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**Short Running Title:** Synchronous RCC with Ca Breast is rare.

**Guarantor of Submission:** The corresponding author is the guarantor of submission.
TITLE: Synchronous carcinoma breast with renal cell carcinoma: a case report and review of literature

ABSTRACT

Introduction
Incidence of Double malignancy (synchronous or metachronous) has increased significantly. Renal cell cancer or Breast Cancer as second primaries are reported in the literature, but synchronous Carcinoma Breast with Renal cell Carcinoma is extremely rare. We are reporting a case of Carcinoma Breast with synchronous Renal Cell Carcinoma.

Case Report
A 38 years old female was investigated for a lump in right breast. Biopsy from Breast lump was reported as Infiltrating Duct Carcinoma. Metastatic workup revealed a large mass at lower pole of right kidney. Right MRM and Right Radical Nephrectomy were done for synchronous Carcinoma Breast and Renal Cell Carcinoma.

Conclusion
Genetic predisposition, tobacco, HPV, improvement in survival and long term surveillance after first primary cancer treatment, history of radiation or chemotherapy can be associated with second cancer but exact cause of second cancer is still unknown. Larger studies and research is warranted as the risk of double malignancy has been increased substantially. The plausible mechanisms behind the synchronous cancers have to be investigated.

Keywords: Synchronous, Carcinoma Breast, Renal cell Carcinoma, Rare
TITLE: Synchronous carcinoma breast with renal cell carcinoma: a case report and review of literature

INTRODUCTION
With the availability of effective cancer therapy and improvement in survival, the incidence of double malignancy has risen [1]. Double malignancy now comprises of the sixth most common cancers and it makes 16% of all incident cancers [2]. Renal cancer is known to be associated with multiple tumours involving bladder, prostate, rectum, lung, non-Hodgkin’s lymphoma, stomach and melanoma etc [3]. Breast cancer is also associated with increased risk of second tumor involving colon, vulva, lung, larynx, liver, uterus and thyroid etc [4]. All these associations can be metachronous (develop consequently) or synchronous (tumors coexist at the time of diagnosis). Synchronous breast and renal cell carcinoma (RCC) can occur rarely [3]. We hereby report a case of Carcinoma Breast with synchronous Renal Cell Carcinoma.

CASE REPORT
A thirty-eight year old premenopausal, multipara female with no significant family history presented with a lump in right breast since eight months duration. Sonomammography of ipsilateral breast showed a fibroadenoma of 23x18 mm at 9o’clock position, surrounding fibroadenosis and reactive axillary lymph nodes. Excision Biopsy was done by a surgeon at a peripheral hospital and it was reported as pT 4.5 x 3cm, Infiltrating Duct Carcinoma with predominant Ductal Carcinoma in situ (cribriform pattern). She was referred to our hospital for further management. CT scan - abdomen for metastatic workup showed a 45x42 mm mass in mid-lower pole of right kidney with small exophytic component and associated perilesional fat density suspected to be malignant (Figure 1). Bone Scan, CT chest and other routine investigations were within normal limits. Right Modified Radical Mastectomy and Right Radical Nephrectomy were done. Histopathology of breast specimen was reported as lumpectomy cavity of size 6x3.5x3 cm, no residual primary tumor, 4/26 lymph nodes positive for metastatic duct carcinoma (Figure 2), immunohistochemistry profile of axillary lymph node showed positivity for GCDFP
and negativity for ER/ PR/ Her 2 neu/ CD 10/ PAX 8 and Vimentin. Gross size of the right kidney specimen was 12.5x7x3 cm with ureter 4 cm in length. On cutting a well circumscribed tumor identified in middle region of kidney measuring 4.5x3.2x3 cm, with variegated cut surface, and Gerota’s facia adherent to the tumor at one focus measuring 3x1.2 cm. Histopathology of renal mass was reported a well-circumscribed tumor, grade I, clear cell renal cell carcinoma, Gerota’s fascia uninvolved, vascular and ureteric cut end unremarkable, renal sinus and perinephric fat free of tumor (Figure 3). Immunohistochemistry of renal mass was positive for CD 10, PAX8, Vimentin and negative for GCFDP. She was finally diagnosed as a case of Synchronous Carcinoma Right Breast (pT2pN2cM0) along with Conventional Renal Cell Carcinoma Right Kidney (pT1bpN0cM0, Grade I). She received adjuvant chemotherapy (FEC x 4 followed by Taxol x 4 cycles). She further received external beam radiotherapy to ipsilateral chest wall and SCF.

**DISCUSSION**

Renal Cell Carcinoma and Breast cancer are associated with increased risk of double malignancy [3,4]. Sato et al [3] al found multiple primary malignant tumors in upto 12% of patients with Renal Cell cancer. Rabbani et al [5] also reported 30% to 40% incidence of other primary malignancies on autopsy series in patients with renal cell carcinoma. Synchronous breast and renal carcinomas are rarely reported [3]. The exact mechanism of double malignancy is not well understood. The predisposing risk factors for dual malignancy include tobacco and alcohol, genetic predisposition (Li Fraumeni and Beckwith Weideman Syndrome, Cowden Syndrome and BRCA mutations), improved survival, history of prior radiation or chemotherapy, enviromental risk factors, old age [1]. PTEN gene is associated with Cowden syndrome which has high risk of developing tumors of the thyroid, breast, kidney, endometrium [6].

Detection bias may be another important factor as metastatic work-up or long term surveillance for first malignancy increases chances of detection of second primary tumor.

Hormone-ER complex may be playing a role in development of RCC. Di Silvero et al [7] reported a series of 17 cases of Renal cell Carcinoma associated with primary
tumors of steroid hormone target tissue such as Breast, Ovary and endometrium.

Liu Z et al[8] in a study of differentially expressed genes (DEGs), reported that ER target genes were closely associated with Renal cell carcinoma development. Tanaka et al[9] investigated that exposing the Syrian hamsters to estrogens results in the development of kidney cancer and aneuploidy in renal cells. Henriksson R et al[10] found no difference in survival for metastatic renal cell carcinoma patients treated with immunotherapy (interleukin 2/interferon alpha) and tamoxifen arm versus tamoxifen alone arm in a multicentric randomized controlled trial. These results suggest that the role of endocrine manipulation for renal cell cancer needs to be investigated more. Epidemiological studies of survivors of atomic bomb irradiation links the Radiation as potential carcinogenic but the proportion of second cancers that attributes to radiotherapy is still unknown. Radiotherapy techniques have changed significantly in last two decades. These rapidly evolving techniques (Intensity Modulated Radiotherapy (IMRT), Volumetric Arc Therapy (VMAT) Tomotherapy, Cyberknife, Stereotactic Radiotherapy, Proton therapy) have different acute and late toxicity profiles compare to conventional radiotherapy. IMRT delivers more conformal radiation doses to the target tumor volume but it involves more number of radiation fields and exposes a larger volume of normal tissue to lower doses. IMRT and its implication as increased second cancer incidence is a matter of debate.

Methodological Research is required on association of Dual malignancy with late side-effects of chemotherapy/Radiotherapy, Genetic Modifiers, Environmental risk factors.

**CONCLUSION**

As the survival of cancer patients has improved due to early detection and availability of advance treatment options, the risk of second cancer or double malignancy has also increased significantly. Long term surveillance and high index of suspicion of double malignancy by treating physician and reviewing pathologist is warranted for early detection of second tumor. Further research is required to quantify the association between second malignancy and Genetic, Environmental and treatment related factors like IMRT and newer chemotherapy.
CONFLICT OF INTEREST
None

AUTHOR’S CONTRIBUTIONS
Tej Prakash Soni
Group 1 - Conception and design
Group 2 - Drafting the article
Group 3 - Final approval of the version to be published

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Group 1 - Acquisition of data
Group 2 - Drafting the article
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Anil Kumar Gupta
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Group 2 - Critical revision of the article
Group 3 - Final approval of the version to be published

REFERENCES


**FIGURE LEGENDS**

Figure 1: CT Abdomen showing a mass in mid-lower pole of right kidney with small exophytic component and associated perilesional fat density
Figures 2: (400x view) H & E stained slide showing malignant ductal cells diagnostic of Infiltrating duct carcinoma.

Figure 3: (400x view) H & E stained slide showing clear cells diagnostic of clear cell Renal cell carcinoma

FIGURES

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Figure 3: (400x view) H & E stained slide showing clear cells diagnostic of clear cell Renal cell carcinoma.