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Increased risk of breast cancer development after diagnosis of salivary gland tumour ☆

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Abstract

The aim of this study was to evaluate whether patients with salivary gland tumours are at increased risk of developing breast cancer. A retrospective cohort study was performed. Female patients ($n = 439$) with a salivary gland tumour (major and minor) were included. The diagnosis was confirmed histologically. The median follow-up was 5.4 years. Fifteen patients out of 439 with a salivary gland tumour subsequently developed breast cancer, with a mean time interval of 64 months. On the basis of incidence rates in the general population 5.93 breast cancers would be expected. The standardised incidence ratio (SIR) was 2.5 (95% confidence interval: 1.4–4.2; $P = 0.003$). Increased SIRs were also observed for other solid malignancies, but the numbers were small ($n < 5$). It is concluded that female patients with a salivary gland tumour have a 2.5 times increased risk of developing breast cancer. Breast screening of these patients is therefore recommended.

Keywords: Salivary gland; Breast cancer

1. Introduction

The risk of cancer patients developing other primary malignancies is an important issue in oncology, especially now that survival for many cancers has improved. The occurrence of multiple primary malignancies may reflect the operation of numerous influences, such as long-term complications of modern chemotherapy and radiotherapy, genetic predisposition, common carcinogenic influences, diagnostic surveillance, a chance event or the interaction of these factors. The temporal trend of excess second cancer risk may provide an important clue to aetiology [1]. Continuous exposure to carcinogens, such as tobacco, smoke and alcohol, contributes to a well-known increased risk of developing multiple primary cancers in the upper aero-digestive tract [2]. For salivary gland carcinomas, an association with subsequent carcinomas has also been described. Several reports describe a unique association between salivary gland tumours and second primary breast cancer. The first study on this association was published in 1968 by Berg *et al.* [3], who found that out of 396 women with major salivary gland cancer, seven developed breast cancer whereas only 0.9 cases were predicted, representing

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an approximately 8-fold increased risk of developing second primary breast cancer. Since then, seven other groups have evaluated this finding, of which two reported on a statistically significant correlation, with standardised incidence ratio (SIR) values ranging from 2.3 to 4.8 [4,5]. In the other series no such correlation between salivary gland tumours and breast cancer could be found [6–11]. These discrepant outcomes may be explained by the fact that cases not treated in registry hospitals were missed [8,9]. Table 1 briefly summarises the results of these reports.

Knowledge about the risk of developing second primary malignancies is of great importance for patient counselling and screening purposes. For making valid estimates in multiple primary studies the selection of patient series is crucial. Since breast cancer is a common malignancy in the Netherlands, with crude incidence rates in 2000 exceeding 139 cases per 100,000 women (Comprehensive Cancer Centres, www.ikcnet.nl), while the incidence of salivary gland tumours is rather low (0.6 cases per 100,000 women), a huge cohort of breast cancer patients would be needed to achieve sufficient data to analyse the association between these two different primary malignancies. Therefore, in our study salivary gland tumours were selected as the index tumour. Patients treated in our department between 1977 and 2000 were identified by the Institutional Tumor Registry, in order to address the hypothesis that patients with benign or malignant salivary gland tumours have an increased risk of developing a subsequent primary breast cancer.

2. Patients and methods

2.1. Patients

Through a computer search of the Netherlands Cancer Institute Tumor Registry all 439 female patients who had been treated for a salivary gland tumour between 1st January 1977 and 15th February 2000 were identified and included in the study. No distinction was made between the different anatomical sites and both major and minor salivary gland tumours were included in the initial selection procedure. Both malignant (142 patients) and benign (297 patients) salivary gland tumours were included in the study, because of the well-known risk of malignant transformation observed in various benign salivary gland tumour types.

In all patients the diagnosis was confirmed histologically, either primarily or by revision of histological specimens taken elsewhere, and all patients received their treatment in the institute. The Tumor Registry routinely collects yearly follow-up data on all patients diagnosed with malignant tumours. For patients known to have benign tumours, second primaries are also registered when diagnosed. For patients lost to follow-up, the general practitioner was approached with a request to provide information on recurrence(s), treatments, multiple primary tumours, vital status and cause of death. Thus, details of the occurrence of primary breast cancers and other malignancies both before and after the diagnosis of salivary gland cancer were obtained from files of the individual cases of salivary gland tumours included in the study. Other data retrieved included date of birth, dates of histological diagnoses of the salivary gland tumour and breast cancer and date off loss to follow-up or death.

2.2. Statistical analysis

A comparison was made between the incidence of breast cancer and other malignancies in our patient group and breast cancer incidence and other malignancies in the general Dutch population. In this person-years type of analysis, the ratio of observed (O) and expected (E) numbers of breast cancers and other malignancies in the study population is determined. In the accumulation of person-years of observation in the study population, time at risk for second cancer began immediately after the diagnosis of the salivary gland tumour and ended at the date of diagnosis of second cancer, date of death, or date of most recent medical follow-up examination, whichever occurred first.

Taking into account the person-years of observation in the salivary gland group cohort (by age, sex, and calendar period), expected numbers of specific second cancers were computed with the use of age-, sex-, and calendar-period-specific cancer incidence rates from the

Table 1
Comparison of various cohorts of women with salivary gland tumours

Reference	*n*	Malignant/benign (M/B)	Major/minor (M/m)	Women-years at risk	Observed breast cancer (O) (*n*)	Expected breast cancer (E) (*n*)	O/E ratio	*P* value
Berg *et al.* [3]	396	M	M	1651.75	7	0.9	7.8	0.00004
Moertel and Elveback [9]	297	M	M	3033.0	4	4.0	1.0	–
Dunn *et al.* [6]	349	M	M	2443.0	8	4.2	1.9	0.6
Prior and Waterhouse [4]	453	M/B	M/m	2315.0	6	2.6	2.3	<0.05
Biggar *et al.* [10]	367	M	M	2868.0	7	5.4	1.3	–
Abbey *et al.* [5]	190	M/B	M/m	628.83	4	0.83	4.8	0.01
Schou *et al.* [11]	930	M/B	M/m	11504.0	24	18.78	1.3	–
Chung Sun *et al.* [18]	1718	M	M	10789	30	28	1.07	–

Eindhoven Cancer Registry up to 1989 and from the Netherlands Cancer Registry for the period 1989–2000 (as cancer incidence data for the whole country were not available for the total study period). Confidence limits of O/E were obtained with the use of the Poisson distribution of O numbers. O/E ratios were calculated for all second malignancies combined and for selected sites such as breast cancer. Results from the person-years analysis were also used to calculate the absolute excess risk of breast cancer per 10,000 person-years. This was done by subtracting the expected numbers of cases from the numbers observed, dividing by person-years at risk, and multiplying by 10,000.

3. Results

In 26 out of 439 female patients with salivary gland tumour the diagnosis of breast cancer had been made, of whom 15 developed a second primary breast cancer after the diagnosis and/or treatment of the index tumour. The distribution of salivary gland tumour histologies involved was as follows: pleomorphic adenoma ($n = 8$), Warthin's tumour ($n = 1$), basal cell adenoma ($n = 1$), adenocarcinoma ($n = 1$), adenoid cystic carcinoma ($n = 1$), acinic cell carcinoma ($n = 1$), muco-epidermoid carcinoma ($n = 2$). All index tumours except 1 adenoid cystic carcinoma of the submaxillary gland originated in the parotid gland. The variation of associated breast cancer histologies was more restricted. Benign parotid tumours were correlated with the following histologies: infiltrative duct carcinoma ($n = 7$), duct carcinoma *in situ* ($n = 2$) and adenocarcinoma not otherwise specified (NOS) ($n = 1$). Breast cancer histologies after malignant parotid tumours were as follows: mucinous adenocarcinoma ($n = 1$), infiltrative duct carcinoma ($n = 3$) and duct carcinoma *in situ* ($n = 1$).

On the basis of incidence rates in the general population, only 5.93 patients with breast cancer were expected after the diagnosis of salivary gland cancer. The number of breast cancers occurring in our study was 2.5 times higher (95% confidence interval (CI): 1.4–4.2) than the expected number, representing a statistically significant increased risk ($P = 0.003$). For the 439 patients included in the study, the mean duration of follow-up was 7.7 years, with a total of 3382 person-years observed overall. The median follow-up time for the study population was 5.4 years. Table 2 summarises the histological diagnoses, sites and ages at diagnosis of both the primary salivary gland tumour and the second primary breast cancer, which occurred among patients who developed both tumours. The time interval between the date of diagnosis of the first primary salivary gland tumour and the second primary breast cancer ranged from 0 to 380 months (mean 64 months). The first primary salivary gland tumour was diagnosed at a mean age of 58 years (range 23–82 years) and the age at diagnosis of the second primary breast cancers ranged from 43 to 89 years, with a mean age of 63 years. The absolute excess risk of second malignancies per 10,000 person-years was 27 breast cancers.

We also examined the occurrence of other secondary malignancies. Overall, the risk of developing any second

Table 2
Summary of characteristics of the cohort studied for development of a second primary breast cancer after a primary salivary gland tumour

	Salivary gland tumour			Interval	Breast cancer		
	Age (years)	Site	Histological type	Months	Age (years)	Site	Histological type
1	58	Left, parotid	Pleomorphic adenoma	0.0	58	Right	Infiltrative ductal
2	48	Left, parotid	Acinic cell carcinoma	0.0	48	Left	Infiltrative ductal, ductal carcinoma *in situ*
3	48	Right, parotid	Basal cell adenoma	0.2	48	Left	Infiltrative ductal
4	59	Right, parotid	Warthin's tumour bilateral	64	64	Left	Adenocarcinoma NOS
5	40	Left, parotid	Pleomorphic adenoma	36	43	Left	Infiltrative ductal
6	23	Right, parotid	Pleomorphic adenoma	381	55	Right	Ductal and lobular carcinoma *in situ*
7	80	Right, parotid	Pleomorphic adenoma	5.1	81	Right	Infiltrative ductal
8	71	Left, parotid	Pleomorphic adenoma	55	75	Right	Infiltrative ductal
9	82	Left, parotid	Muco-epidermoid carcinoma	87	89	Left	Infiltrative ductal
10	67	Right, parotid	Muco-epidermoid carcinoma	0.1	67	Left	Infiltrative ductal
11	64	Left, submandibular	Adenoid cystic carcinoma	179	79	Left	Infiltrative ductal
12	44	Right, parotid	Pleomorphic adenoma	4.2	44	Right	Ductal carcinoma *in situ*
13	47	Right, parotid	Pleomorphic adenoma	146	59	Right	Infiltrative ductal
14	75	Right, parotid	Pleomorphic adenoma	8	75	Right	Infiltrative ductal
15	67	Right, parotid	Adenocarcinoma	0.1	67	Right	Mucinous adenocarcinoma
Mean	58			64	63		

NOS, not otherwise specified.

Table 3
Risk of second primary malignancies after a salivary gland tumour in our study

Tumour localisation	O/E	SIR	(95% CI)	*P* value
All tumours	29/18.02	1.6	1.1–2.3	0.021*
Solid tumours	29/16.60	1.7	1.2–2.5	0.007*
Solid without breast	14/10.68	1.3	0.7–2.2	0.378
Mouth and pharynx	3/0.22	13.4	2.8–39	0.005*
Respiratory tract	4/0.91	4.4	1.2–11	0.030*
Nasal cavity	1/0.02	40.1	1.0–223	0.073
Lung	3/0.81	3.7	0.8–11	0.101
Melanoma	2/0.47	4.3	0.5–15	0.164
Breast	15/5.93	2.5	1.4–4.2	0.003*
Urogenital tract	4/3.24	1.2	0.3–3.2	0.809

O/E, observed/expected; SIR, standardised incidence ratio.
* $P < 0.05$.

malignancies following a salivary gland tumour was 1.6-fold increased (95% CI: 1.1–2.3; $P = 0.021$) compared with the population at large. There were 14 non-breast cancers *vs*. 12 expected. Three patients developed oral/oropharyngeal cancer (SIR: 13.4; $P = 0.005$) and four patients developed cancer of the respiratory tract (SIR: 4.4; $P = 0.030$) (Table 3).

4. Discussion

In this study, we found an approximately 2.5 times increased risk of breast cancer among women with salivary gland tumours (benign and malignant). Our study group was unselected and 439 consecutive patients were diagnosed and treated over a period of 23 years according to standardised institutional protocols. It is interesting to note that we observed this correlation in a completely different patient population, more than 15 years after the last international publication on this issue [11]. In the literature increased risks for women with salivary gland tumours subsequently developing breast cancer range from approximately 1.3-fold [10] to 8-fold [3]. There are studies presented with negative findings, although follow-up periods were among the longest of all published series [9,11].

As in other series [12–18], an association was also demonstrated between salivary gland tumours and other types of malignancies. Significantly increased SIRs were also found for second primary malignancies in the oral cavity and respiratory tract. However, numbers were small for other non-breast second malignancies and some of our results may be chance findings. Salivary gland tumours, with a majority of benign lesions, might share a common external carcinogenic influence, such as the smoking- and drinking-related aero-digestive tract tumours [19–23], but dietary factors [24], ionising radiation [19,25] and occupational factors [24] have also been described. Our observation of an increased risk of mouth and pharynx carcinoma (Table 3) may point to a shared role of Epstein–Barr virus (EBV) [26]. However, studies on the role of this ubiquitous herpesvirus in breast cancer have had inconsistent results, with regard to varying EBV presence and absence of viral characteristics found in other EBV-related malignancies [27].

Both benign and malignant salivary gland tumours were included in our study, assuming that any benign salivary gland tumour harbours the chance of malignant transformation. This is well known for pleomorphic adenomas, which have a 3–4% chance of developing into malignant salivary gland tumours in cases of increased tumour size [28]. Also, malignant transformations have been described for Warthin's tumours [28–33]. These observations lead us to include these tumour types in the analyses.

At a microscopic level there may be morphological mimicry between salivary duct carcinomas and ductal mammary carcinoma [34]. In addition, both histological and immunohistochemical similarities have been found between adenomyoepithelioma of the breast and epithelial–myoepithelial carcinoma of the salivary gland [35]. This morphological homology may give a differential diagnostic problem in the distinction between primary and metastatic breast carcinoma lesions. However, metastatic carcinoma of the breast rarely involves the salivary glands [36,37]. This, in addition to the fact that breast cancer developed in association with the diagnosis of salivary gland tumours, renders it very unlikely that this phenomenon occurred in our series of patients.

So far we do not have a sound explanation for the rather consistent finding of the association between salivary gland tumours and breast cancer. It does not belong to the breast cancer syndromes such as BRCA1, BRCA2, Li-Fraumeni syndrome or Cowden's syndrome [38,39]. Yet, it is plausible to assume that a genetic association plays a role in the origination of these tumours. This is supported by recent findings on the involvement of the pleomorphic adenoma gene 1 (*PLAG1*) gene in the development of salivary gland tumours and mammary glands in mouse mammary tumor virus (MMTV)-*Cre*/*PLAG1* double transgenic mice [40]. Although, we do not yet have a clear biological explanation for the increased occurrence of second primary breast cancers in patients who have had first primary salivary gland tumours, we think that the observed increased risk should be considered as an indication for screening of patients who have been treated for a salivary gland tumour. If general screening recommendations for women at moderately increased risk for breast cancer (2–3 times) are followed, women under the age of 50 years are advised to have an annual mammogram, arbitrarily starting at the age of 35 years or after the diagnosis of the salivary tumour. For women of 50 years and older a mammogram every 2 years is generally advised [41–43].

Conflict of interest statement

None declared.

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