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Independent multiple primary tumors and second primary neoplasms. Relationship between smoking

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A B S T R A C T

Multiple primary tumors and second primary neoplasms have been increasing in incidence in recent decades and are reviewed in this paper. The reasons attributed to this significant increase are fundamentally the best diagnosis of multiple concurrent cases and increased overall survival of patients diagnosed with cancer, allowing surface new primary tumors in other organs during or after standard monitoring. At the same time the widespread use of radio and chemotherapy for the first tumor are invoted as possible causes. The genitourinary system is frequently involved in cases of multiple neoplasms; urological organs are one of the few settlement sites of primary tumors in almost a quarter of cases. This suggests a susceptibility/genitourinary system increased target for neoplastic disease. For this same reason, the urologist has a fundamental role in managing these patients and especially during follow up. We believe that the concept of clinical monitoring of this subset of patients should be revised, and should entail a screening of the most common second primary neoplasms since the risk of developing a subsequent independent cancer after presenting a urothelial tumor is considerably increased.

Tumores primarios múltiples independientes y segundas neoplasias primarias. Relación con el hábito de fumar

Palabras clave:
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Segundas neoplasias primarias
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R E S U M E N

Los tumores primarios múltiples, así como las segundas neoplasias primarias, han experimentado un aumento de la incidencia en estas últimas décadas y son objeto de revisión en este trabajo. Los motivos que se atribuyen a este aumento significativo son fundamentalmente el mejor diagnóstico de los casos múltiples concomitantes y la mayor supervivencia en general de los pacientes diagnosticados de cáncer, lo que permite que afloren nuevos tumores primarios en otros órganos durante o después del seguimiento estándar. Al mismo tiempo, se invocan como posibles causas el extenso

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uso de radioterapia y quimioterapia para el primer tumor. El sistema genitourinario está muy frecuentemente implicado en los casos de neoplasias múltiples; los órganos urológicos son uno de los sitios de asentamiento de algunos de los tumores primarios en casi una cuarta parte de los casos. Esto sugiere una susceptibilidad/diana incrementada del sistema genitourinario para la enfermedad neoplásica. Y, por esta misma razón, el urólogo tiene una responsabilidad esencial en el manejo de estos pacientes y de manera especial durante el seguimiento. Creemos que el concepto de seguimiento clínico de este subgrupo de pacientes debe ser revisado y debe comportar un cribaje de las más frecuentes segundas neoplasias primarias, ya que el riesgo de desarrollar un cáncer independiente subsiguiente después de presentar un tumor urotelial está considerablemente incrementado.

Definition

Multiple primary tumors are defined as the coexistence of more than one primary cancer in different organs, or the coexistence of two or more primary cancers of different cell types in the same organ. It excludes all multifocal neoplasms in the same organ (bladder tumors), simultaneous neoplasms in the same organ or in paired organs (breast cancer), asynchronous neoplasms in the same organ or in paired organs (colon polyps), and progressive cancer (*in situ* cervical carcinoma and subsequent carcinoma of the cervix).

Incidence

The prevalence of two or more malignant primary tumors in one patient has increased over the past decades; this increase is more marked for epithelial tumors, especially those associated with smoking[1,2].

Several reasons have been suggested to explain the fact that multiple primary tumors are being diagnosed more frequently: a) better treatment options for other conditions such as high-mortality heart and vascular diseases, which prolongs life expectancy and thus clearly affects the incidence of malignant diseases in general, and b) the widespread use of radiation and/or chemotherapy to treat cancer seems to increase significantly the number of secondary tumors.

As far as urology is concerned, and regarding patients with urothelial non-muscle infiltrative cancer (who usually have long survivals), the most common subsequent malignant tumors are in the prostate, lung, colon, and stomach, followed at a certain distance by laryngeal, pharyngeal, esophageal, rectal, pancreatic, liver, parathyroid, and skin (basocellular

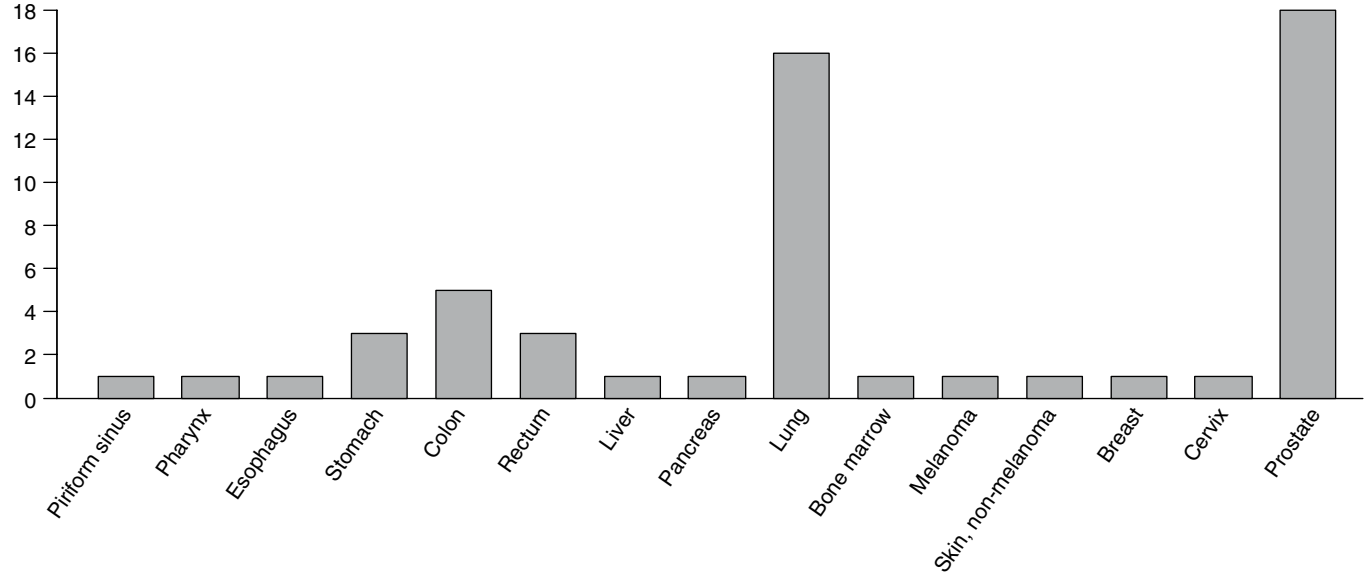

Figure 1 – Type and number of second primary cancers.

carcinoma) cancers (fig. 1), according to data from the Tumor Registry of Hospital del Mar, 1998-2005.

Etiologic factors

For lung and bladder cancer, the independent risk factors are the following:

1) Environmental factors: a) Smoking is the most important causal factor for these neoplasms, increasing the risk three-fold for heavy smokers compared to non-smokers; additionally, the risk of bladder cancer increases with the duration and intensity of smoking, declines immediately after quitting, and continues to decrease up to 60% after 25 years; b) Exposure, occupational, and labor factors;
2) Intrinsic factors: a) Age over 60 years; b) Hereditary, and c) Immune system disorders.

Relationship with smoking

Augustine et al[3,4] have studied the effect of the duration of smoking and the number of cigarettes smoked per day (cpd) on the development of bladder cancer. In these studies, the exposure categories were non-smokers, smokers, and former-smokers. The number of years smoking (2-7 years, 7-12 years and >13 years) and the mean cpd (11-21 cpd, 21-31 cpd, >31 cpd) were recorded for each group. For smokers, the effect was analyzed in relation to the number of cpd and the duration of the habit, which were adjusted to each other and to other covariables not related to smoking. Among men, a significant effect was found for number of cpd, which was directly associated with a higher incidence of bladder cancer. Among women, the effect of the number of cpd in the non-adjusted odds ratio (OR) analysis disappeared after adjusting for the same covariables; this is in agreement with the lower incidence of urothelial carcinoma among women and their lower genetic susceptibility supported by the medical literature. When the data for men and women are combined, the effect of cpd is significant, with an increase in the incidence of bladder cancer for both genders in the three upper levels (11-21 cpd, 21-31 cpd, >31 cpd), after adjusting for covariables. The effect of the duration of the habit was significant only for the higher levels (7-12 years, >13 years); in other words, the longer the duration of smoking, the higher the incidence of bladder cancer.

Former smokers presented an interesting risk pattern. The decrease of the OR is similar in each category of former smokers: approximately 0.6-0.7. The decrease observed among those who quit smoking only 6 years before diagnosis is similar to that of those who had quit 13 years or more before diagnosis. However, former smokers have a high OR compared to individuals who have never smoked.

Curiously, in this study the risk pattern per cpd among men shows a threshold of risk after the 20-30 cpd level. When the development of bladder cancer is compared between men and women smokers, there is an interesting difference in incidence between the two groups. As Skov et al[5] showed when they compared series over a period of around 50 years in the Danish population, the risk of bladder cancer among women increased 3.7-fold since the first cohort per year of birth to the last cohort, which presented the highest risk; among men, the risk of bladder cancer increased 6.1 times[6].

On the other hand, the increased incidence of lung cancer in a cohort followed for 50 years in Norway[7] shows the same magnitude for both genders, and is approximately 45 times higher. These differences cannot be explained by the type of tobacco used or occupational exposure. The data seem to support the idea that women are less susceptible than men to smoking-induced bladder cancer.

Salminen et al[8] first studied a registry of 10,014 bladder cancer patients followed-up for a mean of 4.6 years after the diagnosis of the first primary tumor; they found second primary tumors in 517 men (6.8%) and 135 women (5.7%) and a significant increase in the accumulated risk for lung cancer of 1.31 (95% confidence interval: 1.13-1.50), calculated with a standardized incidence ratio[9-11]. Lung cancer was the most common second primary tumor (30% of the total) among patients with bladder cancer.

A more recent study conducted with a smaller cohort but with a practically identical follow-up period and with similar tumors, found a much higher incidence and prevalence[12]; the cumulative incidence of lung cancer in this group of patients, calculated with the standardized incidence ratio, was 9.35%.

Tumors epidemiologically associated with smoking appearing during follow-up constituted 44% of all secondary cancers. Significantly, there was an increase of risk for lung cancer among patients of both genders aged 45-74 years. The authors attributed these data to the fact that cancer patients have a more frequent medical follow-up and consequently undergo more tests, which facilitates finding a significant secondary condition. In the Finnish study, the most common secondary cancers were lung, prostate, and stomach cancer, followed by laryngeal and renal cancer.

Exposure factors

Nieuwenhuijsen et al[13] presented data showing an increased incidence of multiple tumors caused by environmental factors, such as the association between bladder and lung cancer and arsenic in drinking water (which leads to a failure in the DNA repair mechanisms). Smith et al[14] obtained similar results. The treatment of the first tumor (radiation and/or chemotherapy [especially cyclophosphamide]) and certain surgical procedures (ureterosigmoidostomy) may induce a second primary cancer[15]. It is not surprising that the combination of radiation and chemotherapy is synergistic and results in a large arithmetic sum of the incidences of secondary tumors[16]. An important theory often used to explain multiple tumors is “field cancerization”, which proposes that in systems of organs exposed to the same carcinogenic agents, there is a higher likelihood of a carcinogenic mechanism being activated.

Age

The development of specific types of second tumors is strongly determined by the patient's age at the time of diagnosis of the first tumor and by survival after treatment of the initial lesion. Young patients are followed up longer than older ones, until the period when there is a natural higher incidence of second primary tumors. Thus, the risk for lung cancer increases throughout follow-up. Wynder et al[17] showed that the more a person smoked before the initial tumor, the higher the probability of developing a second primary tumor, and that a long follow-up increases the likelihood of this finding. They also suggest that continuing to smoke after the diagnosis of the first tumor increases the risk of a second primary cancer. This increased risk for second primary tumors associated with smoking suggests that it is important to continue educating patients about smoking and that it is necessary to remind them of this risk when the follow-up guidelines are planned and assessed.

Another theory about the relationship between cancer and old age suggests that each daughter cell is somewhat altered compared to the mother cell, with DNA changes that are not incompatible with cell survival. These abnormal cells produce subsequent daughter cells, which may also present cumulative DNA damage, and so forth. The final result is that these subsequent generations of cells are significantly different from the original mother cell, and therefore so are the mechanisms of RNAm and protein production. If DNA repair systems are damaged by age, these abnormal cells may induce cancer[18,19].

Another factor that may allow the development of tumors throughout the years, especially during the later decades, is the accumulation of free radicals that facilitate DNA replication errors. Another cause of tumors in old age are lipid-loaded macrophages, which are elevated in the elderly and injure the host's immune system.

Heredity

Multiple primary tumors in a person may be the result of host-related factors such as a particular hormonal environment, immune status, and genetic heredity. Genes so far unrelated have been found in different tumors, which would explain the possibility of a common genetic pathway; however, this involves tumors with an altered *locus* in different chromosomes, so it is difficult to associate these lesions with a common genetic pathway. However, the possibility of damaged tumor suppressor genes that allow the expression of the more susceptible *loci* seems to be a more reasonable and acceptable mechanism[20,21].

Immune status

Klippel et al[22] analyzed a sample of 55 patients with single and multiple tumors who underwent immunological testing of B and T lymphocytes. They found a diminished immunity in the cancer patient groups compared to the non-cancer patients. Interestingly, they did not find significant differences between the multiple and the single cancer groups. However, when adding this finding to the increased probability of DNA errors during replication due to free radicals, other mechanisms could be speculated that explain the incidence of cancer developing at a certain age.

Survival data

After presenting with a second primary lung tumor, the 5-year survival from the time of diagnosis of the second tumor was only 23%. Vainrib[23] also concluded that the interval between the diagnoses of the second primary tumor is significantly different between the group with a first lung cancer and the group with a first bladder cancer. They found that the interval between the diagnosis of a bladder tumor after a lung tumor is 4 years, and the interval between lung cancer after bladder cancer is 6 years. Due to the aggressive nature of most lung cancers and the expectations of low survival among these patients, it is natural that the interval is shorter among patients with prior lung cancer.

More than half the patients with lung cancer developed a second primary tumor on the first year shortly after diagnosis of lung cancer, and only a few (17.6%) developed the second tumor after 5 years. Conversely, lung cancer as a second primary tumor after a non-lung tumor appeared in 40.1% of patients after 5 years into the course of the disease[24]. This is attributed to the fact that patients with advanced lung cancer probably do not survive long enough to develop a second primary bladder tumor unless the interval is very short. However, second primary tumors, including bladder cancer, can be detected after successful treatment (resection or chemotherapy) of the primary stage III cancer.

Conclusions

The review of the medical experience reported in the scientific literature suggests that individuals with a first malignant cancer are at higher risk of developing a second tumor. This is because the first tumor was probably caused by genetic, hormonal, iatrogenic, environmental, or immune factors or agents, most of which continue to be active when the second cancer appears. According to Vainrib[23], the incidence of multiple primary tumors is 5-8%, which is 31% higher than the development of malignancy in the general population[4]. The genitourinary system is often involved, and the organs in this system are the site of at least one of the primary tumors in 13.5% of cases of multiple primary malignant cancers. This suggests that the genitourinary system is more susceptible to neoplastic disease. Another important point is that the frequency of multiple primary tumors is approximately 3.6%. The incidence of cancer in the USA is 0.32%, so the probability of developing a second malignant tumor is higher in a person who already had cancer.

Urologists play an essential role in the management of patients with multiple and second primary tumors, and should become aware of this responsibility[12].

Oncological follow-up is currently done almost exclusively in terms of relapse or metastasis of the primary tumor, and subsequent malignancies developing during follow-up have not been considered relevant. Based on the retrospective analysis of our cohort, our data show that it is necessary to revise this concept of follow-up because the risk of developing an independent tumor after bladder cancer is considerably increased. For this reason, we propose that in order to reach an early diagnosis of independent subsequent cancer after primary bladder cancer, instead of doing a rigid follow-up focused only on the primary urologic cancer, the follow-up should include screenings for the common second cancers; this would perhaps significantly improve the survival of these patients[25].

Constant education on smoking cessation should be continued to prevent second primary cancer[26] with the purpose of eliminating persistent causal factors.

Conflict of interest

The authors state that they have no conflicts of interest.

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