Screening for Occupational Cancer

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Background and Definitions

Many known and potential human carcinogens are related to workplace exposures; the practice of occupational health is founded upon the key concept that virtually all such exposures can be prevented [1–3]. Primary prevention is the optimal prevention strategy for occupational cancer control through activities intended to eliminate harmful exposure(s) in the workplace [4].

Given the above, secondary prevention provided by medical screening remains an important component of sound occupational health practice in many instances. Such instances may include provision of medical screening for (1) workers with occupational exposures experienced before introduction of more recently enacted (and more protective) occupational exposure limits; (2) workers in workplaces where efforts are being made, but remain incomplete, in controlling exposures to acceptable levels; and (3) workers in occupations or industries known to be associated with cancer but with unknown specific causative exposure [3]. Medical screening can also detect breakdowns in protection of worker populations that might otherwise go unnoticed. Screening is among the tools available to complement exposure control for the prevention of occupational cancer. The fact that most cancers caused by occupational exposures are pathologically and clinically indistinguishable from cancers not caused by these exposures [5] supports the role of screening for occupational cancer in workplaces. Health professionals with the ability to recognize the role that exposures may be playing in the development of cancer are crucial to this process [2]. Early detection of cancer via screening is a component of a complete strategy for cancer control [6]. One of the aims of secondary prevention is to reduce morbidity and mortality through the detection of illness at an early stage when treatment may succeed in altering progression of disease.

Appropriate implementation of screening activities requires an understanding of the principles of screening and of the related activities of hazard and medical surveillance. The terms *surveillance* and *screening* have sometimes been used interchangeably (and sometimes inconsistently) in the past—it is important to understand distinctions between these activities [7–9]. Gochfeld provides useful distinctions for the medical terms and defines *medical surveillance* as an activity that targets health events or a change in a biologic function of an exposed person or persons, with recurrent longitudinal examinations and data analysis over time. *Medical screening* is a complementary activity designed to detect early signs of work-related illness by administering tests to apparently healthy persons in a repeated cross-sectional approach [7]. Medical screening for occupational cancer therefore involves the application of physical examination or medical tests to detect medical effects of exposure to cancer-causing agents [4, 10]. Screening activities have a clinical focus—the screened person may be directly evaluated and treated in response to a screening test. Medical screening data, ideally collected in a standardized manner, aggregated, and evaluated over time, can also be evaluated as a part of a surveillance program and play an important role in primary prevention. However, screening and surveillance activities without follow-up do not prevent occupational disease [11].

Biomarkers and Biomonitoring

A topic directly related to both screening and surveillance is biomonitoring using biomarkers of exposure or response. Biomarkers of exposure measure workplace agents or metabolites in biological specimens. Biomonitoring using these

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tests may allow for assessment of exposure via all routes of exposure and absorption [12]. Biomarkers of response are objective measures of normal physiologic processes, pathologic processes, or pharmacologic responses to a therapeutic intervention [13]. The two types of biomarkers can be used in screening and surveillance to assess exposure, effects of exposure (including preclinical, early, or clinically apparent disease), and susceptibility to illness [14–17]. Biomonitoring for carcinogens can involve testing for changes in deoxyribonucleic acid (DNA) or chromosomes, presence of markers of exposure in cells or body fluids, or detections of mutagens in biologic samples [4] and has long held potential as a form of medical screening [10]. As with any medical test, health professionals should understand what question the test is intended to answer and whether the biomarker is validated (validity is the best approximation of the truth of a test or the degree to which the results correspond to the endpoint or phenomenon being measured), so that the results can be accurately interpreted and informative [17]. Validation of biomarkers for use in screening for carcinogenicity remains an important issue both for occupational and environmental carcinogens [18, 19]. Frameworks for the use of biomarkers as clinical screening tools, particularly when other sources of medical data are not readily available, have been published [17]. The utility of biomarkers remains primarily in the area of research, as established and emerging biomarkers are used in clinical, etiologic, and hypothesis-generating studies [19]. For example, the efficacy of a multimodal screening strategy has been investigated for ovarian cancer mortality reduction [20] but remains investigational [21, 22].

A broad range of biomarkers have been used to assess exposures to potential carcinogens. Assays to detect DNA damage and DNA adducts have been used in epidemiologic and laboratory studies and have been among the most informative biomarkers of exposure to genotoxic agents [23–25]. Fibulin and high mobility group box protein 1 (HMGB1) are examples of biomarkers currently being investigated related to asbestos exposure and mesothelioma [26, 27]. 1-Hydroxypyrene and adducts of N-nitroso compounds are among biomarkers of genotoxicity being investigated for research and regulatory applications [18, 28, 29]. Although a number of biomarkers remain important research tools for investigations at the population level [18], poor specificity and positive predictive value (PPV) (among other issues) currently preclude their routine use as workplace screening tools for early detection of cancer in individuals. Ongoing research to augment available data concerning biomarkers of exposure with data related to biomarkers of effect will greatly enhance risk assessment efforts [23]. Research into biomarkers of genetic susceptibility is an emerging field; the evolving science is prompting important considerations related to ethical and social concerns [30–32].

Initiation of Screening for Occupational Cancer

The initiation of workplace screening for occupational cancer involves consideration of a number of factors.

Nature of the Health Outcome: Burden of Disease

Important diseases are candidates for screening [10]. Cancers, including occupational cancers, clearly represent illnesses posing substantial burden across the world. The global burden of cancer is increasing, with more than 8.2 million cancer deaths in 2012 [33]. Twelve million cancer deaths have been predicted for 2030, making primary and secondary prevention of great importance [6, 34]. In the United States, more than 1.6 million people were expected to be diagnosed with cancer in 2016; more than 590,000 people in the United States were expected to die from cancer in that year [35]. Estimates of the burden of occupational cancer have been published, recently summarized for Great Britain in 2012 [36], and well described in other parts of this text. Estimates of the percentages of occupational cancer among the total are widely considered underestimates due to several factors; nevertheless, it is clear that successful prevention activities could have major impact [2, 37].

Impact on the Health Outcome

An overarching consideration related to the initiation of screening relates to expected benefit to workers from the screening, and specifically, that there is a preclinical state of the health condition of concern that can be identified prior to the presence of symptoms [38]. If the health condition of concern is cancer, an additional factor important to realizing benefits from screening is that identification at an early stage may improve treatment outcomes. Adequate evidence of reduction in mortality has been a gold standard measure of efficacy when applying evidence-based methods to assess the value of screening tests. For cancer in the general population, recommendations for screening are often made on the basis of such considerations [22, 39, 40]; however, it has been pointed out that evaluations that assess improved survival as a measure of the value of screening activities are subject to known biases [41].

Experts have proposed different levels of evidence, including expert opinion [42], to support screening or other types of preventive health examinations, and screening may be recommended for subgroups on a case-by-case basis taking into account more qualitative aspects of importance to

those groups [22]. For example, preventive health examinations or testing can play an important role in occupational safety and health even in the absence of direct evidence of benefit to the screened individuals [10, 12, 16].

Availability of Tests to Detect the Health Outcome

Tests considered for screening must be able to detect cancer early in the illness, during the detectable preclinical phase [41]. The goal of screening is to increase the time between detection of cancer and the usual onset of symptoms (lead time). Ideally, this increased lead time would allow for intervention (e.g., treatment) to beneficially modify the clinical course and ideally to cure the illness. In addition to being practical and feasible [43], several defined characteristics of the screening tests are important when considering the initiation of a screening program. Sensitivity, specificity, and PPV (the proportion of persons with the health outcome among all persons who test positive) are important characteristics. PPV varies with the burden of the illness in the group being screened. Therefore, a screening test judged as having inadequate PPV for a cancer outcome in the general population may have adequate PPV in a group of workers at risk related to occupational exposure if that exposure leads to increased prevalence of illness in the tested workers.

Assessment of Medical Benefits and Concerns

In addition to the above, other benefits of screening include improved access to counseling for workers, exposure reduction or other modifications of the workplace, and contributions to medical surveillance efforts in the relevant workplace [10]. The benefits of a screening program should be considered against potential concerns. Concerns include direct complications from the screening test itself, complications from follow-up testing performed because of a positive screening test, and the potential emotional impact on a person receiving a false-positive test. Concerns also include monetary costs to the individual workers or to the employer. For employers, resources devoted to poorly planned screening programs may have been put to better use for other methods of prevention such as exposure control. Analyses of costs may be done in a qualitative or quantitative (in cost–benefit or cost-effectiveness analyses) manner. Another consideration is potential impact on the employment status of a worker who has been found to have an abnormal screening test (whether true or false positive) [4, 10]. Genetic biomonitoring that assesses potential predisposition to cancer has been raised as an ethical concern and a potential risk to workers [10, 44], and such concerns have contributed to current recommendations for caution in the use of genetic screening [30, 32]. In spite of rapid technologic advances in the ability to use genetic biomarkers in workplace screening programs, the program administrator must still consider the test characteristics (i.e., usefulness for screening) [45].

Component of a Sound Occupational Health Practice

Sound occupational health practice around the world includes elements of screening for many occupational exposures. Screening for occupational cancer is a component of a comprehensive approach for prevention among groups of workers exposed to occupational carcinogens [46, 47]. This comprehensive approach to prevention may need to be balanced with clinical approaches to prevention in which complete consensus is commonly not achieved relative to recommended screening tests for cancer [22]. In the United States, elements of screening are included in many standards and recommendations related to agents known or suspected to cause cancer [48–50].

Occupational Cancer and Latency

The factors noted above should be considered with knowledge of temporal relationships between exposure to occupational carcinogens and detection of cancer. Most cancer-related health effects among workers exposed to occupational carcinogens are not observed until 10–45 years after exposure. This observed latency presents a challenge to effective screening for occupational cancers in the workplace [4]; workplace-based screening programs should consider screening not only of currently exposed workers but also of workers previously exposed. Ideally, screening programs should be organized in employer-independent manner (e.g., based on exposure registries).

Components of a Medical Screening Program

The following factors are important components to consider in all types of workplace medical screening programs [8, 10, 12]:

1. Purpose and objective
2. Target population
3. Testing modalities and frequency of testing
4. Data maintenance and interpretation
5. Communication
6. Intervention
7. Program evaluation

A medical screening program should have a clearly defined purpose or objective. The target population should be clearly defined and may include that subset of workers with the highest potential for exposure. Testing modalities must be available to accomplish the defined objective. Testing modalities may include such tools as symptom questionnaires, medical histories, physical examinations, or medical testing. These types of evaluations should be used within the target population to gain data concerning a specific organ system(s) or health effect(s). A plan for initiation of testing (e.g., periodically and/or post-incident) should be formulated at the start of the program. The frequency of the screening test will depend in part on some or all of the following: test characteristics, the incidence of disease in the exposed group, information related to latency of the disease of concern, the length of the preclinical detection period, and the level and frequency of exposure [10].

Screening activities should be undertaken with a plan in place that ensures confidentiality of the medical data and of the interpretation of results. Privacy concerns related to collection of screening data have become more prominent with recent advances in and discussion of genetic screening [30, 32].

Several issues related to data interpretation should be considered. For example, screening test results may not be simply positive or negative. For data that may be interpreted as borderline, the level of abnormal test results that triggers some follow-up or intervention should be defined. Follow-up may include diagnostic evaluation and treatment (including medical removal if appropriate). In addition, for most tests, availability of baseline (ideally, before exposure) medical tests is important, so that those test results can be compared with results from testing at a later date. Furthermore, those persons conducting medical screening should understand the concepts of *sentinel events* [51] and should watch carefully for unusual clinical findings which may be important indicators of failure of prevention in the workplace. The detection of a malignancy that may be related to an occupational exposure may be considered a sentinel health event. When screening data are aggregated and analyzed over time and used for surveillance, such analysis may alert practitioners to elevated rates of an illness that warrants follow-up investigation. For example, the data may signal when an illness such as a malignancy occurs in excess or in a "cluster" in time and space. Finally, expertise in epidemiology is useful when analyzing and interpreting medical screening data, cancer rates, and potential cancer clusters and when conducting surveillance [12, 52].

An effective medical screening program requires several levels of communication with individuals being screened and with other relevant groups. If the screening is based in a workplace, communications with workers and management should include the objectives of the screening program and limitations of the data as well actual communication of the results. Screening test results should be understandable, and workers being screened should receive them promptly, as effective and timely communication is key to avoid creating false anxiety or false assurance. An explanation of the level of uncertainty associated with test results should be routinely included in communications about screening test results. With the individual workers' consent, results of medical tests may be shared with those workers' personal physicians. Communication of summary information should only be done in accordance with privacy and confidentiality protections. Communication of screening test results with professionals coordinating other aspects of the workplace hazard and medical surveillance provides for an effective, complete occupational health program. As discussed above, the availability of effective clinical follow-up is an important consideration in a screening program. For workplace-based screening programs, consideration should be given to whether analysis of screening program data may result in a need for workplace intervention. A final phase of a medical screening program is assessment of the program effectiveness over time. Quality assurance and control should be considered for all workplace screening programs.

Considerations Related to Screening: Updates on Specific Cancers

On the basis of the rationale and principles reviewed above, screening activities are currently components of sound occupational health practice for a number of exposure scenarios and in relationship to several types of cancer. Current information related to screening for several types of occupational cancer is described below.

Lung Cancer

Lung cancer is the leading cause of cancer death worldwide [33] and an important cancer in working populations [1, 3]. The prognosis of lung cancer is markedly improved by diagnosis at an early stage, so there has been great interest in early detection [53]. The National Lung Screening Trial (NLST) showed that annual low-dose computed tomography (LDCT) screening reduced lung cancer mortality in high-risk individuals followed up for up to 5 years after their last annual screen by 20% relative to a control group receiving chest X-ray (CXR) [54]. The NLST is a national randomized controlled trial launched by the US National Cancer Institute in 2002 which used the following risk criteria for entry—age 55–74 years, 30 or more pack-years of cigarette smoking history, and former smokers had to have quit smoking within the previous 15 years [54]. In 2013 the American Cancer Society (ACS) revised its lung cancer screening guidelines,

recommending that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients with the same risk profile as used for the NLST [55]. The ACS emphasized that (a) a process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with LDCT should occur before any decision is made to initiate lung cancer screening; (b) smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer; and (c) screening should not be viewed as an alternative to smoking cessation [55]. The US Preventive Services Task Force (USPSTF) has similar recommendations, differing primarily in the age at which to discontinue screening [22, 56].

In order to provide evidence-based guidance for LDCT screening for early detection of lung cancer in populations that have been exposed to lung carcinogens, it is important to document that such screening will achieve a favorable balance between benefits and harms. In order to assure that potential benefits of early detection exceed potential harms such as causing radiation-induced lung cancer or related to false positive studies, it is important to assure that the screened population is at sufficiently high risk for lung cancer. Studies are ongoing in the attempt to refine screening protocols to improve the efficiency and cost-effectiveness of population-based lung cancer screening programs [57].

Lung cancer risk related to smoking is an important consideration in lung cancer screening. Workers with combined exposures to tobacco smoking and an occupational carcinogen such as asbestos are at greater risk for lung cancer than nonsmokers with the same occupational exposure [58, 59]. Thus, in potential future guidance for LDCT screening, it will be important to identify and consider different thresholds for level of exposure to an occupational carcinogen that triggers screening among nonsmokers as compared to smokers. A recent report by the Finnish Institute of Occupational Health (FIOH) on LDCT screening for lung cancer in asbestos-exposed workers provides guidance on a potential risk threshold. The FIOH recommended LDCT screening of workers "... with any asbestos exposure and a smoking history equal to the entry criteria of the {NLST} study; and workers with asbestos exposure, with or without a smoking history, which alone or together would yield an estimated risk level of lung cancer equal to that in the entry criteria of the NLST study" [58]. The reason for this recommendation was that LDCT screening of the NLST population, which had a high risk for lung cancer, was documented to result in a favorable balance of benefits and harms. Quantitatively, the absolute risk for lung cancer in the NLST study population (and thus the threshold absolute risk for lung cancer proposed by FIOH as a trigger for LDCT screening for early detection of lung cancer) was 1.34% over 6 years [60]. If it is documented that a working population has this high level of risk (or greater) for lung cancer, it will be possible to justify an evidence-based requirement for LDCT screening.

Dissemination of LDCT technology that allows chest scans to be completed using less radiation is changing the risk–benefit calculation in a way that favors screening requirements. For example, it is now feasible to screen with ultralow-dose CT using amounts of radiation similar to a conventional CXR [61]. Widespread availability of this technology would reduce risks from radiation and improve the balance between benefits and risks.

There are several additional aspects of LDCT screening for lung cancer to consider as guidance is refined in the future. Access to appropriate counseling is a very important part of an LDCT screening program—just being identified as being at sufficiently high risk for lung cancer to be eligible for LDCT screening can lead to a need for counseling. Counseling may also be needed to help patients through the screening process as screening results often lead to follow-up tests (often repeat chest CT scans) to assess changes in nodules over a period of many months. It is important that those being screened be fully informed about the process, including the significance of screening findings and the approach to follow-up. Also, since follow-up is so frequently necessary and so critical to the success of an LDCT screening program, future guidance should take into account the provision of appropriate clinical care in follow-up to LDCT screening [62].

Bladder Cancer

It has been estimated that more than 429,800 new cases and 165,100 deaths from bladder cancer occurred worldwide in 2012 [33]. Although occupational exposures rank behind smoking as important risk factors for bladder cancer, a number of occupational agents are known bladder carcinogens [63–65]. Issues related to screening of higher-risk persons, such as those with occupational exposures associated with bladder cancer, have been an important topic for many years [66] and remain an area of active work [67, 68].

Clinical evaluation by cystoscopy, an invasive test, is commonly used as the diagnostic test for bladder cancer among the screened population. Individually, urinalysis for hematuria may have adequate sensitivity (particularly with repeated testing) but specificity is low. Urine cytology has been the primary test employed for bladder cancer screening among workers exposed to agents raising the risk for bladder cancer [63], but has been shown to have low sensitivity, even among those with high-grade cancers [69]. Cytology with other tests such as urinalysis and cell-based tests has been used in well-described screening and surveillance programs

as part of research studies [66, 70], and research continues in developing cell- and urine-based bladder cancer tests [71, 72]. The unique clinical characteristics of transitional cell bladder cancer and inadequate test characteristics of current screening tests, along with inability to demonstrate reduced mortality among the screened groups, all contribute to the current determination that further research on bladder cancer markers is needed to inform screening programs for occupational bladder cancer [73–76]. Further research is underway to identify appropriate target populations (thereby increasing the PPV of subsequent screening tests) for bladder cancer screening [68, 73, 75]. There are a variety of noninvasive tests (along with assessment of risk factors such as smoking history and/or occupational exposure to bladder carcinogens) that may be used to identify high-risk populations within which to perform subsequent screening [71–73, 77–79]. While models have been developed incorporating known factors such as smoking and selected tests (such as urinalysis) to identify high-risk populations likely to benefit from screening, clinical judgment remains an important factor which considering screening of populations who may be at risk from occupational exposures [68]. Recent studies of bladder cancer screening programs among specific occupational groups are informative and can help guide future work [75, 80], but further research is needed before bladder cancer screening can be recommended in any systematic manner. The USPSTF concluded that additional research is needed to determine whether screening for bladder cancer improves clinical outcomes [81].

Skin Cancer

Skin cancers are the most common cancers [82] with both nonmelanoma skin cancers (more common but not commonly associated with mortality) and melanoma (less common and accounting for most mortality from skin cancers), representing significant health problems worldwide [83, 84]. Environmental and occupational exposures are known to be associated with several types of skin cancer, with exposure to ultraviolet radiation an important occupational risk factor [83, 85]. Examination of the skin is an established prevention activity for clinicians [86, 87]. However, limited evidence that skin cancer screening in the general population, particularly with regard to benefits of skin cancer screening on melanoma mortality, has led to calls for future research on the effectiveness of targeted screening in those considered to be at higher risk for skin cancer [88–90]. New approaches to screening for skin cancer, such as tele-dermatology, are being studied [91, 92]. The substantial burden of morbidity and mortality associated with melanoma have particularly focused calls for improvements in melanoma prevention activities which can include screening programs [83, 84].

Other Cancers

Although exposures to a number of agents (including ionizing radiation, benzene, and cytotoxic drugs) are associated with acute leukemia, clinical screening tests to detect the health outcome (leukemia) or cytogenetic abnormalities associated with leukemia are not routinely used for workers exposed to these agents [93]. Investigations continue into the molecular mechanism of benzene toxicity and into potential biomarkers for early diagnosis of toxic effects [94, 95]. Potential future clinical application of these techniques in screening programs will be informed by continued research in these areas.

Pleural mesothelioma, primarily associated with occupational exposure to asbestos, is a cancer for which there has been a high level of interest in early detection due to the associated generally poor prognosis and high mortality [96]. Radiologic tests (CXR, CT) have not been shown to be useful screening tests for mesothelioma in the past. Serum biomarkers have also been considered, sometimes in conjunction with radiologic tests, as screening tools. Recent studies have investigated blood biomarkers such as fibulin-3 and N-ERC/mesothelin [26, 97]. To date, the use of biomarkers as screening tools for persons at risk of mesothelioma remains investigational, and future work to improve their diagnostic performance may help increase their clinical usefulness for this indication [96].

Considerations Related to Screening: Integration with Other Program Elements

From a workplace perspective, screening for occupational cancer should be occurring as a component of a complete occupational health program [10]. From an individual's perspective, screening for occupational cancer should be occurring as component of complete clinical care for the individual [50]. Among the factors to consider here is that a worker may be exposed to multiple agents and that such agents may be associated with both malignant and nonmalignant illness. Approaches to integration of screening for health effects related to exposure to multiple agents in the workplace are described in the literature [98]. When agents are known or suspected to be associated with both malignant and nonmalignant illness, issues related to latency will need to be considered as the screening program develops over time. For example, the unprecedented occupational exposures that occurred related to the attack on the World Trade Center (WTC) in New York City are being partly addressed by a screening, surveillance, and medical treatment program for established cohorts [99, 100]. Issues concerning cancer endpoints related to potential occupational exposure during the WTC attack and subsequent work may become of increasing

importance in the future [101]. Emerging occupational exposures also present a challenge in the consideration of medical screening and prevention of occupational cancer as a component of a complete occupational health program. For example, health concerns and issues related to medical screening have been raised relative to the increasing development and use of nanomaterials [102, 103]. The principles underlying the rationale for screening and how screening for endpoints including occupational cancer fit into a program of prevention should be carefully considered for those workers potentially exposed to agents for which evidence of toxicity is emerging [104, 105].

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