Introduction

Multiple-primary cancers are defined as primary malignant tumours of different histological origins in a single patient. Recently, there has been an increase in the number of patients diagnosed with multiple-primary cancers; attributed to improved diagnostic techniques and prolonged life span of patients with malignancy. Now we are aware that most multiple primary cancers are double primary cancers [1-2-3].

The incidence of Multiple-Primary Malignancies has been common among cancer patients [4]. One of the earliest statistical analyses of Double-Primary Malignancies was carried out by Bugher in 1934, he derived an equation for the probability of death from cancer during a specified period of age with a coincidental Second Malignancy [5]. According to the definition used, the overall reported frequency of Multiple-Primary Cancers ranges from 2% to 7% [6].

The criteria used for the diagnosis of Double-Primary
malignancies has been primarily given by Warren and Gates [7]. While, the two most commonly used definitions were provided by the SEER Program (Surveillance, Epidemiology, and End Results) and the IACR/IARC (International Association of Cancer Registries and International Agency for Research on Cancer) [8]. The SEER database considers single tumours at different sites in the same organ (e.g., colon) as multiple sites. The IACR/IARC rules are more limited; only one tumour is recorded for an organ, regardless of time, unless there are histologic differences. Additionally, The SEER database advocates the use of a 2-month period to distinguish between Synchronous and Metachronous Multiple-Primaries, whereas IARC recommends a 6-month period [9-10]. The theory regarding the origin of the majority of Multiple-Primary cancers is that they arise due to random chance, but different mechanisms have been suggested to be involved in Multiple-Primary Cancers, such as the family history, immunologic, genetic defects, exposure to carcinogens, radiation, chemotherapy, and field cancerization [11]. Germline mutations in mismatch repair genes can produce susceptibility to cancers of the colorectum, ovary, stomach, small bowel, upper uroepithelial tract, hepatobiliary tract, and brain. Li-Fraumeni syndrome (LFS), an autosomal- dominant disorder, features the occurrence of breast cancer in young women and of soft tissue sarcomas, osteosarcomas, brain tumours, acute leukaemia, and adrenocortical tumours in children and young adults [12]. Germline mutations in the p53 tumour suppressor gene (also known as TP53) have been identified in approximately one-half of LFS families in the literature [13] and cigarette smoking that affects the risk of several cancer types. All the information about double malignancy came from case reports with very few centers reporting their experience and none from our region. We needed to collect our experience in treating those cases. Collecting information will aid us in expecting the impact of prior therapies and teach us how to best treat them. This is a retrospective study with a single medical facility’s experience with Multiple-Primary cancer cases. This study aims to report cases of Double-Primary Malignancy in our society and see if we have a special predilection of certain Double-Primary cancers based on different geographic and environmental risk factors.

Materials and Methods

This was a retrospective observational study carried out at King Abdullah Medical City, Makka, Saudi Arabia, from January 2012 to December 2019. All Patients with malignant tumors of different histological origins were defined as histologically confirmed Multiple-Primary Malignancy cases. Patients were identified through a retrospective review of medical records excluding patients with insufficient histopathological data. The data collected were the patients’ characteristics, pathological data, and outcome information. Moreover, this research protocol was approved by the Institutional Review Board Committee. Since the study performed is retrospective, we obtained a waiver of informed consent from IRB.

Results

We collected 53 cases of Multiple-Primary malignancies 26 were synchronous (48%) and 27 were metachronous (52%). Out of 53 patients, 29 (60%) were females and 14 (40%) were males. The most common sites for synchronous, Table 1, are breast and endometrial cancer. Metastasis at diagnosis was present in 7 patients (23%). The median age of diagnosis for synchronous tumours was 61 years (range: 27 to 83 years), 4 patients were male (26%). CT scan for staging workup resulted in the detection of a second tumour in 21 patients 5 patients of which was diagnosed during pathological examination. Curative treatment could be offered in 19 patients (73%). For metachronous tumours, Table 2, the median age of diagnosis for the second primary neoplasm was 54years (range: 34 to 82years) 3 patients of which where male. The median interval of six years was observed, the most common sites of a primary tumour were breast, the most common second malignancy was colorectal cancer and Metastasis at diagnosis were present in 7 patients (25%). Curative treatment could be offered in 15 patients (53%).

Discussion

Multiple primaries [14] are more than one tumour arising in different sites and or of different histology either synchronous or metachronous depends on the duration between them, 2-month according to SEER data [15] and 6 months according to IARC. In our study, we used the definition of IARC. The burden of multiple tumours is expected to increase due to the use of accurate imaging techniques. In a single facility in Saudi Arabia, we collected 54 cases over 7 years. Multiple-Primary did not always signify a bad prognosis as we treated all non-metastatic cases with curative intent. It is most imperative to diagnose it early before the patient reaches the metastatic stage. This means that we should have a high degree of suspicion. The role of the radiologist is crucial as usually, radiologists are first to flag for suspicion of multiple tumours. In our study, most of the synchronous tumours were detected initially by CT scan then confirmed pathologically. Examples from our study as CT scan done for a patient with ovarian cancer showed a breast mass or CT scan showed a speculated lung lesion in a patient with breast cancer or showed renal mass in a patient with nasopharyngeal cancer. The response to therapy is always an alarm for the physician to review his pathology by repeating the biopsy of the metastatic disease. In our study a patient with breast cancer who developed lung nodules treated with chemotherapy as. Metastatic breast then the poor response to chemotherapy urged us to biopsy the largest metastatic nodule and to our surprise came to be second primary.
| Age At diagnosis | sex | Primary                          | Secondary                          | Detected by | Treatment                                      | Metastasis at presentation | State of last follow up | Outcome /duration from diagnosis to death |
|------------------|-----|----------------------------------|------------------------------------|-------------|-----------------------------------------------|----------------------------|--------------------------|-------------------------------------------|
| 79               | F   | Stage II breast cancer           | Stage IV ovarian cancers           | CT scan     | Mastectomy and chemotherapy                    | yes                        | dead                     | Refused surgery for the ovary then received paclitaxel weekly then palliative care |
| 68               | F   | Right breast IDC 11/2017         | Stage IIIC high grade serous cancer | CT scan     | TAH & BSO Omentectomy. Adjuvant Carboplatin/ Paclitaxel | No                         | Alive                    | Under follow up                           |
| 61               | F   | Right breast IDC stage IIIB      | Stage IIA colon cancer             | CT scan     | BCS ALND Chemotherapy FEC/ Docetaxel Sigmoidectomy letrozole | No                         | free                     | Under follow up                           |
| 44               | F   | Right breast cancer IDC          | Appendicular mucinous adenocarcinoma stage IV | CT scan     | MRM Tamoxifen                                  | yes                        | dead                     | 5 months                                  |
| 52               | F   | Left breast stage IIIA IDC       | Stage IA endometrioid adenocarcinoma of the uterus | CT scan     | TAH & BSO omentectomy PLND Left MRM Chemotherapy FEC/docetaxel Radiotherapy Letrozole | No                         | free                     | Positive family history of ovarian cancer BRCA mutation positive Under follow-up |
| 63               | F   | Breast IDC                       | Endometrial endometrioid adenocarcinoma | CT scan     | Neoadjuvant with dual anti-HER 2 therapy. Followed by surgery for both | No                         | Alive                    | The patient currently under adjuvant therapy |
| 63               | F   | Triple negative left breast IDC   | Hormone receptor positive right breast cancer | Path exam   | Neoadjuvant AC/ docetaxel Bilateral MRM         | No                         | Alive                    | Currently under adjuvant hormonal therapy |
| 65               | F   | Right breast IDC                 | Stage IV Rectal adenocarcinoma     | CT scan     | Right MRM Chemotherapy for rectal cancer       | yes / Yes liver            |                          | Still under chemotherapy                  |
| 75               | F   | Stage IVB endometrioid adenocarcinoma | Stage I mucinous carcinoma of the breast | CT scan     | Carboplatin paclitaxel. But Refused surgery    | yes                        | Dead                     | Refused surgery for the endometrium after very good response to chemotherapy |
| 49               | F   | Stage IA endometrial endometrioid adenocarcinoma | Stage IA mucinous borderline tumour | Path exam   | TAH & BSO infracolic omentectomy                | No                         | free                     | Under follow up                           |
| 36               | F   | Stage IA endometrial adenocarcinoma | Papillary thyroid cancer          | CT scan     | TAH & BSO Total thyroidectomy                   | No                         | free                     | Under follow up                           |
| 64*              | F   | Stage IA endometrial endometrioid adenocarcinoma NSCLC stage T1bN0 | Cancer rectum                    | CT scan     | TAH & BSO Omentectomy + Cholecystectomy Right lung lobectomy and hilar lymph node excision LAR | No                         | free                     | Under follow up                           |
| 56               | F   | Stage I Uterine leiomyosarcoma    | Stage IA Ovarian endometrioid borderline tumour | Path exam   | TAH & BSO Omentectomy 7/2018                   | No                         | alive                    | Under follow up                           |
| 72               | F   | Stage IA carcinosarcoma of the uterus | Stage I mucinous carcinoma of the breast | CT scan     | TAH & BSO Followed by Adjuvant carboplatin/paclitaxel, Radiotherapy External pelvic Right MRM Adjuvant Letrozole | No                         | free                     | Relapsed 6 years later with metastatic carcinosarcoma shifted to palliative care after two cycles of chemotherapy |
Lung Cancer.
Cancer patients who survive their primary tumour always have a high risk to develop a second primary and this is due to many reasons like genetic predisposition as one of our patients who has Double Synchronous Primary Breast Cancer and Endometrial Cancer gave a strong family history of ovarian cancer and her BRCA genetic testing came to be positive.
Cancer treatment is carcinogenic. We are reporting leukaemia in ovarian cancer patients treated with chemotherapy, breast cancer patients treated for DLBCL, and breast and thyroid cancer in Hodgkin’s lymphoma patients treated at a young age.

| Age At diagnosis | Sex | Primary Diagnosis | Secondary Diagnosis | Detected by | Treatment | Metastasis at presentation | State of last follow up | Outcome /duration from diagnosis to death |
|------------------|-----|-------------------|---------------------|-------------|-----------|---------------------------|-------------------------|------------------------------------------|
| 27               | F   | Left foot leiomyosarcoma | CT scan | Surgery for both | No free | Under follow up |
| 39               | F   | Low grade brain glioma large infiltrative mass | CT scan | Bilateral V/P shunt | No | dead | 21 months |
| 78               | M   | Stage IV nasopharyngeal cancer undifferentiated | Hepatocellular carcinoma Cirrhosis, LCF | CT scan | Radiotherapy incomplete course | yes | dead | 6 months |
| 47               | F   | Colon cancer high grade adenocarcinoma | Hodgkin’s disease classical type stage IV | CT scan | ABVD | yes | dead | 9 months |
| 83               | M   | Rectal moderately differentiated cancer | Metastatic Prostate cancer GS4+4 | CT scan | Goserelin / bicalutamide | yes | dead | 8 months |
| 69               | M   | Sigmoid adenocarcinoma T2N1 | stageIIB Lung adenocarcinoma Lung carcinoid tumour low grade | CT scan | Surgery for both then adjuvant chemotherapy for lung carboplatin/ pemetrexed | no | Alive | Under follow up |
| 60               | F   | Gastric adenocarcinoma T4N3M0 | Lung mucinous adenocarcinoma | CT scan | Neoadjuvant chemotherapy ECF for gastric cancer, Gastrectomy then Lung lobectomy | N0 | Dead | 13 months |
| 78               | M   | Prostate cancer undifferentiated Sarcoma left femur | CT scan | Orchiectomy radiotherapy | no | Alive | Lost follow up |
| 59               | M   | Renal cell carcinoma | Metastatic nasopharyngeal cancer | CT scan | Target therapy plus chemotherapy | yes | Alive | localized RCC refused surgery received pazopanib changed to sunitinib metastatic NPC received gemcitabine 10 cycles then start 2nd line docetaxel |
| 68               | F   | Stage I gastric leiomyosarcoma | Stage I ovarian serous cancer | CT scan | Partial gastrectomy, ovarian cystectomy then Neoadjuvant carboplatin/paclitaxel then debulking surgery | no | free | Under follow up |
| 34               | F   | stage IA high grade ovarian mucinous cancer | Stage IA endometrioid adenocarcinoma | Path exam | TAH&BSO and omentectomy. Chemotherapy carboplatin/paclitaxel | no | free | Under follow up |
| 45               | F   | Stage IC mucinous ovarian cancer | Stage IB endometrioid adenocarcinoma | Path exam | TAH&BSO and omentectomy. Chemotherapy carboplatin/paclitaxel Followed by radiotherapy | no | free | Under follow up |
For patients with breast cancer, the incidence of second primaries studied and has been reported to range from 4.1% to 16.4% [15-16]. An excess risk of endometrial cancer is reported with the use of Tamoxifen [17]. Genetic factors as BRCA1 BRCA2 mutations are well-known risk factors for Multiple-Primary [18]. In this study, we reported 7 cases of the Synchronous Second-Primary with breast cancer, 3 cases with ovarian cancer. Also, we reported endometrial cancer in patients with hormone receptor-positive breast cancer with BRCA mutation. AML can be triggered during the first 2 years after radiation therapy and it is also a late effect of chemotherapy. For metachronous tumour in patients with breast cancer, We reported two cases of AML which may be chemotherapy related.

Patients with prostate cancer who received external beam radiotherapy are at increased risk of bladder cancer, rectal cancer and sarcomas within the radiation field after being disease-free for at least 5 years [19]. Second primaries can also occur in patients with prostate cancer owing to genetic factors, especially BRCA mutation [20]. In our study, we reported prostate cancer, rectal cancer, and prostate cancer and sarcoma synchronously.

The most important cause of mortality in Hodgkin’s lymphoma is a Second-Primary cancer [21]. We reported a case of colon cancer synchronously with Hodgkin’s lymphoma and thyroid cancer. Also, breast cancer that occurred 12 years after ABVD for Hodgkin’s lymphoma.

Smoking is an important risk factor not only for lung cancer but also for a Second-Primary Cancer. A 7.9% of lung cancer cases who acquire a second primary have

| Age | Sex | Primary | Treatment | Secondary | Treatment | Metastasis at presentation | Interval between primary and secondary | Recurrence |
|-----|-----|---------|-----------|-----------|-----------|---------------------------|----------------------------------------|------------|
| 53  | F   | Stage I Breast IDC | Surgery hormonal letrozole | Stage II Colon cancer | Surgery, FOLFOX | No | 7 y |          |
| 50  | F   | Stage III Breast IDC | Neoadjuvant chemotherapy EC/T Surgery, radiotherapy | Colon cancer T4N1M0 | SURGERGY | Capectabine / Oxaliplatin | NO | 14 Y | Colon cancer recurrence and received chemotherapy HIPEC and on chemotherapy |
| 64  | F   | Stage II triple negative breast IDC | Surgery chemotherapy radiotherapy | Stage IV pancreatic cancer | Palliative care | yes | 6 y | Died after 3 months |
| 39  | F   | Breast IDC stage II | Surgery FAC Tamoxifen | Endometrium | Surgery radiotherapy | no | 11 y |          |
| 44  | F   | Stage II breast IDC | Surgery TEC radiotherapy Tam /letrozole | Stage III Uterine carcinosarcoma | surgery carbo/paclitaxel | | 6 y |          |
| 42  | F   | STAGE IIA BREAST IDC | RT MRM TEC radiotherapy Tamoxifen | APL M5 | ATRA | no | 2 y | In CR Under follow up on Tamoxifen |
| 35  | F   | Stage II breast IDC | Surgery FEC/ Docetaxel Radiotherapy tamoxifen | AML | FLAG then IDC. | no | 5 y | In CR Under FU |
| 51  | F   | Stage IIIA Breast cancer IDC Her2neu positive disease | Surgery chemotherapy Radiotherapy | Lung squamous cell lung cancer | Chemotherapy | no | 2 y | Still under chemotherapy |
| 47  | F   | ER+ breast cancer | Surgery and adjuvant chemo. Hormonal and radiotherapy | Stage IIA triple negative breast cancer | Surgery and chemotherapy | Yes | 8 y | Under follow up |

45 F Papillary thyroid cancer | Surgery total thyroidectomy, radioactive iodine | Stage III Follicular lymphoma | FCR | 3 y | Under follow up |

41 F Papillary Thyroid Cancer | Surgery radiotherapy | Stage IC Ovarian serous cancer | Debulking surgery Adjuvant chemotherapy | no | 9 y | dead |

72 M Papillary Thyroid cancer | Thyroid surgery and ablation on replacement | Stage IV NSCLC | Chemotherapy and palliative radiotherapy | yes | 20 y | dead |

59 F CML chronic phase | TKI Imatinib, desatinib | Colon cancer | Chemotherapy, Radiotherapy | 9 y | Dead |
| Age | Sex | Primary Tumour | Treatment at Presentation | Secondary Tumour | Treatment | Metastasis at Presentation | Interval between primary and secondary | Recurrence |
|-----|-----|----------------|---------------------------|------------------|-----------|---------------------------|------------------------------------------|------------|
| 35  | F   | CML            | TKI                       | Tracheal adenocarcinoma | Surgery radiotherapy | no | 15 y | In MMR Under follow up |
| 70  | F   | Colon cancer   | Surgery, XELOX            | Breast            | Docetaxel trastuzumab | yes | 5 y | dead |
| 68* | F   | Stage II adenocarcinoma Colon cancer | Surgery radiotherapy chemotherapy | CML Then developed thyroid cancer | TKI Chemotherapy for colon | No | 2 y | dead |
| 80  | F   | HCC            | HA Chemoembolization      | Breast cancer stage IV liver bone Mets | Trastuzumab Hormonal treatment | yes | 2y | dead |
| 70  | F   | Stage IV adenocarcinoma of the gall bladder | Surgery then gemcitabine | Stage colon cancer | Surgery chemotherapy FOLFOX / bevacizumab | yes | 1y | dead |
| 66  | F   | Stage endometrial endometrioid adenocarcinoma | Surgery | Breast DCIS | Surgery Tamoxifen | No | 3 y | free |
| 41  | F   | Stage II granulosa cell tumour of the ovary | Surgery chemotherapy VAC | Stage IV Carcinoid tumour of the pancreas | octreotide | yes | 10 y | Under octreotide |
| 82  | F   | Stage IA endometrial endometrioid adenocarcinoma | Surgery | Stage I breast IDC | Hormonal and radiotherapy | no | 1 y | free |
| 65  | F   | Stage IIIc serous ovarian cancer | Neoadjuvant chemotherapy carboplatin / paclitaxel Interval debuing Adjuvant chemotherapy | Stage IV high grade neuroendocrine tumour | Refused chemotherapy | No | 1y | dead |
| 59  | M   | Cancer larynx T1N0M0 | Radical Radiotherapy | Stage IV gastric cancer | Palliative chemotherapy and radiotherapy | Yes, liver Mets | 2 y | dead |
| 64  | M   | DLBCL stage IV B | Chemotherapy | Stage IIIIB Mesothelioma | Chemotherapy | No | 4 y | Under Chemotherapy |
| 34* | F   | Stage III B Hodgkin’s lymphoma | ABVD | Papillary thyroid cancer And left breast cancer | Surgery radioactive iodine | No | 12 y | Under follow up |
| 55* | F   | Stage IIA DLBCL | Chemotherapy and radiotherapy | Breast cancer stage and follicular lymphoma stage IA | Lymphectomy and ALND Chemotherapy Hormonal therapy for the breast Radiotherapy for FL | No | 2y | Under follow up |
| 54  | F   | Stage IIA NHL follicular GII | Rituximab for 4 weeks and then maintenance | Hodgkin’s lymphoma in axillary lymph node | AVD | No | 2 y | Under follow up |

*Triple malignancies; IDC, Invasive ductal carcinoma; DLBCL, diffuse large b cell lymphoma; TAH BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; BCS ALND, breast conserving surgery and axillary lymph node dissection; MRM, modified radical mastectomy NSCLC, non-small cell lung cancer; ABVD, Adriamycin, bleomycin vinblastine dacarbazine; AML, Acute myeloid leukaemia; APL, Acute promyelocytic leukaemia.
SCLC [22]. In this study, we reported colon cancer 1 year after lung cancer and gastroesophageal cancer that was diagnosed 18 months after the lung cancer diagnosis.

The treatment decision of synchronous tumours is not straightforward and usually requires a multidisciplinary approach, one of our patients had a synchronous breast and endometrial cancer. We discussed the case in our tumour board, and we decided to give her neoadjuvant chemotherapy followed by surgery MRM and TAH&BSO in the operating room by two surgeons.

We treated our patients with curative intent in more than 60% of cases so, we should always be aware of the possibility of a second primary cancer. Late metastatic spread in a patient with triple-negative breast cancer led us to suspect second primary and diagnose pancreatic cancer. Also, low tumour marker in ovarian cancer patient which was initially high was found to have a second primary neuroendocrine tumour, continued smoking history should alert us about this possible important carcinogen.

We should inform our patients about the late side effects of their treatment, particularly Second-Primary Malignancies, by including it in the consent form. Such actions would educate patients on the value of continuous surveillance and avoiding all possible carcinogens especially smoking in addition to encouraging them for a healthy lifestyle [23-24].

Patients with multiple primaries are usually excluded from clinical trials and there are no established guidelines to treat these cases. we need clinical trials to study the new histology non-specific medications like (immunotherapy, biologic therapy, etc)

Finally, in our medical facility, we adopted the policy of referring our cases with Multiple-Primary to our genetic oncology clinic for evaluation and genetic testing; this hopefully will help us gain more knowledge about patients with hereditary cancer. we will report these data separately.

In conclusion, we are expecting an increase in the prevalence of Multiple-Primary tumours due to increased accuracy of diagnostic techniques in addition to novel target therapy that may increase the risk. Hereditary cancer syndrome, smoking, cancer therapy are all risk factors. we need to pick these cases as early as possible before the development of metastasis as this has a marked impact on patient survival. Treatment decisions for these cases should be based on a multidisciplinary approach. Research on this topic is an unmet need particularly the genetic background for developing second primary cancers. To reflect more of a real-life population, we need clinical trials investigating those patients in detail to increase the physician’s awareness that these cases are not rare, and they need to be treated with curative intent in most situations.

References

1. Siegel R, Miller K, Jemal A. Cancer statistics, 2019. CA: A Cancer Journal for Clinicians. 2019;69(1):7-34.
2. Noh S, Yoon J, Ryoo U, Choi C, Sung C, Kim T et al. A case report of quadruple cancer in a single patient including the breast, rectum, ovary, and endometrium. Journal of Gynecologic Oncology. 2008;19(4):265.
3. Lee J, Moon W, Park S, Park M, Kim K, Jang L et al. Triple Synchronous Primary Cancers of Rectum, Thyroid, and Uterine Cervix Detected during the Workup for Hemachozia. Internal Medicine. 2010;49(16):1745-1747.
4. Owen L. MULTIPLE MALIGNANT NEOPLASMS. JAMA: The Journal of the American Medical Association. 1921;70(20):1329.
5. Bugher JC. The probability of the chance occurrence of multiple malignant neoplasms. Am J Cancer. 1934; 21(4):2309.
6. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T et al. Multiple primary tumours: challenges and approaches, a review. ESMO Open. 2017;2(2):e000172.
7. Warren S, Gates O. Multiple primary malignant tumours: A survey of the literature and statistical study. Am J Cancer. 1932; 16:1358-414.
8. Coyte A, Morrison D, 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(1).
9. Amer M. Multiple neoplasms, single primaries, and patient survival. Cancer Management and Research. 2014.;119.
10. Ferretti S. Airtum cancer registration handbook. Florence, Italy, 2009.
11. Kim S, Kim H, Lee J, Lee Y, Kang W, Park J et al. Multiple Primary Cancers Including Colorectal Cancer. Journal of the Korean Society of Coloproctology. 2008;24(6):467.
12. Hartley A, Birch J, Kelley A, Murshed H, Harris M, Teare M. Are germ cell tumours part of the Li-Fraumeni cancer family syndrome?. Cancer Genetics and Cyto genetics. 1989;42(2):221-226.
13. Frebourg T, Barbier N, Yan XY, Garber JE, Dreyfus M, Fraumeni Jr., et al. Germline p53 mutations in 15 families with Li-Fraumeni syndrome. Am J Hum Genet 1995; 56:608-15.
14. Shah SA, Riaz U, Zahoor I, et al. Carcinoma multiplex. J Coll Physicians Surg Pak 2013; 23:290–2.
15. Amer M. Multiple neoplasms, single primaries, and patient survival. Cancer Management and Research. 2014.;119.
16. Weir H, Johnson C, Thompson T. The effect of multiple primary rules on population-based cancer survival. Cancer Causes & Control. 2013;24(6):1231-1242.
17. Riccieri F, Fasanelli F, Giraudo M, Sieri S, Tumino R, Mattiello A et al. Risk of second primary malignancies in women with breast cancer: Results from the European prospective investigation into cancer and nutrition (EPIC). International Journal of Cancer. 2015;137(4):940-948.
18. Molina-Montes E, Pérez-Nevet B, Pollán M, Sánchez-Canalejo E, Espin J, Sánchez M. Cumulative risk of second primary cancers: results from a retrospective population-based study. Cancer Causes & Control. 2015;26:608-15.
19. Friedenson B. BRCA1 and BRCA2 mutation carriers with a first breast cancer: A systematic review and meta-analysis. The Breast. 2014;23(6):721-742.
20. Shah P et al. Second malignancies after radiotherapy for prostate cancer: systematic review and meta-analysis. BMJ. 2016;;i851.
21. Mofina Elemam, et al: Multiple Primary Tumours, How Frequent we Can Offer Curative Therapy? Asian Pacific Journal of Cancer Care• Vol 5• Issue 2
22. Bhaskarla A, Tang P, Mashtare T, Nwogu C, Demmy T.
Adjei A et al. Analysis of Second Primary Lung Cancers in the SEER Database. Journal of Surgical Research. 2010;162(1):1-6.

23. Hewitt M, Greenfield S, Stovall E, editors. From cancer patient to cancer survivor: lost in transition. Washington, DC: The National Academies Press; 2006.

24. Demark-Wahnefried W, Pinto B, Gritz E. Promoting Health and Physical Function Among Cancer Survivors: Potential for Prevention and Questions That Remain. Journal of Clinical Oncology. 2006;24(32):5125-5131.

This work is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License.