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ARTYKUŁ ORYGINALNY / ORIGINAL RESEARCH ARTICLE

The value of pedigrees and clinical assessment in identification of a high risk cancer group – our experience

Znaczenie badań rodowodowo-klinicznych w identyfikacji grup wysokiego ryzyka raków – doświadczenia szczecińskiego ośrodka

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Article history: Received: 06.05.2016 Accepted: 23.05.2016 Published: 15.06.2016

ABSTRACT: Pedigree and clinical data are still very important diagnostic tool useful in estimation of a high risk of a cancer development, molecular basis research and also determining optimal screening for a single family. In this study the own experience was presented in identification of the risk of cancer prevalence with different organ location among the first degree relatives of 760 patients with laryngeal cancer.

KEYWORDS: laryngeal cancer, genetic susceptibility, risk factors, pedegrees

STRESZCZENIE: Dane rodowodowe i kliniczne nadal stanowią bardzo istotne narzędzie diagnostyczne przydatne zarówno w ocenie ryzyka zachorowania na nowotwór i poszukiwaniu jego podłoża molekularnego, jak również przy ustalaniu optymalnych dla danej rodziny badań przesiewowych. W pracy przedstawiono doświadczenia własne w identyfikacji ryzyka występowania raków o różnej lokalizacji narządowej wśród krewnych pierwszego stopnia w oparciu o dane rodowodowe 760 pacjentów z rakiem krtani.

SŁOWA KLUCZOWE: rak krtani, genetyczna predyspozycja, czynniki ryzyka, badania rodowodowe

Laryngeal cancer is strongly associated with environmental factors. The main and most commonly recognized factors include smoking and alcohol abuse. In recent years, the importance of other factors has been emphasized, including HPV infection and gastroesophageal reflux. [1,2,3,4,5,6] However, there is a subgroup of patients with laryngeal cancer, where the risk is probably associated with genetic factors. [1,6,7] The well-known genetic factors include genes involved in xenobiotic metabolism and detoxification, such as: P450 cytochrome (CYP-1A1, 1B1, 1A2, 2D6, 2E1), glutathione transferase (GST-M1, T1, M2, P1) and N-acetyltransferase genes (NAT1, NAT2). The studies published thus far show that single genes coding carcinogen metabolism and repair enzymes influence risk of laryngeal cancer only to a certain degree. Most often, only coincidence of certain gene variants increases the risk significantly. [8-18] The role of the genetic factor is clearly shown in case of moderate exposure to cigarette smoke, while great exposure masks the genetic influence. Furthermore, the role of genetic factors is highlighted for a second primary tumor. [11]

The research considering the role of genes associated with high monogenic risk of cancer, such as e.g. BRCA1, is very limited for laryngeal cancer. [19-25] It is a known fact that genes relating to strong predisposition are a relatively rare cause of cancer development in the general population, and the number of mutations identified as directly connected with increased cancer

risk is fairly small. It should be remembered that a characteristic feature of such an inheritance pattern is familial aggregation of malignant tumors. In some instances, it can be connected with accumulation of mutations within a family, which causes moderate increase in risk of developing cancer in various locations.

In search for genetic basis of diseases, considerable progress can be achieved when association studies are conducted on patient subgroups with specific clinical features. Distinction of subgroups with different family history and clinical presentation can have high practical value for early diagnosis and prevention.

It should be born in mind, however, that in many cases of familial aggregation of cancer in various organs, neither pathogenesis nor clinical presentation are known. It applies to head and neck tumors as well. Therefore, it is important to assess the type and occurrence of each cancer in such families, thus allowing to determine the risk of developing cancer in the studied organs. The risk assessment is usually based on pedigree analysis and constitutes the main task of genetic counselling. Properly taken family history is still an important diagnostic tool, but it also proves helpful for choosing optimal screening tests for the family. It may be expected that, due to introduction of appropriate diagnostic strategies, chances of early diagnosis of cancer increase and the use of adequate treatment leads to permanent cure.

For many years, Otolaryngology and Laryngological Oncology Department has collaborated with the Department of Genetics of PUM [Pomeranian Medical University] in terms of finding genetic factors for laryngeal cancer development. This article, based on family history and clinical presentation of a large group of patients with laryngeal cancer, shows a possible practical application of those data for identifying the risk of cancer.

AIMS:

The primary aim of the study was to answer the questions: 1. is there any characteristic family history trait in laryngeal cancer? and 2. is there, and if yes - how high is, a risk of developing cancer in various organs among first-degree relatives of patients with laryngeal cancer and cancer aggregation? The study was conducted in a few stages, therefore, the sample size differed in each stage.

MATERIALS AND METHODS:

1. Clinical characteristics of familial laryngeal cancer [26]:

The study was performed on a group of 753 non-selected consecutive patients with laryngeal cancer, who were diagnosed in the Otolaryngology Department of PAM [Pomeranian Medical Academy] in Szczecin between 1998-2005. Family history was determined based on the history taken at the admission. Patients with laryngeal cancer were classified as familial laryngeal cancer (FLC), if this condition was present in at least one first-degree relative. Patients who had at least two first-degree relatives suffering from any other cancer (not laryngeal) were categorized as cancer familial aggregation (CFA). The rest were counted as sporadic (see above).

The family history and clinical data included: sex, age at diagnosis, size and site of tumor, metastases to lymph nodes, clinical staging, morphological signs of malignancy, type of cancer in patient's relatives and their age at diagnosis.

It is well known that familial cancer aggregation of laryngeal cancer may indicate genetic predisposition to such type of tumors. In order to differentiate, whether the observed familial aggregation of laryngeal cancer is random or stemming from constitutional genetic factors, clinical features of laryngeal cancer in patients presenting familial aggregation and patients with no family history were compared. The frequency of those features, individually or combined, were compared between FLC and CFA patients and sporadic cases, for men and women separately. In multi factor statistical analysis, chi-squared test was applied to test differences between groups of patients.

2. Risk assessment of breast cancer in young patients with laryngeal cancer. [27,28]

The study was conducted on a series of 683 successive patients with laryngeal cancer, from whom the family history was taken. Evaluation of this association was related to the fact that, in the previous study regarding predisposition to breast cancer performed by Department of Genetics of PUM in Szczecin, a molecular relationship between NOD2 3020insC mutation and both laryngeal and breast cancer in young patients, as well as 2-fold increase in risk of early breast cancer in women and 2-fold for men aged 50-59 in carriers of CYP1B1 355TT mutation was established. [29,30]

Based on data obtained from family history, analysis was performed of early (diagnosed before age of 50) and late (diagnosed over age of 50) breast cancer occurrence in first-degree relatives of patients with laryngeal cancer, with respect to age (<50, 50-59, >59). The occurrence observed in families of laryngeal cancer patients were compared with expected population prevalence, obtained from the Polish National Cancer Registry. [31] Additionally, mean age of onset of laryngeal cancer in patients, whose relatives suffered from breast cancer before age of 50, was compared with mean age of laryngeal cancer diagnosis in

patients, whose female relatives had breast cancer over age of 50; similarly, mean age of breast cancer diagnosis in first-degree relatives was compared with subgroups of patients with laryngeal cancer diagnosed before and over age of 50.

3. Risk assessment of tumors of various organ location in relatives of patients with laryngeal cancer [27,32]

In the previous studies, it has been established that the risk of breast cancer at young age in relatives of patients with laryngeal cancer may be increased, although its basis has not been fully explained, and thus the aim of the next study was to investigate the relationship, not only between laryngeal cancer and early breast cancer, but also between other types of cancer. The study involved 760 non-selected consecutive patients with laryngeal cancer and was based on family history and clinical data.

2 839 first-degree relatives of patients from a group of 760 were assessed in terms of cancer risk from birth to the current age (or age of death), in the case of the relative not being diagnosed, or the age of onset if he suffered from cancer. The expected number of cancer cases was obtained based on current cancer registry for Polish population. [31] Standardized incidence ratio (SIR) was calculated, which is a ratio of number of observed to expected cases multiplied by 100. The ratio has been analyzed with respect to various locations of a tumor (larynx, stomach, lung, breast, intestines), taking into consideration the age of diagnosis, sex of the patients and number of relatives suffering from cancer.

RESULTS:

Re 1. Family history of laryngeal cancer [26]

In the group of 754 successive patients with laryngeal cancer, it was found that 5.8% of cases of familial laryngeal cancer (FLC) – i.e. at least one case of laryngeal cancer was present among first-degree relatives of patients diagnosed with laryngeal cancer. 9.7% of cases came from families, where at least two first-degree relatives were diagnosed with any other cancer (cancer familial aggregation – CFA).

The comparative analysis of clinical features showed that in women with laryngeal cancer from FLC families, more aggressive course of the disease, i.e. considerable local advancement of the tumor, metastases to lymph nodes, high grading (T3-T4, N1-N3 and G3; OR = 10.0, p = 0.0003), was observed significantly more often than in other groups. Therefore, the risk of laryngeal cancer was 10 times greater for first-degree relatives of female patients presenting the above-mentioned features. Such relationship has not been found in the group of males with FLC.

It has also been established that mean age of diagnosis in females from FLC group with T3, T4, N1-N3 and G3 characteristics was lower than in women with a tumor with less aggressive features, and they amounted to 52.5 and 58.6 years respectively, but the difference was not statistically significant.

Re 2. Risk assessment of breast cancer at young age in relatives of laryngeal cancer patients

The analysis showed that the total count of breast cancer cases in laryngeal cancer patients' relatives was lower than expected. However, the result was dependent on the patient's age. Number of patients over 50 diagnosed with breast cancer was significantly lower than expected. Contrary, the higher than expected number of cases was observed in relatives of patients diagnosed with laryngeal cancer before the age of 50.

Statistically significant relationship was found between familial aggregation of laryngeal cancer and early breast cancer, while analyzing the age of patients diagnosed with breast cancer. Mean age of patients diagnosed with laryngeal cancer, who had a case of breast cancer before 50 in their family, was significantly lower, compared to patients who had a case of breast cancer over age of 50 in their family. The mean age was 57 and 66 respectively (p=0.0064). Also, a reverse relationship was observed in relatives of patients diagnosed with laryngeal cancer before the age of 50, a mean age of a patient diagnosed with breast cancer was 47. However, in relatives of patients with laryngeal cancer that were diagnosed over 50, the age of onset of breast cancer was higher and amounted to 53. The difference was statistically significant (p=0.02).

Re 3. Risk assessment of tumors of various organ location in relatives of patients with laryngeal cancer [27,32]

The occurrence of cancer in various locations was assessed in 2 839 first-degree relatives of 760 successive patients with laryngeal cancer. In 540 out of 760 patients, tumors were found among first-degree relatives, including 47 cases of laryngeal cancer, 117 of lung cancer, 63 of stomach cancer, 45 of breast cancer, 26 of colorectal cancer and 242 of cancer in other locations. For each location, the SIR was calculated. Statistically significant increase in cancer incidence was noted for laryngeal (SIR:400), lung (SIR:135), stomach cancer (SIR:271) (Tab. I.). For breast cancer, no increase was observed (SIR:96). However, having separated early (before age of 60) and late (over 60) diagnosis of breast cancer, two new groups emerged. For early diagnosis of breast cancer, the SIR was 287. The relationship

between laryngeal cancer and early breast cancer was not modified by age nor sex of the laryngeal cancer patient (Tab. II.). The association of laryngeal and breast cancer was enhanced when additional cases of cancer in other locations were present within the family. For example, if the laryngeal cancer patient had 2 or more first-degree relatives with cancer (other than breast cancer), the SIR reached 520, indicating 5-fold increase in risk (Tab. III.).

Tab. I. Standardized incidence ratio (SIR) for tumors of various location in first-degree relatives of laryngeal cancer patients

LOCATION OF TUMOR	OBSERVED	EXPECTED	SIR	95%CI
Larynx	47	11,8	400	221–721
Stomach	63	23,4	271	172–428
Lung	117	86,9	135	102–179
Breast	45	46,8	96	64–145
Intestines	26	46,6	56	35–89

Tab. II. SIR for breast cancer diagnosed under the age of 60, with respect to age and sex

PARAMETERS	OBSERVED	EXPECTED	SIR	95%CI
All patients	33	11,7	287	151–545
Age of patient with laryngeal cancer <60 >60	20 13	7,1 4,6	284 290	125–647 104–810
Sex K M	5 28	1,9 9,8	289 272	144–582 53–1381

Tab. III. SIR with respect to patient's family history.

EXPECTED	OBSERVED	EXPECTED	SIR	95%CI
Healthy relatives	15	6,4	236	96–582
1 diseased relative	10	3,7	276	87–875
2 or more diseased relatives	8	1,6	520	111–2437

DISCUSSION

Environmental factors, especially cigarette smoking and alcohol consumption, are long recognized risk factors of laryngeal cancer. Contrary to them, genetic factors have not been fully explained, despite years of research. Due to the association of laryngeal cancer with smoking, genetic factors are being searched for among genes relating to xenobiotic metabolism and detoxification.

Many authors emphasize that a positive family history can also constitute a risk factor. Therefore, evidence for genetic predisposition to laryngeal cancer was studied by means of pedigree analysis. Cooper et al. [33] analyzed cancer occurrence in first-degree relatives of laryngeal cancer patients. The analysis showed approximately 3.5-fold increase in the risk of upper respiratory tract cancer in relatives of laryngeal cancer patients, and 15 times in siblings. Similarly, the study by Bonda indicated 2-fold increase in cancer risk in first-degree relatives of patients with upper respiratory tract cancer, who also proved sensitive in bleomycin test. [34]

Increased risk of laryngeal cancer, if the family history of cancer in the same location was positive, is reported in the newest multicenter case-control studies and amounts to 2.1 – 8.0. The risk is even greater if the patient is younger than 60. [6,7]

In the pedigree analysis of 753 patients diagnosed and treated in our department, it has been found that 5.8% of patients reported having at least one relative with laryngeal cancer, and 9.7% had at least two first-degree relatives with cancer of other location. Considering the fact that familial aggregation of cancer may increase genetic predisposition, we decided to investigate whether familial aggregation of laryngeal cancer is random or it stems from constitutional genetic factors, and we compared clinical features of laryngeal cancer in patients with aggregation of such tumors with patients who did not present any relevant family history.

The results of the study appear to be significant, owing to the fact that thus far, clinical features of familial laryngeal cancer have not been the subject of many studies, and its genetic basis has not been explained. The analysis showed that in women with laryngeal cancer coming from families with familial laryngeal cancer (FLC), more aggressive course of the disease was observed considerably more often (T3-4, N1-N3 and G3; OR = 10.02, p=0.0003), which suggests that they are at particular risk of aggressive cancer. It was accompanied by lowered age of onset, which can be associated with genetic predisposition. This result seems to have practical value, as it shows that the risk is 10 times greater for first-degree relatives of women presenting aggressive features of the tumor. In practice, it indicates the necessity for standard monitoring of such relatives. Moreover, the knowledge of familial laryngeal cancer characteristics may be helpful in search for its molecular basis.

The later part of the study regarded the relationship of laryngeal cancer with other types of cancer. Based on the literature data suggesting association of laryngeal cancer with breast cancer [20,21], as well as on the previous molecular studies conducted by the Department of Genetics of PUM [29,30],

we assessed the association with respect to pedigree data. The study showed the relationship between early breast cancer and early laryngeal cancer. The relationship was particularly threatening when there were two or more tumors of other location, because it led to 5-fold increase of the risk.

The association of laryngeal cancer and breast cancer cannot be explained by smoking, because it is not considered a risk factor for breast cancer. It may therefore indicate that there are common genetic factors for both types of cancer. Furthermore, the established increase in risk of developing cancer in other locations such as stomach and lungs in first-degree relatives may indicate that familial laryngeal cancer has heterogeneous presentation, in terms of both genome and phenotype. In this case, it seems reasonable to initiate research aimed at finding molecular basis of cancer in families, where a few family members have been diagnosed with laryngeal cancer, or with confirmed cancer aggregation. From the practical point of view, it is advisable to design screening tests and systematically monitor patients from those three high risk locations.

SUMMARY:

The conducted studies allow us to draw the following conclusions:

1. Families with multiple cases of laryngeal cancer may indicate that genetic factor contributes to the development of this tumor.

2. Knowledge of specific phenotype of familial laryngeal cancer in women should be helpful for identification of new genes relating to predisposition to laryngeal cancer.

3. Due to significantly increased risk of familial laryngeal cancer, relatives of female patients with laryngeal cancer presenting aggressive features require standard monitoring for early detection of the disease.

4. Probably similar genetic, and possibly also environmental, factors increase the risk of both laryngeal and breast cancer at young age. In search for genetic basis of laryngeal cancer, it is reasonable to include, as a candidate markers, genetic mutations associated with increased risk of breast cancer.

5. Similar environmental, and possibly also genetic, factors probably increase the risk of laryngeal, lung and stomach cancer. It is reasonable to perform further multi-center studies in that field.

6. The established increased risk of lung, stomach, laryngeal and breast cancer at young age requires that the families be covered by a special screening program.

7. Pedigree analysis and clinical examination are diagnostic tools that are very useful for risk assessment of cancer development, search for molecular basis of diseases, as well as setting optimal screening test for a given family.

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Word count: 3000 Tables: 3 Figures: – References: 33

Access the article online: DOI: 10.5604/20845308.1202618 Full-text PDF: www.otorhinolaryngologypl.com/fulltxt.php?ICID=1202618

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Competing interests: The authors declare that they have no competing interests.

Cite this article as: Jaworowska E.: The value of pedigrees and clinical assessment in identification of a high risk cancer group – our experience; Pol Otorhino Rev 2016; 5(2): 51-56