

Chapter 2

Principles of Primary and Secondary Cancer Prevention

Keywords Primary prevention • Secondary prevention

2.1 Primary Prevention

The main goal of primary prevention of cancer is to reduce the incidence through the reduction of exposure to risk factors for cancer at population level. Where feasible, primary prevention programmes are demonstrated to be largely cost-effective, i.e. the reduction of the burden of disease is achieved with a reasonable money investment, while this is not always the case for secondary prevention programmes.

Many determinants of malignant neoplasms, including UV radiation, ionizing radiation, tobacco smoking, alcohol drinking, a number of viruses and parasites, and a number of chemicals, industrial processes and occupational exposures, are sufficiently well established to constitute logical priorities for preventive action. Two more reasons add weight to this priority: some of the agents are responsible for sizeable proportions of the cancers occurring today, and for many agents it is in principle feasible to reduce or even to completely eliminate exposure. If this is taken as the objective of preventive action, some practical points are helpful in guiding such action.

First, although epidemiological data in most cases do not allow a direct estimate of the risk of cancer at low doses, it is reasonable (at least from a preventive point of view) to assume that the dose (exposure)-risk relationships for agents acting through damage to DNA is linear with no threshold (Peto et al. 1991). Second, the carcinogenic effect is not equally dependent on the dose rate (dose per unit of time) and on duration of exposure. For example, in regular smokers, the incidence rate of lung cancer depends more strongly on duration of exposure, increasing with the fourth power of it, than on dose rate, increasing only with the first or second power of it (Peto 1977).

The attribution of causality to specific agents (as done when, for instance, smoking is said to be the cause of some 30 % of all cancers deaths; see Sect. 5.1) is complicated by their interactive effects. This is particularly relevant when considering the relative effectiveness of removing (or reducing) exposure to one of two (or more) jointly-acting agents. Whenever a positive interaction (synergism) occurs between two (or more) hazardous exposures, there is an enlarged possibility of preventive action; the effect of the joint exposure can be attacked in two (or more) ways, each requiring the removal or reduction of one of the exposures; moreover, the larger the size of the interaction relative to the total effect, the more these ways of attack tend to become equal in effectiveness.

Finally, reducing exposure to carcinogens can be implemented in two major ways: by elimination of the carcinogen or its substitution with a non-carcinogen, or by impeding by various means the contact between the carcinogen and people. Reduction of exposure depends in each case on technical and economical considerations.

Cancer prevention strategies have evolved from a predominant environmental and lifestyle approach to a model that matches individual-oriented actions with public health interventions. Advances in identifying, developing, and testing agents with the potential either to prevent cancer initiation, or to inhibit or reverse the progression of initiated lesions support this approach. Encouraging laboratory and epidemiologic studies, along with studies of secondary endpoints in prevention trials, have provided a scientific rationale for the hypothesis promising results have been reported for various types of cancer, in particular among high-risk individuals (Greenwald 2005; Boffetta and La Vecchia 2009; Zhang et al. 2014).

2.2 Secondary Prevention

Given the limitations still constraining the primary prevention of many cancers, early detection needs to be considered as a secondary and alternative option, based on the reasonable expectation that the earlier the diagnosis and the stage at which a malignancy is discovered, the better the prognosis. This implies that an effective treatment for the disease exists and that the less advanced the cancer at the pre-clinical stage, the better the scope for treatment, and the better the prognosis. This latter aspect cannot be taken for granted.

Before a screening programme can be adopted on a large scale, a number of other requirements need to be fulfilled. First of all, a screening test (that is, a relatively simple and rapid test aimed at the presumptive identification of pre-clinical disease) must be available that is capable of correctly identifying cases and non-cases. In other words, both sensitivity and specificity should be high, approaching 100 %. While high sensitivity is obviously important, given that the very purpose of screening is to pick up, if possible, all cases of a cancer in its detectable pre-clinical phase, it is specificity that plays a dominant role in the practical utilization of the test within a defined population. As the prevalence of a pre-clinical cancer to be screened in well-defined populations is often in the range of 1–10 per 1,000, if a test

is used with a specificity of 95 %, then 5 % of results will be false-positives. In other words, for every case which will turn out at the diagnostic work-up to be a true cancer (assuming 100 % sensitivity), there will be 5–50 cases falsely identified as such and ultimately found not to be cancers. This situation is likely to prove unacceptable due to too high psychological and economical costs. One solution is an increase in specificity, for example by developing better tests or combinations of tests, or by changing the criterion of positivity of a given test to make it more stringent (this necessarily decreases sensitivity). In addition, one might select populations with relatively high prevalence of the cancer ('high-risk' groups), so as to increase the number of the true positives. Whatever the group on which the programme operates, additional requirements are that the test is safe, easily and rapidly applicable, and acceptable in a broad sense to the population to be examined. It has also to be cheap, but what is or is not cheap is better evaluated within a cost-effectiveness analysis of different ways of preventing a cancer case or death, an issue not further discussed here.

If these requirements are met, still little is known about the possible net benefit in outcome deriving from the screening programme (in fact, screening test plus diagnostic work-up plus treatment, as applied in a given population). To evaluate benefit, several measures of outcome can be assessed. An early one, useful but not sufficient, is the distribution by stage of the detected cancer cases which, if the programme is ultimately to be beneficial, should be shifted to earlier, less invasive stages of the disease in comparison with the distribution of the cases discovered through ordinary medical care. A second measure of outcome is the survival of cases detected at screening compared with the survival of cases detected through ordinary medical care. This is a superficially attractive but usually equivocal criterion, to the extent that a screening may only advance the time of diagnosis (and therefore the apparent survival time), without postponing the time of death ('lead-time bias'). A final outcome (and the main test of the programme) is the site-specific cancer mortality in the screened population compared with the mortality in the unscreened population.

Correct, unbiased comparison of this outcome, and thus unbiased measure of the effect of the screening programme, should in principle be made within the framework of a randomized controlled trial, in which two groups of subjects are randomly allocated to the screening programme and to no screening (that is, receiving only the existing medical care system) or to two alternative screening programmes, for instance, entailing different tests or different intervals between periodical examinations. However, largely due to pressures to adopt on a large scale screening programmes hoped to be effective, a situation has often arisen where withholding screening to a group has been regarded as unethical or socially unacceptable, thus preventing the conduct of a proper experiment. Very few randomized trials evaluating the effectiveness of screening programmes are available. Comparisons made through non-randomized experiments or through observational studies.

In addition to lead-time bias, three types of bias are peculiar to the assessment of screening programmes. Because of self-selection, persons who elect to receive early detection may be different from those who do not: for instance, they may belong to

better educated classes, be generally healthier and health conscious, and this could produce a longer survival independent of any effect of early detection. In addition, cancers with longer pre-clinical phases, which may mean less biological aggressiveness and better prognosis, are, in any case, more likely to be intercepted by a programme of periodical screening than cancers with a short pre-clinical phase, and a rapid, aggressive clinical course (length bias). Finally, because of criteria of positivity adopted to maximize yield of early cases, a number of lesions which in fact would never become malignant growths are included as 'cases', thus falsely improve the survival statistics (over-diagnosis bias).

Chemoprevention can also be considered for primary and secondary prevention of cancer, but data are negative or inconsistent for most micronutrients or other substances considered. Data are however more promising for aspirin, see Sect. [5.10](#).

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