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ORIGINAL ARTICLE

Risk of skin cancer following tamoxifen treatment in more than 16,000 breast cancer patients: a cohort study

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Abstract
Background Women with breast cancer are at increased risk of developing skin cancer. Little is known about how tamoxifen affects this risk. We aimed to investigate whether tamoxifen treatment following breast cancer is associated with skin cancer.
Methods A cohort consisting of 44,589 women diagnosed with breast cancer during 1977–2007 from the nationwide clinical database of the Danish Breast Cancer Cooperative Group, was followed for a primary skin cancer [basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or melanoma] in the Danish Cancer Registry supplemented by data on BCC and SCC from the Danish Pathology Register. We investigated incidence of skin cancer among 16,214 women treated with tamoxifen compared to 28,375 women not treated with tamoxifen by calculating incidence rate ratios (IRRs) in Cox regression models.
Results Tamoxifen users were followed for a median of 2.9 years. The median duration of tamoxifen treatment increased from around 1 year among women diagnosed before 1999 to nearly 2.5 years among women diagnosed in 1999 or later. Women treated with tamoxifen had an IRR 1.06 (95 % CI 0.72–1.55) for SCC and an IRR 1.40 (95 % CI 0.95–2.08) for melanoma when compared to non-users. The observed number of these types of cancer (37 SCCs and 38 melanomas among users) did not allow stratification on calendar-period. The overall IRR for BCC was 0.96 (95 % CI 0.84–1.09), but the IRR differed by menopausal status and calendar-period at diagnosis of breast cancer.
Conclusions Our overall results indicate that tamoxifen is not associated with skin cancer. However, the inconsistency of results from stratifications prevents a firm conclusion.

Keywords Breast cancer · Tamoxifen · Non-melanoma skin cancer · Melanoma

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Introduction

Studies of second malignancies after breast cancer show that breast cancer patients have an increased risk of developing melanoma [1–3]. Non-melanoma skin cancer (NMSC) has rarely been included as an outcome in such studies. However, two studies found an increased risk of NMSC [1, 4]. Thus, skin and breast cancer may share common etiologic factors such as hormone related factors. In support of this, estrogen receptors (ERs) are expressed in benign naevi [5] as reflected in naevi change during pregnancy [6, 7]. Melanoma also expresses ERs, and the incidence of melanoma is rare before puberty, increases during the reproductive years and decreases among

postmenopausal women [8–10]. Non-melanoma skin cancer carcinogenesis is promoted by the UV induced DNA damage in the skin [11–13] and estrogens may act as photosensitizing agents by potentiating the skins reaction to UV radiation [14, 15]. In addition, keratinocytes express ERs [16, 17].

Tamoxifen has been widely used in the adjuvant treatment of ER positive early breast cancer. In light of the possible hormonal influence on skin cancer, tamoxifen may modify the risk of melanoma and/or NMSC after a diagnosis of breast cancer. In accordance, results from a recent study from Switzerland indicated that breast cancer patients treated with tamoxifen had a lower risk of melanoma than non-users comparing each group to the background population [18]. These findings were, however, not supported by a Danish [19] and a Dutch study [20]. None of these studies investigated the risk of NMSC after tamoxifen use.

The aim of this study is to investigate if tamoxifen is associated with skin cancer. Our study is based on information from the same registers as the Danish study by Andersson et al. but will add further knowledge on the relationship between tamoxifen and skin cancer by performing a direct comparison between users and non-users of tamoxifen, including NMSC as an outcome and extending the follow-up period by approximately 10 years.

Materials and methods

The Danish Breast Cancer Cooperative Group (DBCG) has prepared treatment guidelines for breast cancer since 1977 [21]. A nationwide clinical database under the DBCG has detailed information on almost every woman diagnosed with breast cancer in Denmark. The database includes the personal identification number (incorporates sex and date of birth), date of surgery, menopausal status at the time of diagnosis and tumor characteristics. Information on medical treatment at diagnosis is also available on women who have been enrolled in a treatment program according to the DBCG guidelines. In regard to tamoxifen, the prescribing clinician reports treatment start and end dates on a standardized form. The DBCG database was linked to the Central Population Registry (CPR) for vital status.

In the DBCG database, we identified 57,273 women with invasive breast cancer diagnosed during 1977–2007, who had undergone surgery and were enrolled in a treatment program. Patients with distant metastases at diagnosis are not eligible for treatment programs and were therefore not included. Of the 57,273 women, 217 were excluded because they participated in randomized trials and received tamoxifen succeeded by blinded endocrine treatment. Furthermore, we excluded 4109 women who had been allocated to tamoxifen treatment, but no detailed information regarding the treatment had been reported to the DBCG. Since it is uncertain whether these women actually received tamoxifen, they were excluded from the study. Thus, users of tamoxifen were women for whom treatment dates and doses of tamoxifen were reported to the DBCG, while non-users of tamoxifen were women who had not been prescribed or allocated to tamoxifen treatment according to the DBCG. We also excluded 274 women, because of inconsistencies between the date of surgery for breast cancer and date of initiation of tamoxifen treatment, 5340 premenopausal non-users diagnosed during 1990–1998, because premenopausal women were not allocated to tamoxifen treatment in this period and 19 women with unknown menopausal status.

The Danish Cancer Registry is nationwide and includes records on almost every cancer diagnosed in Denmark since 1943. Tumors are coded according to ICD-10 and ICD-O-3 since 1978. The Danish Pathology Register contains detailed records of all pathology specimens analyzed in Denmark since 1997, as well as records of specimens from some pathology departments dating back to 1970's. Date of request and diagnoses based on the Danish SNOMED codes are reported. The SNOMED codes include information on anatomical location and histology. A database that contains incident cases of basal cell carcinomas (BCC) and squamous cell carcinomas (SCC) was established by including the first recorded incident case of BCC or SCC registered in either the Danish Cancer Registry [ICD-10 topography code = C44 and ICD-O3 morphology = M-807 (SCC) and M-809 (BCC)] or the Danish Pathology Register [SNOMED topography codes = T01 and SNOMED morphology codes = M-807 (SCC) and M-809 (BCC)] between 1978 and 2009 [22].

Cancer diagnoses among users and non-users of tamoxifen were identified in the Danish Cancer Registry and in the database of NMSC described above. Subsequently, 2432 women were excluded because they had been diagnosed with another cancer before the breast cancer surgery. Follow-up for skin cancer began at date of breast cancer surgery and continued until date of diagnosis of melanoma, NMSC or non-skin cancer, start of other endocrine therapy (aromatase inhibitors or megestrol acetate), start of a second tamoxifen course, death, emigration or the end of 2009, whichever occurred first. As aromatase inhibitors or megestrol acetate could potentially affect risk of skin cancer, we censored women when they received these other endocrine treatments. This primarily affected women diagnosed in the most recent period from 1999 to 2007 when aromatase inhibitors were introduced in Denmark. The follow-up period was shortened considerably among these women due to this censoring. Furthermore, we censored at date of second tamoxifen course to

avoid having more than one past user period. Only around 2 % of tamoxifen users were censored for this reason, so it had little impact on the results. During the most recent 10-year period, records of tamoxifen use may be incomplete due to delay in submitting the registration forms to the DBCG. Therefore, we also censored women diagnosed during this period at date of last record of tamoxifen, if they had been prescribed tamoxifen for <5 years and had no subsequent record of non-use.

For 293 women, the censoring date was prior to the entry date and therefore, they were excluded. Users of tamoxifen contributed person-years to the non-user category from date of surgery to start date of tamoxifen treatment and contributed person-years to the user category from the latter date.

Statistics

Direct comparisons of women treated and not treated with tamoxifen were made by calculating incidence rate ratios (IRR) for BCC, SCC and melanoma in Cox proportional hazard models with time since breast cancer surgery as the underlying time scale to ensure that the estimation was based on comparisons of individuals who had been followed for the same length of time. The main exposure variable 'use of tamoxifen' was included as a time-dependent covariate with values reflecting use of tamoxifen as either ever or never use. These analyses were adjusted for age at breast cancer surgery (30–39, 40–49, 50–59, 60–69, 70+ years), calendar-period at breast cancer surgery (1977–1989, 1990–1998, 1999–2007), radiotherapy (yes, no) and chemotherapy (yes, no). To eliminate skin cancer that may have arised before breast cancer diagnosis although not yet diagnosed, we performed a subgroup analysis where 5431 users and 19,179 non-users who had ≥5 years of follow-up were included.

In the follow-up for BCC, we stratified the cohort according to calendar-periods of breast cancer surgery (1977–1989, 1990–1998 and 1999–2007) that reflect changes in DBCG protocols and according to menopausal status due to the different treatment guidelines for pre- and postmenopausal women. Within these calendar-year strata, we estimated IRRs of BCC among postmenopausal women by time since start of use of tamoxifen (<1, 1–4, 5–9 and ≥10 years), current and past use, duration (<1.2 and ≥1.2 years) and time since last use (<5, 5–9 and ≥10 years). In a sub-analysis also including only postmenopausal women in the same strata, we investigated whether tamoxifen alone or in combination with radiotherapy and/or chemotherapy was associated with risk of BCC compared to no use of adjuvant therapy. We did not perform these stratifications for SCC and melanoma due to small numbers. Statistical analysis was performed using SAS/STAT version 9.3.

Results

Our cohort from the DBCG consisted of 44,589 women diagnosed with primary breast cancer. Among these, 16,214 (36 %) women became users of tamoxifen during follow-up, while 28,375 (64 %) women remained non-users throughout follow-up. Table 1 shows baseline characteristics of users and non-users of tamoxifen. Among users, 12,470 (77 %) were postmenopausal at diagnosis of breast cancer while 18,963 (67 %) were postmenopausal among non-users.

Median time from date of breast cancer surgery to start of tamoxifen treatment was 1 month (5–95 % percentiles 0.3–11 months). The 16,214 users of tamoxifen were followed for a median of 2.9 years (5–95 % percentiles 0.5–16.8 years), and 2641 (16 %) were followed for more than 10 years. The relatively short median follow-up was due to short follow-up for the many patients with breast cancer during the most recent period, 1999–2007, i.e., a median of 2.5 years among 3441 premenopausal women and 2.5 years among 6234 postmenopausal women despite that 6539 users with breast cancer in earlier periods had median follow-up periods of around 6 years (Table 2). Thus, number of users of tamoxifen clearly increased during the study period. Duration of tamoxifen treatment also increased during the study period from a median around 1 year among patients diagnosed before 1999 to a median around 2.5 years among patients diagnosed between 1999 and 2007.

The adjusted IRR of BCC associated with tamoxifen use was 0.96 (95 % CI 0.84–1.09) based on 318 and 1074 BCCs among users and non-users, respectively (Table 3). Among women treated with tamoxifen, 37 developed SCC during follow-up while the corresponding number among non-users was 115 and the adjusted IRR of SCC was 1.06 (95 % CI 0.72–1.55). Melanoma was identified in 38 users and 97 non-users, and the adjusted IRR was 1.40 (95 % CI 0.95–2.08). The risk estimates associated with tamoxifen use for BCC, SCC and melanoma did not change substantially when we restricted the analysis to ≥5 years of follow-up (Table 3).

Among premenopausal women, we found no significant association between tamoxifen use and BCC in any of the two calendar-periods 1977–1989 and 1999–2007 (Table 4). Among postmenopausal users of tamoxifen diagnosed between 1977 and 1989, the incidence of BCC was higher compared to non-users (IRR 1.43; 95 % CI 1.10–1.85), whereas among users diagnosed during 1990–1998 and 1999–2007, the incidence of BCC was decreased (IRR

Table 1 Characteristics of Danish breast cancer patients included in the study

	Tamoxifen users		Non-users	
	No. of patients	%	No. of patients	%
All	16,214	100	28,375	100
Age at BC (years)				
<40	604	4	1812	6
40–49	2354	15	5558	20
50–59	5263	32	9209	32
60–69	5822	36	8506	30
70+	2171	13	3290	12
Menopausal status				
Premenopausal	3744	23	9412	33
Calendar-period at BC				
1977–1989	303		6492	
1990–1998[a]	–		–	
1999–2007	3441		2920	
Postmenopausal	12,470	77	18,963	67
Calendar-period at BC				
1977–1989	2743	22	5254	28
1990–1998	3493	28	7566	40
1999–2007	6234	50	6143	32
ER status of BC				
Positive	13,561	84	12,375	44
Negative	560	3	7661	27
Unknown	2093	13	8339	29
Chemotherapy of BC				
Yes	4095	25	6557	23
No	12,119	75	21,818	77
Radiotherapy of BC				
Yes	9797	60	11,925	42
No	6417	40	16,450	58
Reasons for censoring				
Other non-skin cancer	1181	7	4179	15
Death	4169	26	10,083	36
Other endocrine treatment	6145	38	0	0
Second period of tamoxifen treatment	325	2	0	0
Uncertainty about duration of tamoxifen	983	6	0	0
Emigration	20	0	83	0
End of follow-up	2998	19	12,739	45

All percentages are column percentages

BC breast cancer, *ER* estrogen receptor

[a] Premenopausal women were not allocated to tamoxifen between 1990 and 1998. Hence, we excluded premenopausal non-users in the time period 1990–1998

0.82; 95 % CI 0.66–1.02 and IRR 0.62; 95 % CI 0.47–0.82, respectively). The risk of BCC mainly differed during the first 9 years after initiation of tamoxifen treatment between postmenopausal users in the first and the two subsequent calendar-periods. In parallel, the IRR by current and past use of tamoxifen differed by calendar-period with increased IRRs during the first period and decreased IRRs during the two next periods though only statistically significant in the most recent period (Table 4). Adding duration to current use and time since last use to past use did not provide a clearer pattern.

The risk of BCC tended to be increased among postmenopausal users diagnosed in 1977–1989 independently of whether tamoxifen was used alone or in combination

Table 2 Percentiles for length of follow-up and for characteristics of use of tamoxifen among pre- and postmenopausal breast cancer patients by calendar-period for the first breast cancer

	1977–1989			1990–1998			1999–2007		
Percentiles	5	50	95	5	50	95	5	50	95
Premenopausal women									
Follow-up time among tamoxifen users (years)	0.94	6.31	25.97	–	–	–	0.50	2.51	7.84
Duration of tamoxifen (years)	0.23	1.42	1.51	–	–	–	0.28	2.43	4.97
Time since last use of tamoxifen at exit (years)[a]	0.17	5.76	24.80	–	–	–	0.14	2.09	6.53
Postmenopausal women									
Follow-up time among tamoxifen users (years)	0.75	6.41	23.86	0.50	6.97	17.00	0.52	2.52	9.03
Duration of tamoxifen (years)	0.48	1.38	1.57	0.49	1.13	5.20	0.50	2.47	5.02
Time since last use of tamoxifen at exit (years)[a]	0.29	5.82	22.61	0.43	6.31	15.99	0.16	2.62	7.86

[a] Among past users

Table 3 Incidence rate ratios (IRRs) for skin cancers associated with tamoxifen treatment among all Danish breast cancer patients included in the study and among patients with follow-up ≥5 years

	BCC	SCC	Melanoma
All			
No. of cases			
Users	318	37	38
Non-users	1074	115	97
Tamoxifen ever versus never			
Age-adjusted IRR[a] (95 % CI)	1.00 (0.88–1.13)	1.07 (0.73–1.56)	1.37 (0.93–2.02)
Further adjusted IRR[b] (95 % CI)	0.96 (0.84–1.09)	1.06 (0.72–1.55)	1.40 (0.95–2.08)
Follow-up ≥5 years			
No. of cases			
Users	167	24	18
Non-users	709	86	53
Tamoxifen ever versus never			
Age-adjusted IRR[a] (95 % CI)	1.08 (0.91–1.29)	1.11 (0.70–1.76)	1.57 (0.91–2.73
Further adjusted IRR[b] (95 % CI)	1.04 (0.88–1.24)	1.10 (0.69–1.77)	1.59 (0.91–2.78)

[a] Adjusted for time since breast cancer surgery and age at breast cancer surgery

[b] Adjusted for time since breast cancer surgery, age at breast cancer surgery, calendar-period at breast cancer surgery, chemotherapy and radiation therapy

with radiotherapy or chemotherapy when compared to patients receiving no adjuvant therapy (Table 5). Among those diagnosed later, there was no excess of BCC in either of the treatment categories shown in Table 5.

Discussion

Our overall results show that women treated with tamoxifen do not have an altered risk of skin cancer compared to women untreated. In relation to BCC, the only subtype of skin cancer for which we had sufficient numbers to carry out stratified analyses, the IRR associated with tamoxifen differed by calendar-period of breast cancer diagnosis among postmenopausal women. Further exploring the risk by time since breast cancer diagnosis, current and past use of tamoxifen, duration of tamoxifen treatment and time since last use of tamoxifen as well as combinations with other therapies did not provide additional information to explain the discrepancy.

The main strengths of our study are the size of the cohort of tamoxifen users and non-users and the relatively large number of skin cancer cases. In addition, due to the existence of the personal identification number, which is used in all health registries and secures correct linkages between registries, we are able to do a follow-up study with virtually no loss to follow-up. Another advantage is the long observation period of ≥10 years for more than 2600 tamoxifen users. Non-melanoma skin cancer data are not routinely collected by cancer registries, but in Denmark,

Table 4 Incidence rate ratios (IRR) for BCC associated with tamoxifen treatment among pre- and postmenopausal Danish breast cancer patients according to calendar-period for the breast cancer diagnosis

	1977–1989				1990–1998				1999–2007			
	No. of BCC				No. of BCC				No. of BCC			
	Users	Non-users	IRR	95 % CI	Users	Non-users	IRR	95 % CI	Users	Non-users	IRR	95 % CI
Premenopausal women												
Overall, age-adjusted	5	261	0.63	0.26–1.53	–	–	–	–	27	46	1.24	0.75–2.03
Overall, further adjusted[a]	5	261	0.67	0.28–1.64	–	–	–	–	27	46	1.36[b]	0.78–2.36
Postmenopausal women												
Overall, age-adjusted	108	213	1.41	1.11–1.78	103	368	0.82	0.66–1.02	75	186	0.66	0.50–0.87
Overall, further adjusted[a]	108	213	1.43	1.10–1.85	103	368	0.82	0.66–1.02	75	186	0.62[b]	0.47–0.82
Time since start of use of tamoxifen[a]												
<1	6	213	1.63	0.56–4.68	4	368	0.45	0.15–1.31	17	186	0.50[b]	0.28–0.89
1–4	26	213	1.48	0.90–2.45	28	368	0.62	0.41–0.94	53	186	0.82[b]	0.58–1.15
5–9	26	213	1.69	1.02–2.81	32	368	0.75	0.51–1.11	5	186	0.25[b]	0.10–0.64
≥10	50	213	1.29	0.90–1.83	39	368	1.30	0.90–1.88	–	186	–	–
Current use of tamoxifen[a]	10	213	2.76	1.13–6.73	16	368	0.64	0.38–1.08	61	186	0.67[b]	0.50–0.94
Past use of tamoxifen[a]	98	213	1.36	1.04–1.79	87	368	0.87	0.68–1.10	14	186	0.45[b]	0.26–0.79
Current use of tamoxifen[a]												
Tamoxifen duration <1.2 years	8	213	2.22	0.85–5.80	4	368	0.41	0.14–1.16	19	186	0.50[b]	0.29–0.86
Tamoxifen duration ≥1.2 years	2	213	9.58	1.03–89.19	12	368	0.75	0.41–1.35	42	186	0.81[b]	0.56–1.18
Past use of tamoxifen[a]												
<5 years since the last use of tamoxifen	31	213	1.41	0.90–2.22	38	368	0.75	0.53–1.06	13	186	0.50[b]	0.28–0.89
5–9 years since the last use of tamoxifen	24	213	1.53	0.92–5.53	27	368	0.86	0.57–1.29	1	186	0.22[b]	0.03–1.56
≥10 years since the last use of tamoxifen	43	213	1.26	0.87–1.84	22	368	1.21	0.76–1.93	–	186	–	–

[a] Adjusted for time since breast cancer surgery, age at breast cancer surgery and radiation therapy

[b] Adjusted for time since breast cancer surgery, age at breast cancer surgery, chemotherapy and radiation therapy

we have an extensive registration of NMSC in two nationwide population-based registries, and thereby a high completeness of NMSC registration. We were not able to adjust for UV dose, frequency of UV light exposure, skin type, number of freckles and eye color which are well established risk predictors for skin cancer [23]. However, it seems unlikely that the distribution of these risk predictors should differ between women treated and untreated with tamoxifen. We lacked information on treatment for recurrence, therefore, tamoxifen given for a recurrence was not taken into consideration in the analyses. An additional limitation is that only few women used tamoxifen for 5 years or more. Five years treatment with tamoxifen was introduced as standard therapy in the late 1990's in Denmark, however, soon after—in 2004—sequential therapy with aromatase inhibitors subsequent to treatment with tamoxifen for 2.5 years was introduced among postmenopausal women, thus reducing the number of women receiving tamoxifen for 5 years. This also affected duration of tamoxifen treatment among premenopausal women since a considerable proportion of these became postmenopausal after the diagnosis, and therefore also received aromatase inhibitors. Other reasons for the short duration among premenopausal women in the most recent period include postponement of start of tamoxifen treatment to after termination of chemotherapy resulting in a shorter time to end of follow-up and a relatively short follow-up among many of the premenopausal users reaching end of study. If long duration of treatment is required for an effect on skin cancer, we would not be able to show this.

A study from Switzerland [18] investigated the risk of melanoma after treatment with tamoxifen by comparing

Table 5 Incidence rate ratios (IRRs) for BCC associated with different combinations of treatments among postmenopausal breast cancer patients according to calendar-period for the breast cancer diagnosis

	Postmenopausal breast cancer patients											
	1977–1989				1990–1998				1999–2007			
	N	BCC	IRR[a]	95 % CI	*N*	BCC	IRR[a]	95 % CI	*N*	BCC	IRR[a]	95 % CI
No adjuvant therapy	4083	181	1.00	–	4649	230	1.00	–	1796	71	1.00	–
Chemotherapy and/or radiotherapy	1171	32	0.94	0.64–1.37	2917	138	1.11	0.90–1.38	4347	115	0.93	0.68–1.26
Tamoxifen only	653	24	1.35	0.88–2.07	2666	77	0.82	0.63–1.06	1684	22	0.52	0.32–0.84
Tamoxifen + radiotherapy	1525	62	1.38	1.04–1.85	827	26	0.93	0.62–1.40	4316	53	0.70	0.49–1.02
Tamoxifen + chemotherapy	564	22	1.46	0.94–2.29	0	0	–	–	19	0	–	–
Tamoxifen + radiotherapy + chemotherapy	1	0	–	–	0	0	–	–	215	0	–	–

[a] Adjusted for time since first breast cancer surgery and age at breast cancer surgery

melanoma incidence among 3358 patients treated and 4002 patients not treated with antiestrogens to that expected in the general population. The majority of the treated women probably received tamoxifen as sole adjuvant hormonal therapy since the cohort consisted of women diagnosed between 1980 and 2005 and according to the authors, aromatase inhibitors were not introduced in Switzerland until 2004. The investigators found an increased risk of MM among non-users of antiestrogens compared to the general population based on 11 cases, while users did not have an increased risk based on 23 cases. In their interpretation, these results suggest that antiestrogen therapy modifies the risk of melanoma after breast cancer. A similar approach with comparison of incidence of melanoma in 7204 tamoxifen users and 24,614 non-users to the general population was used in the previously mentioned Danish study [19]. However, the incidence of MM among both users and non-users was similar to that in the background population.

In a large population based cohort study of breast cancer patients from the Netherlands, comparisons within the cohort were made between different treatments [20]. One hundred and sixty-four women in the cohort developed melanoma after the breast cancer diagnosis, but it is unclear how many of these received treatment with tamoxifen. The investigators found an increased risk of melanoma among all breast cancer patients compared to the background population, but there was no difference between the incidence of melanoma among those who received hormonal treatment and those who did not. Thus, only one study has suggested that tamoxifen modifies the risk of melanoma [18]. We were not able to confirm this. However, the risk estimates were based on few numbers of cases.

In general, NMSC is being studied much more rarely than melanoma, because of no or incomplete registration of NMSC in various cancer registries [24–26]. Hence, to our knowledge, the present study is the first to assess the potential association between tamoxifen treatment and the subsequent risk of NMSC. Our overall results for both BCC and SCC were not in support of an association, however, stratification on calendar-year and menopausal status at breast cancer showed no consistent pattern in relation to BCC, thus questioning this finding. The relatively small numbers of SCC did not allow stratified analyses.

Through the past years, it has been discussed whether skin cancers are hormone related [27]. Expression of ERs in naevi [5], melanoma [5, 16, 28, 29] and keratinocytes [16, 17], certain patterns in melanoma incidence [8–10] and excess risk of skin cancer following breast cancer [1–3] support the relationship. In contrast, one meta-analysis [30] and one review [6] concluded that exogenous

hormones do not increase risk of melanoma, and studies on reproductive factors and risk of melanoma have given inconsistent results [6, 30–33]. In addition, there is no consensus from studies investigating use of exogenous hormones and risk of NMSC [34–37].

Tamoxifen is a selective estrogen-receptor modulator (SERM) that has both estrogen agonist and antagonist effects [38]. According to our knowledge, it is still uncertain whether tamoxifen acts as an agonist or antagonist in melanocytes or keratinocytes, but presence of ERs in both benign naevi and keratinocytes strongly suggest that tamoxifen could affect the likelihood of developing skin cancer. Our results, however, do not provide support for this suggestion, but inconsistencies in the results for BCC challenge this interpretation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts interests.

Ethical standard The study was approved by the Danish Data Protection Agency. Approvals from Ethical Committees and written consent from study participants were not obtained, since in Denmark these are not required for register-based studies that do not involve contact with study participants and collection of biological samples.

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