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Research article

# ASSESSMENT OF THE CONTRIBUTION MADE BY ONCOGENIC FACTORS TO THE RISK OF MALIGNANT NEOPLASMS DEVELOPMENT FOR THE URBAN POPULATION OF WORKING AGE

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*High morbidity and mortality caused by malignant neoplasms in various age groups among urban population remains a pressing issue that public healthcare has to solve in contemporary megacities.*

*This research concentrated on assessing significance of oncogenic risk factors that could cause malignant neoplasms (MNs) occurrence among urban population aged 18–64 inclusively.*

*766 people living in an administrative and industrial center in Siberia took part in the research; MNs were diagnosed in 367 out of them (the test group). The research involved calculating individual carcinogenic risks. Oncogenic factors, both environmental and occupational ones, were examined for each patient; attention was also paid to peculiarities of medical and biological characteristics as well as tobacco smoking and alcohol intake. Impacts exerted by the examined factors on risks of MNs occurrence were determined via odds ratios with estimated confidence intervals.*

*First detected MNs frequency amounted to 638.9 ± 41.9 cases per 100 thousand people among women aged 18–64, and 532.6 ± 41.9 cases among men ($p > 0.05$). The following factors were determined as ones causing elevated risks of MNs occurrence: carcinogenic hazards at a workplace; hereditary predisposition; tobacco smoking; alcohol abuse; female sex; living under exposure to chemical carcinogens in the environment. Women tended to have certain diseases that are conventionally considered possible risk factors (viral hepatitis B and C and pancreatic diabetes) 1.3 and 2.4 times more frequently than men.*

*All the obtained data can be used for developing a targeted program aimed at malignant neoplasms prevention among urban population and they can also become a vital component in a system for managing risks of malignant neoplasms occurrence on a given territory.*

***Key words:*** *urban population of working age, malignant neoplasms, individual carcinogenic risks, oncogenic risk factors, tobacco smoking, sex, heredity.*

Malignant neoplasms (MNs) are among priority diseases as per their medical and social significance; they create negative demographic balance not only in the Russian Federation [1, 2] but also in many countries all over the world [3–5]. According to estimates by the World Health Organization, in 2016 MNs caused 9.0 million death cases accounting for 22 % of mortality due to non-communicable diseases [4]. Statistic data collected in the RF indicated that levels of oncologic morbidity taken as a ratio between male and female population were different in different age groups; these ratios amounted to 0.6 among people aged 15–29; 0.4, among people aged 30–39; 0.6, among people aged 40–49; 1.0, among people aged 50–59; 1.6, among people aged 60–69; 1.9, among people aged 70–79; 1.7, among people aged 80 and older [1].

Partial or total loss of health owing to MNs results in declining working capacities and, consequently, labor resources deficiency, the latter being a serious threat to the national security of the country. Substantial economic expenses on oncologic pathology treatment are a significant aspect related to the issue. In



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2016 integral economic losses caused by malignant neoplasms burden amounted to 241.3 billion rubles which was equal to 0.3 % of the country GDP. And there are hidden or unaccounted losses of working capacities by family members who have to take care of a patient with oncologic pathology and this leads to drastic changes in their working routines [6]. Therefore, issues related to MNs prevention are of great social and economic significance in the Russian Federation.

Primary prevention of malignant tumors occupies a most significant place in fight against cancer. Activities within such prevention should primarily be aimed at eliminating oncogenic environmental factors. At present there are multiple available research works that focus on detecting peculiarities of oncologic pathology occurrence among various population groups [7–12]. It was shown that a great contribution to adverse influence on health was made by chemical contamination of the environment, eating habits, working conditions, living conditions, education, and lifestyle. According to several researchers, environmental factors, primarily occupational ones, play the leading role (up to 75–80 %) in MNs occurrence and development [10, 11]. Ambient air pollution with chemicals is responsible for 41 % of respiratory diseases and more than 13 % of oncologic diseases among employable population [13]. Socioeconomic conditions are also thought to be a significant factor causing a risk of MNs occurrence [12, 14]. Influence exerted by this factor becomes possible due to multiple interrelated elements including material and social resources, physical and psychosocial stressors, and health-related behavior. Tobacco smoking is a basic risk factor of cardiovascular diseases and MNs and has negative social, ecologic, and economic consequences. In 2016 more than 1.1 billion people worldwide aged 15 or older were smokers (34 % of all men and 6 % of all women in this age group); in the RF, 58.3 % and 23.4 % accordingly [15]. Besides, socioeconomic status is tightly associated with smoking and alcohol abuse, the leading causes of malignant neoplasms in the airways and gastrointestinal tract [16]. In 2016 in the USA approximately 42.0 % of all MNs cases and 45.1 % death cases due to tumors were caused by risk factors [12]. According to estimates provided by Islami F. with colleagues, cigarette smoking caused the highest share of morbidity with MNs, 19.05 %, and mortality due to them, 28.87 %; overweight (7.8 % and 6.5 % accordingly) and alcohol intake (5.6 % and 4 % accordingly) were less significant [12]. It should be mentioned that complex effects produced by oncogenic factors result in higher risks [9, 17, 18]. MNs are considered to be more typical among elderly people; however, MNs of breast, ovary, lungs, thyroid gland, and the central nervous system become crucially frequent among people of working age [1, 8, 12] and this predetermines specific social significance of this nosology. It should be noted that knowing basic manageable factors that cause a significant share of morbidity and mortality due to malignant neoplasms gives grounds for primary and secondary prevention and provides relevant information for population and workers who are exposed to technogenic carcinogens. The most significant factors are revealed by using some statistical procedures; experience gained in their application as well as their advantages and drawbacks are described in several papers [19, 20].

**Our research aim** was to estimate significance of oncogenic risk factors for malignant neoplasms occurrence among urban population aged 18–64 inclusively.

**Data and methods.** The research was accomplished in an administrative and industrial center in Siberia with its population being equal to 430 thousand people (women accounted for 54 %); it included three stages. The first stage involved creating the test group (people with diagnosed MNs); to do that, we analyzed 8,206 individual case files on patients provided by a local oncologic dispensary with data collected in 2006–2016. Data were taken from the Form No. 030-6/u "Control case history of regular check-ups (onco)". Primarily diagnosed morbidity with MNs over years was given as an average an-

nual value with value error per 100 thousand people of relevant sex and age. The examined group was made up of 254 thousand people aged from 18 to 64 inclusively and this allowed creating representative samplings to assess risk factors. All patients permanently lived in Ulan-Ude; their age was within 18–64 inclusively.

At the second stage we calculated a necessary sampling to examine significance of risk factors. Given the gender ratio of population in their working age in the examined city, groups should include not fewer than 364 people according to [21]. 367 people were included into this study; they all applied to the local oncologic dispensary in 2014–2016, their diagnoses were confirmed, all medical documents were completed; age of all these people was within the selected range and they all lived in the examined city. The reference group was randomly created using data obtained through regular check-ups in 2016 and included 399 people without any diagnosed MNs.

This stage also involved individual questioning that was accomplished in person. Accounted risk factors included a place of residence, workplace, and bad habits; significant exposure levels were determined for tobacco smoking and alcohol intake and they were as follows: half a cigarette pack smoked daily for not less than 1 year and 1 standard drink 5 times a week [21]. The questioning provided necessary data on etiologically significant communicable diseases in a case history (viral hepatitis *B* and *C*, human papillomavirus); we also were able to find out whether a patient had had tuberculosis, HIV-infection and type II diabetes in the past or had one or several of these diseases at the moment of the research. Hereditary predisposition to MNs was taken into account in case they were diagnosed in patient's parents, children, or siblings.

Individual carcinogenic risks were calculated according to the procedure stipulated by the Guide R 2.1.10.1920-04[1] using data collected at monitoring posts of a hydrometeorology center, environmental monitoring system, production control, and results we obtained in our own examinations of qualitative and quantitative characteristics of workplace air and ambient air as well. Individual carcinogenic risk was assessed taking into account actual place of living for people who didn't work at productions with carcinogenic hazards; this individual carcinogenic risk reflected total aggregated ambient air pollution with substances that had oncogenic properties. We calculated individual carcinogenic risk that reflected total workplace air pollution ($ICR_{wa}$) for workers who were employed at major productions with carcinogenic hazards; the calculation procedure is described in details in our previous research [11, 22]. Frequency of a certain occurrence in examined groups was compared using Fischer's exact test, differences were considered statistically significant at $p < 0.05$.

Odds ratio (*OR*) and its confidence interval (*CI*) were calculated at the third stage to reveal significant risk factors of MNs occurrence in people aged 18–64. Factors with their bottom limit being $OR > 1$ were considered significant. We applied $\chi^2$ test with Yates's correction to confirm that *OR* was statistically significant with critical significance being taken at $p < 0.05$.

MNs of trachea, bronchus, and lungs (ICD10 code is C34) were selected to estimate economic losses related to occurrence of MNs caused by exposure to adverse environmental factors. First of all, it was due to great frequency of this MNs localization (in 2014–2016 there were 70 cases among men and 9 cases among women in the examined age group) and substantial losses that, according to Kontsevaya and others [6], amounted to 73,501.2 million rubles in the RF in 2016. Total losses and ex-

[1] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu [R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals]. Moscow, The Federal Center for State Sanitary-Epidemiologic Surveillance of the RF Public Healthcare Ministry, 2004, 143 p. (in Russian).

penses borne by the examined settlement were calculated for men and women as per the following formula:

$$\text{ELE} = (N/3) \cdot \text{ELE (RF)}, \quad (1)$$

where $N/3$ is average annual number of MNs cases, ELE (RF) (economic losses and expenses) are average expenses per 1 case in the Russian Federation (1,202.675 thousand rubles [6]).

Population-attributed fractions (exposure levels) (*paf*) were calculated for specific risk factors as per the formula [23]:

$$paf = [E\,(OR - 1)] / [E\,(OR - 1) + 1], \quad (2)$$

where $E$ is a population fraction exposed to a factor, $OR$ is odds ratio for a disease developing in an exposed population group.

Bearing in mind that C34 nosology was caused by multiple risk factors, we applied the following formula to calculate combined *paf* in a multi-factor system:

$$\text{Combined } paf = 1 - [(1 - paf_1)(1 - paf_2)\ldots(1 - paf_n)], \quad (3)$$

where $paf_{1,2..,n}$ are exposure levels (population-attributed fractions) for specific factors (1.., $n$).

**Results and discussion.** We established that primarily diagnosed morbidity with MNs amounted to 638.9 ± 41.9 cases per 100 thousand people among women aged 18–64 living on the examined territory; 532.6 ± 41.9 cases among men per 100 thousand people of corresponding sex and age ($p > 0.05$). There were no statistically significant differences in frequency of most risk factors between men and women with MNs in the examined age group (18–64) (Table 1).

Frequency of active smoking was the only exception since each third male patient had this bad habit and it was 8 times more frequently than among women ($p = 0.000$). Certain diseases that the International Agency for Research on Cancer (IARC) considered to be probable carcinogenic risk factors were more frequent among women than among men: viral hepatitis *B, C*, by 1.3 times; pancreatic diabetes, by 2.4 times (however, these differences were not statistically significant). Since sex-dependent differences in frequency of risk factors were not significant, the second stage involved comparison between two groups.

We compared frequency of risk factors among patients who were treated at the local oncologic dispensary and among people who didn't have MNs (the reference group); Table 2 contains the comparison results. People with diagnosed MNs worked at productions with carcinogenic hazards and were occupationally exposed to carcinogenic risk factors 3.4 times more frequently than people from the reference group. The questioning revealed that several risk factors were more frequent among patients of the local oncologic dispensary than among people without diagnosed MNs; MNs were diagnosed in relatives 2.5 times more frequently; tobacco smoking, 2.2 times; alcohol abuse, 1.8 times; living on a territory where $ICR_a$ was high, 1.1 times. Besides, it should be noted that women accounted for 62.3 % among all people of working age who had MNs and only for 53 % in the reference group.

We revealed the most significant risk factors by analyzing randomly selected individual primary medical documents of patients who were treated at the local oncologic dispensary and people who had regular medical check-ups and didn't have any diagnosed oncologic disease (Table 3).

Odds ratio was higher than 1 for all examined risk factors that caused MNs. However, an association between MNs and previous diseases or diseases a patient had at the moment of examination was not statistically significant (*OR* bottom limit was lower than 1). Risk factors were ranked as per their significance in the following way: occupational carcinogens > burdened heredity > tobacco smoking > alcohol abuse > sex > living on a territory with elevated $ICR_i$.

Economic losses were calculated for MNs of trachea, bronchus, and lungs that are

Table 1

Frequency of risk factors causing malignant neoplasms development among people aged 18–64 with diagnosed MNs (per 100 people)

| Risk factors | Frequency (confidence interval) | | | *p |
|---|---|---|---|---|
| | men ($n$ = 3,496) | women ($n$ = 4,710) | both sexes ($n$ = 8,206) | |
| Exposure to chemical carcinogens at workplace | 14.2 (11.7–16.7) | 8.9 (8.4–11.4) | 12.1 (10.3–14.0) | 0.15 |
| Tobacco smoking | 33.3 (29.9–36.7) | 6.5 (4.4–8.6) | 22.5 (20.2–24.8) | **0.00** |
| Burdened heredity | 10.4 (8.3–12.5) | 10.6 (7.9–13.3) | 10.5 (8.9–12.1) | 0.95 |
| Viral hepatitis *B, C* in case history | 3.8 (2.4–5.2) | 4.9 (3.0–6.8) | 4.2 (3.1–5.3) | 0.64 |
| Tuberculosis in case history | 2.7 (1.5–3.9) | 2.4 (1.0–3.8) | 2.6 (1.7–3.5) | 0.87 |
| Pancreatic diabetes in case history | 2.7 (1.5–3.9) | 6.5 (4.4–6.6) | 4.2 (3.1–5.3) | 0.13 |

Note: * is statistical significance of differences between frequency among men and women.

Table 2

Frequency of risk factors causing malignant neoplasms development among urban population aged 18–64 (per 100 people)

| Factors | Frequency (confidence interval) | | *p |
|---|---|---|---|
| | People with oncologic disease ($n$ = 367) | People without oncologic disease ($n$ = 399) | |
| Exposure to chemical carcinogens at workplace | 17.1 (15.2–19.0) | 5 (3.9–6.1) | **0.000** |
| Tobacco smoking | 18.8 (16.8–20.8) | 8.7 (7.3–10.1) | **0.000** |
| Burdened heredity | 12.5 (10.8–14.2) | 5 (3.9–6.1) | **0.000** |
| Viral hepatitis *B, C* in case history | 6.5 (5.2–7.8) | 3.7 (2.8–5.5) | 0.083 |
| Tuberculosis in case history | 2.6 (1.6–3.4) | 1.7 (1.1–2.3) | 0.417 |
| Pancreatic diabetes in case history | 4.2 (3.2–5.2) | 2.3 (1.6–3.0) | 0.118 |
| Living under exposure to chemical carcinogens | 76.4 (74.2–78.6) | 70 (67.8–72.2) | **0.044** |
| Alcohol abuse | 10.4 (8.8–12.0) | 5.7 (4.6–6.8) | **0.019** |
| Female sex | 62.3 (59.8–64.8) | 53 (51.6–55.4) | **0.003** |

Note: * is statistical significance of differences in frequency between the two groups, people with or without oncologic disease.

Table 3

Risk factors that cause malignant neoplasm development among urban population aged 18–64

| Factors | *OR (CI)* | $\chi^2$ | *p* |
|---|---|---|---|
| Exposure to chemical carcinogens at workplace | 3.97 (2.33–6.64) | 28.0 | 0.000 |
| Tobacco smoking | 2.41 (1.16–3.92) | 15.5 | 0.000 |
| Burdened heredity | 2.72 (1.57–4.69) | 12.8 | 0.000 |
| Viral hepatitis *B, C* in case history | 1.79 (0.92–3.47) | 2.5 | 0.114 |
| Tuberculosis in case history | 1.41 (0.52–3.82) | 0.2 | 0.641 |
| Pancreatic diabetes in case history | 1.85 (0.79–4.27) | 1.5 | 0.213 |
| Living under exposure to chemical carcinogens | 1.41 (1.02–1.94) | 3.9 | 0.047 |
| Alcohol abuse | 1.89 (1.11–3.25) | 4.9 | 0.027 |
| Female sex | 1.48 (1.11–1.97) | 7.7 | 0.010 |

considered to be primarily caused by tobacco smoking and exposure to chemical carcinogens in workplace air and ambient air [9, 13, 15]. Contribution of oncogenic factors to economic losses due to malignant neoplasms of trachea, bronchus, and lungs among urban population aged 15–64 was ranked depending on gender [23]. Ranked *paf* for men were as follows: tobacco smoking (*paf* = 0.978), occupational exposure to carcinogens (0.97), exposure to carcinogens in ambient air (0.93); for women, occupational exposure to carcinogens (*paf* = 0.962), exposure to carcinogens in ambient air (0.93), tobacco smoking (0.9).

Growing MNs prevalence in various population groups predetermines not only medical significance of this pathology but also social and economic ones related to demographic issues becoming more and more serious (losses among overall and employable population), persistent loss of working capacities and disability, expenses borne by the society and a person on medical and social aid provided for oncologic patents. All this makes studies aimed at examining both clinical and hygienic and epidemiologic aspects of the issue more and more vital [8, 24].

Prevalence of certain risk factors varies depending on age and race / ethnic group. White M.C. with colleagues provided evidence that in the USA alcohol abuse was typical for each forth man and each eighth woman; tobacco smoking, each fifth and each seventh accordingly [25]. In our examined subpopulation frequency of the examined risk factors was rather different. Thus, one of 10 men and one of 20 women stated that they abused alcohol; each third examine man and one of 15 examined women smoked. It is probably due to a wider age range examined in our research (18–64 against 18–44 in the USA). Age-related factor can be quite significant since a share of people who abused alcohol was established to decline among people from older age groups [25]. Besides, data on frequency of smoking and alcohol abuse in the USA were obtained through a target survey whereas our estimates were based on questioning during a visit to a doctor and this indicates there are certain limitations in accomplished comparisons.

Most types of cancer are considered to be caused by a combination of factors with lifetime influence [26]. Cancer prevention is based on describing cancer burden, detecting reasons that cause it, assessing and implementing prevention activities. Approaches to cancer prevention should take into account non-genetic exposure that changes over time. Actions to reduce prevalence of adverse risk factors among young people can prevent or at least delay new cancer cases in future [27] and it is extremely important to assess contributions made by leading risk factors into morbidity for proper assessment of balance between expenses and benefits.

In the RF structure of morbidity with malignant neoplasms among men aged 30–59 is fundamentally different from the structure of morbidity among women of the same age. Neoplasms of trachea, bronchus and lungs (16.7 %), skin with melanoma (10.5 %), stomach (7.0 %), kidney (6.9 %) and lymphoid and hematopoietic tissue (6.7 %) prevail among men; neoplasms of breast (27.2 %), cervix uteri (10.6 %), skin with melanoma (10.2 %), corpus uteri (9.2 %), and ovary (6.1 %) prevail among women [1].

Our research revealed several most hazardous risk factors among the examined ones including occupational carcinogens and MNs occurrence in relatives (16.6 %), typical bad habits (smoking and alcohol), female sex, and carcinogens in ambient air. Overall, significance of factors available for our analysis doesn't contradict data provided by the WHO experts [9]. Environmental factors, first of all, occupational ones, make a significant contribution to morbidity with MNs and this is in line with research results described in [9, 24, 28]. We should note that our data on several factors are similar to the results obtained by Lezhnin and others; they assessed contributions made to MNs in lungs by various factors and detected that smoking and occupational hazards accounted for 22–23 %; biological agents, 17 %; chronic lung diseases in case history, 15 %; environmental pollution, 10 %; alcohol abuse, 9 %, stove heating, 4 % [29]. These results can be used to give grounds for programs aimed at primary prevention of malignant neoplasms among people of working age; they will help provide control over risk factors, implement sanitary-educational activities to create safety behavioral attitudes, and raise responsibility for personal and public health.

We should note that our research has certain limitations. Thus, we took into account only inhalation exposure to carcinogens although more and more attention is being paid to complex carcinogenic burden on the environment [7, 8, 17]. Vast majority of carcino-

gens can occur in water, air, soils, and food products and a person can contact them both at work and at home. And in most cases exposure to chemical carcinogens in small doses results in additive effects. Besides, uncertainty in estimates is related to genetic predisposition realized against a dominating role in etiology of malignant tumors belonging to environmental factors and lifestyle-related ones [13]. Our results can underestimate overall share of MNs caused by the examined factors since influence of all the established risk factors can't be determined quantitatively and many probable modifiable risk factors haven't been established as causal yet. Nevertheless, these results highlight that there is huge potential for reducing morbidity and mortality caused by MNs and, consequently, for minimizing economic losses and expenses borne by a person and the society as a whole through implementing well-grounded prevention activities

**Conclusion.** There were no statistically significant differences in frequency of most risk factors causing malignant neoplasms among men and women aged 18–64 with diagnosed MNs, excluding tobacco smoking that was much wider spread among men. The most significant oncogenic factors for urban population of working age included exposure to carcinogens at workplace; heredity burdened as per MNs; tobacco smoking; alcohol abuse; female sex; living under exposure to chemical carcinogens. Economic losses and expenses associated with malignant neoplasms of trachea, bronchus, and lungs were by 7.7 times higher among men than among women.

Research results can be used as a basis for making managerial decisions on malignant neoplasms prevention and development of a target program on providing sanitary-epidemiologic safety of the population. This program should be aimed at providing hygienic safety of the environment; protecting health of the most vulnerable population groups; informing public at large about prevention activities and healthy lifestyle; implementing secondary prevention activities.

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**Conflict of interests.** The authors declare there is no any conflict of interests.

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