Pilot study on the occurrence of multiple cancers following cancer-related therapy at the University of Florida, Jacksonville (2011–2016)

Karan Seegobin,[1] Estela Staggs,[2] Robina Khawaja,[2] Satish Maharaj,[1] Shiva Gautam,[3] Carmen Smotherman,[3] Fauzia Rana[2]

[1]Internal Medicine Department, University of Florida College of Medicine, Jacksonville, Florida, USA
[2]Hematology and Oncology Department, University of Florida College of Medicine, Jacksonville, Florida, USA
[3]Center for Health Equity and Quality Research, University of Florida College of Medicine, Jacksonville, Florida, USA

Correspondence to
Dr Karan Seegobin, Internal Medicine Department, University of Florida College of Medicine, Jacksonville, Florida 32209, USA; karanseegobin@hotmail.com

The abstract was submitted to the ASCO Annual Meeting of 2018 for poster presentation, and presented as a poster presentation at the Florida ACP Internal Medicine Chapter in Florida 2018 and the 2018 AFMR Midwestern Regional Meeting.

Accepted 15 May 2018
Published Online First 6 June 2018

ABSTRACT

New primary cancers can occur in patients with a previous cancer. Among the risk factors, therapies such as chemotherapy, radiotherapy, and hormonal therapy have been associated with the development of neoplasms. Second cancers most commonly develop 5–10 years after the initial tumor. We observe the implications of cancer-related therapy in the development of a new tumor. We looked at 602 patients who had their first cancer diagnosed in 2011 and calculated the number of different primary cancers between 2011 and 2016 for each patient. Twenty-four patients had a second cancer within 5 years from the first diagnosis and there were no patients with a third cancer. There was no statically significant difference in the rates of second cancers after exposure to chemotherapy, radiotherapy, hormonal therapy, or any combination of these (p=0.738). Of the second cancers reported after 2011, renal, uterine, cervical, and lung cancers were the most frequently reported. Additionally, there was no statically significant difference among the rates of second cancers in men versus women (p=0.467), as well as among whites versus blacks (p=0.318). We conclude that while new primaries can occur after one cancer, there was no increased risk after exposure to different cancer-related therapies. With increased focus on the primary disease, there is a higher likelihood of missing another primary lesion. This is important as the practical implications of managing multiple primaries are rarely discussed.

Significance of this study

What is already known about this subject?
- New primary cancers can occur in patients with a previous cancer.
- Chemotherapy, radiotherapy, and hormonal therapy have been associated with the development of neoplasms.
- New primaries are most common 5–10 years after diagnosis of the first.

What are the new findings?
- New primary tumors can occur within 5 years after treatment of one cancer.
- There is no significant difference in the rates of second cancers after treatment with chemotherapy, radiotherapy, hormonal therapy, or any combination of these.
- There is no significant difference among the rates of second cancers in men versus women, and whites versus blacks.
- Breast, head and neck, and colon were the most common initial cancers that were associated with the development of a second tumor.

How might these results change the focus of research or clinical practice?
- There should be heightened awareness in uncovering new cancers after 5 years of diagnosing the initial one.
- There should be additional investigation into other factors (mutations, smoking, type and dose of chemotherapy, dose of radiotherapy, hormonal therapy) that contribute to the development of second cancers.
- There should be increased physician education about the patterns of development of second cancers.

INTRODUCTION

Patients with cancer are now living longer due to advancements in therapy.[1] As a result the number of patients developing new primary tumors will increase.[1] In this study we observe the occurrence of multiple cancers among patients with previous chemotherapy, radiotherapy, and hormonal therapy. Having one cancer increases the risk of another tumor.[1] The risk factors include smoking, genetic mutations, chemotherapy, radiotherapy, hormonal therapy and alcohol.[1 2] While use of these cancer-related therapies has improved patients' outcomes, based on prior reports it comes at a cost, as they have been linked with the development of new cancers.[2 3] Second cancers most commonly develop 5–10 years after the initial tumor. We investigate whether there is any increased risk of a second cancer among these cancer-related therapies (chemotherapy, radiotherapy, or hormonal therapy). If any of these therapies confers an increased risk, it may affect our present cancer screening strategies in this

To cite: Seegobin K, Staggs E, Khawaja R, *et al*. *J Investig Med* 2018;**66**:1050–1054.

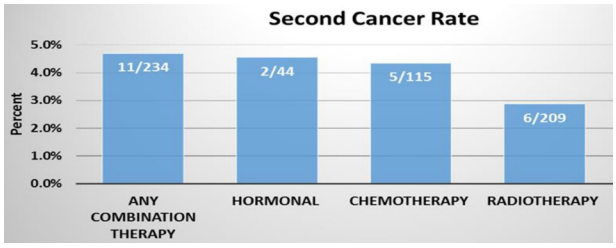

Figure 1 Second cancer rate after therapy.

population. Furthermore, understanding who is at risk will better allocate resources for this subgroup to improve outcomes and guide further research.

MATERIALS AND METHODS

The 5-cancer database, i2b2 system and Epic software were accessed to acquire data on all patients diagnosed with cancer in 2011. We looked at 602 patients who had their first cancer diagnosed in 2011 and calculated the number of different primary cancers between 2011 and 2016 for each patient. Treatment with chemotherapy, radiotherapy, hormonal therapy, or any combination therapy was also recorded for each case. For this study, any combination therapy included chemotherapy and hormonal therapy, chemotherapy and radiotherapy, radiotherapy and hormonal therapy, or all three therapies. Patients with a diagnosis of cancer prior to 2011 were excluded from the study. Additionally, those who did not follow up at our institution after 2011 and those who pursued hospice care were also excluded. Patients who died during the study period without a diagnosis of a second cancer were excluded. A time period from 2011 to 2016 was chosen to limit the sample size with a documented treatment patterns at the 5-year mark, thereby improving the significance of the study.

For this study, new cancers were defined as any tumor of a dissimilar histology type from the first, occurring at any site.[1] Metastasis of the same cancer was not considered as the development of a second type of tumor.[1] Patients without exposure to any of these therapies, as well as those who did not follow up at our institution, were excluded from analysis.

Cancers were classified based on the following sites: oral cavity and pharynx, esophagus, stomach, small intestine, colon, rectum, anus/anal canal/anorectum, liver and intrahepatic bile duct, gall bladder, other biliary, pancreas, retroperitoneum, peritoneum/omentum/mesentery, other digestive organs, nose/nasal cavity, larynx, lung, pleura, trachea, mediastinum, bones and joints, heart, melanoma of the skin, other non-epithelial skin, breast, female genital system, prostate, testis, penis, other male genital organs, urinary bladder, kidney, ureter, other urinary organs, eye and orbit, brain and other nervous system, thyroid, other endocrine including thymus, hematologic cancers, Kaposi sarcoma, and miscellaneous.[1] This classification system was adopted from a prior study on multiple tumors for consistency when comparing our results with prior studies.[1]

RESULTS

Six hundred and two patients had either radiotherapy, chemotherapy, hormonal therapy, or a combination of these.

Of this 602, 24 (4.0%) patients had a second cancer within 5 years from the first diagnosis and there were no patients with a third cancer. The rates of second cancers (figure 1) are as follows: patients with chemotherapy alone 4.4%, radiotherapy alone 2.9%, hormonal therapy alone 4.6%, and those with any combination therapy 4.7% (p=0.738).

Of the second cancers reported after 2011 (figure 2), lung (3, 12.5%), uterine/cervical (3, 12.5%) and renal (3, 12.5%) cancers were the most frequently reported. Breast, head and neck, and colon were the most common initial cancers that were associated with the development of a second tumor (figure 3). Thyroid and endometrial cancers

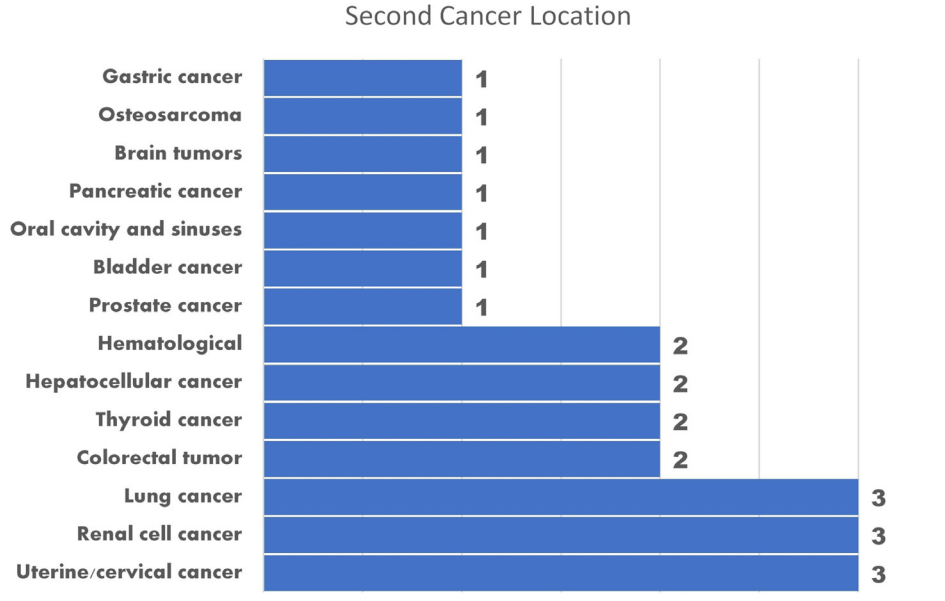

Figure 2 Distribution of second cancer location.

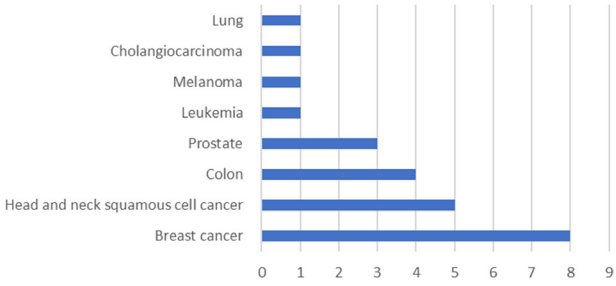

Figure 3 Frequency of initial cancers for those patients with second cancers.

were the most common second tumors in patients with prior breast cancer, while renal and hepatocellular cancers were the most common second tumors after colon and head and neck cancers, respectively (figure 4).

The rates of second cancers in men versus women were 5% and 7%, respectively (p=0.47), and the rates in whites versus blacks were 5% and 6%, respectively (p=0.32). The demographics of these 24 patients, the types of initial cancer diagnosis, treatment of each cancer (hormonal, chemotherapy, surgery, radiation), elapsed time to second cancer diagnosis and the type of cancer diagnosis are further highlighted in table 1.

DISCUSSION

Multiple primary cancers are not common and are usually defined as primary malignant tumors of different histologic origins in one person.[4] They were first described by Billroth in 1889.[5] More cancers are being frequently reported at present due to advancement in technology, prolonged life span, and longer survival.[4] In 2014, 14.5 million people with a history of cancer were alive in the USA.[6] Our study supports other reported data that new primary cancers can occur within 5 years after being diagnosed with cancer.[4] With increased focus on the primary disease, there is a higher likelihood of missing incidental coexistence of another primary malignant lesion.[4] In light of this, the importance of screening procedures should be emphasized for early detection before the appearance of clinical symptoms.[4] This topic is of increasing importance as the practical implications of managing patients with multiple primaries are rarely discussed.[6]

Cancer therapies such as chemotherapy, hormonal therapy, and radiation therapy have been implicated in the development of neoplasms.[4] Other factors include family history, prolonged exposure to carcinogens, field cancerization, and immunologic and genetic defects.[4] Our study however did not reveal an increased risk of cancer with exposure among the different therapies (chemotherapy, radiotherapy and hormonal therapy).

Compared with the overall population, patients with cancer are at about a 10% risk of developing another cancer in any site.[5] Location has a role, with most new primary malignant neoplasms arising in the respiratory and gastrointestinal systems (table 2).[5] Other reports indicate the breast followed by cervix were the most common sites for second tumors (table 2).[4] Our study showed similar results, with lung cancer being one of the most common second cancers reported.

We looked at the significant relationships between the first and second cancers in our study.

Second cancers after breast cancer

Gastrointestinal, lung, breast and cervical cancers were among those listed as the most common second tumors following initial breast cancers (table 2). Our study, on the other hand, showed that thyroid and endometrial cancers were the most common after breast cancer (figure 4). The occurrence of thyroid cancer can be related to radiotherapy used in the treatment of breast cancer.[6] Both patients who

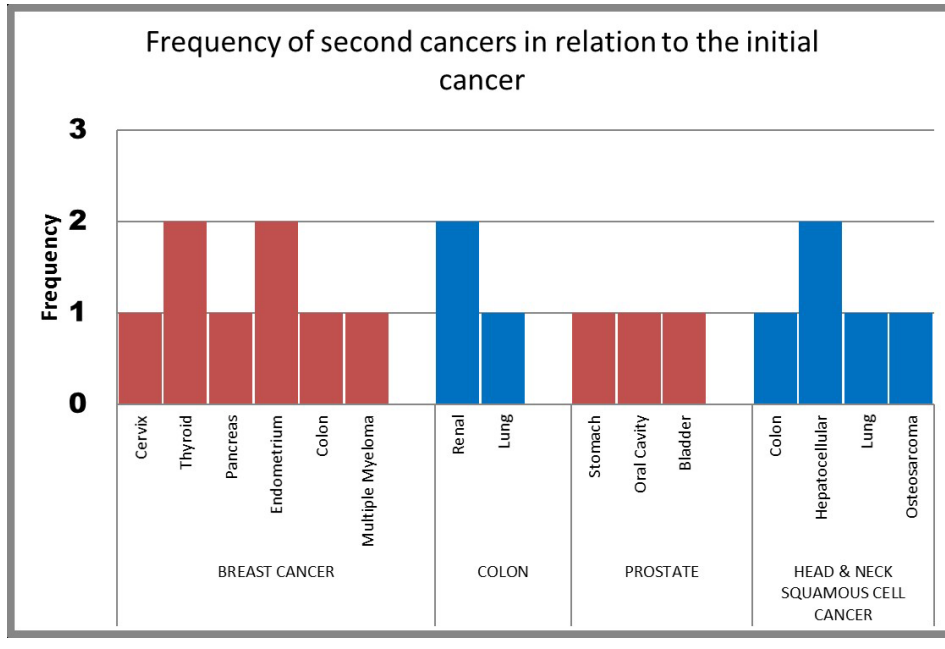

Figure 4 Frequency of second cancers in relation to the initial cancer.

Table 1 Characteristics of patients with multiple cancers

Patient	Age	Gender	Ethnicity	Type of initial cancer	Treatment	Elapsed time to second cancer diagnosis	Type of second cancer diagnosis
1	81	Female	White	Invasive duct and lobular carcinoma breast cancer	Radiotherapy and surgery	54 months	Squamous cell cancer of the cervix
2	56	Female	White	Invasive ductal breast cancer	Chemotherapy, radiotherapy, hormonal therapy, and surgery	5 months	Papillary thyroid cancer
3	57	Female	Black	Colon adenocarcinoma	Chemotherapy and surgery	21 months	Papillary renal cell cancer
4	75	Male	White	Squamous cell cancer of the pharynx	Radiotherapy and surgery	29 months	Adenocarcinoma of the colon
5	65	Female	Black	Squamous cell cancer of the tongue	Chemotherapy, radiotherapy, and surgery	18 months	Hepatocellular cancer
6	60	Male	Black	Chronic myeloid leukemia	Chemotherapy	45 months	Renal cell cancer
7	73	Male	White	Adenocarcinoma of the prostate	Radiotherapy	1 month	Squamous cell cancer of the soft palate
8	82	Male	Black	Prostate adenocarcinoma	Hormonal therapy	3 months	Adenocarcinoma of the stomach
9	77	Female	Black	Squamous cell cancer of the maxillary sinus	Chemotherapy, radiotherapy, and surgery	32 months	Hepatocellular cancer
10	89	Female	Black	Invasive ductal breast cancer	Radiotherapy, hormonal and surgery	47 months	Adenocarcinoma of the pancreas
11	70	Female	White	Invasive ductal breast cancer	Chemotherapy, radiotherapy, hormonal and surgery	9 months	Endometrial cancer
12	67	Male	White	Melanoma of the skin	Chemotherapy	1 month	Adenocarcinoma of the prostate
13	68	Female	Black	Invasive ductal breast cancer	Hormonal and surgery	5 months	Endometrial cancer
14	77	Male	White	Adenocarcinoma of the colon	Chemotherapy	6 months	Small cell cancer of the lung
15	77	Male	White	Squamous cell cancer of the larynx	Chemotherapy and radiotherapy	17 months	Squamous cell cancer of the lung
16	49	Female	White	Invasive ductal breast cancer	Chemotherapy, radiotherapy, hormonal and surgery	5 months	Papillary cancer of the thyroid
17	50	Female	Black	Adenocarcinoma of the colon	Chemotherapy and surgery	21 months	Renal cell cancer
18	75	Male	Black	Cholangiocarcinoma	Chemotherapy and radiotherapy	1 month	Multiple myeloma
21	60	Female	White	Invasive ductal breast cancer	Chemotherapy, radiotherapy, hormonal and surgery	5 months	Adenocarcinoma of the colon
20	46	Male	White	Squamous cell cancer of the larynx	Radiotherapy and surgery	14 months	Osteosarcoma of the knee
21	73	Male	White	Adenocarcinoma of the prostate	Radiotherapy	2 months	Transitional cell cancer of the bladder
22	58	Female	White	Invasive ductal breast cancer	Chemotherapy, radiotherapy, hormonal and surgery	14 months	Multiple myeloma
23	50	Male	White	Squamous cell cancer of the lung	Chemotherapy and radiotherapy	32 months	Small cell cancer of the lung
24	66	Male	White	Adenocarcinoma of the prostate	Radiotherapy	28 months	Rhabdoid meningioma of the brain

Table 2 Second cancer occurrence after the initial cancer

Reference	Patients studied (n)	Second cancers (n)	Time frame of study	Types of initial cancer diagnosis	Most common second cancer in descending order of frequency
Buiatti *et al*[9]	4275	75	Mean 2.5 person-years	Colon	Stomach, lung, rectum
Buiatti *et al*[9]	4275	75	Mean 2.5 person-years	Breast	Colon, rectum, stomach
Coyte *et al*[10]	56,564	2137	5 years	Colorectal	Lung, colon prostate
Coyte *et al*[10]	56,564	2137	5 years	Breast	Breast, lung, colon
Coyte *et al*[10]	56,564	2137	5 years	Prostate	Lung, colon
Coyte *et al*[10]	56,564	2137	5 years	Head and neck	Lung, head and neck, esophagus
Gaskin *et al*[11]	1953	42	10 years	Breast	Breast, cervical
Gaskin *et al*[11]	1953	42	10 years	Colon	Colon

developed thyroid cancer after initial breast cancer in our study were treated with radiotherapy (table 1). Treatment with tamoxifen increases the risk of developing endometrial, gastric, colon and ovarian cancers.[5 6] In our study both patients who developed endometrial cancer were also treated with tamoxifen.

Second cancers after colon cancer

Our study reported renal cancer among the most common second cancers after colon cancer. While renal cancer is not the most common second tumors that can occur after colon cancer,[7] previous research has reported that there may be an association between these two cancers.[8] One possible mechanism for this is due to the hereditary non-polyposis colorectal cancer mutation.[8] This mutation was not documented in the medical records of our patients with colorectal cancer; further research is needed on the association between these two entities.

Second cancers after head and neck tumors

While head and neck, lung and esophagus tumors are reportedly common after initial head and neck primaries (table 2), our study reported two cases of hepatocellular cancer occurring after. From our literature review using the search terms 'second tumors' and 'head and neck tumors' on PubMed and Google, we have not found any reports of hepatocellular cancer occurring after head and neck tumors. While smoking and alcohol are linked with both head and neck tumors, and hepatocellular cancers, further research is needed to look at other contributing factors.

CONCLUSIONS

New cancers can develop after treatment of one cancer. There was no significant difference in the rates of second cancers after treatment with chemotherapy, radiotherapy, hormonal therapy, or combination of these at a 5-year mark. Further research may be able to identify other factors contributing to the occurrence of additional primary cancers.

Contributors KS, ES, RK, SM, SG, CS, and FR all equally participated in the drafting of the protocol, collection of data, literature search and writing of the manuscript. KS and FR both revised the final written manuscript.

Funding This study was awarded the Resident's Dean's Grant from the University of Florida College of Medicine, Jacksonville. Funds from this grant was used only for attending conferences and covering the publication fee of the study.

Competing interests None declared.

Patient consent Not required.

Ethics approval University of Florida College of Medicine, Jacksonville, IRB committee.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Mariotto AB, Rowland JH, Ries LA, *et al*. Multiple cancer prevalence: a growing challenge in long-term survivorship. *Cancer Epidemiol Biomarkers Prev* 2007;16:566–71.
2 Aidan JC, Priddee NR, McAleer JJ. Chemotherapy causes cancer! A case report of therapy related acute myeloid leukaemia in early stage breast cancer. *Ulster Med J* 2013;82:97–9.
3 Boice JD, Day NE, Andersen A, *et al*. Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. *J Natl Cancer Inst* 1985;74:1307–75.
4 Jena A, Patnayak R, Lakshmi AY, *et al*. Multiple primary cancers: An enigma. *South Asian J Cancer* 2016;5:29–32.
5 Cercato MC, Colella E, Ferraresi V, *et al*. Report of two cases of quintuple primary malignancies and review of the literature. *Anticancer Res* 2008;28:2953–8.
6 Vogt A, Schmid S, Heinimann K, *et al*. Multiple primary tumours: challenges and approaches, a review. *ESMO Open* 2017;2:e000172.
7 Evans HS, Møller H, Robinson D, *et al*. The risk of subsequent primary cancers after colorectal cancer in southeast England. *Gut* 2002;50:647–52.
8 Calderwood AH, Huo D, Rubin DT. Association between colorectal cancer and urologic cancers. *Arch Intern Med* 2008;168:1003–9.
9 Buiatti E, Crocetti E, Acciai S, *et al*. Incidence of second primary cancers in three Italian population-based cancer registries. *Eur J Cancer* 1997;33:1829–34.
10 Coyte A, Morrison DS, McLoone P. Second primary cancer risk - the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. *BMC Cancer* 2014;14:272.
11 Gaskin HS, Hardy RE, Fletcher RL. Multiple primary malignancies in black patients. *J Natl Med Assoc* 1981;73:1065–8.