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Incidental findings on brain Magnetic Resonance Imaging in long-term survivors of breast cancer treated with adjuvant chemotherapy

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ABSTRACT

Purpose: Incidental brain findings defined as previously undetected abnormalities of potential clinical relevance that are unexpectedly discovered at brain imaging and are unrelated to the purpose of the examination are common in the general population. Because it is unclear whether the prevalence of incidental findings in breast cancer patients treated with chemotherapy is different to that in the general population, we compared the prevalence in breast cancer survivors treated with chemotherapy to that in a population-based sample of women without a history of any cancer.

Patients and methods: Structural brain MRI (1.5T) was performed in 191 female CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil) chemotherapy-exposed breast cancer survivors. A reference group of 1590 women without a history of cancer was sampled from a population-based cohort study. All participants were aged 50 to 80 years. Five trained reviewers recorded the brain abnormalities. Two experienced neuro-radiologists reviewed the incidental findings.

Results: The cancer survivors had completed chemotherapy on average 21 years before. Of the 191 subjects, 2.6% had an aneurysm and 3.7% had a meningioma. The prevalence of meningiomas and aneurysms was not different between the groups. The prevalence of pituitary macro adenomas in the breast cancer survivors (1.6%) was higher than that in the reference group (0.1%) (OR = 23.7; 95% CI 2.3–245.8).

Conclusion: Contrary to commonly held opinions, we did not observe an increased prevalence of meningiomas in cancer survivors. Breast cancer survivors previously treated with chemotherapy are more likely to develop pituitary adenomas than persons without a history of cancer and chemotherapy treatment.

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1. Introduction

Over the past decade there has been an increase in the number of Magnetic Resonance Imaging (MRI) studies investigating chemotherapy associated structural and functional brain changes in cancer patients without central nervous system disease.[1–9] The focus of these studies has been mainly on brain volumes, white matter lesions and integrity of normal appearing white matter. An implication of the use of brain imaging is the chance of discovering incidental findings, defined as previously undetected abnormalities of potential clinical relevance that are unexpectedly discovered and are unrelated to the purpose of the specific outcome measures under study.[10]

The majority of these incidental findings are asymptomatic and little is known about their clinical relevance or prognosis.[11] Frequently detected incidental findings in the general population are benign primary tumours and aneurysms.[11] Whether the prevalence of such abnormalities in cancer patients is similar to that in the general population is unclear. None of the studies that examined structural or functional brain changes associated with chemotherapeutic treatment[1–9] reported on the occurrence of incidental findings.

We evaluated whether breast cancer patients who have been exposed to chemotherapy have an increased prevalence of incidental intracranial findings. We investigated this by comparing the prevalence of incidental findings in a large sample of chemotherapy-exposed breast cancer survivors with that in a large sample of women who had never been diagnosed with cancer from the general population.

2. Materials and methods

2.1. Participants

We used data from a study after the late effects of CMF chemotherapy on brain function and structure in older breast cancer survivors. This study compares chemotherapy-exposed breast cancer survivors with a population-based sample of women without a history of cancer, on several outcome measures and implements including neuropsychological tests and MRI of the brain. We selected a reference group from an ongoing population-based cohort study. Examination of the breast cancer survivors took place in the research centre of this cohort study with the same protocol and by the same technicians.

From the registries of the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital and the Erasmus University Medical Center – Daniel den Hoed Cancer Center we selected consecutive female patients who had been treated between 1976 and 1995 for unilateral invasive breast cancer with six cycles of CMF (Cyclophosphamide 100 mg/m^2 on days 1–14, Methotrexate 40 mg/m^2 on days 1 and 8,5-Fluorouracil 600 mg/m^2 on days 1 and 8) chemotherapy.[12] All women underwent local radiotherapy. We included women who were between 50 and 80 years of age at the time of study enrolment, who had sufficient command of the Dutch language, who had had invasive breast cancer as their first and only neoplasm, and who were disease-free since primary cancer treatment. Exclusion criteria encompassed use of adjuvant endocrine therapy for breast cancer or MRI contra-indications.

On the basis of information from patient files, 359 women were eligible for participation and were hence sent an invitation letter signed by their treating physician. From the 359 patients, 20 (5.6%) could not be reached, 16 subjects (4.5%) had a health related contra-indication for MR imaging, 30 (8.4%) persons were ineligible for MRI assessment due to claustrophobia and two women (0.6%) had insufficient command of the Dutch language. This left us with 291 eligible patients of whom 195 (67.0%) agreed to participate. Four of the 195 participating women aborted the scan session because of claustrophobic complaints. The final number of patients who completed MRI examination was 191. Written informed consent was obtained from all participants. The institutional review boards of the two participating institutions approved the study.

A reference group was selected from the Rotterdam Study; a population-based prospective cohort study ongoing since 1990 in the Ommoord district, Rotterdam, The Netherlands[13] Of the 4058 participants of the Rotterdam Study who completed an MRI examination until September 2009, we selected all women ($n = 2206$; 54.4%) who were between 50 and 80 years of age ($n = 1881$; 85.3%). Next, we excluded all participants with a cancer history based on self-report and record linkage with general practitioners ($n = 291$; 15.5%), leaving a total reference group of 1590 women.

2.2. Methods

2.2.1. Brain MRI acquisition

All scans were obtained at the Rotterdam Study research center in Rotterdam, the Netherlands, using a 1.5-T scanner with an eight-channel head coil (GE Healthcare). Two trained technicians performed all examinations in a standardised way. The MRI protocol was identical for all participants has been described previously by Vernooij et al.[11]

2.2.2. Assessment of incidental findings

All scans were read for incidental findings of potential clinical relevance by one of five trained reviewers. Examples include brain tumours, aneurysms, subdural fluid collections and arachnoid cysts. Reviewers were blinded for information on the subjects. Brain findings that were not considered clinically relevant and were not recorded as incidental findings included simple sinus disease and variations from the norm, such as pineal cysts, ventricular asymmetry and enlarged Virchow–Robin spaces.[11]

Diagnoses were not confirmed by histologic studies but were made on the basis of MRI findings characteristic of each lesion. Case definitions for each incidental MRI finding have been described previously by Vernooij et al.[11]

Two experienced neuro-radiologists reviewed and reached a consensus on all initially reported abnormalities.[11]

The management of incidental findings followed the protocol of the Rotterdam Study and was defined before the start

of the study. Depending on the detected abnormality and after consultation with involved clinicians, persons with incidental findings requiring additional clinical workup or medical treatment were informed and referred to a relevant medical specialist.

2.2.3. *Statistical analysis*

Prevalence of incidental brain findings were compared between the chemotherapy-exposed women and the women from the reference group using age-adjusted binary logistic regression analysis. We subsequently examined the effect of type of menopause and age at menopause on the risk to develop incidental findings. In addition, within the breast cancer survivors we investigated whether radiotherapy field was associated with the development of incidental findings. Alpha levels were set at $p = 0.05$ for all analyses.

3. Results

Eligible breast cancer patients who declined participation were older than subjects who were willing to participate at the time invitation letters were sent (F1, 289 = 11.13, $p < .05$).

Table 1 presents the characteristics of the breast cancer survivors and the reference group. Chemotherapy-exposed subjects were older than women from the reference group ($F = 59.6$; $p = < 001$). The mean age at breast cancer diagnosis was 42.9 years and time since treatment was on average 21.2 years. Of the 191 chemotherapy-exposed participants 161 (85.3%) became menopausal following breast cancer treatment at a mean age of 43.0 years. For the whole sample, breast cancer patients menopause occurred on average at age 43.8 years (sd = 6.1), which is significantly earlier than for women from the reference group who reached menopause at a mean age of 48.6 years (sd = 6.0) ($F = 105.0$; $p = <.001$). Of the 191 breast cancer survivors, 85.3% received parasternal radiotherapy, 9.4% received radiotherapy at the breast or chest wall, 3.7% underwent radiotherapy according to the McWhirter protocol and for three patients (1.6%) radiotherapy field was unknown.

Table 2 presents the prevalence of age-adjusted incidental findings. Of the breast cancer survivors 2.6% had an aneurysm, 3.7% had a meningioma and 1.6% had a pituitary macro-adenoma. There were no significant differences in the prevalence of meningiomas and aneurysms between women who underwent chemotherapy and the reference group. However, chemotherapy-exposed patients had a higher prevalence of pituitary macro adenoma than the reference group (OR = 23.7; 95% CI = 2.3–245.8). Besides aneurysms, pituitary adenomas and meningiomas in this sample of merely 200 women we did not find any other findings such as gangliomas, vestibular schwannomas or subdural haematomas. We found no association between age and type of menopause (chemotherapy induced versus natural) with any of the incidental findings. In the chemotherapy-exposed patients, radiotherapy field was not associated with the prevalence of any of the incidental findings.

4. Discussion

We found no difference in the prevalence of asymptomatic meningiomas and aneurysms identified on MRI scans in 50 to 80-year-old former breast cancer patients who had been treated with chemotherapy, on average 21 years before, and a population-based sample of women of the same age without a history of cancer. However, the former breast cancer patients had a higher prevalence of asymptomatic pituitary macro adenomas than the reference group.

Up till now, a non-significant positive association between pituitary adenomas and benign breast tumours has been reported.[14,15] To our knowledge, no previous data are available on a relationship between pituitary adenomas and invasive breast cancer. Therefore, it remains undermined whether the excess number of pituitary adenomas in the current group of invasive breast cancer survivors could be explained by their first primary neoplasm.

A possible explanation for the elevated prevalence might be the relation of pituitary adenomas and postmenopausal status. In a case-cohort study Schoemaker et al. reported a three-fold risk increase in postmenopausal women, which was even greater for surgically induced menopause compared to natural menopause (OR 6.7), and was greatest in women who entered menopause before the age of 40 years (OR 7.5).[15]

It is known that CMF may induce menopause in a substantial number of patients. A study by Goodwin et al. showed

Table 1 – Characteristics of the breast cancer survivors and the reference group.

	Breast cancer survivors		Reference group		*p*-Value
N	191		1590		
Mean age in years (sd)	64.1	(6.4)	60.2	(6.6)	<.001
Mean age at menopause					
Total (sd)	43.8	(6.1)	48.6	(6.0)	<.001
Spontaneous menopause in years (sd)	47.5	(4.3)	50.2	(4.3)	<.001
Induced menopause in years (sd)	43.0	(7.2)	45.7	(7.1)	.002
Mean age of cancer diagnosis in years (sd)	42.9	(5.3)			
Mean time since treatment in years (sd)	21.2	(4.4)			
Radiotherapy field					
Parasternal (%)	163	(85.3)			
Breast/chest wall (%)	18	(9.4)			
McWhirter (%)	7	(3.7)			
Unknown (%)	3	(1.6)			

Table 2 – Revalence of age-adjusted incidental findings.

	Reference group (N = 1590) n (%)		Breast cancer survivors (N = 191) n (%)		OR	95% CI
Aneurysm	37	(2.3)	5	(2.6)	1.1	0.42–2.91
Meningioma	36	(2.3)	7	(3.7)	1.4	0.62–3.33
Pituitary macro adenoma	1	(0.1)	3	(1.6)	23.7	2.28–245.76

OR = odds ratio; CI = confidence interval.

that use of CMF increased the risk of onset of menopause within 1 year after breast cancer diagnosis in 40-year-old women from less than 5% to more than 40%. In 50-year-old women, this risk was increased from approximately 20% to close to 100%.[16] In our sample of cancer patients 85.3% became menopausal directly after treatment at a mean age of 43.0 years. The relative early and young mean age at menopause may have put these women at a higher risk for pituitary adenomas. However, type of menopause and menopausal age of onset were no predictors for the risk of incidental findings in our models, although this could also be due to the small number of incidental findings.

Several studies have reported an elevated risk of developing a meningioma after breast cancer and vice versa, with standardised incidence rates ranging from 1.57 to 1.90.[17–22] Proposed explanations for the co-occurrence of these tumours include (a) the hormonal dependency of both tumours as oestrogen and progesterone receptor expressions are frequently present in breast carcinomas as well as in meningiomas, and the observation that meningiomas tend to grow rapidly during pregnancy,[23–25] (b) the fact that both tumours have a higher incidence in females,[20] and (c) intake of unsaturated fat as a risk factor for both malignancies.[20]

In contrast with the literature, we did not find a higher prevalence of meningiomas in former breast cancer patients compared to the general population. Potential explanations for the divergent observations are the different study designs and populations. The incidental findings in our studies concerned asymptomatic meningiomas whereas other studies focused on symptomatic meningiomas. Moreover, previous studies used data from regional[22] and national[17–20] cancer registries that include almost all consecutive breast cancer patients in a particular time frame whereas we selected a more homogeneous group of breast cancer patients who were all treated with adjuvant chemotherapy and who never developed recurrent breast cancer nor a second malignancy.

Some epidemiologic studies showed that increased oestrogen levels are associated with a higher risk for breast cancer in pre- and post-menopausal women.[26–29] Because oestradiol also might stimulate growth of meningiomas[30] one might expect a higher prevalence of these neoplasms in breast cancer patients. However, the fact that our breast cancer survivors went through menopause much earlier than women from the general population may have decreased the prevalence of meningiomas in our study group as a result of a significant period of lower oestrogen levels. Furthermore, Wigertz et al. postulated that sex hormones influence tumour growth rather than tumour initiation.[31] These arguments may explain why we did not find a difference in the prevalence of asymptomatic meningiomas between breast cancer survivors and the general population and also the discrepancy of the prevalence of menigiomas that we observed in the breast cancer survivors and the prevalences of symptomatic meningiomas in the published studies.

No difference in the prevalence of aneurysms was observed between chemotherapy-exposed breast cancer survivors and the reference group. *In-vitro* studies have showed that chemotherapy might induce endothelial cell damage,[32,33] which in rats has been related to cerebral aneurysm formation.[34] Data in humans hereon are lacking. Radiotherapy to the head, neck and brain has been associated with intracranial aneurysms.[35] To our knowledge, no studies have investigated if ionising radiation scatter from radiotherapy for breast cancer, for example at the supraclavicular field, is also associated with the formation of intracranial aneurysms. Our results, however, indicate no association between breast cancer and CMF chemotherapy or radiotherapy-field and the development of intracranial aneurysms.

We are aware that our study has some drawbacks. As a result of the inclusion criteria that we applied, our population under study is a selection, since we have only included breast cancer patients who underwent cytotoxic treatment, who did not develop breast cancer recurrence and who were never diagnosed with a second primary cancer. This limits the generalizability of the study results, because breast cancer patients who have developed a second malignancy may be at higher risk to subsequently develop intracranial neoplasms than those who have not.[36]

Moreover, we cannot separate the effect of chemotherapy and breast cancer itself on the risk of developing intracranial neoplasms or aneurysms. Finally, although our sample of former breast cancer patients was large enough to investigate the more common incidental findings, the number of subjects was too small to investigate less common incidental findings e.g. gangliomas.

Another point of discussion is whether the findings of this study apply to breast cancer patients treated with contemporary regimens, since it is unclear whether the current observation on the associations between adjuvant chemotherapy for breast cancer and the development of incidental findings is exclusively linked to the CMF regimen. If cancer rather than its treatment is a risk factor for incidental findings, risk differences between the CMF regimen and contemporary regimens may not exist. If differences in hormone levels are in the causal pathway of incidental findings, the risk may be different for contemporary regimens, as the occurrence of premature treatment-induced menopause varies by regimen.[41] When development of incidental findings is caused by cytotoxic treatment itself, similar risks may be expected for contemporary regimens compared to the CMF regimen; both cyclophos-

phamide and 5-fluorouracil are frequently implemented in current regimens and these agents as well as many other commonly applied agents are independently associated with structural brain changes[42,43] and comprised vessel integrity in animals.[44,45]

A major strength of this study is the large reference group from which we obtained a precise estimate of the prevalence of incidental findings in women from the general non-cancer population. Up till now, no other study has looked at the relation between breast cancer or adjuvant chemotherapeutic treatment and asymptomatic intracranial neoplasms or aneurysms. The long time since treatment enabled us to look at neoplasms and aneurysms that normally take a long time to develop and of which the initiation or progression may have been triggered by the cytotoxic treatment.

4.1. *Clinical implications*

The number of studies implementing MRI in the field of cancer and cognition is rapidly increasing and as a result the number of incidental findings will progress similarly. No strict guidelines on the management of incidental findings are available and investigators vary greatly in the way they handle them.[11,37] For the interpretation of the prevalence of incidental findings data from an appropriate reference population are of crucial importance. Up till now three studies have presented data on the prevalence of incidental findings in healthy adults,[38–40] and only one study has described prevalences of incidental findings in the general population.[11] This is the first study that presents the prevalence of incidental findings in breast cancer survivors who have been treated with chemotherapy. The observation of an increased incidence of pituitary macro adenomas, possibly in relation to an early postmenopausal status needs confirmation as with the current treatment strategies the number of long-term breast cancer survivors is increasing.

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Conflict of interest statement

None declared.

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