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Incidence and Clinical Behaviour of Patients with Second Primary Cancers - Single Institution 17 Years Observation

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Abstract

Aim: The present study was done to study the incidence and clinical behavior of patients with second primary cancers.

Materials and Methods: This study is a retrospective study of all patients with second primary cancers treated in the Department of Radiotherapy at Christian Medical College and Hospital -Ludhiana during the period 1990 to 2007. They were assessed with respect to sex, site of primary malignancy, histological type, site of second malignancy and interval of presentation. Patients with primary breast malignancy who developed malignancy in the opposite breast were not included in the study.

Results: Of the total 27 patients assessed, the Male: Female ratio is 1:1.7; Breast Cancer was the most common primary in females who presented with second primary in cervix and ovary; while head and neck cancer was the most common in males presenting with second primary in upper aero-digestive tract. In a primary breast carcinoma the mean interval of presentation of cervical cancer was 5 years, while that of ovarian cancer was 12.3 years. The mean interval of presentation of second primary in upper aero digestive tract was 8.6 yrs. The overall mean time interval of presentation of second primary cancers was 5.66 years while the median time interval was 5.5 years.

Conclusion: This study demonstrates that survivors of carcinoma breast besides the risk of contra lateral breast cancer are at increased risk of developing second primary in cervix and ovary. Male survivors of Head and neck cancer have an increased predilection for tumours of upper aero-digestive tracts. The substantial increase in solid tumor risk with greater follow-up time necessitates lifelong medical surveillance of these patients for early detection and management of second primary.

Keywords: Second primary; Cancer survivors

Introduction

Man in his search for cure has made tremendous achievements in the field of medicine. Cancer which was once thought an incurable disease has progressed through stages of prolongation of life, incomplete cure to even complete cure in some cancers. With prolongation of life, these patients developed other problems like second malignancies and late effects of cancer treatment.

Second primary cancer refers to a new primary cancer in a patient with history of cancer. For a definition of second primary tumors, most clinicians use the criteria of Warren and Gates [1], which were published in 1932: (a) each of the tumors must present a definite picture of malignancy, (b) each must be distinct, and (c) the probability of one being a metastasis of the other must be excluded. Histological examination will often find that a tumor is malignant, but with this method, it is difficult to prove that the lesions are distinct. To exclude the possibility of a local recurrence, most studies use a distance of at least 2 cm between the first tumor and the second primary tumor [2]. An additional criterion of a second primary tumor at the same or an adjacent anatomical site is that it should occur at least 3 years after the diagnosis of the primary tumor [3].

The occurrence of multiple tumors can be explained by two competing hypothesis: (a) multiple transforming events give rise to genetically unrelated multiple tumors, or (b) a single cell is transformed and through mucosal spread gives rise to genetically related multiple tumors [4]. It has been reported that 87-100% of all of the loco regional recurrences and distant metastases have occurred within 3 years [5]. Therefore an

additional criterion of a second primary tumor at the same or an adjacent anatomical site is that it should occur at least 3 years after the diagnosis of the primary tumor [6]. It has been hypothesized that the hypersensitive patients develop a second primary tumour by a second hit, possibly as a result of the continuation of smoking combined with their increased intrinsic susceptibility [7]. Overall, cancer survivors have a 14 -20 percent higher risk of developing a new primary malignancy compared with the general population [6].

Second primary cancers can be divided into two groups: synchronous second primary cancers, which develop simultaneously with or within 6 months after the index tumour, and metachronous second primary cancers, which develop >6 months after the initial tumour [8]. The term "field cancerization" was used for the first time by slaughter et al in a study of 783 patients with oral cancer [9,10]. Based on histological examinations, field cancerization was described as follows: (a) oral cancer develops in multifocal areas of precancerous change, (b) histologically abnormal tissue surrounds the tumours, (c) oral cancer often consists of multiple independent lesions that sometimes coalesce, and (d) the persistence of abnormal tissue after surgery may explain second primary cancers and local recurrences.

A population based cohort study of 75087 patients of Head and Neck Cancers showed the standardized incidence rate of second primaries was 2.2 while excess absolute risk (EAR) per 10,000 person-years at risk was 167.7 [11]. In case of primary Head and Neck cancers, the effect of treatment suggest no significant difference between radiotherapy and surgery within five years after treating the primary tumour [12-16]. Beyond five years, however, the incidence of second malignant tumours seems to be higher in those who received radiotherapy14,15. The common sites of second tumors in a patient with Head and neck cancer were in another focus of Head and Neck or lung16. Patients with primary lung cancer are at significant risk for second malignancies throughout the entire aerodigestive tract [10].

Breast cancer patients are at a increased risk of contralateral breast cancer [17]. The risk of endometrial malignancy following a primary breast cancer is increased 2-4 fold in postmenopausal women who use tamoxifen while the risk of ovarian cancer increases with age and is linked to hereditary/genetic syndromes. Among women with BRCA1-associated cancers the lifetime risk of ovarian malignancy is 15% to 45% whereas in BRCA2-associated cancers the risk of ovarian cancers is 10% to 20%10.

Patients with gynaecological malignancies like cervical, endometrial and ovarian cancer have an increased risk of colorectal cancer especially if diagnosed at an early age [18]. Cervical cancer patients also have increased risk of cancers of the upper aerodigestive tract, anus, pancreas, lung, other female genitals, and urinary bladder [19]. Chemoprevention studies have shown that β-carotene and retinoids increase the risk of second cancer in smokers; while retinoids was found to be useful in non-smokers [20-27]. This study is mainly intended at studying the incidence and clinical behaviour of second primary cancers.

Materials and Methods

The study was conducted at department of Radiotherapy, Christian Medical College and Hospital - Ludhiana. The study is a retrospective study with data obtained from department file records and from the medical records section. Patients who presented with second primary tumours during the period of 1990-2007 were included in the study. Of the 4816 newly diagnosed cancer patients attending the out-patient clinic during the period, 27 patients presented with a second primay malignancy.

These 27 patients were studied with respect to age and sex and classified. Histopathology of both primary and second primary tumors was studied. Primary and second primary tumors were also studied with respect to site, stage and treatment received. Patients with contralateral breast cancer were not included in the study. Statistical analysis was done using SPSS (version 16) software.

Results

Among the 27 patients with multiple primary malignancies 2 cases had synchronous double primary malignancy and 25 had metachronous double primary malignancy. These 27 patients comprised 0.56 % of the 4816 newly diagnosed cancer patients attending the out-patient clinic during the period 1990-2007. See table no.1 for patient characteristics (Table 1).

Table 1: Patient Characteristics.

Multiple primary			
Parameter	No. (%)	Median (range)	Mean (SD)
No of patients	27 (100)		
Age		51.5 (25-67)	51.78 (10.4)
Sex			
Male	10 (37.03%)		
Female	17 (62.96%)		

The male: female ratio of second primaries was 1:1.7 suggesting a predominance of second primaries in females. Female patients presented at an earlier median age of 48 years compared to 57 in males. Histopathologically the adenocarcinoma and the squamous cell carcinoma subtypes occurred in almost equal frequencies in both primary and second primary malignancies.

The most frequent type of first primary tumours which developed second tumours were Breast (37.03%), Head and neck (22.22%) and cervical (22.22%) cancers. The distribution by site of the second primary tumours were gastrointestinal tract (18.52%), Head and neck (14.81%), breast (14.81%),

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cervix (11.11%), ovary (11.11%) cancers. Gastrointestinal malignancies were more common as second primaries than first primary malignancy (18.52% vs 3.7%, p=0.023). Breast cancer incidence was more frequent in first primary malignancy than second primary (37.04% vs 14.81 %, p value= 0.001).Primary tumours tend to be at a smaller TNM stage compared to second primary (81.48% of the first primaries was stage I+II vs 33.33% of the second primaries P=0.022) and second primaries present at a higher stage than first primaries (6.66% of the second primaries was stage III+IV vs 18.51% of the first primaries P=0.001) (Table 2).

Table 2: Disease and patient characteristics.

Parameter	1st malignancy No. (%)	2nd malignancy No (%)
Pathology		
Adeno ca.	13 (48.15%)	11 (40.74%)
Squamous cell ca.	14 (51.85%)	13 (48.15%)
Others	0	03 (11.11%)
Type of cancer Head and Neck and lung	**6 (22.22%)**	**7 (25.93%)**
Oral cavity	2 (7.4%)	0
Nasopharynx	0	1 (3.7%)
Hypopharynx	2 (7.4%)	3 (11.11%)
Larynx	2 (7.4%)	0
Salivary glands	0	1 (3.7%)
Bronchi and lungs	0	2 (7.4%)
Gastrointestinal system	**1 (3.7%)**	**5 (18.52%)**
Upper GIT	0	2 (7.4%)
Lower GIT	1 (3.7%)	3 (11.11%)
Breast	**10 (37.04%)**	**4 (14.81%)**
Gynaecological	**8 (29.63%)**	**7 (25.93%)**
Cervix	6 (22.22%)	3 (11.11%)
Ovary	1 (3.7%)	3 (11.11%)
Endometrium	1 (3.7%)	1 (3.7%)
Others	**2 (7.4%)**	**4 (14.81%)**
Stage of cancer (TNM)		
0	0	0
1	5 (18.52%)	3 (11.11%)
2	17 (62.96%)	6 (22.22%)
3	3 (11.11%)	16 (59.26%)
4	2 (7.4%)	2 (7.4%)
Curative surgery performed		
Yes	15 (55.56%)	9 (33.33%)
No	12 (44.44%)	18 (66.67%)
Radiotherapy received		
Yes	23 (85.19%)	14 (51.85%)
No	4 (14.81%)	13 (48.15%)
Chemotherapy received		
Yes	8 (29.63%)	7 (25.93%)
No	19 (70.37%)	20 (74.07%)

When primary malignancy was from breast cancer category, the second cancer was mostly gynaecological cancers (mainly cervical and ovarian malignancy). Gynaecological cancers accounted for 70% of the second primaries in breast cancer and breast cancer accounted for 50% of the second primaries in primary gynaecological cancers (Table 3).

Table 3: Type of second malignancy with regard to first malignancy.

	Head & Neck	Lung	Breast	GIT		Gynecologica			Others			Total
				Upper	Lower	Cervix	Ovary	Endo-metrium	Penis	MMela-noma	Lymphoma	
1st malignancy												
Head & Neck	3	1	0	1	0	0	0	0	1	0	0	06
Breast	0	0	0	0	2	3	3	1	0	1	0	10
GIT	0	0	0	0	0	0	0	0	0	0	1	01
Gynecological	1	0	4	1	1	0	0	0	0	0	1	08
penis	1	1	0	0	0	0	0	0	0	0	0	02
Total	5	2	4	2	3	3	3	1	1	1	2	27

The mean time of presentation of second malignancy is 68 months (5.66 years) and median 66 months (5.5 years) [range, 1-216 months]; with synchronous malignancies having a range between 1 and 4 months and metachronous malignancies in range of 1-18 years. In case of breast cancer the interval of presentation ranged from 1-18 years with a mean interval of presentation of 6.6 years. The average time of presentation of ovarian malignancies was 12.33 years with a range of 5-18 years (Table 4).

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Table 4: Second Primaries in Breast Cancer and their Interval of Presentation.

Second primary	No. of cases	Time interval of presentation (years)
Cervix	3	4
		4
		7
Ovary	3	5
		14
		18
Colorectal	2	2
		6
Endometrium	1	1
Malignant melanoma	1	5
	Total = 10	Mean = 6.6 years, Median = 5 years

In case of head and neck primary cancer, cancers of the upper aero digestive tract contributed 83.33% of the second primaries. The time interval of presentation of another focus of head and neck cancers in a patient with primary head and neck cancer ranged from 6-11 years; with a mean interval of 8.67 years. The mean interval of presentation of second primaries in primary head and neck cancer was 6.5 years and median interval of 5 years (Table 5).

Table 5: Second primaries in Head and neck cancer and their interval of presentation.

Second primary	No. of cases	Time interval of presentation (years)
Head and neck cancer	3	6
		9
		11
Bronchus	1	5
Oesophagus	1	4
Penis	1	4
	Total = 6	Mean = 6.5 years Median = 5 years

Breast cancers in primary gynaecological cancers presented as early as 1 year and as late as 12 years. The mean interval of second malignancies in primary gynaecological cancers is 4.67 years (Table 6).

Table 6: Second primaries in Gynecological cancer and their interval of presentation.

Second primary	No. of cases	Time interval of presentation (years)
Breast	4	1
		5
		5
		12
NHL	1	9
Head and neck cancer	1	3
Oesophagus	1	2
Anal canal	1	4 months
Total	8	Mean 4.67 years

In patients who received radiotherapy for first primary malignancy, there was equal incidence of second primary malignancy in Gynecological (21%), Head and Neck (21%) and gastrointestinal cancer (21%). Gynaecological cancers presented as late as 18 years, while Head and Neck and Gastrointestinal malignancies presented as late as 11 years and 6 years respectively in patients who received radiotherapy (Table 7).

Table 7: Second primaries in patient who underwent radiotherapy and the interval of Presentation.

Second primary	No. of cases	Time interval of presentation (years)
Head and Neck	5	1 month
		3
		6
		9
Gynecological	5	11
		1
		4
		5
		7
		18
GIT	5	4 months
		2
		2
		4
		6
Breast	3	1
		5
		12
NHL	2	8
		9
Lung	1	5
Malignant melanoma	1	5
Penis	1	4
Total	23	Mean = 5.54 years
		Median = 4.5 years

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Discussion

The incidence of 0.56% of second primary malignancy in our series from 1990-2007 is in accordance with literature where the proportion of multiple primary patients in all cancers varied from 0.5 to 7.4% [20-22]. Among the patients with second primary malignancy, women had an earlier median age (48 years) of presentation compared to men (57 years) probably suggesting a hormonal influence in carcinogenesis.

In our study Primary tumours were found to be at a smaller TNM stage compared to second primary (81.48% of the first primaries was stage I+II vs 33.33% of the second primaries P=0.022) and second primaries present at a higher stage than first primaries (66.66% of the second primaries was stage III+IV vs 18.51% of the first primaries P=0.001). Similar findings were found in study done by Mehmet Artec et al [23]. This could also imply the increased survival in early stage cancers which made then prone for second primaries.

In our study Breast cancer was the most common first primary malignancy (37.03%) and Breast cancer cases were more frequent as first primary than second primary malignancy (37.04% vs 14.81 %, p value= 0.001) this is supported by the study done by Mehmet Artec et al [23] which had similar relationships. Mean time interval of presentation of second primary malignancy in Breast cancer patients was 6.6 years; almost similar value of 6.2 years was got in a study done by J S Raymond and C J R Hogue [24]. The same study also got an increased incidence of colorectal, ovarian and lung malignancies apart from contra lateral breast cancer in primary breast cancer patients. Increased incidence of ovarian and colorectal malignancy was also noted in our study. Increased incidence of second primary ovarian cancers in primary breast cancer patients was also seen in a study done by H. Irene Hall et al [25].

In case of head and neck primary cancers, cancers of the upper aero digestive tract accounted for 83.33% of the second primary malignancies. In a study done by Jones AS et al [9], Head and Neck along with lung contributed 84% of the second primaries in primary Head and Neck cancer patients. This high incidence may be because of continued exposure to carcinogen and genetic predisposition.

In case of Gynecological first primary cancers most studies show an increased incidence of colorectal malignancies [18] but our study showed an increase incidence of breast cancers. The mean interval of presentation of second primary malignancy was 5.54 years in our study in those patients who received radiotherapy for first primary malignancy. Literature shows an increased incidence of second primaries after five years in those treated with radiotherapy [14,15].

Multiple primary malignancies have an indolent course. The long median time of 5.5 years and a mean time of 5.66 years indicate that a good amount of time can pass for carcinogenesis to complete before a subsequent malignancy may appear. This indolent course leads to long term survival as shown in the cases of ovarian cancers occuring in case of breast cancer as late as 18 years in this study. Literature also shows that in patients with primary breast cancers the risk for ovarian malignancy remained elevated even 15-24 years after diagnosis25. These findings necessitate long term follow-up for early detection.

Conclusion

Since most recommended guidelines recommend regular follow-up for only 5 years and then only an annual examination, we feel that as there is occurrence of second primary as late as 18 years at least 4-6 monthly follow-up in oncology clinic with good clinical examination and special emphasis on the second primary tumors commonly associated with that primary is recomended even after the 5 years.

Contra lateral prophylactic mastectomy may be considered after the diagnosis of a primary breast malignancy. Bilateral salpingo-oophorectomy also reduces the risk of subsequent invasive breast cancers by about 50% and nearly eliminates the risk of ovarian malignancy [28,29].

The use of MRI as superior to mammography should be evaluated in the detection of second breast malignancies, particularly among premenopausal women carrying a predisposing genetic mutation. We also need to develop new strategies to screen for ovarian cancer among women with genetic syndromes.

The development and validation of tissue-based and cytogenetic markers to predict reliably the risk of recurrence of upper aero digestive malignancies should continue as a high priority. Genomic tumour profiling techniques should be developed not only in selecting treatment for primary cancers but also to identify individuals at risk for second primary. To conclude, the bulk of second malignancy is a reflection of age of patient, treatment modalities used and continuation of presence of high risk factors like poor living style, continuation of tobacco usage as well as nutritional stresses like pesticides. Primary health care providers should be educated about development of second primaries in patients treated for malignancy and taught clinical screening procedures like breast examination.

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