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# Indicators of Cellular and Developmental Disorders in Multiple Primary Cancers

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## ABSTRACT

*In human organism development is a very complex and highly regulated system that enables the functional balance of each organ in a whole body. Disorders and tumor micro-environment weaken host immune system that is not able to recognize the tumor as a unknown body and fight against its uncontrollable forces. Tumor avoids the immune system in a way that promotes immunosuppression and orientation cytokine production towards Th<sub>2</sub> immune responses which are responsible for infection appearances. Some of infectious agents (viruses) can cause oncogene activation and inhibition of tumor suppressor genes. It is also known that oncology treatment can be detrimental to the host immune system. The drugs or radiation can activate different signaling pathways which lead to a vicious circle from which there is no return. Experimental models of tumor biology and molecular events in vivo are patients who have multiple primary cancers (MPC) diagnosed during life. Such patients confirm the complexity of disorders that occur in the cell and explain all the influences and contributions to developmental tumor cascade.*

**Key words:** multiple primary cancers, breast cancer, cellular disorders, immune system, chemotherapy

## Introduction

In the tumor cell, the major cellular processes are disturbed at the level of genes, chromosomes, signaling pathways, immune system. Disorders present at the level of the genes are point mutations, translocations, deletions and amplification. These changes mostly lead to the appearance of gain or loss of chromosome, microsatellite instability (MSI), DNA (Deoxyribonucleic Acid), mutation in DNA repair mechanisms and telomere maintenance<sup>1</sup>. Patients who have multiple tumors diagnosed during life can be *in vivo* models and they can show us complexity of tumor biology and molecular events like investigations *in vitro* on experimental models. Multiple primary cancers were first described by Billroth in 1889<sup>2</sup>. In 1932, Warren and Gates published the first study of 1,259 patients with multiple neoplasms<sup>3</sup>. Ever since, there have been numerous reports addressing the occurrence of second primary neoplasms. Synchronous cancers occur at the same time or within an interval of two months, while metachronous cancers follow in sequence and more than two months apart. There is the most used classification of multiple tumors (Table 1)<sup>4</sup>.

## Epidemiology and Etiology of MPC

In the literature the prevalence of MPC is estimated between 0.73% and 11.7% and the incidence is increasing with age<sup>5</sup>. Breast cancer was found to be one of the most frequent malignant tumors associated with other primary cancers. The most frequent malignant associations are breast-breast, breast-endometrium and breast-ovary. It was showed that twenty-one patients developed the first breast cancer at an early age under 50 years, before menopause<sup>6</sup>. So it is suggested that Oncotype Dx testing is useful in MPC. Oncotype Dx testing on multiple primary breast cancers altered management in regards to chemotherapy recommendations and should be considered for multiple primary breast cancers. The median period of time between the two primary cancers was 10.69 years. The most frequent synchronous malignant tumors are breast cancers, mostly because of the use of mammography as a screening method. Usually the metachronous breast malignant lesions were discovered because of the follow-up of the first malignant tumor<sup>7</sup>. Qualitatively, there seems to be a greater difference in genetic profile in tumors appearing simultaneously on different breasts

**TABLE 1**  
CLASSIFICATION OF MULTIPLE TUMORS

GROUP I	multiple primary tumors occurring in organs with the same histology: <ul style="list-style-type: none"> <li>– including cancers that occur in the same tissue and organ (Group IA).</li> <li>– including cancers that are from the same tissue and different organs (Group IB)</li> <li>– including cancers that occur in bilateral organs (Group IC).</li> </ul>
GROUP II	multiple primary tumors originating from different tissues
GROUP III	multiple tumor originating from different tissues and organs that concurrently exist with group I forming multiple primary cancer of three or more cancers.

when compared to multiple tumors on the same breast. There was no association between distance between tumors and difference in Oncotype Dx scores for tumors on the same breast<sup>8</sup>. New South Wales Central Cancer Registry revealed an increased risk between 1972–1991 to develop a second primary after a colon cancer: small bowel cancers in both sexes, prostate and kidney cancer in men, breast, endometrial, ovarian cancer and thyroid cancer in women. After a rectal cancer, the risk is increased for another colon, prostate and pancreas cancer<sup>6</sup>. In Japan other primaries are described as well (stomach, lung, prostate, larynx, liver, esophagus and urinary bladder in men; uterus, stomach, breast, and liver in women). Also, in the colorectal synchronous cancers group there were patients diagnosed with pancreatic cancer and prostate cancer, as other new primaries<sup>9</sup>. Carcinogenic insults, such as tobacco and alcohol, may increase the likelihood of multiple independent malignant foci developing in the mucosa epithelium. Smoking-related cancers, prostate cancers and renal cell carcinoma are most commonly associated with MPC<sup>10</sup>. Head and neck cancer survivors are at an increased risk of developing another cancer of the respiratory or digestive tract<sup>11</sup>. A ‘field cancerization effect’ was assumed to explain this phenomenon, with carcinogens to which the organ has been exposed initiating the proliferation of numerous clones of cells<sup>12</sup>. The Japanese population appears to have a higher likelihood of developing MPC. This may be caused by genetic susceptibility, longer average life span or medical advances in chemotherapy and radiotherapy. The increasing effectiveness of cancer therapies and the improvement of diagnostic tools have led to better survival rates among cancer patients. The risk of developing any second cancer 3.8 % at 10 years versus 7% at 15 years for patients receiving a doxorubicin-based regimen for breast cancer<sup>5–7</sup>.

### Cellular and Molecular Disorders in MPC

The pathogenic mechanisms of multiple primary lung cancer are rather complicated, but currently available clinical and fundamental study data are rare. Analyses on the main reasons for increased incidence of multiple primary lung cancer can help improve the understanding on the pathogenic mechanisms of the disease. Besides environmental factors, genetic factors also have important role in the occurrence of malignant tumors. At present,

more than 30 genes are known to be related to the occurrence of malignant tumors, and those closely related to increased risk for MPC are tumor suppressor genes and DNA repairing genes. Latest studies found that genomic instability and changes in gene expression profile (such as tumor suppressor genes and DNA repairing genes) and even mutation and deletion of chromosomes were closely related to the occurrence of multiple primary cancers<sup>5,6</sup>.

### Breast cancer in MPC

The epidermal growth factor receptor (EGFR) is implicated in breast cancer progression and is associated with an aggressive phenotype. The presence of EGFR mutations in exons 18–21 in breast cancer, as in non-small-cell lung cancer<sup>7</sup>. 50% of TP53 (mutations within the *TP53*-coding region), associated lung cancers were squamous cell carcinoma and 20% of TP53 mutations associated with ‘high differentiation’ cancers and 25.9% of TP53 mutations were ‘mid differentiation’ cancers<sup>12</sup>. Data suggested that EGFR mutations in concert with P53 mutations accelerate cancer development and lead to evolution of therapeutic resistance<sup>13</sup>. In the second patient in case report 2 all four tumors are associated with mutation of p53<sup>14,15</sup>. In CLL, p53 mutation is much more frequent in patients who have received chemotherapy prior to sample extraction<sup>16,17</sup>. The excessive skin melanoma in breast cancer survivors was attributed to the relationship with Breast Cancer genes 2 (2 BRCA2) and cyclin-dependent kinase inhibitor 2A (CDKN2A) mutation-positive patients. CDKN2 has a critical target or targets in the retinoblastoma (RB) pathway which mutations are associated with breast cancer, melanoma and lung cancer<sup>17</sup>. While most human solid tumors neutralize this tumor-suppressive pathway at the level of p53 itself (TP53) melanoma provides a notable exception to this rule. It became clear that functional inactivation of p53 could be achieved by the melanoma cell through other signaling pathways. In fact, concomitant deletion of the CDKN2A locus does occur in the face of activating Cyclin-dependent kinase 4 (CDKN4) mutations suggesting that abrogation of the RB pathway through cyclin dependent kinases mediated mechanism is still insufficiently explored<sup>18</sup>.

MSI was noticed to occur more frequently in cases of MPC than in sporadic cancers<sup>19</sup>. Cancer does not occur

from a single gene mutation in a single gene. Instead, the development of cancer involves multiple mutations within several key genes, including mutations in proto-oncogenes, tumor suppressor genes, and DNA repair genes<sup>1</sup>. So we can assume that when one mutation happened it can lead to numeral different tumors associated with that mutation. The drugs or radiation can activate different signaling pathways which lead to a vicious circle from which there is no return. It is also known that tumor evade host immune system and that our treatments can cause deeper host immunity deprivation<sup>20</sup>. Lian et al. showed 51-year-old female developed 6 metachronous primary malignant neoplasms in a period of 10 years. This patient had no familial or hereditary tendencies but, definite impairment of the cellular immunity had been identified<sup>21</sup>. Merkel cell carcinoma frequently appears in immunocompromised especially in recipient of great number of chemotherapy protocols and radiotherapy and in patients with polyoma virus infection<sup>22,23</sup>. Anaplastic lymphoma kinase (ALK-1) mutation associated with non-Hodgkin lymphoma. ALK protein was detected with high frequency in Merkel cell carcinomas and was useful in distinguishing Merkel cell carcinoma from small cell lung carcinoma<sup>24</sup>. It was shown that one reason may be our chemotherapy or radiotherapy used for the first malignancy<sup>3</sup>. That treatment could result some damage of specific regions of DNA with chromosome rearrangement or loss responsible for tumorigenesis<sup>5</sup>.

## Conclusion

Most patients with MPC are geriatric. The majority of the patients with quadruple cancers present with breast and upper aero-digestive tumors<sup>25</sup>. The reports on patients with multiple primaries include patients at an earlier stage 0 (carcinoma in situ), while others limit the study to invasive cancers (stage I and above)<sup>26</sup>. Patients with multiple primaries are usually of Caucasian ancestry, have less aggressive malignancies, present at earlier stages of disease, and frequently have a strong family history of similar malignancies and predisposition genes in Caucasians. They tend to have cancers with indolent clinical behavior and longer overall survival, especially in those

developing second malignancies more than 5 years after the initial primary diagnosis<sup>14</sup>. The possibility of multiple primary malignancies should always be considered during the treatment and follow-up of cancer patients, especially those of Caucasian ancestry and those having a strong family history of cancer. Because of advances in the early detection, treatment, and supportive care for cancer, the number of cancer survivors has been gradually increasing, and this has led to an increase in the possible occurrence of subsequent malignancies<sup>3</sup>. According to the Surveillance, Epidemiology and End Results cancer registries of the National Cancer Institute, cancer survivors had a 14% higher risk of developing a new malignancy than would have been expected in the general population<sup>6</sup>.

## Concluding Remarks

The body is made up of a community of individual cells, each of which has a specific job to ensure that the community functions correctly. Cancer is not one disease, but literally hundreds of different diseases<sup>1</sup>. Cancer forms when genes within a normal cell are damaged and mutated. The development of multiple primaries may possibly be related to genetic disorders of known or an unidentified nature. Because of advances in the early detection, treatment, and supportive care for cancer, the number of cancer survivors has been gradually increasing, and this has led to an increase in the possible occurrence of subsequent malignancies<sup>2</sup>. The early diagnosis of secondary malignancies should not be neglected in patients treated for a primary malignancy, especially when the long clinical period before the diagnosis of subsequent tumors is taken into consideration. With careful monitoring, secondary tumors can be detected earlier, and, with appropriate intervention, might be better managed, without compromising survival. Experimental models of tumor biology and molecular events *in vivo* are patients who have multiple tumors diagnosed during life. Such patients confirm the complexity of disorders that occur in the cell and explain all the influences and contributions to developmental tumor cascade<sup>6</sup>.

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## **POKAZATELJI MOLEKULARNIH POREMEĆAJA U RAZVOJU MULTIPLIH TUMORA**

### **SAŽETAK**

Razvoj organizma u čovjeka vrlo je složen i visoko reguliran sustav koji omogućava funkcionalnu ravnotežu svakog organa u cjelini. Glavni stanični procesi u tumorskoj stanici poremećeni su na razini gena, kromosoma, signalnih putova, imunološkog sustava itd. Na razini gena prisutni su poremećaji u smislu točkastih mutacija, translokacija, amplifikacija i delecija. Navedeno vodi ka nastanku viška ili manjka kromosoma, mikrosatelitnih nestabilnosti, poremećaja mehanizama popravka DNK (deoksiribonukleinske kiseline), dugovječno održavanje telomeraza i slično. Poremećaj stanica vodi ka slabljenju imunološkog sustava domaćina koji bi trebao prepoznati tumor kao nepoznato tijelo i boriti se protiv njegove nekontrolirane snage. Tumor izbjegava imunološki sustav na način da potiče imunosupresiju tj. orijentira imunološki odgovor ka stvaranju Th2 citokina. Tumorski mikrookoliš omogućava nastanak i rasplamsavanje infekcija (npr. virusa) koji potiču onkogene a koče tumor supresor gene. Također je poznato da i onkološka terapija dodatno može smanjivati imunitet domaćina i aktivirati signalne putove koji naše bolesnike vode u začarani krug iz kojeg nema povratka. Eksperimentalni modeli tumorske biologije i molekularnih zbivanja in vivo jesu bolesnici koji imaju multiple tumore dijagnosticirane tijekom života. Takvi bolesnici nam potvrđuju svu složenost poremećaja koji nastanu u stanicima i što sve može utjecati i doprinosti nezaustavljivoj tumorskoj kaskadi.