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Lung cancer in women: is gynecological and obstetrical history important?

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ABSTRACT

Introduction. Lung cancer remains the most frequent cause of death related to cancers, reaching 1.8 mln worldwide. We observe globally that the incidence of lung cancer in the never smokers affects women disproportionately more often than men.

Material and methods. The aim of the study was to analyse the data about women suffering from lung cancer, with particular emphasis on their gynecological and obstetrical history. Women with confirmed primary lung cancer were evaluated ($n = 29$). Information about smoking, gynecological and obstetrical history was obtained from a self-administered questionnaire. Demographic data were also collected.

Results. The most frequent lung cancer was adenocarcinoma (51.7%), followed by squamous-cell carcinoma (31.0%) and small-cell lung cancer (17.2%). Epidermal growth factor receptor (EGFR) mutations were present in 3 cases. The vast majority of women were smokers (89.7%) with median 30 pack years (IQR 20–48). Evaluating the TNM classification, the highest number of patients was classified to stage III (44.8%).

The median age of menarche was 14 years, menopause — 50 years, the number of days with bleeding in the menstrual cycle — 4 and the length of the menstrual cycle — 28 days. An overwhelming majority of women have given birth to a child. Women reported extended menstrual cycles as the most frequent menstrual disorder (6 cases, 20.7%). Hormone replacement therapy and intrauterine contraceptive device use were declared in 10.3%.

Conclusions. The results based on the small group of patients did not reveal any significant gynecological dysfunctions in our sample group with lung cancer.

Key words: lung cancer, women, gynecological history, estrogen, smoking

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Introduction

The increasing number of cancers worldwide should prompt a search for relationship between cancers and various risks factors. The WHO data show that the number of new cases of lung cancer is around 2 million globally, which represents approximately 11.6% of all cancers and puts it in the first place. Lung cancer remains the most frequent reason of death related to cancers, reaching 1.8 million worldwide. The figures for women are as follows: 725 thousand cases and 576 thousand deaths due to that reason in 2018. In Europe, the age-standardized incident rate in females oscillates between 11.9–26.9 per 100 thousand [1]. Analyzing the data in Poland, the number of new diagnoses of lung

cancer among women in last years is calculated to be 7,000 per year which represents approximately 10% of all cancer cases. Unfortunately, in Poland the number of deaths due to lung cancer in females is higher than the number of new cases (7,500 deaths per year which corresponds to 17% of all deaths caused by cancers) and the five-year survival rate for lung cancer is about 13.5% [2].

These calculations are worrying and encourage the world of science to find new interrelations of medical history with risk factors and endogenous causes.

Undoubtedly smoking still remains the main reason for lung cancers in the western populations, being responsible for more than 80% of cases [3]. Currently estimated global prevalence of tobacco smoking ac-

According to WHO is 18.7% for both sexes and is much higher for men than women (31.9% for males and 5.4% for females). Data from the Global Adult Tobacco Survey disclosed that the male/female prevalence ratio for smoking was the highest in Egypt and the Asian countries and was the lowest among others in Poland [4].

Moreover, we observe the incidence of lung cancer in the never smokers which affects women disproportionately more often than men. The incidence of females with non-smoking lung cancer is estimated to be 14.4–20.8/100,000 and in contrast in males the rate is — 4.8–13.7/100,000 [5, 6]. This difference between men and women indicates that, besides smoking, there are other factors influencing the development of non-small cell lung cancer (NSCLC) in women. The most often non-smoking patients suffer from adenocarcinoma [7].

In a few articles the attention was drawn to some differences in lung cancer depending on sex. These are the following: the median age of diagnosis of lung cancer is lower among females than among males; females have better outcomes at all diagnosis stages; *EGFR* gene mutation is more common in females [8–10]. The association between carcinogenesis of lung cancer and female hormones, aromatase expression, pituitary sex hormone receptors are investigated [11].

Searching for the reasons of these differences, scientists investigated the role of female hormones. The results show that estrogens seem to play a role in development of lungs in both sexes — two types of estrogen receptors ($ER\alpha$ and $ER\beta$) were found in lungs [12]. Rodriguez-Lara et al. [13] revealed that estrogen receptors ($ER\beta$) are overexpressed in adenocarcinomas compared to normal lungs. Additionally, they noticed that premenopausal women with adenocarcinoma exhibited higher signals for $ER\beta$ compared to postmenopausal women and to men, who showed lower signals for these proteins.

In many reports the ER status was taken into consideration as a factor of non-small cell lung cancer patient survival. Some studies show that in particular nuclear $ER\beta$ positivity, which was observed in the majority of lung cancer cases, is assumed to be a favorable prognostic indicator [14]. In another study, significant survival benefit was showed among patients suffering from adenocarcinoma who had positive expression of hormonal receptors (among others $ER\alpha$) [15].

Considering the influence of female hormones on lung cancer, we obviously should check the contribution of hormone replacement therapy (HRT).

When investigating the subject of female hormones, we cannot ignore the role of aromatase (the enzyme that catalyzes androgen aromatization into estrogen). Aromatase staining by immunohistochemistry is detected in up to 86% of NSCLC [16]. Niikawa et al. [17]

found a significantly higher concentration of estradiol in the intratumoral NSCLC than in the non-neoplastic lung tissues and it was positively correlated with the intratumoral aromatase expression [17, 18].

The aim of the study was the analysis of information on women suffering from lung cancer, with particular emphasis on their gynecological and obstetrical history.

Material and methods

Women admitted to the Department with principal diagnosis of lung tumor were evaluated in this study. All patients were anticancer treatment-naive. Demographic data were collected and information about smoking history, gynecological and obstetrical history was obtained from a self-administered questionnaire. Patients were also evaluated according to the 8th edition of the TNM classification for lung cancer. All women gave their informed consent to participate in the study. The study was approved by the local bioethics committee.

Results

Finally, 29 women with pathologically confirmed primary lung cancer were enrolled. The median age of women with lung cancer was 67 (IQR 62–72). The most frequent lung cancer was adenocarcinoma (51.7%), followed by squamous-cell carcinoma (31.0%) and small-cell lung cancer which was diagnosed in 5 cases (17.2%). Activating mutations in the *EGFR* gene were found in 3 patients. The vast majority of women were smokers (89.7%) with median 30 pack years (IQR 20–48). Evaluating the TNM classification, the highest number of patients was classified as stage III (44.8%) (Table 1).

The median age of menarche was 14 years, menopause — 50 years, the number of days with bleeding in menstrual cycle — 28 and the length of the menstrual cycle — 4 days. An overwhelming majority of women have given birth to a child (natural labor — 86.2%, caesarean section — 10.3%). Miscarriage and gynecological operations were present in 31.0% of cases. Women reported extended menstrual cycles (defined as more than 35 days) as the most frequent menstrual disorder (6 cases, 20.7%). Hormone replacement therapy and intrauterine contraceptive device use were declared in 3 cases. The precise results are presented in Tables 2 and 3.

Discussion

The aim of the study was to analyse possible association of gynecological and obstetrical history with

Table 1. Characteristics of the study group

| | |
|---|--|
| Number of women | 29 |
| Adenocarcinoma | 15 (51.7%) |
| Squamous cell carcinoma | 9 (31.0%) |
| Small cell lung cancer | 5 (17.2%) |
| EGFR mutations | 3 (10.3%) |
| TNM (I/II/III/IV) (% all cases) | 3 (10.3 %)/5 (17.2 %)/ /13(44.8 %)/8 (27.6 %) |
| Smokers/non-smokers (% all cases) | 26 (89.7%)/3 (10.3%) |
| Median pack years of smoking | 30 (IQR 20–48) |
| Median age for a diagnosis of lung cancer | 67 (IQR 62–72) |

Data presented as number of cases (% all cases) or median; IQR — interquartile range

Table 2. Characteristics of menstrual cycle of women with lung cancer

| | |
|---|----------------|
| Menarche (years old) | 14 (IQR 13–15) |
| Menopause (years old) | 50 (IQR 46–52) |
| The length of the menstrual cycle (days) | 28 (IQR 28–30) |
| Number of days with bleeding in the menstrual cycle | 4 (IQR 4–6) |

Data presented as number of cases (% all cases) or median; IQR — interquartile range

Table 3. Gynecological and obstetrical history of women with lung cancer

| | |
|---|--------------|
| Natural labor n (%) | 25 (86.2%) |
| Miscarriage n (%) | 9 (31.0%) |
| Week of miscarriage (week) | 8 (IQR 7–12) |
| Gynecological operations n (%) | 9 (31.0%) |
| Extended menstrual cycles n (%) | 6 (20.7 %) |
| Intrauterine contraceptive device n (%) | 3 (10.3%) |
| Caesarean section n (%) | 3 (10.3%) |
| Hormone replacement therapy n (%) | 3 (10.3%) |
| Shortened menstrual cycles n (%) | 1 (3.4 %) |
| Intermenstrual bleeding n (%) | 1 (3.4 %) |

Data presented as number of cases (% all cases) or median; IQR — interquartile range

the risk of lung cancer among women. The rationale for this work comes from the knowledge on a possible role of steroid hormones in lung carcinogenesis [19, 20]. The clinical investigation of a relationship between hormonal status and lung cancer is worth undertaking in different populations. However, our results show that the simple gynecological and obstetrical history of lung cancer women was not specific and did not differ from Polish women.

Many studies have tried to evaluate the association of lung cancer with some menstrual and reproductive factors, but the results have been generally inconsistent. The pooled analysis of these factors was conducted in the international lung cancer consortium where data were collected from 8 different studies (from North America and Europe) involving more than 4,000 women. The majority of studied population was Caucasian (> 80%). The results showed that the mean age of women diagnosed with lung cancer was 63.3 years, adenocarcinoma was the most frequently found histological type (47%), followed by squamous-cell carcinoma (14%), while small-cell lung cancers were represented in 7% of all the cases [21]. The vast majority of women were current (46.3%) or former smokers (38.4%). Comparing to our results, adenocarcinoma was present in 51% cases, squamous-cell carcinoma in 31% and small-cell cancer in 17.2% of patients. In our study cigarette smoking is still an important single factor for lung cancer — these data coincide with national registers. High prevalence of smoking women and high median pack years show that there is still plenty to do in encouraging women to quit smoking in Poland. *EGFR* mutation was present in 10.3% of cases which is also on line with the estimated number for that mutation in Caucasian race [22].

The small number of patients represent main limitation of our study — there were limited possibilities for a deeper statistical analysis of the data. The results based on such a small group of patients did not reveal any significant gynecological dysfunction. The median age of menarche seems to be higher than current global average which is 12 years, but we need to notice that this age is declining in recent years [23].

Late age of menarche was assessed as a risk for lung cancer in many studies. One meta-analysis resulted in slightly, non-significantly decreased risk of lung cancer among women with late age of menarche [24], but it was not confirmed in many currently published studies [21, 25, 26].

The median length of the menstrual cycle (days) and the number of days with bleeding in menstrual cycle was within normal limits, but women reported extended menstrual cycles (> 35 days) as the most frequent disturbance. It is reported that longer length of menstrual cycle can be associated with a decreased lung cancer risk [24].

The median age of menopause in our study was 50 years, comparing to the global data with the mean age of menopause of 51 years (range of variation between 40 and 60 years old) [27]. There was some evidence that postmenopausal status is related to increased lung cancer risk particularly in Europe, what was presented in one meta-analysis concerning menopausal status and risk of lung cancer in women [28]. Also, data from the pooled analysis quoted above showed that menopausal

status was associated with a statistically significant 50% increased risk of lung cancer with minor differences according to the smoking behaviour [21]. That makes us wonder whether postmenopausal females should be taken under special care and appropriate observation in the screening programs.

Hormone replacement therapy (HRT) was not frequently used in our study group. The role of HRT in lung cancer seems to be unclear. Some study results suggest that the association of HRT with lung cancer was dependent on duration, with the highest risk for users of estrogen plus progestin for ≥ 10 years [29]. On the other hand, the meta-analysis of cohort studies has shown that HRT history had no effect on the risk of lung cancer in females [30]. The meta-analysis from 2019 suggests that ever use of HRT is associated with a decreased risk of lung cancer in women [31]. Contraceptive use was not often reported in our study as well. The meta-analysis based on twenty-five articles, representing 24 independent studies from 2012, showed that contraceptive use was not a factor associated with a significant risk for lung cancer [24].

An interesting study related to the topic from 2020 was performed in Korea. The reproductive factors and the risk of lung cancer in postmenopausal Korean women were taken into consideration. The study revealed that the risk for lung cancer was not significantly affected by early menarche age or late age at menopause. Other factors — number of children, duration of breastfeeding and use of hormone replacement therapy — were not associated with the risk for lung cancer [32]. These results are consistent with our observation.

In spite of the limitation in our study and nonconclusive results, we assume that the association between lung cancer and gynecological and obstetrical factors seems to be an interesting issue which needs further well-designed studies.

Conflict of interest

None of the authors have a conflict of interest.

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