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Review

Evidence-based policy recommendations on cancer screening and prevention

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Abstract

Ideally, practice guidelines for cancer prevention should reflect the available empirical evidence. Although the most persuasive arguments for the efficacy of an intervention come from randomized controlled trials (RCTs), such studies are not always feasible because of ethical or logistical reasons. The advent of evidence-based medicine has underscored the need for consortia of researchers specialized in reviewing the biomedical literature on a systematic basis, ranking studies according to their design, quality, and generalizability of results. This review summarizes the recommendations and policies on screening and prevention of specific types of cancers from North American and international organizations such as: the National Cancer Institute's Physicians's Data Query Program, the US Preventive Services Task Force, the Canadian Task Force on the Preventive Health Care Force, and the Cochrane Collaboration.

Keywords: Evidence-based medicine; Cancer; Prevention; Screening; Recommendations; RCTs

1. Introduction

Ideally, clinical and public health practice guidelines should reflect not only the availability of empirical evidence but also the strength of evidence as judged by expert reviews of published data. The most persuasive evidence for the efficacy of a cancer screening or preventive intervention comes from a reduction in mortality and/or incidence of cancers shown in conclusive randomized controlled trials (RCTs). These investigations typically take many years to complete and are not always feasible, however, either because of ethical reasons—e.g. when discovery of the intermediate endpoint is already an accepted basis for treatment or because studies would have to be extremely large to the point of being impractical (e.g. rare cancers such as neuroblastoma). Interventions that have focused on pre-malignant or early cancerous lesions that can be treated or excised, with consequent arrest of neoplastic development, include those searching for high-grade dysplasias of the uterine cervix, oral leukoplakias, and colonic adenomas.

Studies in which baseline screening or primary prevention information on all subjects is subsequently linked with national or regional incidence or mortality databases without intervening surveillance of lesions have served a useful purpose in providing evidence of benefit (or lack thereof) for interventions. However, the increased concern in Western populations about individual privacy has led to a tendency for funding agencies and ethical review boards to require more stringent justification for record linkage studies. In consequence, trials focusing on intermediate endpoints (precancerous lesions or suitable biomarkers) have become more widely accepted, especially because of a better understanding of the use of surrogate markers in cancer research and the fact that they can be carried out in a shorter period of time and with greater statistical power [1,2].

The new era of evidence-based medicine has spawned a number of consortia of biomedical researchers specialized in reviewing published clinical and epidemiological evidence on a systematic basis, and ranking the available evidence in terms of the type of study, the quality of the information, and the generalizability of the results to different health care settings. These consortia are affiliated with government agencies, professional societies, or with private

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non-profit organizations dedicated to the improvement of health care delivery. This review summarizes both the recommendations and policies on screening for and prevention of specific types of cancer from some of the more influential of these organizations in North America and internationally and their assessment of the weight and quality of the scientific evidence in support of these interventions.

2. Evidence for screening interventions

2.1. National institutes of health physician's data query program

The Physician's Data Query (PDQ) database program maintained by the US National Cancer Institute is a permanent review group that continuously monitors the literature to assess the quality of the evidence for oncological practices, including screening interventions and prevention strategies [3,4]. The PDQ program produces summary statements of screening efficacy for specific tests or procedures. The assessment of the evidence and the summaries are prepared by the PDQ Screening and Prevention Editorial Board based upon both continuing review of the published scientific evidence and recommendations by professional bodies. Members of the Editorial Board represent the fields of oncology, cancer prevention, statistics, epidemiology, and economics. This group meets bimonthly to review and update information on cancer screening and early detection. The expertise of the Editorial Board is supplemented by Advisory Boards, which include over 100 specialists who review information regularly and suggest changes or updates to the main Editorial Board.

Table 1 summarizes the levels of evidence for statements of screening efficacy by the PDQ. Proof of mortality reduction in RCTs is assigned the highest level of evidence. Lower levels of evidence are obtained from case-control and cohort studies and other information such as the incidence of cancer before and after introduction of a particular screening intervention. Measures of improved outcome for determining screening efficacy are ranked from the most persuasive to the least persuasive as follows: (1) decrease in cause-specific mortality; (2) reduction in incidence of advanced stage cancers; (3) increase in survival; (4) shift in disease stage [3].

Table 2 presents evidence for the efficacy of specific screening tests for various cancer sites from the PDQ program (with updated information as of May 2002). Many of the screening tests described in the table are able to detect cancer precursor lesions in the respective organs or sites (e.g. Pap test, mammography, sigmoidoscopy, colonoscopy, oral exfoliative cytology, and skin examination), whereas the remainder are able to detect early invasive cancers. RCTs have been conducted for only a few of the more common screening techniques—mammography in breast cancer screening being the one most thoroughly studied in several trials worldwide [5] with evidence of benefit among women aged 40–69 years. Although the PDQ panel judged the evidence as largely unequivocal, a recent Cochrane review has challenged this conclusion [6]. Adding to the controversy, Miettinen et al. [7], using data from one of the studies included in that review, demonstrated that, allowing for the appropriate length of follow-up, mammographic screening in older women ($\geq$55 years of age) provided a 55% reduction in cause-specific mortality.

Pap cytology is often considered the most successful cancer screening test. There is widespread acceptance that Pap screening has reduced mortality from cervical cancer in most Western countries, but the evidence comes from observational epidemiologic studies, such as case-control and cohort investigations [8,9] (level 3), time series analysis showing that mortality decreased after the introduction of organized screening [10] (level 4), and geographical comparisons showing that the reduction in mortality was proportional to screening coverage [11] (level 4). In addition, there are numerous consensus statements from expert groups attesting to the effectiveness of the Pap test as an established medical procedure (level 5). The weight of the evidence in favor of Pap cytology obviates the need to have its screening efficacy scrutinized further in an RCT. In fact, such a proposition would be ethically untenable given that the Pap test is a widely accepted medical procedure.

Table 2 shows that sufficient evidence for screening effectiveness has been obtained for two screening tests other than Pap cytology and mammography: guaiac-based fecal occult blood (FOB) testing, and sigmoidoscopy in colorectal cancer, albeit with quantitatively different levels of evidence. Biennial FOB testing was evaluated in RCTs in Europe [12,13] and in the US [14,15] with a 15–21% reduction in mortality, whereas sigmoidoscopy has been assessed

Table 1
Levels of evidence for statements of screening efficacy from the US National Cancer Institute's Physician's Data Query Program (from [3])

Level of evidence	Assessment of the evidence by expert review
1	Evidence obtained from at least one well-designed and conducted randomized controlled trial
2	Evidence obtained from well-designed and conducted controlled trials without randomization
3	Evidence obtained from well-designed and conducted cohort or case-control analytic studies, preferably from more than one center or research group
4	Evidence obtained from multiple-time series with or without intervention
5	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Table 2
NCI-PDQ program's summaries of evidence for the efficacy of specific screening tests in reducing mortality from cancer (from [3])

Cancer site	Screening test	Evidence of benefit	Level of evidence*
Bladder	Hematuria, cystoscopy, cytology	Insufficient	5
Breast	Mammography with or without clinical breast examination	40–49 years: yes	1, 3–5
		50–69 years: yes	1, 3–5
		70+ years: uncertain	5
		<40 years: no data	5
		High-risk groups: uncertain	5
Colorectal	Fecal occult blood	Yes	1
	Sigmoidoscopy	Yes	3–5
	Colonoscopy	Insufficient	3
	Digital rectal examination	No	3
Endometrium	Endometrial sampling or transvaginal ultrasound	Insufficient	4, 5
	Pap cytology	No	5
Esophagus	Endoscopy and cytology	No	5
	Chromoendoscopy, laser-induced fluorescence spectroscopy	Insufficient	5
Liver	Alpha-fetoprotein and/or ultrasound or CT	Insufficient	5
Lung	Chest X-ray and/or sputum cytology	No	1, 3
	Spiral CT	Insufficient	5
Neuroblastoma	Vanillylmandelic acid and homovanillic acid	No	3, 4, 5
Oral	Oral examination or cytology	Insufficient	5
Ovary	CA 125, transvaginal ultrasound, pelvic examination	Insufficient	4, 5
Prostate	Digital rectal examination, transrectal ultrasound, or prostate-specific antigen	Insufficient	3, 5
Skin	Physical examination	Insufficient	5
Stomach	Endoscopy	Insufficient	3 + 4 (limited), 5
Testicular	Physical examination	Insufficient	5
Uterine cervix	Pap cytology	Yes	3, 4, 5

* See Table 1 for explanation on levels of evidence.

in observational studies and by expert review groups [16]. Removal of adenomas found on sigmoidoscopy, particularly the ones with severely dysplastic areas, decreases subsequent colorectal cancer risk [17,18]. Colonoscopy is being used as a complementary screening maneuver when distal lesions are found during sigmoidoscopy. However, evidence is mounting for the inclusion of colonoscopy as a screening method for colorectal cancer, as two recent studies demonstrated that up to 50% of patients with advanced proximal disease do not have distal adenomas/polyps and would be missed by sigmoidoscopy [19,20].

As yet there is no evidence of benefit for the remaining screening tests in reducing cancer mortality (Table 2) but many continue to be investigated in a variety of study designs in clinical and population-based settings (e.g. the National Institutes of Health (NIH)-coordinated prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial [21]). Conclusive evidence of absence of benefit has been obtained for Pap cytology in endometrial cancer, for chest X-ray and sputum cytology in lung cancer, and for urinary metabolite tests in neuroblastoma [3].

A number of novel screening tests not included in Table 2 are currently being evaluated in epidemiologic studies and RCTs. Noteworthy among them are automated cytology methods and human papillomavirus (HPV) testing for detecting preinvasive cervical lesions [22,23] and spiral computerized tomography (CT) for detecting incipient, potentially precancerous lung lesions [24]. As yet, there is insufficient evidence to support automated cytology methods and HPV testing to replace Pap testing in cervical cancer screening, although both seem to have higher sensitivity and at least comparable specificity to the latter when older women are screened [22,23]. Spiral CT is being evaluated clinically and has been introduced into clinical practice in the US on a limited basis amidst considerable controversy surrounding the long-term follow-up results of the Mayo Lung Project [25], an RCT that showed no reduction in lung cancer mortality in men receiving frequent chest X-ray examinations. Chest X-ray detected many incipient lesions that did not progress to cancer in the latter trial, which underscores the concern that with spiral CT, owing to its much greater imaging sensitivity, many more such lesions will be unveiled. Consequently, a relatively greater proportion of patients would have to undergo unnecessary, invasive treatment procedures. A feasibility trial was funded recently by NIH (NCI-P00-0171) to examine the acceptability by current and former smokers of participating in a subsequent larger RCT that will compare spiral CT with chest X-rays for lung cancer screening [21].

2.2. US and Canadian Task Forces

Two other organizations noteworthy for their systematic approach in reviewing the evidence for the effectiveness of cancer screening interventions are the US Preventive Services Task Force (USPSTF) [26] and the Canadian Task Force on Preventive Health Care (CTFPHC) [27]. These two organizations have cooperated in reviewing the appropriateness of a wide range of clinical preventive services in use in North America, including screening tests for early detection of disease, immunizations to prevent infections, and counseling for disease risk reduction. Both task forces rank the quality of the published evidence via the same descriptors adopted by the PDQ program (Table 1). However, these organizations do not merely rank the quality of the evidence but go one step further, by making specific graded recommendations for or against adoption of procedures as part of standard clinical practice. The strength of the recommendations for adoption of a particular screening intervention is graded according to the classification shown in Table 3 [26,27]. Assessment of screening test accuracy and the documentation of favorable clinical outcomes in addition to reduction in mortality from cancer are important criteria guiding the recommendations by these two task forces. Unfortunately, unlike the PDQ Editorial Board, which meets bimonthly, these two groups do not meet regularly to review the published evidence that accumulates continuously in most areas of screening and prevention.

Table 4 summarizes both task forces' recommendations concerning the application of cancer screening tests among asymptomatic persons [26,27]. The quality of the evidence is shown in parentheses next to the scores for practice recommendations. A grade "A" recommendation (good supporting evidence) was given in only one instance by the USPSTF—Pap cytology—and only twice by the CTFPHC: to mammography for women of 50–69 years and to FOB in colorectal cancer. The Canadian Task Force assigned a "B" recommendation (fair supporting evidence) to the Pap test and to sigmoidoscopy. Mammography for women 40 years of age and older, FOB and sigmoidoscopy attained "B" grade recommendations by the USPSTF. Most of the screening tests shown in the table attain at most a "C" recommendation (or "I" in the most recent revision by the USPSTF), with several noteworthy negative recommendations, such as urine sediment tests for bladder cancer, and biochemical and clinical tests for ovarian, pancreatic, and prostate cancer, which received "D" scores (fair evidence against). The only frankly negative recommendation ("E" grade: good evidence against) was assigned by the CTFPHC for sputum cytology in lung cancer screening.

During the past year, the CTFPHC has updated recommendations for colorectal and breast cancer screening [28–31]. The changes proposed recently by the CTFPHC upgrades previous statements of efficacy, with one most prominent exception: the CTFPHC has downgraded breast self-examination (BSE) to a "D" recommendation given that there is recent evidence documenting the lack of benefit and evidence of harm as there is an increased number of medical visits and benign biopsies associated with the practice [31]. More recently, the USPSTF has reviewed recommendation guidelines for breast and skin cancer screening (Table 4).

Table 3
Recommendations used by the US Preventive Services Task Force (USPSTF) and by the Canadian Task Force on Preventive Health Care (CTFPHC) for assessing clinical preventive services, including screening for cancer (from [26,27])

Recommendation grade		
USPSTF*	CTFPHC	Description
A	A	There is good evidence to support the recommendation that the condition** be specifically considered in a periodic health examination.
B	B	There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
I	C	There is insufficient evidence to recommend for or against the inclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.
C	D	There is fair evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.
D	E	There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

* According to 2002 guidelines: "(A) The USPSTF strongly recommends that clinicians routinely provide (the service) to eligible patients. (The USPSTF found good evidence that (the service) improves important health outcomes and concludes that benefits substantially outweigh harms.); (B) The USPSTF recommends that clinicians routinely provide (the service) to eligible patients. (The USPSTF found at least fair evidence that (the service) improves important health outcomes and concludes that benefits outweigh harms.); (C) The USPSTF makes no recommendation for or against routine provision of (the service). (The USPSTF found at least fair evidence that (the service) can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.); (D) The USPSTF recommends against routinely providing (the service) to asymptomatic patients. (The USPSTF found at least fair evidence that (the service) is ineffective or that harms outweigh benefits.); (I) The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing (the service). (Evidence that (the service) is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.)". Recommendation grades adopted by the USPSTF corresponded to those for CTFPHC up to 2002. The USPSTF grades its recommendations according to one of the five classifications (A, B, C, D, or I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

** 'Condition' in the context of this chapter implies a particular screening test.

Table 4
Summary of recommendations (with quality of the evidence*) by the US Preventive Services Task Force (USPSTF) and by the Canadian Task Force on Preventive Health Care (CTFPHC) with respect to the effectiveness of cancer screening tests (from [26,27])

Cancer site	Screening test	USPSTF (1996 or 2002**)	CTFPHE (1994)
Bladder	Dipstick for hematuria	D (II-2, III)	D (II-2)
	Urine cytology	D (III)	D (II-2)
Breast**	Mammography with or without clinical breast examination	40+ years: B (fair)	40–49 years: C (I) 50–69 years: A (I) 70+ years: not assessed
	Annual clinical breast examination	I	Not assessed
	Routine breast self-examination	I	40–69 years: D (I)
Colorectal	Fecal occult blood (FOB)	B (I, II-1, II-2)	A (I)
	Sigmoidoscopy	B (II-2, II-3)	B (II-2, III) High risk: B (II-3)
	Colonoscopy	C (III)	C (II-3) High risk: B (II-3)
	Genetic testing	Not assessed	High risk: B (II-3)
	Digital rectal examination	C (III)	Not assessed
	Barium enema	C (III)	Not assessed
Lung	Chest X-ray	D (I, II-1, II-2)	D (I)
	Sputum cytology	D (I, II-1, II-2)	E (I)
Mouth	Oral examination	C (III)	C (II-2)
Ovary	CA 125, transvaginal ultrasound, pelvic exam	D (II-3, III)	D (II-2)
Pancreas	Abdominal palpation, ultrasound, serum markers	D (III)	D (II-2)
Prostate	Digital rectal examination	D (II-2)	C (II-2)
	Transrectal ultrasound	D (II-2, III)	D (II-3)
	Prostate-specific antigen	D (I, II-2, III)	D (II-3)
Skin**	Physical examination	I	C (II-3)
Testicular	Physical examination	C (III)	C (III)
Uterine cervix	Pap cytology	A (II-2, II-3)	B (II-2)
	Cervicography or colposcopy	C (III)	Not assessed
	HPV testing	C (III)	D (III)

* Quality of evidence indicated in parentheses correspond to scores for the descriptions in Table 1 based on the following equivalency: I = 1, II-1 = 2, II-2 = 3, II-3 = 4, III = 5. The CTFPHC assessment includes only the highest attained score. See also Table 3 for descriptions of recommendations. Lately, the USPSTF began to grade the quality of the overall evidence for a service on a 3-point scale (good, fair, or poor), as follows: "Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes; Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes; Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes."

** Cancer sites affected by the 2002 revision.

2.3. Other systematic reviews

Of paramount importance among the international consortia of clinicians and epidemiologists producing reviews of evidence for health care interventions is the Cochrane Collaboration. This group was inspired by the work of Archie Cochrane, a British epidemiologist who proposed continuous, systematic reviews of all relevant RCTs of health care interventions. The Cochrane Centre began with seed funds from the United Kingdom's National Health Service and was initially based at Oxford University in 1992. The initiative quickly expanded to include centers around the world and in 1993 the 'Cochrane Collaboration' was founded [32]. Cochrane reviews are the principal output of the Collaboration and are published electronically in successive issues of the Cochrane Database of Systematic Reviews [33]. Preparation and maintenance of Cochrane reviews is the responsibility of international collaborative review groups which cover most of the important areas of health care and follow a rigidly defined set of guidelines for reviewing the evidence from RCTs in their specific areas. Whenever appropriate, Cochrane reviews provide a meta-analysis of study results, that is, summary estimates of screening benefit (for instance, the net percent reduction in mortality due to the intervention) averaged across all RCTs with comparable design and outcomes.

Many of the Cochrane reviews cover relevant areas in cancer control and prevention. However, unlike the dedicated function of the PDQ program at NCI and the periodic task force evaluations in North America described above, Cochrane reviews have to rely on the ad hoc assembly of volunteer experts who agree to target specific tests or

Table 5
Screening interventions and related procedures relevant to cancer control that either have been evaluated or are under review by the Cochrane Collaboration as of May 2002 (from [33])

Review status	Screening intervention or related procedure	Conclusion
Completed	Screening for colorectal cancer using the fecal occult blood test	Average reduction in colorectal cancer mortality: 16% (95% CI: 7–23%) but harmful effects and costs need to be assessed.
	Surgery for cervical intraepithelial neoplasia	No differences among seven techniques in disease eradication; large loop excision of the transformation zone yields best specimens for histology.
	Collection devices for obtaining cervical cytology specimens	Extended tip spatulas of various designs are better than Ayre's spatule for sampling endocervical cells specially in combination with a cytobrush.
	Mammographic screening for breast cancer	Mammographic mass breast cancer (BC) screening does not lead to improved survival; evidence of its impact on BC mortality is still inconclusive.
	Strategies for inviting women to participate in breast cancer screening	Various interventions, alone or in combination, to increase recruitment in BC screening programs are effective whereas some more costly strategies do not have an impact.
	Screening for lung cancer	There is no evidence to support screening for lung cancer using chest X-rays or sputum cytology and frequent chest radiography might even be harmful.
	Interventions for treating oral leukoplakia	Treatment of oral leukoplakia is not effective in preventing malignant transformation.
	Dietary fiber for the prevention of colorectal adenomas and carcinomas	There is no evidence to suggest that increased dietary fiber intake will reduce the incidence or recurrence of adenomatous polyps within a 2–4-year-period.
	Interventions for encouraging sexual lifestyles and behaviors intended to prevent cervical cancer	Providing information and sexual negotiation skills to underprivileged women encourages reduction of sexual risk behaviors at least in the short-term.
Under review	Interventions for relieving the pain of screening mammography	
	Regular physical or self-examination for early detection of breast cancer	
	Prophylactic mastectomy for the prevention of breast cancer	
	Tamoxifen for the primary prevention of breast cancer	
	Interventions to encourage the uptake of cervical cancer screening	
	Oophorectomy with or without hysterectomy for preventing ovarian cancer in women with a familial history	
	Screening for prostatic cancer	
	Adenoma surveillance on incidence and mortality from colorectal cancer	
	Strategies for detecting colon cancer and/or dysplasia in inflammatory bowel disease patients	
	Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps	
	Therapies for the eradication of *Helicobacter pylori*	
	Alpha-fetoprotein and/or liver ultrasound for liver cancer screening among hepatitis B carriers	
	Drugs for preventing lung cancer	
	Influencing people's experiences of screening	

interventions for assessment. As of May 2002, of the 23 cancer screening-related procedures that were listed in the Cochrane database of systematic reviews, 9 had been completed (Table 5).

In addition to the above systematic reviews, several others, undertaken by different expert panels assembled by government agencies in North America and in Europe, have focused specifically on certain screening interventions. The US Agency for Healthcare Research and Quality (formerly, Agency for Health Care Policy and Research) has produced systematic reviews of the efficacy and costs of Pap cytology in cervical cancer screening [34] and of different screening methods for the detection of colorectal lesions [35]. In Canada, the Canadian Coordinating Office for Health Technology Assessment has produced a comprehensive review of the techniques available for cervical cancer screening including conventional and automated cytology methods and HPV testing [36]. In the UK, the National Coordinating Centre for Health Technology Assessment has reviewed the evidence for the efficacy of HPV testing [37] and of liquid cytology methods [38] in cervical cancer screening. The latter reviews are more extensive in scope and in their

review of study methodology than the PDQ program and North American Task Forces and include detailed analyses of costs for the various procedures. On the other hand, the conclusions are more qualitative than quantitative in terms of specific recommendations.

3. Evidence for interventions aiming at primary prevention

The same agencies or consortia described above have also produced systematic reviews of evidence for the effectiveness of primary prevention strategies. A compilation of these systematic reviews is presented below.

3.1. National Institutes of Health Physician's Data Query program

The PDQ program defines cancer prevention as the reduction of cancer mortality via reduction in the incidence of cancer. Its panel of experts has assessed a number of plausible interventions, such as avoiding intake of carcinogens or altering their metabolism and modifying lifestyle or dietary practices that affect cancer risk. These assessments have taken into account not only the potential benefit of the strategy in the general population but also among high-risk individuals who carry genetic predispositions. The summaries are updated bimonthly by the PDQ Editorial Board as new evidence becomes available in the published literature [39].

As with the statements about screening efficacy described above, the PDQ assessments are summarized by varying levels of evidence that support a given statement. Table 6 shows the different degrees of quality of evidence assigned to these assessments [40]. The most convincing evidence is that obtained from well-designed and well-conducted RCTs with cancer-specific mortality as the endpoint (level 1ai). Frequently, however, mortality endpoints are not realistic and other relevant endpoints are utilized, such as cancer occurrence (level 1aii) or an intermediate endpoint such as a cancer precursor (level 1b), e.g. a dysplastic, preinvasive lesion of the cervix or an adenomatous polyp of the colon. RCTs are also more the exception than the rule among the study designs used to ascertain the role of risk factors or preventive strategies. In general, preventive practice has to rely on evidence obtained from non-randomized trials with sufficient follow-up (level 2) or, more often, from observational epidemiologic studies with individuals as the unit of observation, that is, cohort or case-control investigations (level 3). Less convincing evidence (due primarily to the possibility of confounding due to other variables) is that obtained from ecologic studies (level 4) that examine variation in cancer morbidity or mortality in entire populations or groups of individuals as a function of the putative average exposure to risk factors. Also included in this category of evidence are studies that establish temporal or geographical relations, or migrant studies. The same suffix assignment based on the type of outcome (ai: mortality; aii: cancer; or b: intermediate endpoint) is made to levels 2, 3, and 4 (as described in Table 1) by PDQ reviewers. Finally, the weakest level of evidence is that concluded by expert panel assessments produced without the availability of the latter study types (level 5).

Table 7 summarizes the levels of evidence for specific prevention strategies for individual sites of cancer. For most statements, the evidence comes from observational epidemiologic studies and/or opinions of expert panels. Whenever a level 1-type evidence (RCTs) is lacking, the rationale for the strategy relies mostly on the fact that increased risk was

Table 6
Levels of evidence for summary statements on the efficacy of prevention strategies assessed by the US National Cancer Institute's Physician's Data Query Program (from [40])

Assessment of the evidence by expert review	Type of endpoint	Outcome	Level of evidence
Evidence obtained from at least one well-designed and conducted randomized controlled trial with	Cancer	Mortality	1ai
	Cancer	Incidence	1aii
	Intermediate endpoint*	Incidence	1b
Evidence obtained from well-designed and conducted non-randomized controlled trials with	Cancer	Mortality	2ai
	Cancer	Incidence	2aii
	Intermediate endpoint	Incidence	2b
Evidence obtained from well-designed and conducted cohort or case-control analytic studies, preferably from more than one center or research group with	Cancer	Mortality	3ai
	Cancer	Incidence	3aii
	Intermediate endpoint	Incidence	3b
Ecologic (descriptive) studies (e.g. international patterns studies, migration studies) with	Cancer	Mortality	4ai
	Cancer	Incidence	4aii
	Intermediate endpoint	Incidence	4b
Opinions of respected authorities based on clinical experience or reports of expert committees (e.g. any of the above study designs using non-validated surrogate endpoints)			5

* A generally accepted intermediate endpoint (e.g. large adenomatous polyps for colorectal cancer prevention; high-grade squamous intraepithelial lesions of the cervix).

Table 7
NCI-PDQ program's summaries of evidence for the efficacy of specific prevention strategies for cancer (from [40])

Cancer site	Prevention strategy	Level of evidence*
Breast	Tamoxifen in women at increased risk for breast cancer	1aii
	Avoidance of unnecessary breast irradiation	3aii, 4aii
	Controlling exposure to alcohol	3aii
	Exercise at certain ages	3aii
	Avoidance of hormonal replacement therapy	3aii, 4aii
	Bilateral prophylatic mastectomy (in women with strong family history of breast cancer)	3ai, 3aii
Colorectal	Diets high in fiber, fruits, and vegetables do not reduce rate of adenoma recurrence	1b
	Non-steroidal anti-inflammatory drugs (piroxicam, sulindac, aspirin) to prevent adenoma formation or cause adenomatous polyps to regress among familial adenomatous polyposis patients	1b, 3ai, 3aii
	Smoking cessation to prevent adenomas and cancer	3aii
	Postmenopausal female hormone use	3aii
	Reducing dietary total fat, protein, calories, alcohol, and meat	3aii, 4aii
Endometrium	Progestins to prevent cancer associated with estrogen replacement	1aii, 2aii, 3aii, 5
	Use of combination oral contraceptives	3aii, 5
	Avoidance of tamoxifen use	1aii, 3aii, 5
	Controlling of obesity, diabetes, hypertension, and avoidance of diet high in fat	3aii
	Increasing breast feeding and physical activity	3aii
Esophageal	Smoking cessation and decreasing alcohol consumption	3aii, 4aii
	Increasing dietary intake of vegetables and fruits	3aii
	High intake of vitamin C and carotenoids	3aii
	Reducing intake of *maté*	3aii
	Regular use of aspirin	3ai, 3aii, 4ai, 4aii
	Elimination of gastroesophageal reflux by surgical or medical means	4aii
Lung	Smoking cessation	3ai, 4ai, 5
	Avoidance of pharmacological doses of beta-carotene among smokers	1a
Oral	Smoking cessation and avoidance of smokeless tobacco	3aii, 5
	Reducing alcohol consumption	3aii, 5
	Increasing dietary intake of fruits and vegetables	3aii, 5
	Avoidance of sunlight exposure (lip cancers)	3aii, 5
Ovary	Sustained use of combination oral contraceptives, multiparity, breast feeding	3aii
	Tubal ligation, hysterectomy, and a low-fat diet	3aii
	Avoidance of hormonal replacement therapy	3aii
	Prophylactic oophorectomy (in women with inherited ovarian syndrome)	5
Prostate	Reducing dietary fat consumption	3aii, 4ai, 5
	Vitamin E, selenium supplementation	1ai/aii
Skin	Reducing ultraviolet radiation exposure (non-melanoma skin cancer)	1b, 3aii, 5
	Avoidance of sunburns, especially in childhood and adolescence (melanoma)	3aii, 4aii, 5
Stomach	Avoidance of excessive salt intake	3aii, 5
	Increased dietary intake of whole grain cereals, carotenoids, allium compounds, green tea	3aii
	Increasing intake of vegetables, fruits and other plants containing vitamin C	3aii, 4aii, 5
	Beta-carotene, vitamin E, selenium supplementation	4aii
Uterine	Barrier methods of contraception	3aii, 4aii, 5
cervix	Smoking cessation	3aii, 4aii, 5
	Increased intake of micronutrients and carotenoids	3aii
	Health education to lead to behavior modification with diminished exposure	5

* See Table 6 for explanation of levels of evidence.

found for a given exposure in epidemiologic studies and that decreasing the exposure intensity or eliminating it completely will lead presumably to a reduction in cancer incidence (e.g. dietary modifications leading to a reduction of the constituent associated with risk). Alternatively, the exposure itself may appear to lead to a reduction in risk—e.g. exercise in relation to breast cancer—and this observation underscores the rationale for a preventive benefit. Assuming that a truly causal relation is established, observational epidemiologic studies are able to estimate the actual impact of the elimination of an exposure that leads to increased risk of cancer, e.g. smoking cessation in lung and upper aero-digestive tract cancers, by calculating attributable fractions.

Of particular interest in recent years is research on chemopreventive agents to reduce cancer risk. Table 7 lists

a few such chemopreventive strategies in which favorable RCT-type evidence (level 1) is already available, e.g. tamoxifen in breast cancer [41], non-steroidal anti-inflammatory drugs (NSAIDs) in adenomatous polyps [42], and progestins in endometrial cancer associated with hormone replacement therapy [43]. The original rationale for incorporating the latter preventive maneuvers in RCTs was based on the results from epidemiologic studies and of secondary clinical outcomes in therapeutic trials of cancer treatment. On the other hand, RCTs of chemoprevention can also lead to results that are dramatically different from what would be expected on the basis of epidemiologic evidence from observational studies. A case in point is the evolution in the understanding of the role of beta-carotene as a micronutrient with cancer preventive potential. During the last quarter century, a substantial body of epidemiologic evidence from case-control and cohort studies has implicated a high dietary intake of fruits and vegetables, a high estimated beta-carotene index diet, and high serum levels of beta-carotene with a lower risk of many malignant epithelial tumors, particularly lung cancer. This provided the rationale for chemopreventive RCTs of beta-carotene to prevent mortality from lung cancer among high-risk persons. As shown in Table 7, the unequivocal conclusions from two well-conducted RCTs, the NCI Alpha-Tocopherol Beta-carotene (ATBC) Trial [44] and the Beta-Carotene and Retinol Efficacy Trial (CARET) [45] have led the PDQ program to assert with a '1a' level of evidence that intake of beta-carotene supplementation at pharmacological doses is to be avoided because it could lead to an increased risk of lung cancer among smokers [40,46]. Interestingly, both studies found inverse associations between plasma beta-carotene levels and lung cancer rates, which is consistent with the epidemiologic evidence that formed the basis for these trials. This indicates that high levels of beta-carotene in plasma may be a marker of increased dietary intake of fruits and vegetables, which in itself may confer the health benefit. These results have led to a rethinking of the rationale for chemopreventive trials of lung and other cancers.

3.2. US and Canadian Task Forces

The two North American Task Forces tend to view preventive strategies differently in terms of how globally the evidence is assessed. While the CTFPHC examined each maneuver in the context of specific cancers [27], the USPSTF examined the overall potential benefits for many different clinical outcomes simultaneously, i.e. cancer, cardiovascular, etc. [26]. The latter also tends to provide separate assessments for the effects of the risk determinant itself and of counseling to modify exposure to it.

The USPSTF assigns an 'A' grade recommendation with level of evidence II-2 (refer to Tables 3 and 4 for an explanation of the score system) to the efficacy of a multiple outcome risk reduction secondary to cessation of tobacco use. On the other hand, this agency provides different recommendations concerning counseling strategies to curb tobacco use: A, level I, for clinician counseling of all smoking patients and use of nicotine patches or gum as adjuncts to counseling; C, level I, for clonidine as an adjunct to counseling; and C, level III, for clinician counseling of children and adolescents [26]. The Canadian Task Force assigns an 'A' grade recommendation of level I for smoking reduction for preventing oral and lung cancers (B for pancreatic cancer) and 'A' and 'B' grades for counseling and referral strategies to prevent or reduce smoking [27].

Regarding interventions for gynecologic cancers, the USPSTF assigns an 'A' grade recommendation with level II-2 for avoidance of high-risk sexual activity and use of barrier methods of contraception to prevent cervical cancer. A 'B' recommendation (level II-2) is assigned to the use of oral contraceptives to prevent ovarian and endometrial cancers. On the other hand, the agency views counseling measures to reduce risk of these diseases somewhat less confidently by assigning them a 'C' recommendation with level III evidence [26].

3.3. Other systematic reviews

Most Cochrane reviews that are applicable to cancer prevention have focused on tobacco cessation strategies. As of May 2002, the Cochrane database contained 26 completed reviews dealing with tobacco addiction that ranged from counseling interventions to techniques involving specific aids, both conventional and unconventional (acupuncture, antidepressants, aversive smoking, nicotine replacement therapies, and various forms of counseling). A number of these interventions were deemed efficacious by the review groups, such as prescription of the antidepressants bupropion and nortriptyline; of drugs that aid withdrawal from nicotine, e.g. clonidine, mecamylamine, nicotine replacement therapy; individual counseling by health care providers; group therapy; and self-help interventions [47]. An additional completed review on interventions for encouraging sexual behavior modification intended to prevent cervical cancer concluded that sexual education interventions involving women of low socioeconomic status are effective in leading to short-term reduction of sexual risk behaviors and thus have the potential to reduce transmission of HPV infection [48]. The Cochrane database also contained several ongoing review protocols covering the following interventions that are germane to cancer prevention: regular physical or self-examination of early detection of breast cancer, prophylactic mastectomy or use of tamoxifen for the primary prevention of breast cancer, oophorectomy for prevention of ovarian cancer in women with a familial history, screening for prostatic cancer, adenoma surveillance and other strategies for detecting colorectal cancer, such as dietary calcium supplementation, therapy for the eradication of *Helicobacter pylori* infection, alpha-fetoprotein and/or liver ultrasonography for liver cancer screening in hepatitis B carriers and drugs for preventing lung cancer (Table 5).

4. Practice recommendations

Numerous government and non-governmental agencies, medical professional societies, and health care organizations have established specific practice recommendations concerning screening and prevention. While some of these groups adopt policy guidelines based solely on scientific evidence that was carefully reviewed as per the mechanisms described in this chapter, others have a more liberal interpretation of the published data or consider additional circumstances such as delivery costs, prevailing practices, etc. Even when agencies adopt practice guidelines based on careful review of the evidence, pressure from the public and professionals may eventually contribute to the reversal or retraction of such recommendations. In cancer screening, the best example was the retraction by NIH of the conclusions from its consensus conference on mammography among women aged 40–49 years [49]. The original main conclusions ("*... data currently available do not warrant a universal recommendation for mammography for all women in their forties ... each woman should decide for herself whether to undergo mammography*.") created substantial controversy and political pressure from the US Congress [50]. Another round of controversy surrounding mammographic screening [6,7] has recently added to the challenging task of weighing the scientific evidence in order to develop practice guidelines.

Equally noteworthy is the recent debate concerning pressure from advocacy groups to maintain existing recommendations in favor of breast self-examination [51] despite conclusions of lack of benefit for the procedure [31].

A key factor in the implementation of policy guidelines based on best available evidence is the general structure of the health care delivery system. Many countries with a universal payor system of socialized medicine tend to examine overall benefits of screening and prevention strategies in relation to delivery costs and are generally more restrictive in their acceptance of novel technologies. Health technology assessments by Canadian and west European agencies tend to give far more weight to evidence of effectiveness from RCTs that show reductions in mortality from cancer as the endpoint. On the other hand, in the US, with its decentralized health care system that is free of direct governmental control, policy agencies tend to accept evidence from a broader spectrum of sources and tend to view more favorably RCTs with cancer precursor or cancer occurrence endpoints. A case in point is the traditionally liberal (in the sense of adopting recommendations more broadly) stance taken by the American Cancer Society, arguably the most influential private organization in the US in setting standards of oncological practice. This agency advocates prostate cancer screening including DRE and PSA testing for all men age 50+ years and yearly mammography among women 40–49 years [52], two examples of recommendations that are yet to be supported by solid evidence, although the latter was recently upgraded from a "D" to a "C" level by the CTFPHC. In addition, a key driving force in health technology assessments in the US has been the climate of medical malpractice litigation, which leads the medical profession to consider the sensitivity of screening tests as a more important parameter than specificity given the potential legal costs of false negative results.

5. Conclusions

Progress in our understanding of the natural history of cancer and in developments in testing technology and epidemiologic methods have led to an increased reliance on intermediate endpoints as outcomes in screening and primary prevention studies [1,2]. However, empirical demonstration that preventive strategies have an impact on the detection of (in the case of screening) or on the incidence of (in the case of chemoprevention) cancer precursors does not equate with proof of benefit from a public health standpoint. The standard of proof for practice guidelines is more restrictive; preventive strategies have to produce a reduction in mortality or at least in cancer incidence to be deemed worthy of being adopted on a populations basis. Nevertheless, screening and prevention studies using cancer precursor endpoints play a valuable role in providing the necessary proof of principle to justify the considerable costs and resources required for investigations of cancer incidence or mortality endpoints.

The practice by many health technology assessment groups of conducting rigorous, systematic reviews of primary and secondary strategies for cancer has contributed greatly to the establishment of scientifically sound practice guidelines. As reviewed here, these systematic reviews of evidence indicate that many screening and preventive strategies fall short of their expected or promised impact.

Most successful secondary prevention (screening) strategies for cancer are based on the detection and effective treatment of cancer precursors, leading to a reduction in the incidence of and mortality from invasive cancer. With the exception of the Pap test in cervical cancer, which was proven largely successful on the basis of systematic epidemiologic observations, the other success stories, namely, mammography in breast cancer screening and FOB in colorectal cancer, underwent verification by a higher standard of proof: the RCT paradigm. Also with noted exceptions (chest X-ray and sputum cytology in lung cancer and urinary metabolytes in neuroblastoma), lack of evidence of benefit for other screening approaches does not indicate that the benefit may not exist, but rather, that current technology and lack of availability of well-designed studies are hampering our understanding of a possible public health impact of these screening strategies.

Primary prevention approaches are all based on the premise that the natural history of cancer must be arrested in its very early phase, by blocking exposure to carcinogens before it leads to cancer initiation. Except for a few approaches involving chemoprevention and dietary modification, maneuvers whose efficacy in cancer prevention have been tested in RCTs, the expected benefit for most other

primary prevention strategies discussed in this chapter is backed up by the lesser standard of proof of observational epidemiologic studies, albeit with substantial consistency across studies. Consistency in epidemiologic findings for a particular cancer risk association forms the rationale for testing the putative preventive strategy in RCTs. The fact that this has led to an occasional paradoxical result—e.g. beta-carotene in lung cancer prevention among smokers—does not indicate that epidemiologic studies were pointing to the wrong opportunity for intervention but rather, that the putative maneuver was an oversimplification of the role of the factor(s) (e.g. dietary fruits and vegetables) in cancer causation.

Systematic reviews of published results of evidence in cancer screening and prevention do not necessarily form the only knowledge base that health care agencies and medical professional societies use when formulating practice guidelines. A variety of factors influence the adoption of recommendations, including the system of health care delivery in a given country or region, pressure from unconvinced health professionals and patient groups, and fear of medical malpractice litigation. As health and legal professionals and the public become more aware of the value of scientific evidence for or against preventive interventions, the latter situation may change and such comprehensive reviews may eventually become the main criterion used to influence changes in health care practices. However, evidence-based medicine is far from being an exact science. No matter how much of the evidence may come from RCTs, a healthy dose of controversy will always exist when it comes to making sense of information on cancer control and prevention.

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