

Association of tamoxifen with meningioma: a population-based study in Sweden

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Previous studies suggest that hormone therapy may play an important role in the development of meningioma. However, it is unclear whether medication with tamoxifen can prevent meningioma. Our study cohort included all women who were diagnosed with breast cancer between 1961 and 2010, and a total of 227 535 women were identified with breast cancer with a median age at diagnosis of 63 years. Women diagnosed with breast cancer after 1987 were defined as tamoxifen exposed; those diagnosed with breast cancer before or during 1987 were defined as not exposed to tamoxifen. Standardized incidence ratios (SIRs) were used to calculate the risk of subsequent meningioma. Of these women, 223 developed meningioma. For women without tamoxifen exposure, the risk of meningioma was significantly increased, with an SIR of 1.54 (95% confidence interval 1.30–1.81); the risk was not increased in those with tamoxifen exposure (SIR = 1.06, 95% confidence interval 0.84–1.32). The increased risk of meningioma in women without tamoxifen exposure persisted during 10 years of follow-up. In this historical cohort study, we found that

women diagnosed with breast cancer but not treated with tamoxifen had an increased incidence of meningioma, whereas the incidence was close to that of the general population in patients treated with tamoxifen. This suggests that tamoxifen may prevent the development of meningioma. *European Journal of Cancer Prevention* 25:29–33 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Meningioma is a common tumour in the central nervous system, and it accounts for 13–26% of all intracranial tumours (Barnholtz-Sloan and Kruchko, 2007; Wiemels *et al.*, 2010). The only known risk factor for meningioma is ionizing radiation (Preston *et al.*, 2002; El Ghissassi *et al.*, 2009); other environmental and lifestyle risk factors show inconclusive results (Barnholtz-Sloan and Kruchko, 2007; Wiemels *et al.*, 2010). Given the higher prevalence of meningioma in women than in men (ratio 2 : 1) (Hsu *et al.*, 1997; Carroll *et al.*, 2000; Claus *et al.*, 2008), it was hypothesized that hormones may be a risk factor for meningioma. Its association with hormones was further supported by evidence from women receiving hormone replacement therapy, who were found to have an increased risk of meningioma (Claus *et al.*, 2007; Benson *et al.*, 2010; Korhonen *et al.*, 2012). A possible association was also observed among women using oral contraceptives (Custer *et al.*, 2006; Claus *et al.*, 2007; Korhonen *et al.*, 2010), and pregnancy and menopausal status were reported to influence the risk of meningioma (Lambe *et al.*, 1997; Wigertz *et al.*, 2008). Women diagnosed with breast cancer have an increased risk of meningioma and vice versa (Custer *et al.*, 2002; Rao *et al.*, 2009). Some studies confirmed the expression of oestrogen receptors in some meningiomas (Black *et al.*, 1996; Carroll *et al.*, 1999; Claus *et al.*, 2008).

All the above observations suggest that oestrogen may play an important role in the development of meningioma. It is thus important to examine whether medication with tamoxifen, a selective oestrogen receptor modulator with an antioestrogenic effect (Al-Mubarak *et al.*, 2014; Nazarali and Narod, 2014), can inhibit or prevent the development of meningioma. Tamoxifen has been used widely to treat patients with oestrogen receptor-positive breast cancer (Al-Mubarak *et al.*, 2014; Nazarali and Narod, 2014), and was first used in Sweden in the late 1980s (Fornander *et al.*, 1989; Chandanos *et al.*, 2006). To study its influence on the development of meningioma, we tested in this study whether women diagnosed with breast cancer and treated with tamoxifen have a lower incidence of meningioma compared with women without tamoxifen treatment using a nationwide population-based cohort study.

Methods

This historical cohort study was approved by the Regional Ethical Review Board of Lund University, Sweden, in 2013 (Diarienummer 2012/795). Patients diagnosed with breast cancer during the period 1 January 1961 to 31 December 2010 were identified from the Swedish Cancer Registry. The Swedish Cancer Registry was founded in 1958, and has had nationwide coverage since 1961. The Swedish Cancer Registry is currently

estimated to have close to 100% coverage at the national level (Hemminki *et al.*, 2010). It is maintained by the National Board of Health and Welfare. In Sweden, all clinicians and pathologists/cytologists are obliged to report all newly diagnosed primary cancers to the Cancer Registry. A validation study showed that 99% of the recorded cancer cases are morphologically verified (Hemminki *et al.*, 2010). Only primary tumours are recorded in this register; metastases are excluded. Women with breast cancer were identified from the Swedish Cancer Registry using the ICD-7 code 170. Only patients with a first primary breast cancer were included; patients with a previous cancer, including breast cancer, were excluded.

All the patients in our cohort were followed until the diagnosis of meningioma, which was identified from the Swedish Cancer Registry using the ICD-7 code 1930. Histological confirmation was determined using the pathological anatomic diagnostic codes 461, 465 and 466. These codes were used during the entire study period. Additional linkages were made to the Swedish National Population and Housing Census (Population and Housing Census 1960–1990, 2011) to obtain information on individual-level characteristics, such as year of birth and sex; to the Cause of Death Register to identify date of death; and to the Emigration Registry to identify date of emigration. All linkages were performed using individual national identification numbers, which were replaced with serial numbers to preserve anonymity.

We calculated person-years at risk for our cohort from the date of diagnosis of first primary breast cancer to the earliest of the following: date of diagnosis of meningioma, death, emigration and end of the study period (31 December 2010). We estimated the risk of meningioma in our cohort using standardized incidence ratios (SIRs), which were calculated as the ratio of the observed to expected numbers of cases (Breslow and Day, 1987; Rothman and Greenland, 1998). The expected number of cases was calculated by multiplying the observed person-years at risk by the incidence rate of meningioma for all individuals without a diagnosis of primary breast cancer. SIRs were standardized by 5-year age group and 5-year time interval. For the SIRs, 95% confidence intervals (CIs) were calculated assuming a Poisson distribution and rounded to two decimal places (Esteve *et al.*, 1994). To exclude surveillance bias, all meningiomas diagnosed within 1 year of follow-up after the primary breast cancer were excluded. As tamoxifen has been used widely in Sweden since the late 1980s, we defined patients with a diagnosis of breast cancer before the end of December 1987 (years 1961–1997) as not exposed to tamoxifen and those diagnosed with breast cancer in 1988–2010 as tamoxifen exposed. As this study is a nationwide study with a total of 227 535 patients with breast cancer, we have 100% power to detect an increasing prevalence of tamoxifen between the two

cohorts on the basis of the assumption that the prevalence of tamoxifen was 5 and 50% before and after the year 1987, respectively.

In our exposure definition, all the patients diagnosed with breast cancer in 1988–2000 were defined as being tamoxifen exposed, which may lead to misclassification of exposure. In particular, only those breast cancer patients with ER⁺ could be treated with tamoxifen, and around 85% could be diagnosed with ER⁺ according to the published literature (Ferno *et al.*, 2000). We thus calculated the adjusted risk ratio on the basis of the following formula:

$$1.06 = 1.54 \times (1 - \text{percentage of misclassification}) \\ + \text{percentage of misclassification} \times \text{adjusted risk ratio.}$$

We assumed that all the patients with ER⁻ will not be treated with tamoxifen, and they will have the same incidence as those breast cancer patients diagnosed before 1988 (SIR = 1.56). All analyses were carried out using SAS, version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

In Table 1, we present the basic characteristics of Swedish women diagnosed with breast cancer from 1961 to 2000. A total of 227 535 women were diagnosed with breast cancer, with a median age at diagnosis of 63 years. Among these women, 223 developed meningioma during 1 715 497 person-years of follow-up. The number of

Table 1 Basic characteristics of Swedish women diagnosed with breast cancer in 1961–2010

	N (%)	Person-years of follow-up	Number of meningioma cases
Not tamoxifen exposed (1961–1987)			
Breast cancers	98 681	964 859	145
Age at diagnosis (years)			
< 50	19 067 (19.3)		
50–59	20 054 (20.3)		
60–69	24 466 (24.8)		
70+	35 094 (35.6)		
Tamoxifen exposed (1988–2010)			
Number of breast cancers	128 854	750 638	78
Median age at entry (years)	63		
Age at diagnosis (years)			
< 50	22 777 (17.7)		
50–59	28 890 (22.4)		
60–69	31 550 (24.5)		
70+	41 277 (32.0)		
Total cohort (1961–2010)			
Number of breast cancers	227 535	1 715 497	223
Median age at entry (years)	63		
Age at diagnosis (years)			
< 50	41 844 (18.4)		
50–59	48 944 (21.5)		
60–69	56 016 (24.6)		
70+	76 371 (33.6)		

women without tamoxifen exposure (diagnosed between 1961 and 1987) was 98 681; 128 854 women (diagnosed between 1988 and 2010) had tamoxifen exposure. A total of 145 meningiomas were found in women without tamoxifen exposure and 78 meningiomas were found in women with tamoxifen exposure.

The risk of meningioma in our cohort is presented in Table 2 according to tamoxifen exposure status. For women without tamoxifen exposure, the risk of meningioma was significantly increased, with an SIR of 1.54 (95% CI 1.30–1.81). By contrast, the risk of meningioma was not increased in women with tamoxifen treatment (SIR = 1.06, 95% CI 0.84–1.32). The risk of meningioma was further analysed by follow-up interval and age at diagnosis of breast cancer. For women without tamoxifen exposure, the increased risk of meningioma can persist for 10 years after the first breast cancer, and the risk was increased for women diagnosed with breast cancer before 50 years and after 59 years. In addition, we calculated the risk of meningioma among breast cancer patients diagnosed between 1988 and 2000 and those between 2001 and 2010, separately. The SIR was 1.08 ($N=55$, 95% CI 0.81–1.41) for those diagnosed between 1988 and 2000 and 1.01 ($N=23$, 95% CI 0.64–1.51) for those diagnosed between 2001 and 2010.

In Table 3, we present the adjusted risk ratio on the basis of the percentage of misclassification of exposure. The adjusted risk ratio decreased with an increased percentage of misclassification of exposure. The risk ratio was 1.01 when misclassification of exposure was 10%.

Discussion

In this historical population-based cohort study, we identified a total of 227 535 women diagnosed with breast cancer during 1961–2010. The main finding is that the incidence of meningioma was significantly increased in women diagnosed with breast cancer between 1961 and 1987, when tamoxifen was not used for the treatment of breast cancer in Sweden. In addition, we found that the

Table 2 Risk of meningioma in Swedish women with a breast cancer diagnosis in 1961–2010

	Not tamoxifen exposed (1961–1987)			Tamoxifen exposed (1988–2010)		
	O	SIR	95% CI	O	SIR	95% CI
Overall	145	1.54	1.30 1.81	78	1.06	0.84 1.32
Time after breast cancer diagnosis (years)						
1–4	46	1.73	1.27 2.31	31	0.95	0.64 1.35
5–9	50	2.10	1.56 2.77	27	1.10	0.72 1.60
10+	49	1.12	0.82 1.48	20	1.22	0.74 1.88
Age at diagnosis of breast cancer (years)						
< 50	32	1.46	1.00 2.07	20	1.32	0.81 2.05
50–59	30	1.33	0.90 1.90	25	1.04	0.67 1.54
60+	83	1.66	1.32 2.06	33	0.95	0.66 1.34

Bold type: 95% CI does not include 1.00.

CI, confidence interval; O, observed number of cases; SIR, standardized incidence ratio.

Table 3 Adjusted risk ratio according to the percentage of misclassification of the exposure

Misclassification (%)	Adjusted risk ratio
0.95	1.03
0.90	1.01
0.85	0.98
0.80	0.94
0.75	0.90
0.70	0.85

incidence of meningioma in women diagnosed with breast cancer during 1988–2010, when tamoxifen was used widely in Sweden, was close that in the general population, suggesting that tamoxifen may prevent the development of meningioma.

The increased risk of meningioma in women diagnosed with breast cancer before 1987 is in agreement with a few previous reports (Markopoulos *et al.*, 1998; Malmer *et al.*, 2000; Custer *et al.*, 2002; Rao *et al.*, 2009). One Swedish study found the relative risk of meningioma to be around 1.6 after the diagnosis of breast cancer (Malmer *et al.*, 2000). Another study in the USA using the Washington State Cancer Registry found that the risk of meningioma in women with breast cancer and the risk of breast cancer in women with meningioma were increased (Custer *et al.*, 2002). One subsequent study confirmed the observed association between meningioma and breast cancer in women, but not in men (Rao *et al.*, 2009). The strong association between meningioma and breast cancer suggests that the two tumour types share aetiological factors. One explanation for the increased incidence of meningioma after breast cancer could be related to the radiation and chemotherapy used to treat primary cancers. However, the observed increase in the risk of meningioma in our study persisted for 10 years of follow-up. This suggests that the treatment effect may only play a small role because therapeutic effects are usually observed in the late follow-up period instead of the initial follow-up period (Ji and Hemminki, 2006). Another explanation is that the two primary cancers share genetic or environmental risk factors. However, a previous study suggests that the contribution of BCRA1 and BCRA2 mutations to the development of meningioma is minimal (Kirsch *et al.*, 1997). On the basis of our discussion above, the strong association between breast cancer and meningiomas may be related to oestrogen, which could contribute to the development of these two types of tumour.

Women with breast cancer have been treated with tamoxifen since the late 1980s in Sweden (Rutqvist, 2004), and the prognosis has been found to be markedly improved among patients with oestrogen receptor-positive tumours. In addition, many studies have examined the effectiveness of tamoxifen in preventing breast cancer (Freedman *et al.*, 2003; Kramer and Brown, 2004). It was found that administration of tamoxifen to women

daily for 5 years can reduce their risk of developing breast cancer by about one-half (Freedman *et al.*, 2003; Kramer and Brown, 2004). However, it is not known whether tamoxifen can prevent the development of meningioma, although oestrogen may play an important role in the development of meningioma.

In this study, we found that the incidence of meningioma in breast cancer patients diagnosed after 1987 and treated with tamoxifen was close to that in the general population. To our knowledge, no previous study has examined whether tamoxifen can inhibit the development of meningioma. Our data suggest that tamoxifen may inhibit the development of meningioma, which may be helpful for individuals at high risk of meningioma, such as those with neurofibromatosis type 2 gene (*NF2*) mutations: mutations in the *NF2* gene may account for half of all meningioma cases (Simon *et al.*, 2007). Two small studies explored the effect of tamoxifen treatment on meningioma, but the results were inconclusive (Markwalder *et al.*, 1985; Goodwin *et al.*, 1993). A study by Markwalder *et al.* (1985) in which six meningioma patients were treated with tamoxifen found no significant improvement in tumour growth. Another study by Goodwin *et al.* (1993), based on 21 patients with non-resectable refractory meningiomas, did not recommend the use of tamoxifen in refractory meningioma.

The present study has some important strengths. First, all primary breast cancers and subsequent meningiomas were identified from the Swedish Cancer Registry, which has high quality and nationwide coverage. Diagnostic bias is unlikely because the Swedish Cancer Registry is based on the compulsory clinical reports provided by physicians, pathologists, and cytologists, ensuring diagnostic accuracy at the national level. In addition, this study is a nationwide study and enough patients were included to ensure reliable risk estimates. The prospective study design and the completeness of the follow-up of patients are other major advantages of the present study.

One major limitation of this study is that data on medication with tamoxifen in our cohort at the individual level were lacking, and we defined tamoxifen exposure by year of diagnosis of breast cancer on the basis of evidence that tamoxifen has been used widely in Sweden since the late 1980s. However, such a definition may have led to non-differential misclassification of tamoxifen exposure, thereby diluting the true observations and biasing our results towards the null. The adjusted risk ratio decreased with an increased percentage of misclassification (Table 3), providing further evidence that non-differential misclassification will bias our results towards the null. The use of tamoxifen was infrequent in Sweden before 1990, but increased continuously during the 1990s (Kemetli *et al.*, 2009). In 2005, the proportion of operable breast cancer patients treated with adjuvant endocrine therapy was around 60–80%, although the prevalence

varied somewhat depending on the age at diagnosis (Kemetli *et al.*, 2009). In addition, treatment with tamoxifen at the beginning lasted only for 2 years, and then increased to 5 years (Ferno *et al.*, 2000). The increased prevalence and time for the treatment of breast cancer with tamoxifen suggest that the risk of meningioma could be varied depending on the time period. Indeed, our study found that the risk of meningioma was somewhat higher among those patients diagnosed between 1988 and 2000 compared with those between 2001 and 2010, further supporting the evidence that treatment with tamoxifen may decrease the risk of meningioma. It is known that the therapy and diagnosis of meningioma have changed during the study period, but the SIR in this study was adjusted for the time period, which can minimize the confounding effect. In addition, adjuvant chemotherapy for breast cancer has also increased during the study period (Kemetli *et al.*, 2009), but no evidence suggests that adjuvant chemotherapy could protect against the development of meningioma. The mortality of breast cancer has decreased continuously during the past decades (Schopper and De Wolf, 2009), but the risk of meningioma could be higher among women with low mortality because of the long duration of follow-up compared with those with high mortality. Data on individual-level risk factors such as alcohol consumption, smoking and dietary factors were lacking, which may have partly confounded our conclusion. However, there is no conclusive evidence that these factors are associated with meningioma, which suggests that their effects are minimal.

Conclusion

Women diagnosed with breast cancer who were not treated with tamoxifen had an increased risk of meningioma, suggesting that the two types of tumour may share aetiological factors such as oestrogen. By contrast, the incidence of meningioma in women with breast cancer who were treated with tamoxifen was close to that in the general population, which suggests that tamoxifen may prevent the development of meningioma.

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J.J., K.S. and J.S. were responsible for the study concept and design. J.S., K.S. and J.J. obtained funding. K.S. and J.S. acquired the data. J.J. analysed and interpreted the data. J.J. drafted the manuscript. J.J., K.S. and J.S. revised the manuscript for important intellectual content.

Conflicts of interest

There are no conflicts of interest.

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