abstract

Second malignant neoplasms (SMN) are nonmetastatic malignancies occurring in patients previously diagnosed with another malignant neoplasm. This clinical entity is becoming increasingly more frequent with the aging of the overall population and better diagnosis and treatment of cancers. Although a reasonable percentage of cases may be explained by genetic, iatrogenic, and/or shared environmental exposure, it is estimated that the majority of cases are sporadic. Recognizing the possibility of SMNs is essential for appropriate and timely diagnosis and treatment, but even more important for the development of preventive strategies.

Key words: *oncology, second malignant neoplasms, ophthalmology, eye tumours*

Second Malignant Neoplasms

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A second malignant neoplasm (SMN) may be defined as a nonmetastatic malignancy that was diagnosed after another malignant neoplasm. This definition includes new primary cancers with one or more of the following features: located in a different organ, located in a different site of the same organ with a different histological type, or affecting the second of paired organs (e.g., lungs, breasts, kidneys, ovaries, testicles, or eyes).

SMNs have become increasingly important because they now represent one of the most common malignancies. In fact, SMNs rank sixth among the most frequent malignant neoplasias behind skin, prostate, breast, lung, and colorectal cancer. Data from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program in 1995 revealed that SMNs constitute 13.1% of cancers in men and 13.7% of cancers in women. Moreover, these frequencies had doubled over the previous 20 years.[1,2] The increased incidence of SMNs in the past few decades can be attributed to some basic factors (Table 1).

The risk factors for SMNs fall into three major categories: shared environmental exposures, genetic predisposition, and iatrogenic.[2]

Environmental exposures may be chemical, physical, or biological. Sunlight, smoking, alcohol, and dietary habits, to name a few, are all important risk factors for the development of a number of cancers, such as those of the skin, lungs, head and neck, and gastrointestinal tract. Primary cancer survivors may still be exposed to and influenced by the same risk factors. Alternatively, they may even be subject to new environmental hazards. This increases the risk for SMN. Moreover, even if the patient is no longer exposed to a certain factor, its carcinogenic consequences may still be in effect and are manifested by a higher than normal risk of multiple cancers. For instance, cessation of smoking decreases the risk of lung cancer; however, the lifetime risk for lung cancer is still higher than that observed in nonsmokers.[5–7] Additionally, smoking is also a shared risk factor for head and neck, esophageal, bladder, and renal cancer (among others).[8]

Genetic abnormalities, such as those related to oncogenes, tumour-suppressor genes, and DNA repair mechanisms, may cause multiple cancer syndromes. Over 40 genes implicated in the development of these syndromes have been described. Patients with genetic multiple cancer syndromes must be regularly screened for new cancers. Conversely, patients newly diagnosed with certain cancer types should be assessed for the presence of genetic abnormalities. The presence of a defined inheritance pattern aids the screening of family members and genetic counselling.

Radiation therapy and chemotherapy employed in the treatment of primary cancers may lead to a number of iatrogenic complications, including SMNs. The first observations were made in the pediatric cancer survivor population.[9] As more potent treatment regimens are introduced, the number of cancer survivors in both the adult and pediatric population increases. However, more toxicity, including SMNs due to cancer

Table 1: Factors Influencing the Increased Incidence of SMNs

General aging of the population	Better life conditions and health care have resulted in increased life expectancy. A larger component of the population now comprises older individuals, and the risk of developing cancer increases with age.
Improved cancer treatment	More cancer survivors are observed in all age groups because of more successful treatment options for different types of cancers. Cancer survivors are twice as likely to develop new primary cancers as cancer-free individuals of the same age and sex.[3,4]
Detection bias	Better systemic work-up of cancer patients for metastasis and/or associated malignancies in certain risk groups also leads to early detection and increased diagnosis of SMNs.

treatment, is also expected.[10,11]

Although the association between two or more primary cancers may point to a more specific etiology, it is estimated that most SMNs are related to random distribution in the population. And despite the seemingly more dramatic impact of genetic predisposition and iatrogenic influences, shared environmental risk factors probably play the major role in causation of SMNs.[2]

Clinically, most SMNs behave quite similar to their de novo counterparts and have the same response to standard therapy. A few SMNs, however, are more aggressive and less responsive to therapy than primaries of the same histologic type. The typical example is iatrogenic acute myelocytic leukemia, which develops after chemotherapy and carries a worse prognosis than primary acute myelocytic leukemia.[12,13]

Geriatrics and SMNs

Cancer is a major problem in the aging population. Approximately 60% of all cancers and two-thirds of all cancer deaths occur in patients over 65 years old. Accumulation of genetic mistakes, cumulative exposure to environmental risk factors, and decreased immune surveillance are among the factors underlying this high incidence. Skin, prostate, lung, breast, colorectal, ovarian, brain, leukemia, lymphoma, and multiple myeloma are the most commonly diagnosed tumours in this age group.[1]

SMNs are also commonly found in the older population as a result of the interplay among the factors discussed above. Different relationships between primary and secondary neoplasms have been described for the adult population and most probably apply to the older population as well.

These relationships are clear in analyses of the standardized incidence ratio (SIR) from the SEER Program data.[3] The SIR compares the observed incidence of new cancers in cancer survivors with the expected incidence of the same type of tumour in age and sex-matched individuals. For instance, men diagnosed with lung cancer have a 3.39 SIR of head/neck cancer. Therefore, an individual diagnosed with lung cancer is 3.39 times more likely to develop a head/neck cancer than a member of the general population of the same sex and similar age. Conversely, a man diagnosed with head/neck cancer is 3.04 times more likely to develop a lung cancer than a member of the general population of the same sex and similar age. In women diagnosed with breast cancer, there is a 1.40 SIR of lung cancer, 1.59 SIR of leukemia (if the breast cancer was treated with radiotherapy), 1.27 SIR of ovarian cancer, and 1.08 SIR of uterine cancer.

Bidirectional associations like the one cited above between lung and head/neck cancer may give clues as to the etiology of the cancers in question. In this example, it is well known that lung cancer and head/neck cancer have a major common etiologic factor: smoking.

Ophthalmology and SMNs

Retinoblastoma

Retinoblastoma is the most common primary intraocular malignancy in children with an average incidence of 1 in 15 to 20,000 live births and the first gene to be linked to multiple cancers was the retinoblastoma (RB) gene.

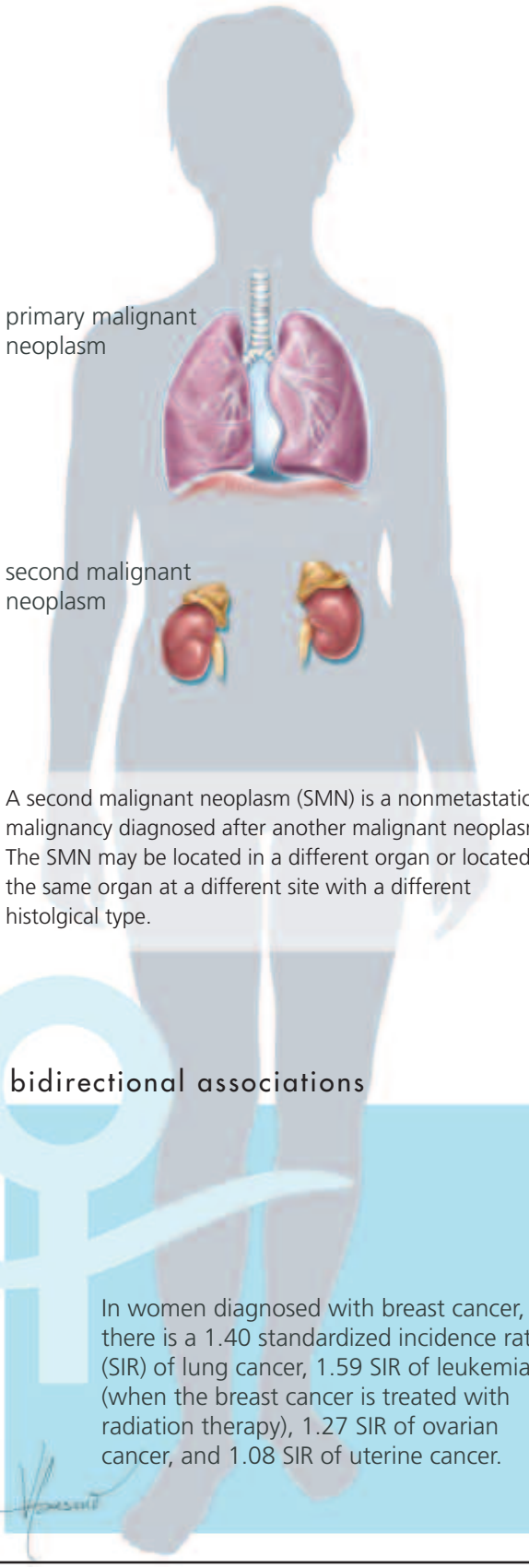
The RB gene is a tumour suppressor gene found in the long arm of chromosome 13, region q1.4. It is a tumour suppressor gene; therefore, both alleles have to be deleted for the tumours to develop. In patients with the heritable or familial form of the disease, all cells of the body have one mutant allele. If the second allele becomes mutated, multiple cancers may arise.[14,15] In addition to multiple retinoblastomas that are usually diagnosed before three years of age, these patients may also develop pinealoblastoma, osteogenic sarcoma, chondrosarcoma, melanoma, and sebaceous cell carcinoma (among others). The incidence of SMNs, especially osteogenic sarcoma and other sarcomas, is increased when radiotherapy is used for treatment of the ocular tumours.[16–18]

With earlier diagnosis and treatment of the eye tumours, the systemic prognosis is very good. There is an increasing number of retinoblastoma survivors, and many of these survivors have children and reach advanced age (thus increasing the incidence of SMNs).

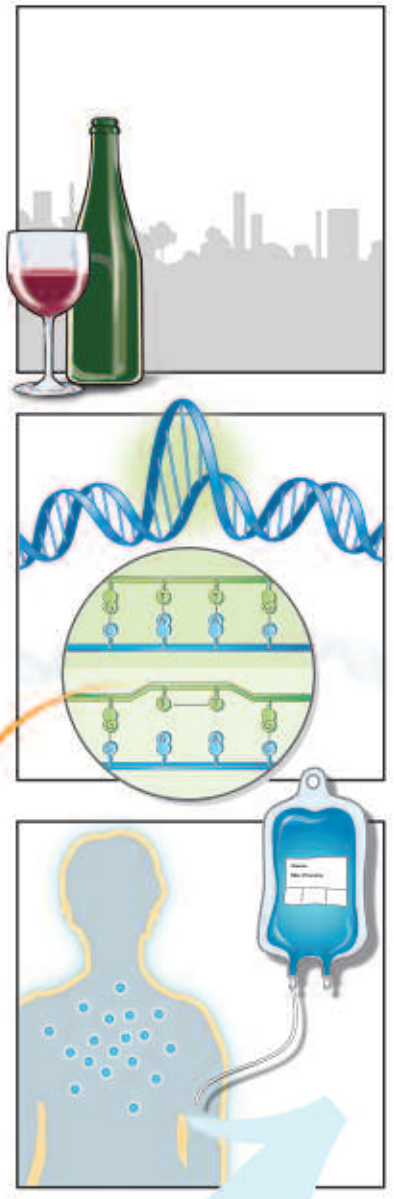
Uveal Melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults with an incidence of 5 to 10 cases per million people per year. It arises in the melanocytes of the uveal tract (iris, ciliary body, and choroids) and the mean age at diagnosis is 55 years old.[19] In a recent epidemiologic study of a Canadian population cohort, 18 out of 129 uveal

Figure 1:
The Risk Factors for Second Malignant Neoplasms



A second malignant neoplasm (SMN) is a nonmetastatic malignancy diagnosed after another malignant neoplasm. The SMN may be located in a different organ or located in the same organ at a different site with a different histolgical type.



environmental

Environmental exposures may be chemical, physical, or biolgical. Sunlight, smoking, alcohol, and dietary habits are examples of environmental risk factors.

genetic

Genetic predisposition to abnormalities, such as those related to oncogenes, tumour-suppressor genes, and DNA repair mechanisms, may cause multiple cancer syndromes.

iatrogenic

Radiation therapy and chemotherapy employed in the treatment of primary cancers may lead to a number of iatrogenic complications.

bidirectional associations

In women diagnosed with breast cancer, there is a 1.40 standardized incidence ratio (SIR) of lung cancer, 1.59 SIR of leukemia (when the breast cancer is treated with radiation therapy), 1.27 SIR of ovarian cancer, and 1.08 SIR of uterine cancer.

Men diagnosed with lung cancer have a 3.39 SIR of head/neck cancer. Therefore, an individual diagnosed with lung cancer is 3.39 times more likely to develop a head/neck cancer than a member of the general population of the same sex and similar age.

melanoma patients had multiple cancers. Nine patients had uveal melanoma as the first cancer, while the other nine had uveal melanoma as a SMN. Despite the occurrence of multiple cancers in 14% of the cohort, no pairwise association indicating increased risk of SMNs in comparison to the general population could be demonstrated.[20]

Sebaceous Cell Carcinoma

Sebaceous cell carcinoma is a rare tumour of the skin. Most cases affect the eyelids. Clinically, eyelid sebaceous cell carcinoma presents in older patients and may mimic chalazion, an inflammatory condition. Sebaceous cell carcinoma may be part of Muir-Torre syndrome, a genetic multiple cancer syndrome. It is a rare autosomal dominant disorder and is currently considered a subtype of the more common hereditary nonpolyposis colorectal cancer syndrome. It is characterized by sebaceous neoplasms and visceral malignancies, especially in the gastrointestinal tract.[21]

Conclusion

Early detection and treatment equals better prognosis for all types of cancer. SMNs are no different. Therefore, physicians have to be aware not only of possible recurrence and/or metastasis of a primary cancer, but also about the possibility of SMNs. In certain scenarios, such as in older patients, genetic cancer syndromes, postchemotherapy and/or radiation therapy, and certain environmental exposures (e.g., smoking), surveillance for SMNs is paramount.

Possible interventions to decrease the incidence of SMNs include avoidance of environmental carcinogens, genetic counseling, and modification of cancer treatment regimens (chemotherapy and radiation therapy) to improve effectiveness while minimizing the frequency of SMNs.

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References

1. Ries LAG, Eisner MP, Kosary CL, et al. SEER Cancer Statistics Review, 1975–2001. Bethesda, MD: National Cancer Institute, 2004.
2. Rheingold SR, Neugut AI, Meadows AT. Secondary cancers: incidence, risk factors, and management, 6th ed. In: Kufe DW, Holland JF, Frei E, editors. Cancer medicine 6. Hamilton, ON; Lewiston, NY: BC Decker, 2003: 2623–31.
3. Ashan H, Insel BJ, Neugut AI. Risk estimates for second primary cancers. In: Neugut AI, Meadows AT, Robinson E, editors. Multiple primary cancers. Philadelphia: Lippincott Williams & Wilkins, 1999: 27–53.
4. Dong C, Hemminki K. Second primary neoplasms in 633,964 cancer patients in Sweden, 1958–1996. Int J Cancer 2001;93:155–61.
5. Ebbert JO, Yang P, Vachon CM, et al. Lung cancer risk reduction after smoking cessation: observations from a prospective cohort of women. J Clin Oncol 2003;21:921–6.
6. Ando M, Wakai K, Seki N, et al. Attributable and absolute risk of lung cancer death by smoking status: findings from the Japan Collaborative Cohort Study. Int J Cancer 2003;105:249–54.
7. Burns DM. Primary prevention, smoking, and smoking cessation: implications for future trends in lung cancer prevention. Cancer 2000;89:2506–9.
8. Levi F, Randimbison L, Te VC, et al. Second primary cancers in patients with lung carcinoma. Cancer 1999;86:186–90.
9. Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. Nat Rev Cancer 2002;2:124–32.
10. Thirman MJ, Larson RA. Therapy-related myeloid leukemia. Hematol Oncol Clin North Am 1996;10:293–320.
11. Sigurdson AJ, Jones IM. Second cancers after radiotherapy: any evidence for radiation-induced genomic instability? Oncogene 2003;22:7018–27.
12. Schoch C, Kern W, Schnittger S, et al. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. Leukemia 2004;18:120–5.
13. Rund D, Ben-Yehuda D. Therapy-related leukemia and myelodysplasia: evolving concepts of pathogenesis and treatment. Hematology 2004;9:179–87.
14. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971;68:820–3.
15. Friend SH, Bernards R, Rogelj S, et al. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 1986;323:643–6.
16. McLean IW, Burnier MN, Zimmerman LE, et al. Tumors of the retina. Tumors of the eye and ocular adnexa. Washington, DC: Armed Forces Institute of Pathology, 1994:97–154.
17. Moll AC, Imhof SM, Bouter LM, et al. Second primary tumors in patients with hereditary retinoblastoma: a register-based follow-up study, 1945–1994. Int J Cancer 1996;67:515–9.
18. Moll AC, Imhof SM, Schouten-Van Meeteren AY, et al. Second primary tumors in hereditary retinoblastoma: a register-based study, 1945–1997: Is there an age effect on radiation-related risk? Ophthalmology 2001;108:1109–14.
19. McLean IW, Burnier MN, Zimmerman LE, et al. Tumors of the uveal tract. Tumors of the eye and ocular adnexa. Washington, DC: Armed Forces Institute of Pathology, 1994:155–214.
20. Callejo SA, Al-Khalifa S, Ozdal PC, et al. The risk of other primary cancer in patients with uveal melanoma: a retrospective cohort study of a Canadian population. Can J Ophthalmol 2004;39:397–402.
21. McLean IW, Burnier MN, Zimmerman LE, et al. Tumors of the eyelid. Tumors of the eyelid and ocular adnexa. Washington, D.C.: Armed Forces Institute of Pathology, 1994:7–48.