

Burden of Malignancy After a Primary Skin Cancer: Recurrence, Multiple Skin Cancers and Second Primary Cancers

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ABSTRACT

The current paper summarizes relevant recent research on the high risk of recurrence, multiple skin cancers and second primary cancers in the growing number of people with a history of skin cancer; the ultimate purpose is to better assess the burden of malignancy following skin cancer.

A number of challenges exist in identifying and tracking both melanoma and non-melanoma skin cancer (NMSC) cases. Most jurisdictions do not routinely track NMSC cases and, even if they do, it is customary to only include the first diagnosis. There are variable rules for counting multiple melanoma cancers, and recurrences are not considered for either major type of skin cancer. Applying insights from recent studies of this issue to Canadian cancer statistics would increase reported diagnoses of NMSC by about 26% and melanoma by 10% in this country. This approach to a fuller assessment of the burden of skin cancers has been called a "diagnosis-based incidence approach" as compared with a "patient-based incidence approach". A further issue that is not usually taken into account when assessing the burden of skin cancers is the 20% to 30% elevated risk of non-cutaneous second primary cancers following a primary skin tumour.

In summary, individuals with skin cancer are subject to a high risk of recurrence, multiple skin cancers and second primary cancers. This burden should be a special concern in the large and growing pool of individuals with a history of skin cancer, as well as among prevention planners.

Key words: Skin neoplasms; second primary neoplasms; recurrence; prevention & control

La traduction du résumé se trouve à la fin de l'article.

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Skin cancers are the most common form of cancer. Current estimates suggest that 78,250 Canadians will be given a diagnosis of skin cancer in 2009, and that 1,200 will die from the disease.¹ This represents 31.8% of the new cases of cancer in the country each year but just 1.6% of deaths due to cancer.² The vast majority (93.7%) of skin cancers are non-melanoma skin cancers (NMSC), the balance of cases being cutaneous malignant melanoma (hereafter referred to as melanoma). Whereas it is relatively common for melanoma to turn deadly, the mortality rate of NMSC has been estimated at just 0.4%.¹

The combination of high incidence and generally successful treatment, and therefore high survival rates, has led to a large and growing population with a history of skin cancer. This especially applies to NMSC. In New Brunswick, the lifetime risk of having basal cell carcinoma and squamous cell carcinoma, the two most common types of NMSC, has been calculated at 13% and 5%, respectively.³ In Manitoba, 2.9% of people 20 years and older living in that province on December 31, 2004, had been given a diagnosis of NMSC between 1984 and 2004 (personal communication: Drs. Alain Demers and Zoann Nugent, CancerCare Manitoba, July 17, 2009).

The impact associated with the incidence and prevalence of skin cancer is substantial; however, the full burden related to skin cancer in Canada is, in fact, higher still. Specifically, there is an elevated risk of various categories of subsequent cancer following a primary skin cancer. This includes the risk of a) recurrence, b) a multiple skin cancer of the same type or c) a second primary cancer (SPC). The plan of this paper is to provide a summary of relevant recent research on the high risk of recurrence, multiple skin cancers

and SPCs among individuals with a primary skin cancer, with the ultimate aim of better assessing the burden of malignancy associated with skin cancer.

Definitions

A recurrence is defined as a cancer that represents a re-emergence of the original malignancy (see Figure 1). In its simplest manifestation, recurrence refers to a cancer (such as a skin tumour) that reappears at a site after an attempt to remove it by surgery or some other means. Recurrences are sometimes classified as a local recurrence, a regional recurrence (usually related to lymph node metastases) or a distant recurrence (metastases in other organs).⁴

A multiple skin cancer is clinically different from a recurrence. Although similar to a local recurrence in that it appears in the same type of skin tissue as the original tumour (e.g., basal cells, squamous cells or melanocytes), a multiple skin cancer is defined as a tumour found at a different site and/or after a delay in time. The most commonly used term for a multiple primary cancer in melanocytes is "multiple primary melanoma".

The issue of timing of multiple skin cancers is most relevant in the case of a new tumour developing in the same tissue at or near

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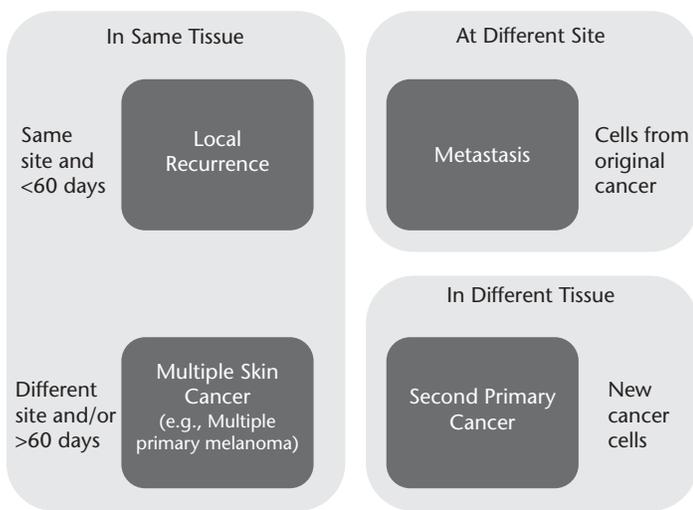
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Figure 1. Terminology for cancer subsequent to a primary skin tumour



the site of the original skin tumour. According to the rule adopted for the Surveillance, Epidemiology and End Results (SEER) program in the US, for a newly identified invasive tumour to be classified as a multiple skin cancer it must emerge 60 days or more after the first primary; otherwise, it should be considered a local recurrence.⁵

An SPC arises independently as a new primary in a different tissue and/or body site, rather than having spread (or metastasized) to that area from an original primary tumour.⁶ Second primaries following skin cancer fall into two broad categories: second primary skin cancers (e.g., a melanoma following a case of basal cell carcinoma) and second primaries in an organ other than the skin.

Challenges in tracking skin cancers

In Canada, counts of cancer incidence (including melanomas) are kept by the various provincial/territorial cancer registries, which obtain their data from a variety of sources and may use different approaches to coding and recording instances of, for example, multiple skin cancers.⁷ To address this variation, Statistics Canada assembles two files with the information it receives from the provincial/territorial cancer registries. The first is the Canadian Cancer Registry tabulation master file. This file includes data based on a mix of rules used by the Canadian Cancer Registry and the International Agency for Research on Cancer (IARC) to determine multiple skin cancers. The second file is the IARC master file, which is ultimately used in preparing and disseminating Canadian cancer statistics (for example, those included in Cancer Surveillance Online).

IARC coding rules tend to be conservative in terms of counting multiple cancers. Comparison between the IARC approach and, for example, the SEER approach indicates that the difference in capturing multiple primary cancers has the greatest impact on the incidence rates of breast, colon and melanoma cancer. Various researchers have found that using the SEER approach increases the number of melanoma cases by 2.0%, 3.7% and 4.0%/5.2% (female/male).⁸⁻¹⁰

In addition to a possible undercount of multiple primary melanomas in Canadian cancer statistics, most cancer registries, including all systems using IARC or SEER coding rules, do not count recurrent cases. In a review of 72 articles published between 1985

Table 1. Percentage of Basal Cell Carcinoma and Squamous Cell Carcinoma After a Primary Diagnosis, by Sex and Age Group

	Male	Female
Basal cell carcinoma		
0-39	0.0%	0.0%
40-59	2.4%	18.6%
60-79	36.5%	41.8%
≥80	59.0%	22.6%
All ages	32.7%	31.3%
Squamous cell carcinoma		
0-39	0.0%	0.0%
40-59	0.0%	0.0%
60-79	0.0%	0.0%
≥80	55.6%	21.4%
All ages	17.2%	11.3%

Source: Stang A, Ziegler S, Buchner U, et al.¹⁷

and 2004, Francken and co-authors found that, on average, 6.6% of melanomas are, in fact, recurrences that would not be captured in cancer registries according to standard rules.¹¹

A final issue with respect to tracking melanoma cases in Canada is the fact that the number of melanoma cases in the Quebec cancer registry is underestimated by 35%, because of that province's dependence on hospital data for tracking melanoma cases, as noted in *Canadian Cancer Statistics 2008*.^{12,13}

The challenges associated with tracking NMSCs are even more substantial than those related to melanomas. Indeed, few cancer registries routinely track NMSCs, in part because of their frequent occurrence coupled with a high rate of successful treatment.¹⁴ Estimating the true incidence of NMSCs in Canada is therefore difficult. Even if NMSCs are recorded, only the first diagnosis is usually included.^{3,15} Yet individuals with an initial case of squamous cell carcinoma, for example, have a 16-fold increased risk that another skin cancer of the same type will develop.¹⁶ The absolute impact of the elevated risk is notable. Research by Stang and colleagues from Germany suggests that, within a five-year period after the original diagnosis, more than 30% of basal cell carcinomas and 14% of squamous cell carcinomas are a second or subsequent skin cancer of the same type, as indicated in Table 1.¹⁷ The difference is particularly relevant in elderly populations, where as many as one third to half of all NMSC may be a recurrent or multiple skin cancer.

A more comprehensive estimate of the burden of skin cancers in Canada

Adjusting for these various challenges leads to a more complete assessment of the burden of skin cancer that is consistent with adopting a "diagnosis-based incidence approach" as compared with a "patient-based incidence approach".¹⁷ A patient-based incidence approach leads to a significant underestimate of the true burden of skin cancers in the population, since both recurrences and SPCs will be undercounted. A recent Canadian report has estimated that a diagnosis-based incidence approach would raise the estimated number of NMSC in 2009 from 73,300 to 92,200, representing a 26% increase. A similar approach for melanoma would result in 5,460 diagnoses in 2009 rather than the 4,950 estimated using a patient-based incidence approach (an increase of 10%).¹

Second primary cancer

As noted earlier, SPCs following skin cancer fall into two broad categories: second primary skin cancers (e.g., a melanoma following a case of basal cell carcinoma) and second primaries in an organ other

Table 2. Standardized Incidence Ratio (95% Confidence Interval) of Non-Cutaneous Second Primary Cancers at Elevated and Reduced Risk Following First Primary Skin Cancers, by Sex

Second Primary Cancer	First Primary Cancer					
	Melanoma		Squamous Cell†		Basal Cell‡	
	Males	Females	Males	Females	Males	Females
Lung	0.65 (0.47-0.86)§		1.7 (1.5-2.0)	1.7 (1.5-2.0)	1.13 (1.06-1.19)	
Colon			1.3 (1.1-1.4)	1.2 (1.0-1.5)	1.30 (1.15-1.46)	1.23 (1.11-1.35)
Rectum					1.17 (1.02-1.33)	
Female breast						1.23 (1.15-1.31)
Non-Hodgkin's lymphoma	1.48 (1.26-1.72)*	1.32 (1.10-1.56)*	1.8 (1.5-2.3)	2.0 (1.5-2.8)	1.37 (1.11-1.66)	1.48 (1.25-1.74)
Leukemia			1.8 (1.3-2.3)	1.8 (1.1-2.9)	1.50 (1.27-1.75)	1.24 (1.03-1.46)
Prostate					1.22 (1.15-1.29)	
Stomach			1.2 (1.1-1.4)	1.4 (1.1-1.7)		1.17 (1.07-1.28)
Kidney	2.11 (1.39-3.07)§				1.23 (1.04-1.43)	
Esophagus				2.1 (1.1-3.5)		
Bladder					1.17 (1.04-1.30)	
Oral		3.06 (1.58-5.35)§	2.5 (1.5-4.1)		1.69 (1.04-2.61)	
Nasopharynx/sinus			3.5 (1.3-7.7)		1.88 (1.07-3.05)	
Hypopharynx/pharynx			2.8 (1.4-5.0)		1.67 (1.16-2.33)	1.75 (1.17-2.51)
Multiple myeloma					1.45 (1.15-1.81)	
Cervix				2.2 (1.4-3.2)		
Hodgkin's disease				2.9 (1.2-5.7)		
Liver	0.28 (0.08-0.71)§		1.2 (1.0-1.5)	1.4 (1.1-1.8)	1.40 (1.12-1.72)	
Small intestine					1.82 (1.20-2.64)	1.88 (1.29-2.65)
Vulva and vagina				2.3 (1.4-3.5)		
Eye						1.91 (1.15-2.97)
Nervous system					1.34 (1.05-1.67)	1.33 (1.11-1.57)
Salivary gland			5.3 (3.2-8.3)	6.1 (2.9-11.2)	4.28 (3.02-5.90)	2.49 (1.62-3.64)
Bone					2.06 (1.03-3.67)	
Lip			4.6 (3.6-5.7)	10.5 (6.3-16.4)	2.07 (1.75-2.43)	2.58 (1.93-3.38)
All Cancers	1.27 (1.19-1.35)§	1.26 (1.15-1.38)§	1.3 (1.2-1.4)	1.3 (1.2-1.4)	1.20 (1.17-1.24)	1.16 (1.13-1.20)

Sources: * Lens & Newton-Bishop²¹ † Adapted from Wassberg et al.¹⁶ ‡ Adapted from Milan et al.¹⁸
§ Crocetti et al.²⁰

than the skin. The elevated risk of another type of skin cancer following a first primary skin cancer has been well demonstrated.⁶ For example, according to various studies an individual with an NMSC has a 2.4 to 3.0 times higher risk of a melanoma,^{16,18} and those with a melanoma have a 3.5 times elevated risk of an NMSC.¹⁹

The topic of SPCs outside of the skin is less well known but arguably of clinical importance from the perspective of surveillance and secondary prevention, as it points to another aspect of the combined cancer burden linked to skin cancer and its risk factors.

Table 2 summarizes the standardized incidence ratio of a non-cutaneous SPC after a first primary skin cancer. The data included in the summary represent the most substantial population-based studies published to date.^{16,18,20,21} Only data indicating statistically significant elevation (or reduction) in risk are noted in the table. To offer some scale of relevance, the inventory of SPCs is ordered in terms of decreasing disease burden (as measured by potential years of life lost across the population for each cancer).²²

Individuals with melanoma have a 27% increased risk of acquiring an SPC compared with the general population. For individuals with squamous cell carcinoma and basal cell carcinoma, the increase in risk is approximately 30% and 19%, respectively.

The specific SPC associations observed by Wassberg et al.¹⁶ (with squamous cell carcinoma) and Milan et al.¹⁸ (with basal cell carcinoma) are consistent with numerous other reports.²³⁻³⁰ The variety of SPCs associated with squamous cell carcinoma and basal cell carcinoma is much greater than found with melanoma. Non-cutaneous SPCs with elevated risk following melanoma appear to be limited to non-Hodgkin's lymphoma, kidney cancers in males and oral cancers in females. It should be noted that this recent inventory of SPCs following melanoma is smaller than the list identified by some older studies.³¹

Time Effects

The risk of SPC developing after a skin cancer does appear to decrease over time, though it does not disappear. For example, the standardized incidence ratio of an SPC following squamous cell carcinoma among men less than 60 years of age is 9.2 (confidence interval [CI]=6.9-12.2) in the first year, 4.4 (CI=3.6-5.4) during years 2 to 4, and 1.3 (CI=1.0-1.7) after 15 years.¹⁶ The risk of non-Hodgkin's lymphoma following melanoma decreases from 1.57 (CI=1.33-1.83) within the first 3 years to 1.25 (CI=1.09-1.42) thereafter, and the risk of a second primary kidney cancer tends to be concentrated during the first 6 months after a diagnosis of melanoma.²¹ Overall, the standardized incidence ratio of SPCs following melanoma decreases from 1.34 (CI=1.25-1.45) during the first 5 years to 1.12 (CI=1.00-1.25) in subsequent years.²⁰ The exception to this time effect appears to be basal cell carcinoma, in which the time elapsed since diagnosis does not "materially influence the overall risk of subsequent cancers".¹⁸ In summary, the data suggest that surveillance for SPCs should be more intensive in the early months and years after a case of melanoma or squamous cell carcinoma; at the same time, for all types of skin cancer, there is no follow-up period over which the increased risk of an SPC is eliminated entirely.

Potential Role of Human Papillomavirus

A review of the data in Table 2 suggests a key clustering of elevated risks among both males and females in head and neck cancers (salivary gland, nasopharyngeal, lip, oral) and, among females, in anogenital cancers (cervix, vagina, vulva). This is suggestive of an association with human papillomavirus and possibly with tobacco consumption (especially in head and neck cancers).

Human papillomavirus is not a single entity. Over 100 types of the virus have been characterized to date. All human papillo-

mavirus types are marked by an affinity for one or other of two categories of epithelial tissues: almost half of the known human papillomavirus types have a tropism for the skin, and the balance have an affinity for the mucosal epithelia in the anogenital and head and neck regions of the body.³² About 20 of the skin-oriented human papillomavirus types have been implicated in the development of skin cancer.³³⁻³⁵ The mechanisms involved in an initial skin infection with one of these viral types may also increase the risk of a persistent infection with other human papillomavirus types elsewhere in the body.³⁶ The additional human papillomavirus infections include those associated with tumours in the anogenital and head and neck regions; this could explain the elevated risk of non-skin second primaries in these regions following skin cancer. The implication is that prevention efforts related to the human papillomavirus, including recently implemented vaccines, could be an important part of controlling certain SPCs after skin cancer.

Protective Effect?

The decreased risk following melanoma for lung and liver cancers observed by Crocetti et al.²⁰ (see bolded results in Table 2) is consistent with some other research. For example, studies by Soerjomataram and colleagues in the Netherlands suggest a decreased risk of prostate, colorectal and breast cancers following a diagnosis of skin cancer.^{37,38} A mechanism posited to explain this phenomenon involves the connection between sun exposure and vitamin D production, and a consequent decreased risk of solid internal tumours.^{39,40} However, the reliability of the basic conclusion about a protective effect has been questioned by other researchers.⁴¹ In fact, there are studies that have found no reduction in risk for carcinomas of the prostate, colon or breast following melanoma.⁴² Furthermore, research in Switzerland actually detected an increased risk of cancers of the breast (standardized incidence ratio of 1.18; CI=1.08-1.30), colon (1.15; CI=1.06-1.25) and prostate (1.20; CI=1.11-1.29) following a histologically confirmed diagnosis of skin cancer.⁴³ The mixed results suggest that further investigation is required. The posited protective effect has public health implications. Evidence of such an effect, even if not confirmed, could lead to a reduction in sun protection behaviours, as has recently been observed in Australia.⁴⁴

Clinical and public health implications

Individuals with skin cancer are at a high risk of recurrence, of multiple skin cancers and of SPCs. This burden, including the 20% to 30% higher risk of non-cutaneous SPCs, should be a special concern in the large and growing pool of individuals with a history of skin cancer.

The data presented in this paper point to three priorities:

- The need for additional research in a number of areas, including the relationship between human papillomavirus infection and SPC following skin cancers and the posited “protective” relationship between skin cancers and certain solid organ tumours.
- Enhanced risk factor control and secondary prevention measures among individuals with skin cancer in order to reduce the additional burden specific to SPC development. While the risk of an SPC does decline with time after certain types of skin tumour, surveillance and protective behaviours continue to be important throughout the life of an individual with a history of skin cancer.

- An increased emphasis on primary prevention of known risk factors for skin cancer in order to reduce the combined burden associated with first primary skin cancers, recurrences, multiple skin cancers of the same type, and SPCs in a different tissue from the first primary.

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RÉSUMÉ

Cet article résume les récents travaux de recherche sur le risque élevé de récurrence, les cancers de la peau multiples et les seconds cancers primitifs chez le nombre croissant de gens ayant eu un cancer de la peau, ceci afin de mieux évaluer le fardeau des tumeurs malignes après un cancer de la peau.

Recenser et suivre les cas de cancer de la peau, tant les mélanomes que les non-mélanomes (NM), présente des difficultés. La plupart des autorités ne font pas le suivi systématique des cas de NM; même lorsqu'elles le font, elles n'incluent d'habitude que le premier diagnostic. Il y a différentes règles pour compter les mélanomes multiples, et l'on ne tient pas compte des récurrences pour les deux grands types de cancer de la peau. Si l'on appliquait aux chiffres canadiens sur le cancer les éclairages apportés par les études récentes sur la question, on augmenterait d'environ 26 % les diagnostics déclarés de NM et de 10 % les diagnostics déclarés de mélanome au Canada. Cette évaluation plus globale du fardeau des cancers de la peau s'appelle « approche de l'incidence fondée sur le diagnostic », par opposition à une approche fondée sur les patients. Un autre aspect dont on ne tient généralement pas compte lorsqu'on évalue le fardeau des cancers de la peau est le risque de 20 % à 30 % plus élevé de second cancer primitif non cutané après une tumeur primitive de la peau.

Pour résumer, les sujets ayant un cancer de la peau présentent un risque élevé de récurrence, de cancers de la peau multiples et de second cancer primitif. Ce fardeau devrait être un sujet de préoccupation pour le bassin vaste et grandissant des sujets ayant eu un cancer de la peau, ainsi que pour les planificateurs en prévention.

Mots clés : tumeurs de la peau; secondes tumeurs primitives; récurrence; prévention et contrôle