trial of WBSE found that SSE could reduce the development of advanced cutaneous melanoma.

3. In practice, WBSE is a luxury for most health care systems, as WBSE takes time and health professionals have little extra time available for such screening.

4. Many individuals will have new or in situ melanoma removed instead of invasive melanoma, and this will contribute to further increasing costs of screening, lead to disfiguring scars and finally negatively impact quality of life.

5. Many screen-detected cutaneous melanomas will consist of indolent cancer that would most probably never have become life-threatening.

6. Mortality from cutaneous melanoma concentrates in the elderly, mainly men over 60 years of age, because of delay to consult a doctor when a pigmented lesion develops, or because the melanoma develops on a hidden skin area such as the back and the shoulders. Also, it is known that elderly men would have low compliance to skin screening.

7. Evaluation of pilot programmes have shown that individuals attending screening often constitute a selected fraction of the population that are more concerned about their health, and also are healthier than non-attenders.

8. Following logically from the previous point, costs of screening may be considerably in comparison to eventual health benefits. It may appear more appropriate to test the efficacy of screening for melanoma in a subset of high-risk subjects, for instance individuals with a strong family history of melanoma or of melanoma patients, or of nevi appearance. Promotion of SSE requires ensuring rapid accessibility to medical services for checking (and eventually removing) self-detected suspected lesions. Simply disseminating a message about SSE will have little impact on early detection without providing opportunities to have lesions examined and excised will seriously hamper preventive efforts and lead to reduced reducibility in health messages given to the population. One case-control study found that SSE could reduce the development of advanced cutaneous melanoma, but results on screening efficacy from this kind of study design require verification by more robust designs such as a randomised trial.

REFERENCES


Genetic Testing: Genetic testing of high-risk cancer susceptibility genes is becoming an important part of clinical cancer genetics in some high-income countries, but is not always available in middle- or low-income countries.

The main benefactors of the genetic information gleaned from this type of genetic testing are the unafflicted relatives of the individuals who are tested.

The most commonly tested high-risk susceptibility genes are BRCA1 and BRCA2 (primarily for breast and ovarian cancer) and MSH4 and MSH2 (primarily for colon and endometrial cancer). However, there are many other genes for which testing is available under specific circumstances.

Medical and surgical interventions have been proposed for mutation carriers to help prevent high-risk mutations in the more often tested genes. Although the interventions involve quality of life tradeoffs, they do, on average, add years to the lives of these at-risk patients.

The vast majority of genetic testing of cancer susceptibility genes is directed towards the established high-risk breast and colon cancer susceptibility genes. De novo mutations of an unaffected patient usually involves a mutation screen of the whole open reading frame of the underlying susceptibility gene, often augmented with a screen for duplications or deletions of individual exons. Consequentially, these are generally laboriously demanding and relatively expensive. In order to maximize testing efficiency, the first individual from an at-risk family to be tested will usually be a cancer case considered to have a high prior probability of carrying a mutation based on age at diagnosis, family history, and perhaps tumour immunohistochemical profile. If the index case is found to be a mutation carrier, the genotype information may well influence their subsequent medical and surgical management. Two further consequences flow from the identification of a specific mutation in an index case. First, it must be understood and emphasized that the main beneficiaries of the genetic information will be the unaffected relatives of the index case. This is because for unaffected mutation carriers there are alternative interventions that can either reduce the risk of disease or aid in early detection thus improving survival. Second, with increasing understanding of the a priori risks of the index case, testing of the at-risk relatives of the index case only need be tested with a specific test targeting the exact mutation that was identified in the index case. Mutation-specific tests are much less expensive, and have higher sensitivity and specificity, than do whole gene tests.

Colon cancer

The two best-understood colon cancer susceptibility syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC or Lynch syndrome). The majority of cases of FAP are due to germ-line mutations in the colon cancer susceptibility gene APC, identified as such by Ordóñez et al. and Nöthwehr et al. in 1991 [9,12,13]. Patients who carry fully penetrant mutations in FAP will typically present with hundreds of adenomas or even a few colorectal cancers. While testing for mutations in colon polyps by their mid-20s, and the incidence of colon cancer in these individuals is essentially 100%. Accordingly, the preferred treatment for these patients is prophylactic colectomy, which can therefore add decades to the lives of patients who are detected and treated early as compared to those who are detected and treated with FAP until they present with colon cancer [14-16]. For this syndrome, the genetic counseling for mutation carriers includes FAP, MSH2, MSH6, and PM2 that that patients and APC mutation carriers need to be assessed very early in the key to adding years to their lives.

HNPCC is due to germline mutations in the DNA mismatch repair genes MLH1 and PMS2, with about 90% of explained cases arising due to germline mutations of one of these four genes. The proteins encoded by these genes help repair small single-strand DNA lesions that occur constantly due to endogenous and exogenous mutagens. Tumours arising due to loss of function in these genes exhibit increased frequencies of point mutations and instability in the length of microsatellite repeats, termed microsatellite instability. Cumulative risk of colon cancer due to germline mutations in these genes has not been studied as thoroughly as has been the case for FAP and BRCA1.

However, a recent population based case-control study concluded that the cumulative risk of colon cancer for carriers of mutations in one of these HNPCC genes is slightly greater than 40%, whereas the risk for patients with the index case is found to be a mutation carrier, the genotype information may well influence their subsequent medical and surgical management. Two further consequences flow from the identification of a specific mutation in an index case. First, it must be understood and emphasized that the main beneficiaries of the genetic information will be the unaffected relatives of the index case. This is because for unaffected mutation carriers there are alternative interventions that can either reduce the risk of disease or aid in early detection thus improving survival. Second, with increasing understanding of the a priori risks of the index case, testing of the at-risk relatives of the index case only need be tested with a specific test targeting the exact mutation that was identified in the index case. Mutation-specific tests are much less expensive, and have higher sensitivity and specificity, than do whole gene tests.

Breast cancer

The principal high-risk breast cancer susceptibility genes are BRCA1 and BRCA2, predisposition due to inherited mutations in either of these genes is often referred to as Hereditary Breast-Ovarian Cancer Syndrome (HBOC). The genes were first characterised in 1994 and 1995, respectively [3-5]. Although the absolute risks conferred by inheritance of high-risk breast cancer susceptibility genes have been relatively modest (when contrasted with other high-risk conditions), a combined analysis of 22 studies estimated that BRCA1 mutation carriers had a cumulative lifetime risk of over 85% of developing breast cancer by age 70. For BRCA2 carriers, the cumulative breast cancer and ovarian cancer risks are by approximately 45% and 11%, respectively [6]. Because these risks are high, particularly for BRCA1 mutation carriers in these genes will often be applied for surgical intervention as a form of primary prevention. At this time, and after much debate, there are some medical and surgical criteria for these two genes.

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### Dominant Inheritance

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<th>GENE SYMBOLS</th>
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### Recessive Inheritance

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<thead>
<tr>
<th>SYNDROMES</th>
<th>GENES</th>
<th>GENE SYMBOLS</th>
<th>CHROMOSOMAL LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Hippel-Lindau syndrome (VHL)</td>
<td>Renal cancer, vascular tumors</td>
<td>VHL</td>
<td>3p25</td>
</tr>
<tr>
<td>Familial melanoma</td>
<td>Melanomas, other tumors</td>
<td>NF16A</td>
<td>9p</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Basal cell carcinoma</td>
<td>PTCH</td>
<td>9q31</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and renal cell cancer (HLRCC)</td>
<td>Leiomyomatosis, renal cell tumors</td>
<td>FH</td>
<td>1q42-3:4q3</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>Gastrointestinal hamartomatous polyposis, gastric, colon, breast, ovarian cancer</td>
<td>STK11</td>
<td>19p</td>
</tr>
</tbody>
</table>

Table 4.14.1: Cancer susceptibility syndromes and underlying high-risk susceptibility genes.
CANCER IN THE SOUTH-EAST ASIA REGION (SEA)

Rapidly progressing epidemiological transitions taking place in the South-East Asia Region (SEA) of WHO has reached an advanced stage, characterised by predominance of chronic non-communicable diseases (NCDs). With an age-standardised mortality rate of 111 per 100,000 and 9% share in total deaths, chronic diseases are by far the most important public health priority. In 2000, there were an estimated 1.3 million cases and 0.9 million deaths from cancer in SEA. Among the leading causes of morbidity in the SEA Region, cardiovascular disease, liver, and lung cancer has been the fastest. Unlike in more developed regions of the world, where most cancers are related to lifestyle and environmental risk factors, in the SEA Region, infectious factors, caused by Human papillomavirus (HPV), hepatitis B and C viruses, Helicobacter pylori and beer are also of high importance.

Effective cancer control requires a comprehensive national cancer control policy and programmes with adequate resource allocation, development, diagnosis and therapeutic capacity and global resource utilisation in palliative care. High levels of female illiteracy, gender discrimination and other socio-economic inequalities, as well as lack of awareness of the risk factors and poor enforcement of tobacco, alcohol and food legislation, all hinder the efforts of cancer control programmes. Widespread inaccessibility of preventive, curative and rehabilitative services for large segments of the population in the Region due to the geographical and financial constraints contribute to poor health outcomes. As out-of-pocket payment for the treatment of cancer could economically devastate families, making cancer care a public health priority. In 2000, there were an estimated 6.6 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.5 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.6 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.5 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.6 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.5 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.6 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.5 million deaths, cancer has become an important public health priority. In 2000, there were an estimated 6.6 million deaths, cancer has become an important public health priority.
In Thailand, the WHO collaborative work includes assessment of exposure to occupational carcinogens, development of an occupational and environmental cancer surveillance system, networking of community health personnel and volunteers and strengthening of communities and local authorities to assess and tackle environmental threats. Also, in other Member States of the SEA Region, including Bangladesh, Bhutan, DPR Korea, Maldives and Sri Lanka, WHO country offices are providing technical support in development of NCCPs and in implementing specific cancer control activities.

Figure 1. Minimum incidence of all cancers in India (men) 
Source: Cancer Atlas (ICMR)

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<table>
<thead>
<tr>
<th>Area</th>
<th>Indicator</th>
<th>No. of countries (total 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Policy/programme</strong></td>
<td>National health policy addresses cancer and other major NCDs</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>National plan/ programme for cancer control</td>
<td>8</td>
</tr>
<tr>
<td><strong>Infrastructure</strong></td>
<td>Presence of a NCD unit or department in ministry of health</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Presence of national cancer reference centre</td>
<td>9</td>
</tr>
<tr>
<td><strong>Legislation/regulation</strong></td>
<td>Anti-tobacco</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Food and nutrition (related to NCDs)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Surveillance</strong></td>
<td>Surveillance systems for major cancers</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Population-based cancer registries</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Hospital-based cancer registries</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>NCD risk factor (STEPS) surveys conducted</td>
<td>9</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Availability of guidelines for cancer management</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Anti-neoplastic medicines accessible and affordable for low-income groups</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 1. Capacity of SEA Member countries to prevent and control cancer: select indicators
Modified from “Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region. Capacity for noncommunicable disease prevention and control in countries of the South-East Asia Region: results of a 2006-2007 survey.” SEA/RC60/9 -INF DOC1

<table>
<thead>
<tr>
<th>Country/site</th>
<th>Current smokers (%)</th>
<th>Current consumers of alcohol (%)</th>
<th>Proportion (%) eating &lt; 5 servings of F &amp; V</th>
<th>Proportion (%) physically inactive</th>
<th>Proportion (%) overweight and obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh – R</td>
<td>25.3</td>
<td>NS</td>
<td>NR</td>
<td>NR</td>
<td>8.6</td>
</tr>
<tr>
<td>Bangladesh – U</td>
<td>21.9</td>
<td>NS</td>
<td>NR</td>
<td>NR</td>
<td>36.5</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>31.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NR</td>
</tr>
<tr>
<td>India – R</td>
<td>17.8</td>
<td>26.4</td>
<td>84.6</td>
<td>10.0</td>
<td>13.3</td>
</tr>
<tr>
<td>India – U</td>
<td>15.7</td>
<td>20.7</td>
<td>81.4</td>
<td>23.8</td>
<td>39.4</td>
</tr>
<tr>
<td>Indonesia*</td>
<td>32.0</td>
<td>3.3</td>
<td>94.5</td>
<td>7.8</td>
<td>22.3</td>
</tr>
<tr>
<td>Maldives</td>
<td>22.7</td>
<td>NS</td>
<td>84.6</td>
<td>NR</td>
<td>44.2</td>
</tr>
<tr>
<td>Myanmar – R</td>
<td>24.4</td>
<td>18.0</td>
<td>98.2</td>
<td>3.5</td>
<td>23.3</td>
</tr>
<tr>
<td>Myanmar – U</td>
<td>22.9</td>
<td>18.4</td>
<td>99.1</td>
<td>7.3</td>
<td>36.5</td>
</tr>
<tr>
<td>Nepal</td>
<td>20.6</td>
<td>40.5</td>
<td>99.1</td>
<td>NR</td>
<td>16.5</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>19.6</td>
<td>40.5</td>
<td>96.8</td>
<td>14.9</td>
<td>28.8</td>
</tr>
<tr>
<td>Thailand*</td>
<td>18.6</td>
<td>40.1</td>
<td>85.0</td>
<td>NR</td>
<td>37.5</td>
</tr>
<tr>
<td>TOTAL (range)</td>
<td>16-32</td>
<td>3-41</td>
<td>81-99</td>
<td>4-24</td>
<td>9-44</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of select behavioural risk-factors in the SEA Region (age 25–64, both sexes)
Source: “Scaling up prevention and control of chronic noncommunicable diseases in the SEA Region: Risk factors: results from surveys using the STEPS approach.” SEA/RC60/9 -INF DOC 2
*Only national surveys, other are sub-national surveys; F & V – fruits and vegetables; NR – not reported; NS – not studied; R – rural; U – urban