Double Primary Malignancies: A Clinical & Pathological Analysis Report from a Regional Cancer Institute in India

Puneet Kumar Bagri[1], Daleep Singh[1], Mukesh Kumar Singhal[1], Guman Singh[1], Gaurav Mathur[2], Shankar Lal Jakhar[1], Surender Beniwal[3], Neeti Sharma[1], Harvindra Singh Kumar[1], Ajay Sharma[1], Megh Raj Bardia[1]

Abstract

Background: Patients which have diagnosed with a cancer, have a life time risk for developing another de novo malignancy depending on various inherited, environmental and iatrogenic risk factors. Cancer victims could survive longer due to settling treatment modalities, and then would likely develop a new metachronous malignancy.

This article aims to report our observed trend of increasing, in prevalence of both synchronous and metachronous second primary malignancy, among the cancer victims, and to review the relevant literature.

Methods: A hospital based retrospective gathering of prospective data, among the patients that have diagnosed with second de novo malignancy.

The study has conducted over a 4 years period from 2009 to 2012. All patients that have diagnosed with a histologically proven second malignancy as per Warren and Gates criteria have included. Various details which have regarded site, age at presentation, sex, synchronous or metachronous, treatment have recorded.

Results: Among 41 cases of multiple primary malignancies that have observed, 8 were synchronous (19.51%) and 33 were metachronous (80.49%). Out of 41 patients, 25 (60.98%) were females and 16 (39.02%) were males. The most common sites of primary tumor were head and neck cancers that have followed by gynecological cancers, breast cancer, lung cancer, esophageal cancer, and then the others. Among the second malignancy, the most common site was breast and gastrointestinal tract that have followed by lung and gynecological cancers. Out of the total number of cases with double location, 14 tumors (34.15%) have belonged to the breast, out of which 5 (12.20%) have represented first locations and 7 (17.07%) have been second locations. Both locations have belonged to the breast in 2 patients (4.9%). In 5 cases (12.20%), there were associations of breast-cervix and in 6 cases (14.63%), there were association of lung-head & neck cancers.

Conclusion: The incidence of multiple primary malignancies has not been rare at all. Screening procedures have especially been useful for the early detection of associated tumors, whereas careful monitoring of patients has treated for primary cancer, and then a good communication between patients and medical care team would certify not only an early detection for secondary tumors, but only finally & subsequently, an appropriate management.

Keywords: Double primary malignancy; Synchronous; Metachronous; Second malignancy

Please cite this article as: Bagri PK, Singh D, Singhal MK, Singh G, Mathur G, Jakhar SL, et al. Double Primary Malignancies: A Clinical & Pathological Analysis Report from a Regional Cancer Institute in India. Iran J Cancer Prev. 2014; 7(2):66-72.

1. Dept. of Radiation Oncology; Acharya Tulsi Regional Cancer Treatment & Research Institute, Bikaner-334003, Rajasthan, India
2. Dept. of Medicine; PBM hospital, Bikaner-334003, Rajasthan, India
3. Dept. of Medical Oncology; Acharya Tulsi Regional Cancer Treatment & Research Institute, Bikaner-334003, Rajasthan, India

Corresponding Author:
Puneet Kumar Bagri, MBBS; PGT; MD Radiation Oncology
Tel: (+91) 7737072711
Email: drpuneetkb@yahoo.com
Received: 1Sep. 2013
Accepted: 19 Dec. 2013
Iran J Cancer Prev. 2014; 2:66-72

Introduction

The incidence of double primary malignancy has not been rare at all [1-4]. One of the earliest statistical analyses of double primary malignancies has carried out by Bugher in 1934, which has derived an equation for the probability of death from cancer during a specified period of age with a coincidental second malignancy [5].

The presence of dysplastic changes in the second primary site strongly has suggested a new primary. The aim of this study was the report of our observation about increasing incidence of multiple primary malignancies. Further, with recently treatment modalities, cancer patients have survived much longer to be able to develop metachronous new primary, which might partly related to the treatment of earlier malignancy. It was also obvious, which with the recently improved diagnostic modalities such as Positron Emission Tomography (PET), that amounts of picking up indolent tumors have increased contributing, further to the obvious increase of multiple primary malignancies incidence [6, 7].

Double primary malignancies could be divided into two categories, depending on the interval between tumor diagnoses [8]. Synchronous malignancies were second tumors have been occurring either simultaneously, or within 6 months after the first malignancy while metachronous malignancies were secondary tumors that have developed after 6 months, or even more than that from the first malignancy.

The criteria have used for the diagnosis of double primary malignancies, have primarily given by Warren and Gates (Table 1) and refined later [9-12].

Materials and Methods

The study was a retrospective collection of the prospective data from the hospital database of patients either presenting with histologically proven synchronous or metachronous double primaries as defined by above criteria over a 4 years period, from 2009 to 2012. The time interval to differentiate between synchronous or metachronous has taken as 6 months as reported by several authors [8, 12, 13].

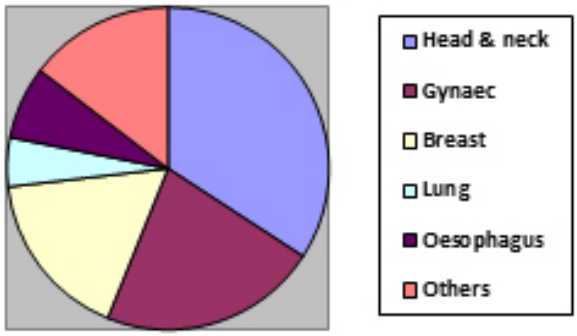

Figure 1. Site distribution of primary malignancy

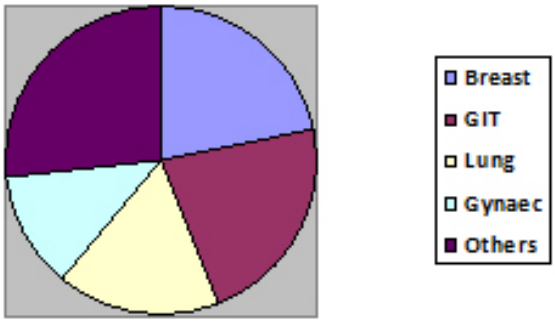

Figure 2. Site distribution of secondary malignancy

The inclusion criteria of patients in this study were the presence of at least two neoplastic locations, that confirmed by histopathological examination, with distinct histopathology in the two locations. We have excluded patients without a clear histopathological confirmation of each tumor, and then also the patients whom the second tumor has suspected to be a metastasis of the first location.

Various details like patient age at time of each tumor diagnosis, sex, synchronous or metachronous, site of origin, diagnosis method, histology, detection clinical stage, and treatment regimen have been recorded.

Table 1. Warren and Gates Criteria for Diagnosis of Double Primary Malignancies.

1. Histological confirmation of malignancy in both the index and secondary tumors.
2. There should be at least 2 cm of normal mucosa between the tumors. If the tumors are in the same location, then they should be separated in time by at least five years.
3. Probability of one being the metastasis of the other must be excluded.

Table 2. Summary of synchronous double malignancies

S. No.	Age (years)	Sex	Primary site	Histopathology	Treatment	Second site	Histopathology	Treatment
01	45	F	Cervix	Moderately differentiated Squamous cell carcinoma	Chemoradiation	Right breast	Invasive ductal carcinoma	Neoadjuvant chemotherapy, Modified radical mastectomy, Radiotherapy
02	37	F	Left gluteal region	Leiomyosarcoma	Surgery	Right breast	Invasive ductal carcinoma	Modified radical mastectomy, Chemotherapy, Radiotherapy
03	55	F	Thyroid	Papillary carcinoma	Total thyroidectomy	Oesophagus	Moderately differentiated Squamous cell carcinoma	Surgery
04	65	M	Lung	Squamous cell carcinoma	Chemotherapy, Radiotherapy	Prostate	Adenocarcinoma	Surgery
05	27	F	Brain	Cerebello pontine angle tumor	Surgery, Radiotherapy	Breast	Invasive ductal carcinoma	Neoadjuvant chemotherapy, Modified radical mastectomy, Radiotherapy
06	39	F	Breast	Invasive ductal carcinoma	Modified radical mastectomy, Chemotherapy, Radiotherapy	Urinary bladder	Transitional cell carcinoma	Surgery
07	53	M	Pyriform fossa	Squamous cell carcinoma	Chemoradiation	Oesophagus middle 3rd	Squamous cell carcinoma	Chemoradiation
08	64	M	Tongue	Squamous cell carcinoma	Surgery	Buccal mucosa	Well differentiated Squamous cell carcinoma	Surgery, Radiotherapy

Results

More than a 4 years period, between 2009 and 2012, total 23,260 cancer patients have registered to Regional Cancer Institute, out of which 41 cases (0.18%) of multiple primary malignancies have observed.

Out of 41 cases, 8 were synchronous (19.51%) and 33 were metachronous (80.49%). Six months (180 days) has considered as the maximum period for the synchronous tumors occurrence. The occurrence interval of metachronous tumors have ranged from 1 to 26 years, with an average of 5.08 years for the entire group. Out of 41 patients, 25 (60.97%) were females and 16 (39.03%) were males.

The median age at the primary malignancy diagnosis, was 48 years (range 27-65 years). The most common site of primary tumor was head and neck (14 cases; 34.15%) followed by gynecological cancers (9 cases; 21.95%), breast (7 cases; 17.07%), lung cancer (2 cases; 4.9%), esophageal cancer (3 cases; 7.3%) and then other tumors (6 cases; 14.6%) (Figure 1). The age range for the second primary tumor was between the 31-71 years. Among the second malignancy, the most common site was breast (9 cases; 21.95%) and gastrointestinal tract (9 cases; 21.95%) followed by lung (7 cases; 17.07%) and gynecological cancers (5 cases; 12.20%) (Figure 2).

Out of the total number of cases with double location, 14 tumors (34.15%) have belonged to the breast, out of which 5 (12.20%) have represented first locations and 7 (17.07%) were second locations. Both locations belonged to the breast in 2 patients (4.9%). In 5 cases (12.20%), we have observed association of breast-cervix, and in 6 cases (14.63%), there were association between the lung-head & neck cancers.

Table 3. Summary of metachronous double malignancies

S. No.	Age at primary malignancy (years)	Sex	Primary site	Histopathology	Treatment	Second site	Histopathology	Time interval (years)	Treatment
01	45	M	Lung	Squamous cell carcinoma	Chemotherapy, Radiotherapy	Ascending colon	Adenocarcinoma	2.5	Surgery, Chemotherapy
02	62	M	Larynx	Squamous cell carcinoma	Radiotherapy	Kidney	Renal cell carcinoma	2	Surgery
03	55	F	Right Breast	Invasive ductal carcinoma	Surgery, Chemotherapy, Radiotherapy	Vulva	Squamous cell carcinoma	7	Surgery, Radiotherapy
04	52	M	Larynx	Squamous cell carcinoma	Surgery	Gall bladder	Adenocarcinoma	1	Surgery
05	41	M	Hypopharynx	Squamous cell carcinoma	Chemoradiation	Lung	Squamous cell carcinoma	1	Chemoradiation
06	58	F	Urinary bladder	Transitional cell carcinoma	Surgery, Radiotherapy	Gall bladder	Adenocarcinoma	2	Surgery
07	46	F	Right Breast	Invasive ductal carcinoma	Surgery, Chemotherapy, Radiotherapy	Cervix	Squamous cell carcinoma	2	Chemoradiation
08	45	F	Cervix	Moderately differentiated Squamous cell carcinoma	Surgery, Radiotherapy	Right breast	Infiltrative ductal carcinoma	3	Surgery, Chemotherapy, Radiotherapy
09	50	F	Cervix	Squamous cell carcinoma	Chemoradiation	Lung	Squamous cell carcinoma	2	Chemotherapy, Radiotherapy
10	45	M	Right testis	Seminoma	Surgery, Chemotherapy	Base of tongue	Squamous cell carcinoma	2	Chemoradiation
11	40	F	Cervix	Squamous cell carcinoma	Chemoradiation	Ovary	Adenocarcinoma	1	Surgery, Chemotherapy
12	44	F	Cervix	Squamous cell carcinoma	Chemoradiation	Ovary	Adenocarcinoma	26	Surgery, Chemotherapy
13	57	M	Pyriform fossa	Squamous cell carcinoma	Radiotherapy	Hard palate	Squamous cell carcinoma	14	Chemoradiation
14	57	M	Base of tongue	Moderately differentiated Squamous cell carcinoma	Chemoradiation	Lung	Squamous cell carcinoma	3	Chemotherapy, Radiotherapy
15	42	F	Uterus	Adenocarcinoma	Surgery, Radiotherapy	Sigmoid colon	Adenocarcinoma	2	Chemotherapy
16	27	F	Oesophagus	Moderately differentiated Squamous cell carcinoma	Chemotherapy, Radiotherapy	Leukaemia	AML	4	Chemotherapy
17	65	F	Cervix	Squamous cell carcinoma	Chemoradiation	Breast	Invasive ductal carcinoma	2.5	Neoadjuvant chemotherapy, Modified radical mastectomy, Radiotherapy
18	60	F	Left breast	Infiltrative ductal carcinoma	Surgery, Chemotherapy, Radiotherapy	Oesophagus	Squamous cell carcinoma	6	Chemotherapy
19	35	F	Right breast	Invasive ductal carcinoma	Chemotherapy, Surgery, Radiotherapy	Parotid	Mucoepidermoid carcinoma	6	Surgery

20	53	F	Gall bladder	Adenocarcinoma	Surgery	Breast	Invasive ductal carcinoma	4	Neoadjuvant chemotherapy, Modified radical mastectomy, Radiotherapy
21	50	M	Base of tongue	Squamous cell carcinoma	Chemoradiation	Lung	Non-small cell carcinoma	4	Chemotherapy
22	60	M	Right buccal mucosa	Moderately differentiated Squamous cell carcinoma	Surgery, Chemoradiation	Lung	Squamous cell carcinoma	10	Chemotherapy
23	27	F	Oesophagus	Squamous cell carcinoma	Chemotherapy	Brain	Astrocytoma WHO grade II	1	Surgery, Radiotherapy
24	50	F	Cervix	Squamous cell carcinoma	Surgery, Radiotherapy	Right breast	Invasive ductal carcinoma	13	Surgery, Chemotherapy, Radiotherapy
25	50	M	Larynx	Squamous cell carcinoma	Radiotherapy	Lung	Adenocarcinoma	3.5	Chemotherapy
26	37	F	Right breast	Papillary ductal carcinoma	Neoadjuvant chemotherapy, Surgery, Radiotherapy, Tamoxifen	Left breast	Invasive ductal carcinoma	10	Surgery, Chemotherapy, Radiotherapy
27	48	M	Upper lip	Squamous cell carcinoma	Surgery	Oesophagus	Squamous cell carcinoma	4	Chemoradiation
28	29	F	Ovary	Sex cord stromal tumor	Surgery, Chemotherapy	Cervix	Squamous cell carcinoma	8	Chemoradiation
29	48	F	Right breast	Invasive ductal carcinoma	Chemotherapy, Surgery, Radiotherapy	Left Breast	Invasive ductal carcinoma	4	Chemotherapy, Modified radical mastectomy, Radiotherapy
30	46	F	Gall bladder	Adenocarcinoma	Surgery	Stomach	Adenocarcinoma	2	Surgery
31	64	M	Oesophagus	Squamous cell carcinoma	Radiotherapy	Prostate	Adenocarcinoma	5	Surgery
32	41	F	Buccal mucosa	Squamous cell carcinoma	Surgery, Radiotherapy	Thyroid	Papillary carcinoma	8	Surgery
33	57	M	Nasal cavity	Squamous cell carcinoma	Radiotherapy	Lung	Squamous cell carcinoma	2	Chemotherapy, Radiotherapy

Discussion

Among the total cancer patients who were admitted to the Regional Cancer Institute between 2009 and 2012, female to male ratio was 0.8:1, while the analysis of patients with double neoplastic locations have revealed a 1.56:1 female-male ratio; that has reversed. Most of the patients belonged to the 5th to 6th age decades (27 of 41; 65.85%). Most diagnosed tumors were metachronous in comparison to synchronous (33 compared with 8).

With regard to tumor stage and treatment, there was no difference between first primary and second primary malignancies of same anatomical sites. However, primary and secondary tumors have tended to be in an advanced stage and the treatment, depending on the location, involved surgery, radiotherapy and chemotherapy. The advanced stage of secondary malignancies was unusual, in comparison to other studies. It should explained either by the low compliance of patients to follow-up, or by their tendency to neglect symptoms. The results have underscored the importance of a good communication between patients and doctors, whereby the doctors should give warnings regarding the risk of developing secondary malignancies after the primary treatment, and then also about the occurrence of any new symptoms.

Although the responsible mechanisms for the multiple primary cancers appearance have not been

fully explained, but among the most frequent factors that have involved, we could mention: the genetic susceptibility, the immune system of patients, and the intensive exposure to carcinogens including chemo- and/or radiotherapy used in the treatment of tumors.

A secondary malignancy could be defined as a new cancer that has occurred as a result of previous treatment with radiation or chemotherapy. Depending on the schedule of treatment, the most common secondary cancers were skin cancer, breast cancer, acute leukemia, colorectal, lung and stomach cancer, the risk of second cancer developing have been 10% at 20 years and 26% at 30 years after the Hodgkin disease treatment, [14] and 3.8 % at 10 years versus 7% at 15 years for patients receiving a doxorubicin-based regimen for breast cancer [15].

Not only Genetic susceptibility, but also the carcinogenic effects of radio/chemotherapy have been largely proposed for the secondary malignancies development. First, it has known, that people with a cancer family would inherit genetic cancer susceptibility as a risk factor, and then moreover, patients whom have treated, and the survivors of earlier cancers with genetic susceptibility, all have an increased risk of multiple primary malignancies. In addition, the treatment used for the first malignancy has resulted in damage to specific regions of DNA with chromosome rearrangement or loss, responsible for tumorigenesis [16]. The new technologies available could analyze various genetic changes such as punctiform mutations, loss of heterozygosity or genetic instability. Microsatellite instability (MSI) has been noticed that occur more frequently in cases of multiple primary malignancies than in sporadic cancers [17]. The percentage of MSI tumors was similar in patients with synchronous or colorectal metachronous tumors. The mechanisms such as trigger microsatellite instability have differed in mentioned two categories.

Patients with Head and Neck Squamous Cell Cancer (HNSCC) have known for 36% cumulative life time risk of developing second primary malignancy over 20 years [18]. This has attributed to field carcinogenesis related to exposure to common risk factors like tobacco chewing, smoking and alcohol consumption [12, 18]. Also In our study head and neck cancers were the most common group to harbor of develops a new primary (10 of 33 cases). Among the head and neck cancer survivors, the cases whom have developed lung cancer were 50% (5 of 10 cases). As a part of preventive strategy, the patients particularly with HNSCC should be encouraged to stop use of alcohol and tobacco in any form, adopt healthy diet and exercise regularly. At present there is no evidence to recommend use of chemo preventive agents such as beta carotenoids and antioxidants in the prevention of second primary malignancies [19].

The possibility of multiple primary malignancies existence should always be considered during pretreatment evaluation. Screening procedures were especially useful for the early detection of associated tumors, preferably before clinical manifestations occurrence.

There were some evidences that screening would improve outcomes among patients who might develop second malignancies, although the data were limited. The optimal screening modalities and strategies for reducing mortality from second malignancies remained to be defined for most tumor sites [20].

The early diagnosis of secondary malignancies should not be neglected in patients treated for a primary malignancy, especially when the long clinical period before the diagnosis of subsequent tumors has been taken for management. With careful monitoring, secondary tumors could be detected earlier, and, with appropriate intervention, might be better managed, without compromising survival.

Our data could guide oncologists towards a closer follow-up strategy in the management of patients treated for common tumors.

Conclusion

In conclusion, second primary malignancy was not uncommon, could occur synchronously or metachronously. After the recently diagnostic and staging modalities as well as progress in the management of common cancer, the detection of second primary malignancy has increased. A strong clinical suspicion and thorough evaluation would pass a long road in the management of these tumors. Most of the operable synchronously occurring second primary malignancy could be resected in single stage. A regular follow up could detect most of the metachronous second primary malignancies at an early stage.

Acknowledgment

Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment & Research

Institute, Bikaner, Rajasthan, India has gratefully acknowledged.

Conflict of Interest

There were no conflicts of interest regarding this study.

Authors' Contribution

Puneet Kumar Bagri: Concept and design, acquisition of data, drafting the article, analysis and interpretation of data, critical revision of article.
All co-authors: Concept and design, analysis and interpretation of data, critical revision of article.

References

1. Vaslamatzis M, Alevizopoulos N, Petraki C, Vrionis E, Zoumblios C, Stassinopoulou P, et al. Second primary neoplasms (SPN) in cancer patients. Proc ASCO. 2003; 22:3581.

2. Morgenfeld EL, Tognelli GF, Deza E, Santillan D, Ares S, Morgenfeld E, et al. Synchronous and metachronous second (ST) and third (TT) primary tumors (PT) in a large patient population. Proc ASCO. 2003; 22:3152.

3. Hulikal N, Ray S, Thomas J, Fernandes DJ. Second primary malignant neoplasms: A clinicopathological analysis from a cancer centre in India. Asian Pac J Cancer Prev. 2012; 13(12):6087-91.

4. Irimie A, Achimas-Cadariu P, Burz C, Puscas E. Multiple primary malignancies- epidemiological analysis at a single tertiary institution. J Gastrointestin Liver Dis. 2010; 19(1):69-73.

5. Bugher JC. The probability of the chance occurrence of multiple malignant neoplasms. Am J Cancer. 1934; 21(4):2309-2824.

6. Agrawal R. Synchronous dual malignancy: successfully treated cases. J Cancer Res Ther. 2007; 3(3):153-6.

7. Gursel B, Meydan D, Ozbek N, Ozdemir O, Odabas E. Multiple primary malignant neoplasms from the black sea region of Turkey. J Int Med Res. 2011; 39(2):667-74.

8. Suzuki T, Takahashi H, Yao K, Inagi K, Nakayama M, Makoshi T, et al. Multiple primary malignancies in the head and neck: a clinical review of 121 patients. Acta Otolaryngol Suppl. 2002; (547):88-92.

9. Warren S, Gates O. Multiple primary malignant tumors: A survey of the literature and statistical study. Am J Cancer. 1932; 16:1358-414.

10. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms. II. Tumors of different tissues or organs. Cancer. 1961; 14:231-7.

11. Curtis RE, Freedman DM, Ron E, Ries LA, Hacker DG, Edwards BK, et al (eds). New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD, National Cancer Institute. 2006; 9-14.

12. Morris LGT, Sikora AG, Patel SG, Hayes RB, Ganly I. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. J Clin Oncol. 2011; 29(6):739-46.

13. Cheng HY, Chu CH, Chang WH, Hsu TC, Lin SC, Liu CC, et al. Clinical analysis of multiple primary malignancies in the digestive system: a hospital-based study. World J Gastroenterol. 2005; 11(27):4215-9.

14. Bhatia S, Yasui Y, Robison LL, Birch JM, Bogue MK, Diller L, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol. 2003; 21(23):4386-94.

15. Woodward WA, Strom EA, McNeese MD, Perkins GH, Outlaw EL, Hortobagyi GN, et al. Cardiovascular death and second non-breast cancer malignancy after postmastectomy radiation and doxorubicin-based chemotherapy. Int J Radiat Oncol Biol Phys. 2003; 57(2):327-35.

16. Escobar PA, Smith MT, Vasishta A, Hubbard AE, Zhang L. Leukaemia-specific chromosome damage detected by comet with fluorescence in situ hybridization (comet-FISH). Mutagenesis. 2007; 22(5):321-7.

17. Horii A, Han HJ, Shimada M, Yanagisawa A, Kato Y, Ohta H, et al. Frequent replication errors at microsatellite loci in tumors of patients with multiple primary cancers. Cancer Res. 1994; 54(13):3373-5.

18. Morris LG, Sikora AG, Hayes RB, Patel SG, Ganly I. Anatomic sites at elevated risk of second primary cancer after an index head and neck cancer. Cancer Causes Control. 2011; 22(5):671-9.

19. Khuri FR, Kim ES, Lee JJ, Winn RJ, Benner SE, Lippman SM, et al. The impact of smoking status, disease stage, and index tumor site on second primary tumor incidence and tumor recurrence in the head and neck retinoid chemoprevention trial. Cancer Epidemiol Biomarkers Prev. 2001; 10(8):823-9.

20. Vogel VG. Identifying and screening patients at risk of second cancers. Cancer Epidemiol Biomarkers Prev. 2006; 15(11):2027-32.