Increased incidence of second malignancies associated with small bowel adenocarcinoma

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BACKGROUND: Some data suggest that there is an increased incidence of second malignancies associated with small bowel adenocarcinomas, but this has not been reviewed in the context of a tumour registry.

OBJECTIVE: To review tumour registries based on population statistics to determine whether there is an increased incidence of second malignancies associated with small bowel adenocarcinomas.

METHODS: The authors reviewed the tumour registries of two Canadian provinces (British Columbia and Manitoba) for small bowel adenocarcinoma to determine whether an increase in associated malignancies existed compared with those expected in the respective populations.

RESULTS: A greater than eightfold increase in second malignancies was associated with small bowel carcinoma. The majority (73%) occurred before the diagnosis of the small bowel malignancy. Twenty-nine per cent were associated with cancers of the colon, rectum or both.

CONCLUSIONS: There is an increased association of malignancy and the diagnosis of small bowel cancer. Generally, small bowel cancer is the second malignancy to be diagnosed, and the diagnosis is most often made in the elderly. Does this represent a syndrome related to an unstable gene (or genes) or a lack of repair, which makes individuals susceptible to this malignancy as they age?

Key Words: Review, Second malignancies, Small bowel adenocarcinoma

Fréquence accrue de néoplasies secondaires associées au cancer du grêle

DONNÉES DE DÉPART : Selon certaines données, la fréquence des néoplasies secondaires associées aux adénocarcinomes du grêle est à la hausse, mais ce phénomène n'a pas été étudié dans le contexte d'un registre des tumeurs.

OBJECTIFS : Passer en revue des registres de tumeurs sur la base des statistiques de population afin de déterminer si la fréquence de néoplasies malignes secondaires associées aux adénocarcinomes du grêle est en hausse.

MÉTHODES : Les auteurs ont passé en revue les registres de tumeurs de deux provinces canadiennes (Colombie Britannique et Manitoba) pour l'adénocarcinome afin de vérifier s'il y avait augmentation du nombre de néoplasies associées, en comparaison avec les prévisions pour les populations respectives.

RÉSULTATS : Les néoplasies secondaires associées au cancer du grêle ont été huit fois plus fréquentes. La majorité (73%) est survenue avant que soit posé le diagnostic de néoplasie du grêle. Vingt-neuf pour cent ont été associés à des cancers du côlon, du rectum ou des deux.

CONCLUSIONS : On note une augmentation des néoplasies associées au diagnostic de cancer du grêle. En général, le cancer du grêle est la deuxième néoplasie à être diagnostiquée et le diagnostic est souvent posé chez les gens âgés. Cela représente-t-il un syndrome lié à un gène (ou à des gènes) instable(s) ou à une réparation incomplète qui rendrait les individus sensibles à cette néoplasie avec l'âge?

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Adenocarcinomas of the small bowel account for 1% of primary gastrointestinal malignancies (1) and have previously been identified in association with Crohn's disease (2-4), celiac disease (5), Peutz-Jegher's syndrome (6-8), familial adenomatous polyposis (9) and Lynch syndrome II (10). In addition, there is mounting evidence that there is an increased incidence of second malignancies associated with the development of small bowel adenocarcinoma (11-15). No group has reviewed adenocarcinoma of the small bowel in the context of a tumour registry. After initially reviewing the tumour registry for small bowel adenocarcinoma in Manitoba, we similarly reviewed the British Columbia cancer registry to determine the natural history of the disease and patient demographics, and whether there was an increased incidence of second malignancies associated with small bowel adenocarcinoma.

MATERIALS AND METHODS

The British Columbia Cancer Agencies' Cancer Registry and the Manitoba Cancer Treatment and Research Foundation's Registry both list all cancers of residents, reported to them as required by law. A 10-year survey of all small bowel adenocarcinomas reported to either registry from January 1, 1982 to December 31, 1991 was undertaken. Patients with other histologies, such as lymphomas, carcinoid tumours or sarcomas, were excluded from the study. Data extracted were age, sex, date of diagnosis and last follow-up, other malignancy, site of the adenocarcinoma, Duke stage of small bowel cancer and overall survival. Follow-up was calculated from the time of the adenocarcinoma until death, subsequent malignancy or last follow-up appointment, after which patients were censored. Log rank survival curves were determined by the usual methods.

The rate of expected malignancy in the registry population was determined by multiplying the person-years of follow-up in each appropriate decade by the incidence of the particular cancer for each age, sex and period-specific incidence rate for the appropriate province; results were then compared with the observed rate in a two-by-two table using χ^2 statistics. For example, an individual age 55 and followed until the development of a second cancer at age 69 was compared with the registry population $\times$ five years in the decade 50 to 59 years, and with the registry population 60 to 69 years $\times$ 10 years for the incidence of developing the second malignancy.

RESULTS

A total of 128 patients with adenocarcinoma of the small bowel were identified (76 male and 52 female). Mean age of the entire group was 67.3 years (median 68, range 27 to 89). At the time of diagnosis of the adenocarcinoma, 74 individuals (57.8%) were older than 65, and 54 (42.2%) were younger than 65. Mean age of males was 67.4 years (range 27 to 89) and of females was 67.1 years (range 31 to 89) (Table 1). Where Duke stage was known (in 91 of 128 cases), four were Duke A (4%), 20 Duke B (22%), 24 Duke C (26%) and 43 Duke D (48%). Thirty-seven cases were of indeterminate

TABLE 1
Small bowel adenocarcinoma

Case type	Mean age (years)	Range
All patients (n=128)	67.3	27-89
Male (n=76)	67.4	27-89
Female (n=52)	67.1	31-89

TABLE 2
Duke stage of disease

Stage	Number	% stage
A	4	4
B	20	22
C	24	26
D	43	48
Unknown	37	—

TABLE 3
Location of the adenocarcinoma of the small bowel

Location	Number (%)
Duodenum	50 (39)
Jejunum	27 (21.1)
Ileum	17 (13.3)
Unknown	34 (26.6)

Figure 1) Overall survival for males and females following the diagnosis of small bowel cancer

stage (Table 2). Fifty cases occurred in the duodenum (39%), 27 in the jejunum (21.1%), 17 in the ileum (13.3%) and 34 could not be determined from the record (26.6%) (Table 3). Mean survival of the total group was 10.1 months. Males survived an average of 11.4 months and females 8.6 months ($P=0.16$) (Figure 1). The 24 patients with Duke A and B stages had a mean survival of 22.2 months ($SD=19.5$); Duke C cases had a mean survival of 12.5 months ($SD=11.8$) and Duke D, 7.4 months ($P=0.05$) ($SD=6.7$) (Figure 2). Histology was not a significant determinant of survival ($P=0.324$) (Figure 3). Histology slides were not reviewed; a record was kept of whether the reading pathologist viewed the tumour as well differentiated, intermediately differentiated or poorly

Figure 2) Survival by Duke stage following the diagnosis of small bowel cancer. Stages A and B were grouped together. Stage A and B patients survive significantly longer than stage C or D patients

Figure 3) Survival by histology following the diagnosis of small bowel cancer. There is no significant difference noted in survival based on pathological differentiation

differentiated/anaplastic. Only 14 cases were deemed well differentiated (10.9%), while 24 were intermediately differentiated (18.8%) and 13 poorly differentiated (10.2%); 77 cases were not graded (60%). Age group and location of small bowel cancer were not of prognostic importance (Figures 4,5).

Fifty-four patients had a second malignancy (42.2%) and six had multiple malignancies. Twenty-five of 72 cases (34.7%) were in Manitoba and 29 of 39 cases (74.4%) were in British Columbia. Of patients with a second malignancy, mean age was 69.8 years at diagnosis; median age was 72 years, range 30 to 87. In 38 instances (70.4% of cases with second malignancy) small bowel adenocarcinoma was the second malignancy occurring; in eight instances (14.8%), small bowel cancer was detected within six months of another malignancy; and six second malignancies (11.5%) occurred greater than six months after the diagnosis of small bowel cancer.

The 54 second malignancies detected were as follows: 16 colon/rectum (29.6%), nine prostate (16.7%), six female genitalia (11.1%), six lung (11.1%), four skin (nonmelanoma) (7.4%), four genitourinary (nonprostate) (7.4%),

Figure 4) Survival by age following the diagnosis of small bowel cancer. Age was not a determinant of survival

Figure 5) Survival by location of the small bowel adenocarcinoma following diagnosis. Location was not a determinant of survival

TABLE 4
Associated malignancies

Type	Number (%)
Colon/rectum	16 (29.6)
Prostate	9 (16.7)
Female genitalia	6 (11.1)
Lung	6 (11.1)
Skin (nonmelanoma)	4 (7.4)
Genitourinary (nonprostate)	4 (7.4)
Lymphoproliferative	3 (5.6)
Breast	3 (5.6)
Second small bowel	2 (3.7)
Chromophobe adenoma	1 (1.9)

three lymphoproliferative (5.6%), three breast (5.6%), two second small bowel (3.7%) and one chromophobe adenoma (1.9%) (Table 4).

The observed incidence of malignancy in each age bracket was taken from the appropriate tumour registry and was multiplied by the years of follow-up in the patient popu-

lation. The rate of second malignancy was highly significant (observed:expected ratio was 8.4:1, $P < 0.0001$). Removing skin cancers did not change the significance.

DISCUSSION

Small bowel adenocarcinoma is a rare malignancy that often occurs as the second malignancy in individuals who may be prone to develop malignancies as they age. Survival is stage-dependent; approximately 50% of patients have small bowel adenocarcinomas that are in an advanced stage at diagnosis – 25% are Duke stage C and approximately 25% are more localized. Histology as determined by the original reading pathologist, sex and age had no effect on survival.

Our results confirm an increased association of second malignancy in patients ultimately diagnosed with small bowel adenocarcinoma. In the majority of cases (38 of 54 [70.3%]) small bowel cancer was the second malignancy in the patient's course. In fact, six cases had multiple malignancies. Two cases had patterns suggestive of Lynch syndrome, but the mean age of these patients at the diagnosis of small bowel adenocarcinoma was 67.3 years, and almost 60% of the patients were older than 65 years at diagnosis. None of the cases appeared to represent a familial polyposis syndrome. Hence, most of these cases do not appear to be related to known familial or genetically determined cancers. It is suggested, however, that development of small bowel cancer is a reason to investigate genetic changes related to multiple cancers.

More cases of second malignancies associated with small bowel adenocarcinoma were seen in Manitoba than in British Columbia (72 versus 39 cases, respectively) despite that the former is a smaller province. Why? There may be more cases present secondary to some groups that live in fairly isolated areas in Manitoba and therefore they have a relatively greater effect on the small population. Examination of address data found that this does not appear to be the case.

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On the other hand, proportionately more cases were found in those living in a major centre in Manitoba, but in many places in British Columbia the population is not as centralized. In Manitoba, over half the population lives in Winnipeg, the largest city in the province, and many live in the two to three larger centres (16). However, British Columbia had a higher proportion of second malignancy compared with Manitoba (74.4% versus 34.7%).

Since small bowel adenocarcinoma occurred in more elderly patients and because transportation has been shown to be a significant factor related to definitive treatment, the elderly may be operated on more readily in larger centres (16). If one assumes that many second malignancy small bowel cases were operated on for complications, this may explain the higher proportion of secondary malignancy seen in the British Columbia cases. In other words, more operations may have been done in Manitoba because most of the surgeons doing them belonged to one or two centres within the province (unless there was a complication that might have made the proportionate rate higher in British Columbia). This hypothesis cannot be tested but is more likely than a true incidence difference in the province.

In the British Columbia Tumour Registry, group family history of all cases was reviewed, but there were only three cases that suggested familial tendencies. In these cases there were several siblings and a parent with cancers. The rest of the cases did not have histories suggestive of known familial inheritance patterns. The development of small bowel cancer may indicate exposure to elements that can cause other cancers. Diet may be a factor because the majority of cases were associated with large bowel adenocarcinoma. There is no compelling evidence of occupational exposure. In view of the association with other malignancies, genetic investigation of individuals who develop small bowel adenocarcinoma, along with careful dietary history, may be worthwhile.

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