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Spousal Cancer: A Systematic Review and Case Report of a Metachronous Presentation of Breast Cancer in a Genetically Unrelated Couple

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Abstract

We present a systematic review of the literature about spousal cancer, concerning the possible cancer aetiology of synchronous and metachronous, concordant and discordant cancer types in married couples. Synchronous and metachronous breast cancer in spouses are extremely rare. We present here a married couple whom were diagnosed with metachronous breast cancer, with a 10-year delay in onset in the husband. This case of spousal breast cancer may represent a coincidental phenomenon, as breast cancer is quite uncommon in men. It has been postulated that exposure to viral, nutritional and environmental / contamination factors for extended periods of time might facilitate cancer development in the same organ in spouses. However, current cancer incidence rates among cohabitants are relatively low.

Keywords: Spousal cancer; Connubial cancer; Epidemiology; Spouses; Married couples; Breast cancer

Introduction

Synchronous and metachronous tumour presentation in married couples is rare, particularly if the tumours originate in the same organ. As male breast cancer is a rare condition, few spousal breast cancer cases have been reported. Married couples frequently have similar socioeconomic backgrounds, ethnic roots, diets and environments, which might facilitate the development of malignant tumours of similar origin in both spouses. Previous studies have provided conflicting results concerning cancer risk in the spouse of a cancer patient. However, spousal aggregation of cancer might provide clues to unsuspected aetiological factors. Incidences rates for cancer among cohabitants is expected to rise, due to the increase in life expectancy and the steady increase in cancer incidence rates in the general population.

Material and Methods

Clinical and histopathological description of the **wife's** bilateral breast tumours: The female patient was 59 years of age when she was diagnosed with a self-detected breast cancer. Mammography screening identified a 40 x 25 mm large suspected malignancy in the upper lateral quadrant of the *right breast*, 1 cm from the nipple. Total mastectomy was performed with axillary dissection. Histopathological examination revealed a 36 mm large invasive ductal carcinoma, Bloom–Richardson–Elston grading score 7, grade 2. The tumour expressed oestrogen and progesterone receptor (90% respectively 60%). Ki-67 proliferation marker showed 40% positivity and HercepTest was negative (score 0).No metastases were found in 14 axillary lymph nodes. The patient received adjuvant endocrine therapy with an aromatise inhibitor during a five-year period. Two years later, a 5 mm large area with micro calcification was identified medially in the *left breast*, 7 cm from the nipple. Partial mastectomy was performed and histological examination revealed an 8 mm large ductal carcinoma *in situ* grade 3. Axillary dissection was not performed. The patient received post-operative breast radiotherapy with a total dose of 50 Gy. No local or distant relapse was diagnosed at her last hospital visit after 8.5 years of follow-up. The patient has no relatives with breast or ovarian cancer.

Clinical and histopathological description of the **husband's** breast tumour: The 67-year-old

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Table 1: Year of publication.

Year of publication	Number of couples	Organ with cancer	Probable aetiology	Authors
1961	51	Various sites, no breast cancer		[11]
1969	29	29 ♂ penile cancers 8 ♀ cervix cancers 3 ♀ breast cancers 1 ♀ ovarium cancer 9 ♀ upper respiratory tract 5 ♀ skin cancers 3 ♀ other types of cancer		[14]
1972	1	♂ Hodgkin´s disease ♀ Hodgkin´s disease		[12]
1974	1	♀ uterine sarcoma ♂ anaplastic liposarcoma		. [10]
1977	9	9 ♂ lymphoproliferative malignancy 9 ♀ lymphoproliferative malignancy		[9]
1975	1	♀ breast cancer ♂ breast cancer		[8]
1978	3	3 ♂ malignant melanoma 3 ♀ malignant melanoma		[12]
1979	1	♀ squamous cell carcinoma of the cervix ♂ squamous cell carcinoma of penis	Probably HPV infection	[13]
1979	541	541 wives of prostate cancer male patients: 253 ♀ cancer in the female genital tract 288 ♀ other types of cancer (160 wives had breast cancer)		[16]
1980	1	♀ immunoblastic lymphoma ♂ immunoblastic lymphoma		[2]
1980	1	♀ pancreas cancer ♂ pancreas cancer	nutritional	[6]
1980	1	♀ multiple myeloma ♂ multiple myeloma		[6]
1980	11	2 couples malignant melanoma 3 couples breast carcinoma 2 couples renal carcinoma 1 couple fibrosarcoma 1 couple carcinoma of oral mucosa 1 couple colon carcinoma 1 couple carcinoma in nasopharynx		[7]
1981	9	9 ♂ breast cancer 4 ♀ breast cancer 1♀ colon cancer 1 ♀ gall bladder cancer 1 ♀ cancer in papillaVateri 1 ♀ endometrium cancer 1 ♀ vulva cancer		[8]
1982	1	♀ squamous cell carcinoma of the cervix ♂ squamous cell carcinoma of the penis		[9]
1982	1	♀ carcinoma in situ of the cervix ♂ carcinoma of penis	Probably HPV infection	[3]
1982	3	3♀Non-Hodgkin lymphoma 3♂ Non-Hodgkin lymphoma		Kim TH et al.[9]
1983	1	♀ acute non lymphatic leukemia ♂ acute anaplastic anemia		[3]
1986	1	♀ glioblastoma multiforme ♂ glioblastoma multiforme		[3]
1986	1	♀ extrahepatic biliary tract carcinoma (ampulla) ♂ extrahepatic biliary tract carcinoma (gallbladder and common bile duct)		[3]
1986	1	♀ non-Hodgkin lymphoma with monoclonal IgM paraprotein ♂ Hodgkin's disease with monoclonal IgM paraprotein		[4]
1987	1	♀lymphocytic lymphoma ♂lymphocytic lymphoma		[5]
1987	1	♀ multiple myeloma ♂ multiple myeloma		[6]
1989	1	♀ pancreas cancer ♂ pancreas cancer		[7]
1989	1	♀ multiple myeloma ♂ multiple myeloma		[8]
1989	23	1064 ♂ with penile cancer 8 ♀ cervical cancer 5 ♀ endometrial cancer 7 ♀ ovarian cancer 1 ♀ vulvar cancer 1 man who had 2 wives: First wife with coloncancer Second wife with rectumcancer 1 man who had 2 wives: First wife with cervical cancer Second wife with pleuracancer	HPV	[5]

1990	1	♀ breast cancer ♂ breast cancer		[9]
1990	2	239 ♂ with penile cancer 2 ♀ cervix carcinoma		[4]
1996	1	♀ breast cancer ♂ breast cancer		[4]
1997	16	♀ 15 cervix carcinoma(in situ and invasive) and 1 vulvar carcinoma ♂ 16 penile carcinoma		[4]
1998	195	7 various sites of cancer		[8]
1999	834	1 couple had spousal breast carcinoma		[8]
2000	5	♀ colorectal cancer ♂ colorectal cancer		[4]
2002	33	33 ♀ breast cancer 33 ♂ breast cancer		[3]
2006	1	♀ breast cancer ♂ breast cancer		[4]
2008	1	♀ head and neck cancer ♂ head and neck cancer	HPV16	[5]
2012	1	♀ breast cancer ♂ breast cancer		[6]
2012	1	♀ esophageal cancer ♂ esophageal cancer	30 year exposure of cleaning agent	[7]
2013	1	♀ glioblastoma multiforme ♂ glioblastoma multiforme	Trichloro-ethylene solvent	Roviello G et al.[48]
2013	1	♀ gall bladder carcinoma ♂ gallbladder carcinoma	40 year explosure of benzene	[9]
2014	230	- 214 (46.5%) spouses had tumors in the digestive system - 64 ♂ cancer in respiratory system, of whom 20 had wives with the same cancer localisation - 127 (55.2%) spouses had lung and female specific cancers		[7]
2015	1	♀ pancreas cancer ♂ pancreas cancer		[5]
2015	1	♀ squamous cell carcinoma of the cervix ♂ squamous cell carcinoma of the penis	HPV 16	[5]
2015	1	♀ renal cell carcinoma ♂ renal cell carcinoma	♂ >30 years with asbestos exposure	[2]
2016	1	♀ oropharynx cancer ♂ oropharynx cancer	HPV16	[5]
2016	1	Current case report ♀ breast cancer ♂ breast cancer		[6]

male patient presented with a retromamillary located, ulcerated, 36 mm large mass in his left breast. Physical examination found enlarged axillary lymph nodes. A total mastectomy was performed with total axillary dissection. Pathological examination of the specimen revealed a 50 mm large invasive ductal carcinoma in the left breast with BRE-score 9, grade 3. Subsequent immunohistochemical examination of the tumour showed positivity for oestrogen and progesterone receptor (95% respectively 90%). Ki-67 proliferation marker was stained in 60% of the tumour cells. HercepTest showed membranous staining score 2+ and SISH (silver *in situ* hybridization) test revealed amplification of the HER2/*neu* gene. Metastasis of breast cancer was found in 19 of 27 axillary lymph nodes. The patient received adjuvant treatment with anthracycline-taxane based chemotherapy, one year of trastuzumab, loco regional radiotherapy and endocrine treatment planned for five years. He has no family history of breast cancer. Both patients' material was stripped of direct subject identifiers.

Results

Here, we report a case of metachronous spousal breast cancer in a long-standing, but childless married couple of 29 years. Due to nulliparity, the wife had an increased risk of developing breast cancer because she had neither given birth, nor breastfed any children. She developed bilateral breast cancer within a 2-year time span. Ten years later, the husband developed breast cancer with a more aggressive breast cancer subtype: grade 3, 50 mm large, *HER2*-positive, invasive ductal carcinoma with several axillary lymph node metastases. There were no known familial cases of cancer for either spouse, and so, their identical but metachronous breast cancer occurrence can be explained as coincidental. Both male breast cancer and this type of marital malignant comorbidity are extremely rare and the occurrence of metachronous tumours in spouses is exceptional, though having most likely occurred by chance. Due to the low prevalence of spousal breast cancer, the aetiological factors are still open to conjecture.

Discussion

The available cancer epidemiology data for spouses are relatively few and show infrequent occurrence of malignant tumours of the same site and type affectingnonconsanguineous couples. One could expect that shared lifestyle including diet, smoking and drinking habits, as well as, viral infection might be associated with increased cancer incidence rates among spouses. Studies reporting cases of spousal cancer are summarized in Table 1, which includes both large studies and cases reports.

Few studies have beenconductedto evaluate spousal breast cancer epidemiology or connubial cancer with breast cancer in one spouse. No cancer type in one spouse was found to predispose breast cancer development in the other, and vice versa. In alarge, population-based cohort in Sweden [1], all first-degree relatives and wives were investigated, of 153 men who were diagnosed with male breast cancer from 1965 to 1989. There was no significant increase in breast cancer incidence in the wives. Namely, the wives of male breast cancer patients had similar cancer incidence as the general population. These results suggested that shared lifestyle in adulthood did not greatly increase the overall risk of breast cancer and were in accordance

with an Italian study conducted between 1991 and 1994 [2]. In a large-scale Swedish study, covering 10.2 million individuals and over one million tumours, a total of 71,020 couples presented with a concordant or discordant cancer after age 50 years. Among them, 33 couples had concordant breast cancer, which is thus far the highest number of the reported concordant spousal breast cancer cases [3]. The study concluded that no excess cancer risk was found among spouses, which could not be explained by known risk factors. Only the association between gastric and pancreatic cancers represented an exception. In 2008, a Swedish study including over 2 million couples confirmed that lifestyle shared by married couples played a minor role in cancer causation [4]. Only strong environmental risk factors such as smoking seemed to influence cancer development in adulthood, including lung, upper aero digestive tract and oesophageal cancers.

Conflicting results have been reported about risk of spousal cancer in the gastrointestinal tract. In a study conducted between 1951 and 1977, Jensen and colleagues showed that the risk of colorectal cancer and other possibly aetiologically-related diseases was no higher in the spouses than in the matched population [5]. Similar results were shown in a Danish study, where 8,095 spouses of colorectal cancer patients were studied who had no excess risk neither for colorectal cancer nor for other types of cancer, including breast cancer [6].

In contrast, a Swedish study analysing approximately 700,000 spousal cases showed a significant increase in risk for oesophageal, stomach, colorectal, lung, bladder and skin cancer and melanoma but not for breast cancer among cohabitants [7]. After screening 25,670 married couples with up to 31 years follow-up, an American study showed that concordant spousal cancer occurred relatively infrequently, with only 834 couples both having cancer and only one couple had concordant breast cancer. The study only found statistically significant husband-wife associations for cancer of the tongue and stomach and for non-Hodgkin lymphoma [8]. In the case of spousal stomach cancer, *Helicobacter pylori* can emerge as an aetiological factor, whereas chemical and viral agents can play a pivotal role in the emergence of marital non-Hodgkin lymphoma [9,10]. Non-significant, but mildly elevated risk ratios were noted for non-Hodgkin lymphoma and for cancers of the mouth and pharynx, lung, bladder and breast. Although the risk ratio for colon cancer and colon and rectal cancer combined was low for 11 couples concordant for cancer of the colon. Examined site distribution of cancer-related deaths in husband-wife pairs and identified 51 couples with cancer-related deaths of various sites, but not breast cancer [11]. In addition, the authors established that the husband-wife pairings showed excessive cancer-related deaths suggesting common environment to be a plausible explanation for this type of aggregation of cancer. Reported three connubial malignant melanoma cases, but fair skin in all six patients and probably common habit of sun exposure were concluded to be more likely risk factors than common environment [12].

Viral aetiology of different spousal cancers has been debated, primarily in genital cancers and lymphoproliferative malignancies. The role of viral agents in breast cancer development has also been postulated. One study confirmed the presence of mouse mammary tumour virus (MMTV)-like DNA sequences in breast carcinomas of three family members including the husband, wife and their daughter, where first the husband was diagnosed with breast cancer and then six years later both his wife and daughter developed breast cancer [13]. However, MMTV as a common aetiological factor in breast cancer development has not been widely investigated or reported in the literature. If an infectious viral agent were to play a role in breast cancer emergence, the prevalence of male breast carcinoma cases would be expected to increase with the increasing breast cancer incidence in females.

Increasing evidence has emerged connecting viruses, in particular human Papilloma virus (HPV), as an aetiological factor for spousal genital cancer. Martinez examined the wives of 889 husbands with penile cancer and showed a substantial increase in incidence of squamous cell carcinoma of the cervix compared to the control group [14]. The wives (n = 29) of penile cancer patients had various cancer types, among which 28% (n = 8) had cervix cancer where the aetiological role of HPV can be considered. On the other hand, a relatively early Swedish study conducted between 1958 and 1982, at a time when viral aetiology of cervical and penile cancer was still not widely accepted, could not showan association between the occurrence of penile cancer in men and cervical cancer in their sexual partners, compared with the control group [15]. Namely, examining 1,064 men with penile cancer, they found only eight wives with cervical and one with vulvar cancer, whose cancers could be related to sexually transmitted HPV infection. It is interesting to mention that there were 12 wives in this study, who were diagnosed with gynaecological malignant tumours (five with endometrial and seven with ovarian carcinoma), not related to viral aetiology. Similar results were found in a Finnish study, where only two wives of 279 patients with squamous cell carcinoma of the penis were found to have cervix carcinoma. The authors concluded that the low incidence rates of both cancers might mean that transmission of the disease was an unusual event in the studied cohort of patients and some HPV types infecting the genital tract are known to have very low or no malignant potential. The low infectivity of HPV virus can refer to a multifactorial aetiology, and even individual immune protection/immune responses may play a role in tumour prevention.

There is an increased morbidity in patients with prostate adenocarcinomas. published an epidemiological study about widowers with prostate cancer, which indicated no tendency of men with a high prostate cancer risk to marry women with a high risk of breast, endometrial, cervical, ovarian, or other cancer [16]. If we suppose that couples had been exposed to a common carcinogenic agent during marriage, a clustering in time of disease onset could have been expected. Reported 230 husband-wife pairs with malignant tumours. Because of the high cancer incidence rates in the wives, the authors recommended that the wife should be screened for lung, breast, and gynaecological cancers if the husband was diagnosed with cancer [17], also found a potentially higher risk of cancer among spouses of cancer patients. The authors postulated that if one of the spouses was diagnosed with a malignant tumour, it might instil better awareness of health issues and consequently an earlier cancer diagnosis in the other spouse.

Although case reports have been published from various populations around the world, no geographical predisposition was noted in the literature.

Statistical evaluation of connubial cancer occurrence can become more difficult in modern times because of changed marital habits, as many tend to marry more than once during their lifetime. Moreover, the number of cohabitations without official marriage is increasing, which makes searching for spousal cancers in marriage registries more difficult.

The low prevalence of comorbidity among spousal cancer patients may confirm that nutrition and environmental factors only in combination with genetic and epigenetic causes may provoke tumour formation in both partners. This postulation is supported by the evident frequent occurrence of family cancer syndrome, where malignant tumours are detected non-simultaneously in family members whom are genetically related to one another. Taken together, genetic characteristics might contribute to the development of multiple primary malignancies in family members.

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