ОБЗОР ЛИТЕРАТУРЫ

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Towards the elimination of occupational cancers in the Russian Federation: cancer research for cancer prevention

(Part 2)

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Cancer is increasing worldwide. The Russian Federation is no exception in this regard with an increase of the total number of new cases predicted to rise from 529,062 in 2018 to 587,622 in 2040. The present high burden and increase in incident cases at the same time increases the pressure on healthcare infrastructure and related costs. Thus, primary and secondary prevention of cancer becomes essential. Occupational cancers related to exposure at the workplace are among the preventable cancer burden, due to the modifiability of the risk through minimisation of occupational exposures and adequate worker protection. For the Russian Federation, some 20,000 cancers each year may be attributable to occupation, but systematic recording is currently lacking. As information is also lacking on the absolute effect of various occupational carcinogens in the Russian workforce due to lack of large-scale epidemiological studies and because for many suspected occupational carcinogens the evidence may become stronger, the true burden may in fact be higher. The Russian Federation appears particularly suitable for research into occupational cancer given the sizable workforce, the heavy industrialisation as well as the good documentation and workplace surveillance over time, so that results are both informative for the situation in the Russian Federation and on a global scale. Five challenging but not unfeasible steps of nationwide population-based cancer registration, development of a legal framework for record linkage of registries and data collections, recording of occupational cancers, large scale epidemiological occupational cancer research and rigorous implementation of worker protection on known carcinogens, lead the way to a continuously updated cancer control plan that includes the elimination of occupational cancer in the Russian Federation.
Key words: *cancer; occupation, workplace carcinogens; cancer prevention; Russian Federation*
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На пути к ликвидации профессионального рака в Российской Федерации: исследования, направленные на профилактику онкологических заболеваний

(Часть 2)

Международное агентство по изучению рака Всемирной организации здравоохранения (МАИР), Секция окружающей среды и радиации, площадь Альбер Тома, 150, Леон, Франция, F–69372

Количество злокачественных опухолей растет во всем мире, и Российская Федерация не является исключением: ожидаемое число новых случаев составит 587 622 в 2040 г. (529 062 в 2018 г.), что обусловливает актуальность профилактика злокачественных новообразований. Профессиональные злокачественные новообразования, связанные с воздействием канцерогенов на рабочем месте, относятся к числу предотвратимых, поскольку возможна минимизация риска их развития за счет применения соответствующих мер по защите работника.
В Российской Федерации порядка 20 тыс. случаев злокачественных новообразований в год может быть связано с работой, однако из-за недостатка информации о различных профессиональных канцерогенах системный учет не ведется, поэтому истинная распространенность может быть выше.
Российская Федерация выглядит особенно подходящей для изучения распространенности заболеваний профессиональными злокачественными новообразованиями, учитывая значительную численность работающего населения, развитую промышленность и хороший текущий надзор за рабочими местами. Полученные результаты могут быть информативны не только для ситуации в России, но и в глобальном масштабе.
Национальная программы учета злокачественных новообразований должна включать: разработку правовой базы, регистрацию случаев профессиональных злокачественных опухолей, проведение крупномасштабных эпидемиологических исследований профессиональных злокачественных опухолей, разработку эффективных мер по защите работника от

известных канцерогенов. Это приведет к созданию постоянно обновляемой системы контроля, направленной на ликвидацию профессиональных злокачественных новообразований в Российской Федерации.

Ключевые слова: *рак; профессия; производственные канцерогены; профилактика рака; Российская Федерация*

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Numbers have some statistical uncertainty as Europe has no complete cancer registration as well as the Russian Federation has no nationwide population-based cancer registration. Only one cancer registry from the Russian Federation was providing information on incidence rates from 2003–2007 to the most recent volume of "Cancer Incidence in Five Continents" published by the International Agency for Research on Cancer (IARC), namely the St Petersburg cancer registry, covering a population of 4.8 million [5]. So for the figures shown above modelling algorithms were used by the IARC that published the worldwide cancer burden within the Global Cancer Observatory [1]. The Global Initiative on Cancer Registration Development (GICR, http://gicr.iarc.fr) aims at improving the level of cancer surveillance worldwide, as cancer registration is an essential tool in developing cancer control plans and in monitoring the success of preventive action. Cancer registries can also play an important role in understanding the causes of cancer. This is particularly so in the field of occupational cancers, when in epidemiological studies occupational cohorts can be linked with the routinely registered cancer burden in the population, as will be further outlined below.

Cancer prevention strategies in general. As explained above, to stop the high cancer burden and the predicted rise in the coming decades, cancer control plans including rigorous implementation of primary prevention need to be developed [2]. This is not only to avoid premature death and reduce the treatment-related high economic burden, but many cancers come with severe suffering of patients during long time periods and several treatment options have severe side effects and late effects resulting in continued suffering even in some patients surviving the initial cancer diagnosis. As most cancers are only curable at early stage, implementation of organized cancer screening programs is also important. Current scientific evidence suggest that organized screening programs reduce the mortality from cervical cancer, colorectal cancer and female breast cancer, while for other cancers the evidence is controversial or premature and programs are at present not recommended such as for prostate, lung or skin cancer [6] or scientific evidence speaks against any population screening, such as for thyroid cancer, even under special circumstances such as after nuclear accidents [7].

Primary prevention requires knowledge on modifiable risk factors. For Europe it has been suggested that about one third to half of cancer cases are preventable, as most of the established causes are exposures (including chemical, physical or biological agents) or unhealthy behaviours that are modifiable at individual or at population level or a combination of both [4]. As introduced above, this scientific evidence has been translated into a set of public health recommendations targeted to the individual summarizing of what they can do themselves to reduce their risk of cancer, called the "European Code against Cancer" [4]. With for instance stopping smoking, maintaining a healthy body weight, being physically active, having a healthy diet and reducing alcohol intake, the individual has means to significantly reduce their cancer risk; nonetheless, all those actions need to be encompassed in regulatory actions on for instance taxation and price policies on tobacco, alcohol or unhealthy foodstuffs, or urban policies to facilitate physical activity. Smaller but nevertheless relevant contributors to the cancer burden as modifiable risk factors are exposures to environmental pollutants or carcinogens in the work place, where action at a population level is required, such as for air pollution, safe work places or protection guidelines to eliminate or reduce exposures against harmful chemicals [8]. In a review, successful policy frameworks for cancer prevention were identified, related for example to asbestos, persistent organic pollutants (POPs), indoor radon, outdoor and indoor air pollution, second-hand smoke, ultraviolet (UV) exposure including tanning devices, and medical radiation; however these frameworks need further strengthening [9].

Thorough analyses of the contributions of different factors to the cancer burden have recently been made for France and for the UK. For France, it was suggested that 41% of cancer cases are preventable [10]. By far largest contributor remained tobacco with 20% of the cancer burden and thereby causing almost half of all preventable cancers, followed by alcohol consumption with 8%. Other factors were unhealthy diet (5.4%), overweight and obesity (5.4%), infections (4%), occupational exposures (3.6%), UV (3%), ionising radiation (1.9%; radon and medical), lack of physical activity (0.9%), exogenous hormones (0.7%), no or shorter term breastfeeding (0.5%), atmospheric pollution (0.4%), and environmental exposures to chemicals (0.1%). In the UK, they estimated similar impact by tobacco (15.1%), overweight/obesity (6.3%), unhealthy diet (4.8%), UV (3.8%), occupational exposures (3.8%), infections (3.6%), alcohol (3.3%), ionising radiation (1.9%), not breastfeeding (0.7%), exogenous hormones/oral contraceptives (0.6%), and lack of physical activity (0.5%) [11]. Noteworthy differences in comparison to France were the lower relative contribution from alcohol consumption (3.3% versus 8%) and the higher relative contribution by air pollution (1% versus 0.4%). A comparison is shown in Figure 3.

Occupational cancer burden. France and the UK showed similar contributions of occupational exposures to their national cancer burden, namely 3.6% and 3.8% respectively (Figure 3). This aligns with the landmark publication on preventable cancers for the USA by Doll and Peto [12], when they were estimating 3% for occupational exposures in 1981. Lack of significant changes over time suggest a combination of slow implementation of primary prevention of occupational cancers

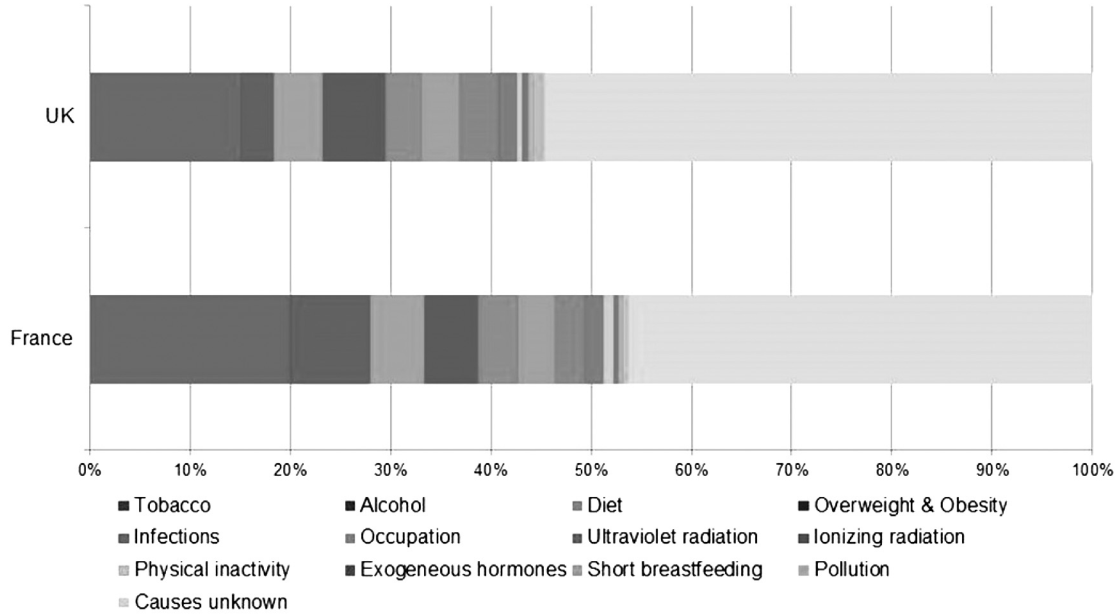

Figure. 3. Population attributable fractions of established modifiable factors to prevent cancer in the UK and in France; in both countries around half of all cancers would be preventable if knowledge of what causes cancer was rigorously implemented in primary prevention actions (ordered by their contributions in France)

Рис. 3. Добавочная доля популяционного риска, связанного с установленными изменяемыми факторами, для предотвращения рака в Великобритании и Франции; в обеих странах примерно половину случаев рака можно было бы предотвратить, если бы знание о том, что вызывает рак, было обязательно включено в меры первичной профилактики (предписано во Франции)

and the long time period elapsing between implementation and observable effects on cancer rates due to the long latency of most cancers between occupational exposure and effect. An example was monitoring time trends of mesothelioma mortality in Germany; although banning asbestos in Germany in the early 1990s, mesothelioma mortality is predicted to rise until 2020–2022 until the trend is ultimately reversed [13].

Applying the estimates from France, UK and the USA to the overall cancer burden in the Russian Federation, suggests that between 16,000 and 21,000 cancers occur every year due to exposure at the workplace. As many cancer types related to occupation are cancers occurring more in the elderly, life expectancy plays some role in this estimation, and — as the life expectancy in the Russian Federation is lower than in the other three countries — the number of occupationally-related cancers may have been somewhat overestimated by this approach. On the other hand, there is a long tradition of heavy industrialisation in the Russian Federation as it was in the Soviet Union, so that both number of exposed workers and their exposure levels may be higher than in the other three countries, which would lead to an underestimation of occupational cancers. Until better hard data collected and studies within the Russian Federation are available, an estimate of 20,000 occupationally-related cancers per year, related to some statistical uncertainty, is perhaps a good starting point for planning how to prevent occupational cancer in the Russian Federation in the future.

Workers are exposed throughout life to a wide range of occupational exposures; exposures that normally cannot be directly controlled by the individual. Several chemicals, metals, dusts, fibres, and occupations have been established to be causally associated with an increased risk of specific cancers, in particular cancers of the lung, skin and urinary bladder, and mesothelioma [8]. The IARC Monograph Program evaluates agents according their carcinogenicity to humans [14]. Table 1 shows common agents classified as carcinogenic to humans, updated from a previous publication [14] and selected with an expectation of having some relevance for the Russian Federation. For the UK a thorough estimation of individual workplace carcinogens has been performed and they identified asbestos as the main cause of occupationally related cancers; mineral oils, silica, diesel exhaust, polycyclic aromatic hydrocarbons (PAH), paints and dioxins also played significant but lesser roles than asbestos [15]. Notably, a proportion of work-related cancers were also not due to workplace chemicals but to natural environmental factors or to behaviours of other people at the workplace, for instance cancers due to solar radiation in outdoor workers, to naturally occurring radon, or to environmental tobacco smoke (passive smoking).

Rationale for more occupational cancer research. With about half of causes of cancer being identified, this leaves the other half of cancers for which the causes are unknown, hence leaving the opportunity open to identify yet undetected environmental or occupational carcinogens [4]. The portion of unknown causes varies considerably by cancer type: it is estimated that for cervical cancer, lung cancer, oral cavity cancer, oesophageal cancer, stomach cancer and melanoma of the skin more than 75% of cases would be preventable using current knowledge, while it was between 50–75% for colorectal cancer, 25–50% for bladder cancer, kidney cancer, liver cancer, cancer of the uterus, pancreatic cancer and breast cancer, 10–20% for ovarian cancer and leukaemia, and even less for Non-Hodgkin lymphoma, prostate cancer and brain cancer [16].

Distinct spatio-temporal incidence patterns and results from migrant studies investigating how cancer risk profiles change in migrants compared to their home country, indicate that in the search of additional causes of cancer environmental factors may have an important role. In addition, epidemiological studies may have underestimated the impact of known carcinogens. When exposure is ubiquitous at similar levels it is in general difficult to identify increased risks in observational

Table 1 / Таблица 1

Selected Agents Classified as Carcinogenic to Humans (Group 1) by the IARC Monographs Program on the Evaluation of Carcinogenic Risks to Humans, Volumes 1–123, with relevance to occupational settings

Избранные вещества, классифицируемые как канцерогенные для человека (Группа 1) на основании программы Международного Агентства по изучению рака, направленной на оценку канцерогенного риска для человека, Тома 1–123, с учетом значимости условий труда

Substance	IARC Monographs volume/s:	Latest Publication year
N-Nitrosonornicotine (NNN)	Sup 7, 89, 100E	2012
4-(N-Nitrosomethylamino)–1-(3-pyridyl)–1-butanone (NNK)	Sup 7, 89, 100E	2012
ortho-Toluidine	Sup 7, 77, 99, 100F	2012
1,2-Dichloropropane	41, Sup 7, 71, 110	2017
1,3-Butadiene	Sup 7, 54, 71, 97, 100F	2012
2,3,4,7,8-Pentachlorodibenzofuran	100F	2012
2,3,7,8-Tetrachlorodibenzo-para-dioxin	Sup 7, 69, 100F	2012
2-Naphthylamine	4, Sup 7, 99, 100F	2012
3,4,5,3',4'-Pentachlorobiphenyl (PCB–126)	100F	2012
4,4'-Methylenebis(2-chloroaniline) (MOCA)	Sup 7, 57, 99, 100F	2012
4-Aminobiphenyl	1, Sup 7, 99, 100F	2012
Acheson process, occupational exposure associated with	111	2017
Acid mists, strong inorganic	54, 100F	2012
Aluminium production	34, Sup 7, 92, 100F	2012
Arsenic and inorganic arsenic compounds	23, Sup 7, 100C	2012
Asbestos (all forms)	14, Sup 7, 100C	2012
Auramine production	Sup 7, 99, 100F	2012
Benzene	29, Sup 7. 100F, 120	2017
Benzidine	29, Sup 7, 99, 100F	2012
Benzidine, dyes metabolized to	99, 100F	2012
Benzo[a]pyrene	Sup 7, 92, 100F	2012
Beryllium and beryllium compounds	Sup 7, 58, 100C	2012
Bis(chloromethyl)ether;	4, Sup 7, 100F	2012
Chloromethyl methyl ether (technical-grade)	4, Sup 7, 100F	2012
Cadmium and cadmium compounds	58, 100C	2012
Chromium (VI) compounds	Sup 7, 49, 100C	2012
Coal gasification	Sup 7, 92, 100F	2012
Coal, indoor emissions from household combustion of	95, 100E	2012
Coal-tar distillation	92, 100F	2012
Coal-tar pitch	35, Sup 7, 100F	2012
Coke production	Sup 7, 92, 100F	2012
Engine exhaust, diesel	46, 105	2014
Erionite	42, Sup 7, 100C	2012
Ethylene oxide	Sup 7, 60, 97, 100F	2012
Fluoro-edenite fibrous amphibole	111	2017
Formaldehyde	Sup 7, 62, 88, 100F	2012
Iron and steel founding (occupational exposure during)	34, Sup 7, 100F	2012
Isopropyl alcohol manufacture using strong acids	Sup 7, 100F	2012
Leather dust	100C	2012
Magenta production	Sup 7, 57, 99, 100F	2012
Mineral oils, untreated or mildly treated	33, Sup 7, 100F	2012
Nickel compounds	Sup 7, 49, 100C	2012
Outdoor air pollution	109	2016
Outdoor air pollution, particulate matter in	109	2016
Painter (occupational exposure as a)	47, 98, 100F	2012
Polychlorinated biphenyls	18, Sup 7, 107	2016
Polychlorinated biphenyls (PCBs 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, 189)	107	2016
Rubber manufacturing industry	28, Sup 7, 100F	2012
Shale oils	35, Sup 7, 100F	2012

End of Table 1 / Окончание табл. 1

Substance	IARC Monographs volume/s:	Latest Publication year
Silica dust, crystalline, in the form of quartz or cristobalite	Sup 7, 68, 100C	2012
Solar radiation	55, 100D	2012
Soot (as found in occupational exposure of chimney sweeps)	35, Sup 7, 92, 100F	2012
Second-hand tobacco smoke	83, 100E	2012
Trichloroethylene	Sup 7, 63, 106	2014
Vinyl chloride	Sup 7, 97, 100F	2012
Welding fumes	49, 118	2018
Wood dust	62, 100C	2012

studies. For many chemicals which are known or suspected carcinogens it remains unclear if and what magnitude of risk they pose at low environmental levels, as there's uncertainty in the estimation of the dose-effect relationship. Ionising radiation is a prominent example, for which it was just recently confirmed in studies of nuclear power workers that there were no safe thresholds of radiation exposure and that the risk increases, albeit very small in magnitude, at cumulative exposures below 100 mSv [17, 18]. Often epidemiological studies apply rather simplifications in exposure modelling as not all pathways are known or can be adequately assessed. Discussing potential exposure scenarios of environmental uranium contamination in the West Rand area of Gauteng, South Africa, inhalation of contaminated dust, ingestion of contaminated soil through geophagy, and ingestion of contaminated drinking water, as well as routes through the food chain due to inhalation and ingestion of uranium by cattle, illustrates the complexity of modelling cumulative exposure [19]. In addition, cancer is multi-causal, and quantifying the effect of one carcinogen requires disentangling it from the effects of other carcinogens. Figure 4 shows results from an international lung cancer consortium looking at lung cancer in certain occupations with taking the smoking history of people into account. As it can be seen, some occupations show an increased lung cancer risk after adjustment for smoking while in others, for example hairdressers, the higher lung cancer risk in this occupation can be attributed to the hairdressers' smoking behaviour [20]. Synergistic effects between carcinogens are also possible, as observed in the case of radon and smoking.

Studying occupational cancer in the Russian Federation. Studying occupational cancer in the Russian Federation is very important for three different reasons. First, as illustrated before, at present the quantification of the occupational cancer burden is hampered by the lack of respective systematic data collection, and extrapolating from figures derived from other countries may hold or not hold true in reality. A prerequisite is the building up of nationwide population based cancer registration that is also urgently needed for developing targeted

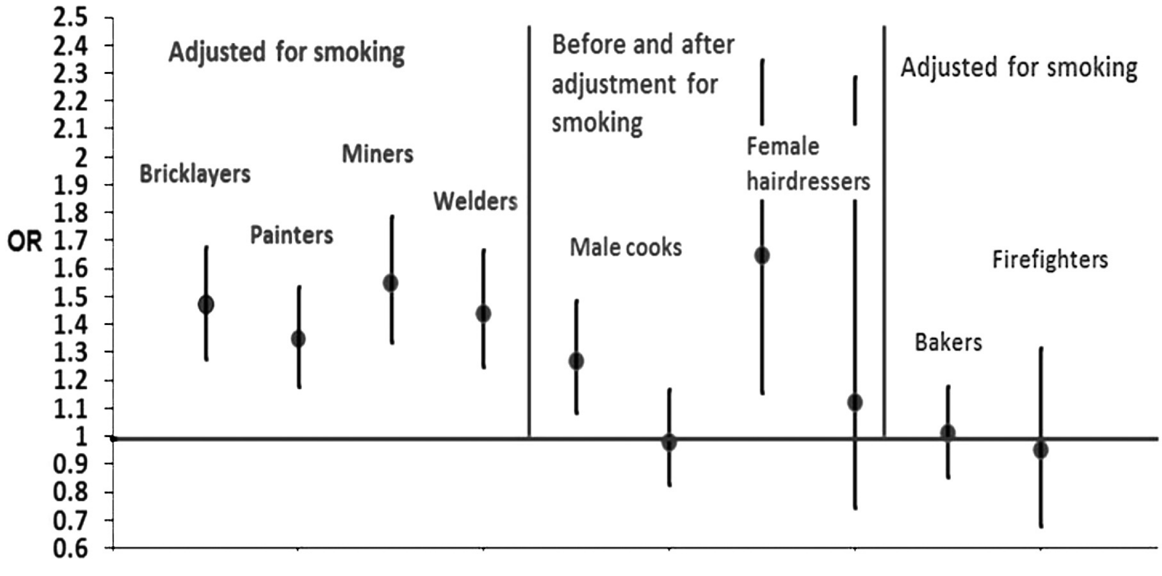

Figure 4. Results from a consortium of lung cancer case-control studies showing the relative risk (estimated by the odds ratio (OR), with circles showing the relative risk and whiskers the statistical uncertainty) of lung cancer in various occupations; bricklayers, painters, miners and welders showed an increase in lung cancer risk even after adjustment for smoking, in male cooks and female hairdressers the association disappeared with adjustment so that the smoking behaviour explains the increased lung cancer risk in those populations, while bakers and firefighters had no increased lung cancer risk with or without adjustment for smoking

Рис. 4. Результаты объединенных исследований рака легких методом «случай-контроль», показывающих относительный риск (оценивался по отношению шансов, на окружностях показаны относительный риск и незначительная статистическая неопределенность) рака легких у представителей разных профессий; у каменщиков, маляров, шахтеров и сварщиков отмечено повышение риска рака легкого даже после поправки на курение, у мужчин-поваров и женщин-парикмахеров поправка на курение снизила силу связи, так что курением можно объяснить повышение риска рака легкого у этих групп населения, тогда как у пекарей и пожарных не было повышения риска рака легкого независимо от поправки на курение

Table 2 / Таблица 2

Steps towards the elimination of occupational cancer in the Russian Federation
Этапы сокращения профессионально-обусловленного рака в Российской Федерации

Action	Description
Population based nationwide cancer registration	Develop nationwide cancer registration from merging collection from regional cancer registries, to inform cancer control plans and to monitor success of preventive action
Develop legal framework for data linkage	Develop legal framework to use registered data for research purposes, by allowing record linkage of registries using personal identifiers under strict data confidentiality, for instance worker archives with the population based cancer registries, and allow access of researchers to death certificate information or population registration (migration) for determination of vital status
Recording of potential occupational cancer cases	Build up occupational cancer recording from linkage of worker populations and cancer registries of those potentially having occupational cancer, allowing identification of individuals with known carcinogenic exposure dose and respective cancer type
Russian Research Initiative into Occupational Cancer as large scale epidemiological research program	Start epidemiological research program of workforces through occupational cohorts or population based case-control studies depending on data availability, to study occupational cancer under Russian working conditions, baseline cancer risk and regional co-factors
Foster worker protection	Rigorously apply worker protection on what is known on occupational cancer already, if not implemented already, as due to long duration of cancer development such measures need long time before becoming fully effective
Elimination of occupational cancer in the Russian Federation	Reduce occupational cancer burden by continuously integrating research results into cancer control plans

cancer control plans and the surveillance of the cancer burden over time. While locally all information may be recorded and archived already, it is the merging and separation of duplicate notifications of the same case from a new case first on regional and afterwards national level that feeds into cancer registration. Creating a legal framework for record linkage between the cancer registry and workforce registries is the first step for the recording of potential occupational cancer cases, as linkage requires access to personal identifying data. Evidently, not every worker develops their cancer because of the workplace exposure, so the plausibility of the exposure-cancer relationship and estimated exposure levels need to be evaluated on individual basis. Direct notifications of presumed occupational cancers should also be requested from the treating hospitals. An impressive systematic approach of evaluating cancer risks in the workforce is the Nordic Occupational Cancer Study (NOCCA) (21).

Second, most of the scientific evidence on occupational cancers comes from North America and Western Europe, hence referring to working conditions in those countries and based on the baseline cancer risk in those populations. To account for potential differences in working situations and conditions, the baseline cancer risk and other co-factors, studies need to be done in the respective population. This will provide insight into the absolute effects of known carcinogens and potentially identify further carcinogens. This reflects the third reason for studying occupational cancer burden, as it will also contribute significantly to the global knowledge on occupational cancer. For example, in an ongoing cohort study of chrysotile miners and millers in Asbest, a substantial proportion of workers are women, while cohorts in other countries around the world had rarely any women enrolled; this allows for the first time in a cohort studying lung cancer in a study population of initially very low smoking prevalence and investigating the chrysotile-related risk for female cancers (22).

Conclusions:

Reducing the occupational cancer burden in the Russian Federation is a challenging but not unfeasible goal. This is why this goal should be an important part of the cancer control plan. It requires a combination of five partially parallel, partially subsequent steps, as summarized in Table 2. Rolling out regional cancer registration to be merged into nationwide population-based cancer registration is an essential tool for successful cancer prevention in general, as is the development of a legal framework based on existing data confidentiality laws to particularly regulate the record linkage across registries. This applies in the context both to the record linkage between workforce registration with the cancer registry for recording of potential occupational cancer cases and to the record linkage of the occupational cancer records or epidemiological studies with cause of death registration and population registration (migration) for assessing the vital status or emigration of persons. A large-scale Russian research program of epidemiological studies on occupational cancer is of utmost importance both from a prevention perspective as well as from a scientific perspective, as it contributes to better knowledge on the absolute risk of known occupational carcinogens in the Russian context as well as to the potential identification of yet undiscovered carcinogens. Rigorously applying of what is known to prevent occupational cancer with at the same time further research to optimize the prevention program, with all of it sufficiently resourced, is the way towards the elimination of occupational cancer in the Russian Federation.

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