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Scand J Work Environ Health 1992;18(1):57-63
Issue date: 1992

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/1411381

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Print ISSN: 0355-3140 Electronic ISSN: 1795-990X

Scand J Work Environ Health 1992;18 Suppl 1:57—63

Proposal for future uses in epidemiology for cohort studies on the prevention of work-related cancer

by Sverre Langård, MD[1]

LANGÅRD S. Proposal for future uses in epidemiology for cohort studies on the prevention of work-related cancer. *Scand J Work Environ Health* 1992;18 Suppl 1:57—63. A new use of the cohort method in cancer prevention is proposed involving individual collection of information on past exposure to dominating cancer determinants. It is assumed that it is possible to determine individual cancer risk and, subsequently, to estimate the individual risks of cause-specific cancers on the basis of accurate individual data on exposure to cancer determinants. Individuals at given risk levels should subsequently be assigned to defined risk categories to establish groups designed for risk-determined screening programs and risk-determined information intervention. As increased risk to work-related cancer is generally more strongly related to past than to current exposure, a large proportion of those who are at high risk are no longer employed and thus not in reach of occupational health physicians. Therefore, risk-determined intervention should be integrated into the daily work routines of both occupational health physicians and primary care physicians.

Key terms: cancer screening, disease risk, risk-determined intervention, risk groups, risk quantification.

Cohort studies on work-related cancer can serve the following major purposes: (i) to identify and characterize the distribution of cancer determinants and the occurrence of cancer in given populations, (ii) to unravel causal exposure-effect relationships between cancer determinants and cancer in populations, (iii) to quantify the relative causative weight of work-related exposure for all cancers in a defined population, and (iv) to serve as a tool in the prevention of work-related cancer.

The cross-sectional study design is generally inappropriate to unravel causes of cancer, mainly because of the long development time between the start of work-related exposure to cancer determinants and the occurrence of exposure-related cancer cases. It can, however, be versatile for identifying populations at high risk.

As a result of the use of the cohort method for about four decades in causality studies, a huge amount of information has been gathered on relations between exposure and the development of site-specific cancer. This is true for exposure factors in the general environment, exposure to personal factors (ie, tobacco), and also for exposure at work. As an illustration I only need to mention some exposure factors, for example, asbestos, nickel, radon daughters, hexavalent chromium, and passive smoking and their significance for lung cancer causation and the significance of nickel compounds for cancer of the nasal sinuses (1—9).

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With only few exceptions the currently known determinants of work-related cancer have been revealed by the use of the cohort method (10). Therefore, up to now the cohort method has been the method of choice in the study of causal relations between work-related exposure and cancer. However, as the case-referent method is becoming increasingly important in revealing causal relations and quantifying relative risks related to exposure, I would like to consider briefly a possible future use of the cohort method as a tool in the prevention of work-related cancer. I expect that during the 1990s the prevention of cancer is likely to become the prime task of those epidemiologists who are preoccupied with work-related cancer.

As scientists have gathered a huge amount of knowledge on causal relations, the time seems appropriate to start using this knowledge for the practical prevention of work-related cancer. However, first, I would like to mention briefly some aspects of design which may become important in current and future cohort studies.

Reduced cancer risk in recent decades

From the 1950s to the 1970s, epidemiologists in the Western world encountered strong relations between exposure to work-related cancer determinants and the occurrence of various cancers. Such high relative or absolute risks can be detected even with crude cohort methods. As a result of various preventive measures during the 1960s and 1970s the high-risk situation has changed dramatically during the 1980s to one with generally low (additional) risks.

Currently in the Western world only minor differences are generally found between the incidence or death rate of cancer in exposed groups as compared with the corresponding rate of the chosen reference population. When more than one reference population is used in a cohort study, the excess cancer incidence or death rate may be present in one comparison but not in another even though the reference populations are presumably appropriate (11). This situation presents the epidemiologist with a much greater methodological challenge than cohort studies some 15—20 years ago did.

Interaction between work-related cancer determinants and determinants from other sources must be taken increasingly into account. Imagine the simple situation of a study performed to quantify the relationship between exposure to asbestos in a given work situation and the occurrence of lung cancer among the persons exposed. Imagine also that the exposure to asbestos is quantified accurately, while the given study circumstances do not permit identification or semiquantification of exposure to other work-related cancer determinants, to smoking or passive smoking, or to other significant determinants. The results of this study turn out to show a much stronger relation between asbestos exposure and lung cancer than do other published results (ie, a rate ratio of 25.0 for the asbestos-exposed group as compared with the reference population). Undoubtedly, these study results falsely ascribe at least a given fraction of the excess lung cancer to asbestos. This fraction should have been ascribed to various other determinants to which the population was exposed.

An example: A group of Norwegian seamen were studied in the early 1980s on the basis of cross-sectional information on work affiliation — work on deck or in the engine room — and smoking habits in 1962 (12). No difference was found between the lung cancer incidence of the engine room workers and the deck workers, while a strong relation was found between smoking and lung cancer, those smoking more than 25 cigarettes a day having a relative risk of 47.0 when compared with those smoking less than five cigarettes a day, a reference level close to the national figures for men. No doubt, this result falsely ascribes some causality to cigarette smoking that rightly should have been ascribed to unidentified lung cancer determinants related to work (ie, asbestos and oil mist).

In cohort studies carried out in the past, when only one prime possible causative determinant has been identified as acting on the study population and such modifying factors were not appropriately accounted for, the aforementioned phenomenon is likely to have occurred frequently.

Significance of the development time of cancer

In general, development (latency) time is considered as the time from a population's first exposure to a cancer determinant and the occurrence of the first exposure-related cancer case in the population. The significance of this phenomenon has been known for decades (13), but in cohort epidemiology it is only during the past 10—15 years that it has been taken into account in the design phase, as well as in the analysis of the data. When development time is accounted for, the cases which occur during that period are excluded, as are the expected figures for that same time period. Even in cases with a short latency period (ie, 10—15 years) the rate ratio can vary by as much as a factor of 1.25 to 2.0 by alternative inclusion and exclusion of the latency period in the analysis (14, 15).

The significance of the development time for the outcome of epidemiologic studies also depends on the potency and level of exposure to the carcinogenic substances of concern. The latency period is generally short after exposure to high levels of potent cancer determinants. Hence, the expected figures cumulated during the latency period are relatively small. Conversely, during the same period, the probability is low that new cancer cases unrelated to exposure will occur. Thus accounting for the latency period in such a situation might be of minor importance.

For exposure to low levels of low potency cancer determinants, (thus a long latency period, ie, 20—25 years or longer) the situation is different. The number of new cancer cases unrelated to the exposure of concern, between the start of exposure and the occurrence of exposure-related cases, may be relatively great. Example: If the development time is 25 years and the "observation period" is 30 years from first exposure, more than 50%, even 75% or more, of the cases occurring during the first 25 years of observation may be unrelated to the exposure of concern. In such a situation the expected figures cumulated during the latency period may also highly contribute to the total number of person-years under observation. Thus it is essential to exclude expected and observed figures from the latency period in particular when the observation period is only slightly longer than the latency period.

Consequences for study design

To meet the challenges resulting from the currently rare high rate ratios for work-related cancer, it is becoming increasingly important to identify and — whenever possible — to semiquantify the exposure to as many as possible of the prime cancer determinants for each cohort member with a much greater accuracy than before. Otherwise the likelihood of detecting small rate differences is small.

Whenever possible one also needs to identify and specify the time periods of the most significant exposure to the presumably most significant cancer determinants on an individual basis. When such detailed exposure characterization is impractical for all members of the cohort, one should identify those members or subgroups for whom such detailed data have been collected. This procedure permits a separate analysis of the occurrence of cancer among these subgroups and to some extent also permits the assessment of possible interactions within the subgroups.

Provided that such detailed exposure characterizations have been carried out for most of the members of the cohort, one has also accounted for the quantification of confounders and modifiers which otherwise could play an uncontrolled role in the possible causal relations occurring in the study population.

The cohort method in prevention

This method provides a tool which the community and the industry need for planning and implementing intervention against work-related cancer and other preventable diseases, as well as for evaluating the outcomes. It seems questionable whether epidemiologists are aware of the need of their knowledge, and whether they are prepared to share their skills with the community and industry. I would like to point out some possible future uses of the cohort method as a tool in the prevention of work-related cancer.

Epidemiologists have been capable advisers on how to use current knowledge on causality in primary prevention. As a result of this advice the community and industry have generally been successful in instigating primary prevention by reducing exposure among current workers (ie, preventing work-related cancer 25—40 years ahead). However, numerous workers have been exposed to cancer-causing agents in their work during the past three to four decades; hence cancer risk has accumulated. This accumulated risk is generally not reduced by a reduction in current exposure.

Consequently, in different countries there are great numbers of people who have accumulated cancer risk in relation to work exposure (ie, asbestos and carcinogenic metals). In a small country like Norway with 4.2 million people there are about 150 000 persons who will continue to have an increased cancer risk during the next two to four decades because of past exposure to asbestos. This risk will contribute 300—350 new lung cancer cases yearly among Norwegian men (ie, 18—20% of all new cases) (16).

Only few epidemiologists have acknowledged this hidden challenge of preventable work-related cancers. The community has succeeded in reducing the accumulated risk of these cancers neither among individuals nor among the groups with past exposure. Therefore, epidemiologists are faced with a challenge. They have to provide their knowledge to the community and participate in preventing these preventable cancers.

Few attempts have been made to instigate early secondary prevention of cancer among people at high cancer risk from past exposure to work-related carcinogens to reduce accumulated cancer risks (17, 18). Some studies, however, have been successful in intervening against accumulated disease risk from other causes (19—21).

To perform such early secondary intervention, one has to identify a sufficiently large number of subjects at increased cancer risk to permit evaluation of the outcome results. Only few currently exposed industrial populations in the Western world are big enough for this purpose, and currently exposed workers are generally not at very high cancer risk. Many — possibly two-thirds — of those at increased cancer risk have already been selected out of work and thus are not within the reach of the occupational physician (16, 22). Hence one must look for those at high risk in other settings than the kinds of workplaces in which workers are currently exposed.

Identification of high-risk cohorts using the cross-sectional method

Inappropriate methods have hampered the identification of subjects who are still healthy and who have exposure-related high risks of work-related cancers. However, some attempts have been made to use self-administered risk factor questionnaires for this purpose, but there are many limitations in their practical application (23, 24). Provided that high-risk groups could be identified, they could be targeted for specific risk-determined intervention programs.

In Telemark experience has shown that cross-sectional studies using comprehensive questionnaires to identify individual past exposure, in combination with a clinical survey and an interview of selected subgroups, can be versatile for identifying subjects at high cancer risk (22, 25). Such cross-sectional studies can easily be carried out on a large scale in the general population, and they permit the identification of a great number of subjects with a priori increased risks to work-related cancers targeted for intervention (25).

Once a large group of people at risk has been identified, it should be possible (i) to identify subjects who are currently at high cancer risks or who later will become at high risk, (ii) to semiquantify these cancer risks at that time and also project for the future, and (iii) to apply these risk estimates to identify target groups for cancer intervention.

Once this has been done, it is possible to start specific intervention programs on risk reduction among identified high-risk subjects and groups. Finally, this approach should also permit the evaluation of the outcome results in terms of reduced a priori risk of site-specific cancer and cause-specific cancer (mortality), short-term as well as long-term.

The cohort concept in prevention

Because environmental factors interact with each other as well as with host factors, cancer cases are rarely caused by one determinant only (26). Hence interaction must be accounted for in the planning of intervention programs. In fact, in absence of exposure to environmental cancer determinants subjects would live longer than today (27).

The relations between exposure and effect is well known for some cancer causes. Therefore, whenever a detailed individual lifetime history on semiquantified exposure to these work-related determinants is available, it should be possible to utilize this information to estimate individual cause-specific risks for work-related cancer. However, before this semiquantification of individual relative or absolute relations between the duration and level of exposure and the incidence and death rates of cancer can be carried out, the data must be available in the literature or in census data. The effects of combined exposure to the cancer causes at issue should preferably also be available. Given both individual exposure and these background data, it is also possible to estimate individual cause-specific cancer risks on the basis of individual exposure.

The purpose of such an operation is to identify and semiquantify the cause-specific risks for major cancers for each member of the group on the basis of individual information on previous and current exposure to significant determinants. As of today few studies have had access to the necessary accurate exposure data required for such studies. With access to a large number of subjects for whom detailed lifetime information on work-related exposure is available, as well as on exposure to other environmental cancer determinants, it should be possible to carry out such intervention studies.

The aims of such intervention should be (i) to reduce cancer risks through intervention aimed at interrupting or reducing exposure to major determinants, (ii) to generate a model to project individual cancer risks 10—30 years ahead, given unchanged exposure to a set of environmental cancer determinants, and (iii) to predict the reduction of risks resulting from a corresponding reduction in the intensity of exposure to the cancer determinants.

Groups of subjects identified and characterized in this way would permit one (i) to estimate individual risks for specific cancers, a procedure which subsequently makes it possible to estimate long-term potential risk reduction of intervention, (ii) to study long-term effects of individual intervention against determinants, as well as the outcomes of intervention against interacting cancer determinants, (iii) to study the results of intervention against exposure to work-related and nonwork-related cancer determinants when they interact in cancer causation, and finally (iv) to semiquantify projected short-term and long-term benefits at various levels of success in reducing the prevalence and intensity of exposure to the cancer determinants at issue.

When individual current and projected risks for work-related cancers have been estimated, each individual can be assigned to cohorts defined by levels of site-specific cancer risks at given times in the future. The specific intervention programs, and inclusion as well as exclusion criteria, characteristic for each risk interval should be decided upon before the intervention program is initiated, thus prior to assignment to the risk interval and intervention program.

Each separate risk cohort can then serve as a target population for individual and group-based "risk-determined information intervention" against cancer risk, and also for risk-determined screening programs. The separate intervention programs should be designed so that they are likely to serve each risk-defined population in reducing individual cancer risk and early cancer detection.

Inclusion criteria for risk-determined information intervention and risk-determined screening

Even in the absence of cancer risks related to genetic characteristics, all humans are at elevated risk for some cancers resulting from environmental exposure. Consequently, it is impossible to offer risk-determined information intervention to all subjects with an increased cancer risk, and some kind of restriction must be implemented. The criteria for such inclusion should be defined at risk levels so that eligible subjects are those among whom risk-determined information intervention is likely to give optimal outcome in terms of reduced cancer risk (25).

Therefore, the aims of a given program for risk-determined information intervention must be defined in advance. Each group-specific and risk-determined program should be designed so that the likelihood is high of reaching the goals. Thus, when the primary objective is a reduced number of unnecessary lost years of healthy life otherwise resulting from preventable cancers, the programs for each separate target population should be designed to meet this objective. Success in this respect would also result in an increased number of years of life.

When the goals are to gain years of healthy life or years of life in a given target population, the efficacy of the intervention can also be judged by the success in reaching these goals.

Basic provisions for successful risk-determined information intervention and risk-determined screening

As indicated elsewhere (25), risk-determined information intervention among high-risk subjects should preferably approach primary prevention. In addition risk-determined information intervention is likely to have a higher success rate in terms of interrupted individual exposure among subjects aged 40 to 50 years or older than among younger subjects, because young people have a low expectation of becoming ill in the next few years, while older subjects have such an expectation (28).

The frequency and content of risk-determined information intervention should take into account the projected levels of high cancer risk(s) at various times in the future for each subject in the risk-determined cohort. As the duration and intensity of exposure to cancer determinants have already been taken into account in the estimates of the a priori cancer risks, these "dose" aspects could be disregarded at this stage. The same is true for the presumed latency period for the cancers at issue.

In contrast to risk-determined information intervention, screening procedures are likely to give the most favorable results when applied late (ie, when the cancer risk approaches its highest peak). Consequently, risk-determined information intervention should be intense in the early phases of the risk increase, and screening should generally be intensified when the projected risk approaches its highest levels (25). If the expectations on illness and healthiness at different ages are taken into account (28), it is possible that programs on risk-determined information intervention should preferably be applied to subjects between the ages of 20 to 45 years and that they should be intensified between the ages of 30 and 35 years. However, the efficacy of risk-determined information intervention and risk-determined screening at various ages should be evaluated as a part of the program.

As indicated, the level of the a priori cancer risks can be estimated if each participant's semiquantified past exposure to cancer determinants is compared with the cancer outcomes at corresponding exposure levels as presented in published studies. These experienced relative or absolute cancer risks at corresponding ages and the levels and durations of exposure can then be multiplied by the absolute age- and gender-specific experienced risk for the appropriate age, year, and time period, as gathered from national or regional cancer incidence data or from cause-specific registers on causes of death.

Supplementary intervention programs

Risk-determined information intervention could be accompanied by other means of intervention, for example, screening for cancer among subjects who meet given risk-determined inclusion criteria. These criteria should be different from those applied for risk-determined information intervention. However, for reasons of efficacy, the criteria for inclusion into screening cohorts should preferably be based on the same determinants of risk.

Subjects who are currently, or are projected to become, at high risk for several cancers should possibly be assigned to a separate high-risk group for "multicause or multieffect." Risk-determined information intervention and screening programs should be more frequent and more comprehensive for these subjects than for subjects with only one major cancer determinant.

The selection of those who should be included in such a multicause high-risk group could be based on the sum of a priori risks for individual cancer sites as projected to given ages (ie, 55, 60, or 65 years) for each subject's major cancer risks (25). The level of this sum of risks could be chosen as the basis for inclusion in a such group. The age to which risks should be projected for summation, which cancer sites should be included in the summation, and the content and the frequency of risk-determined information intervention and screening, respectively, should be decided during the design of the program.

As for the potential to reduce projected cancer risks, it is greater for young subjects than for older ones. Hence, risk-determined information intervention is likely to result in a greater risk reduction when carried out among high-risk subjects at a young age than among older subjects with a corresponding level of risk.

Organization of risk-determined information intervention and risk-determined screening

Some countries have well organized primary health care. In such cases primary health physicians are in a strategic position to carry out counseling, in particular because the patients themselves initiate the visit to the primary health physician (29). It is assumed that primary health physicians, through their close contact with each patient, can conveniently carry out in-depth interviews on smoking and alcohol consumption, dietary habits, and other individual cancer determinants (30). This unique position of the primary health physician could be more appropriately utilized in prevention. Occupational health physicians are also in a unique strategic position which could be utilized for the detailed collection of individual information on work-related cancer determinants. It is also assumed that occupational health physicians have a similar opportunity to interview workers on work-related cancer determinants, permitting in-depth interviews on current and past work-related determinants. Both primary health physicians and occupational health physicians should preferably become increasingly involved in this kind of intervention.

In countries with well organized primary health physicians as well as occupational health physicians there could be a potential conflict as to which of these two groups should take the main responsibility for individual intervention. However, this possible conflict can be avoided if the magnitude of a priori cancer risk is allowed to determine who is to carry out the individual counseling, depending on whether the primary determinants for cancer risk are related to life-style or work exposure.

It is essential that, given an identical risk level for a given illness, the counseling should be practically identical, irrespective of who carries it out. One way to solve this equity problem is to establish units for disease intervention covering populations of appropriate sizes (100 000 to 250 000 people). To permit broad contact and continuous communication between the participating primary health physicians and occupational health physicians and this unit, the unit should have defined functions as indicated elsewhere (31). Direct computerized transfer is preferable for exposure data, individual disease risk assessments, and proposals for individual counseling. Primary health physicians and occupational health physicians should preferably also communicate through computers to supplement each other's exposure data.

Evaluation of results

Short-term evaluation of results of risk-determined information intervention and risk-determined screening could be based on a reduction in the prevalence and intensity of exposure to the targeted cancer determinants, and it could involve comparisons with age-adjusted nonparticipating reference groups.

Long-term evaluation of results from risk-determined information intervention and screening is complicated. One reason is that reference groups may benefit from intervention in different ways. To avoid some of these difficulties, one could carry out a "controlled" study in which half the eligible subjects are assigned "blindly" to risk-determined reference groups. However, as many eligible subjects belong to two or three risk groups, this approach may also result in a complicated situation for the separation of intervention and reference groups. Such an approach may also generate ethical questions such as depriving half the eligible high-risk groups the opportunity of participation.

One could also choose a method for long-term evaluation similar to that used in a study on the effect of smoking cessation on asbestos workers (18). In this study the mortality of lung cancer, and all causes as well, among the persons who quit smoking was compared with that of nonquitters from the same exposure group. This method provides a possibility to offer intervention to all eligible subjects. However, selection may occur which is difficult to control.

To find appropriate reference groups for the short-term evaluation of screening is difficult. For groups eligible for screening (eg, persons with lung cancer), results could be evaluated in comparisons of mortality in the screened groups with that among eligible nonparticipating groups. However, in that case, the small size of the reference population could be a problem.

A reduced prevalence or intensity of exposure to the target determinants may not only reduce the targeted cancers, it may also result in reduced disease incidence and mortality from other exposure-related illnesses. Therefore, such additional gains should be accounted for when the effects of risk-determined information intervention and risk-determined screening are evaluated.

Gained healthy years and gained years of life in the intervention groups should be considered to be the ultimate goals of risk-determined information intervention and risk-determined screening. Therefore, these benefits can be considered appropriate for the ultimate evaluation of the results, and thus a measure of outcome. Projections of long-term changes in disease incidence and rates of cause-specific deaths, which this intervention approach may provide data for, may also become a useful tool for health care planning.

My conclusion is that the suggested use of the cohort method could provide a new field of application for this method. Within the field of preventing work-related cancer, serving as a tool in organizing and evaluating such cancer prevention programs, the method may face a bright future.

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