FULL PAPER

BJC

British Journal of Cancer (2018) 118, 294–298 | doi: 10.1038/bjc.2017.378

Keywords: tetracycline; melanoma; squamous cell carcinoma; basal cell carcinoma; UV exposure; pharmacoepidemiology

Tetracycline use and risk of incident skin cancer: a prospective study

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Background: Tetracycline is a photosensitising medication that increases skin vulnerability to UV-related damage.

Methods: We prospectively examined tetracycline use and risk of incident melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) based on 213 536 participants from the Nurses' Health Study (NHS), NHS2, and Health Professionals Follow-up Study. Information on ever use of tetracycline was asked via questionnaire. Diagnoses of melanoma and SCC were pathologically confirmed.

Results: Tetracycline use was associated with a modestly increased risk of BCC ($n_{case} = 36\,377$), with a pooled hazard ratio (HR) of 1.11 (95% confidence interval (CI) = 1.02–1.21, *P*-trend = 0.05 by duration of use). Tetracycline use was not significantly associated with melanoma ($n_{case} = 1831$, HR = 1.09, 95% CI = 0.94–1.27) or SCC ($n_{case} = 3332$, HR = 1.04, 95% CI = 0.91–1.18) risk overall. However, we observed positive interactions between tetracycline use and adulthood UV exposure on SCC risk (*P*-interaction = 0.05).

Conclusion: Tetracycline use was associated with a modestly increased risk of BCC, but was not associated with melanoma or SCC.

Excessive sun exposure and UV radiation is the most recognised risk factor for skin cancer (Li *et al*, 2016). Individuals with a sun-sensitive phenotype, such as sunburn susceptibility and poor tanning ability, have significantly increased risk of melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) (Li *et al*, 2016). Tetracycline is known to induce photosensitivity, specifically phototoxic dermatoses, increasing the vulnerability of the epidermis and dermis to UV-induced damage (Stern, 1998; Drucker and Rosen, 2011). Tetracycline may therefore act as a co-carcinogen with UV radiation and increase the risk of skin cancer. Only a limited number of epidemiologic studies have been published on tetracycline use and skin cancer (Kaae *et al*, 2010; Robinson *et al*, 2013). Although these studies suggest a possible association between tetracycline use and particularly BCC risk, whether tetracycline use may increase the risk of all skin cancer types remain to be elucidated. We prospectively examined the associations between tetracycline use and risk of incident melanoma, SCC, and BCC in two cohorts of women, the Nurses' Health Study (NHS) and NHS2, and a cohort of men, the Health Professionals Follow-up Study (HPFS).

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Received 23 May 2017; revised 2 October 2017; accepted 4 October 2017; published online 26 October 2017

Table 1. Baseline characteristics of the study population (1982 in NHS, 1993 in NHS2, and 1992 in HPFS) according to ever use of tetracycline[a]

	NHS ($n=89\,168$)		NHS2 ($n=85\,714$)		HPFS ($n=38\,654$)	
	Never use ($n=84\,770$)	Ever use ($n=4398$)	Never use ($n=47\,121$)	Ever use ($n=38\,593$)	Never use ($n=37\,471$)	Ever use ($n=1183$)
Age, year, mean (s.d.)	48.6 (7.2)	45.4 (7.1)	37.9 (4.8)	38.3 (4.5)	59.0 (9.5)	57.1 (9.6)
Body mass index, kg m^{-2}, mean (s.d.)	24.7 (4.6)	24.5 (4.6)	25.3 (5.7)	25.3 (5.8)	25.9 (3.5)	25.8 (3.5)
Current smoking (%)	27.1	25.0	10.4	11.9	7.7	7.9
Alcohol intake, g per day, mean (s.d.)	6.6 (11.2)	7.0 (11.2)	3.0 (5.9)	3.3 (6.3)	10.1 (14.2)	10.9 (15.1)
Citrus consumption, serving per day, mean (s.d.)	0.9 (0.7)	0.9 (0.8)	0.6 (0.6)	0.6 (0.6)	0.9 (0.8)	0.9 (0.8)
Family history of melanoma (%)	2.7	3.1	4.1	4.5	3.4	5.1
Red or blonde hair (%)	15.8	17.1	19.9	21.1	13.7	13.8
$\geqslant$3 Moles on the extremity (%)	12.8	14.3	30.9	33.5	12.7	14.2
Burn or blistering skin reaction to the sun (%)	36.9	38.0	48.0	49.3	69.6	74.6
Childhood tendency to average to deep tanning response (%)	69.1	68.7	NA	NA	NA	NA
History of $\geqslant$6 severe or blistering sunburns[b] (%)	50.7	53.6	9.1	10.9	35.1	39.3
Lifetime average summer time sun exposure $\geqslant$6 h per week (%)	45.2	43.7	42.2	43.4	67.5	65.6
Annual erythemal UV, mW m^{-2}, mean (s.d.)	186.5 (24.0)	188.2 (25.0)	169.9 (34.4)	173.0 (38.3)	195.8 (36.1)	195.3 (35.8)
Severe teenage acne (%)	NA	NA	2.8	14.3	NA	NA
Severe acne (%)	NA	NA	0.9	7.8	NA	NA
Rosacea (%)	NA	NA	0.6	2.0	NA	NA
Periodontal disease (%)	12.0	12.1	NA	NA	18.1	18.7

Abbreviations: HPFS = Health Professionals Follow-up Study; NA = not available; NHS = Nurses' Health Study; NHS2 = Nurses' Health Study 2; UV = ultraviolet.
[a]All values other than age were age adjusted.
[b]NHS and HPFS asked the lifetime number of sunburns, whereas NHS II asked the number of teenage severe sunburns.

MATERIALS AND METHODS

Study population. Details of the three cohorts are presented in the Supplementary Information. In 1982 (NHS) and 1992 (HPFS), participants were asked 'did you ever take tetracycline for at least 2 months at a time (e.g., for acne or other reason)' and for how long they had used tetracycline. In 1993 (NHS2), participants were asked whether they had ever taken tetracycline (without specifying 'at least two months') and for how long they had used tetracycline. In 2006, we sent a supplementary questionnaire to 100 HPFS participants (50 reported $\geqslant$4 years of use and 50 reported $<$4 years) and asked the indications for tetracycline use. Of them, 83 returned the completed questionnaire, with acne (51.8%, 43 out of 83) and rosacea (19.3%, 16 out of 83) reported as the primary indications. Only 12.0% (10 out of 83) denied or could not remember using tetracycline for $\geqslant$2 months (Sutcliffe *et al*, 2007).

Participants reported diagnoses of melanoma, SCC, and BCC on biennial surveys. Related medical records for melanoma and SCC were reviewed and only pathologically confirmed invasive cases were included in our analysis. The BCC diagnoses were not confirmed but previous studies have indicated high validity of self-reports (Colditz *et al*, 1986; Hunter *et al*, 1992).

Among participants with information on tetracycline use, we excluded those reporting any cancer at or before the baseline (1982 in NHS, 1993 in NHS2, and 1992 in HPFS) and all non-whites.

Statistical analysis. Person-years of follow-up were calculated from the return of the baseline questionnaire to the diagnosis date of melanoma, SCC, or BCC, death, or end of follow-up (June 2012 for NHS, June 2011 for NHS2, and Jan 2010 for HPFS), whichever came first. We calculated age- and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazards analysis stratified by age and calendar time in each 2-year interval. Covariates in the multivariate-adjusted models are shown in the Supplementary Information. To address the concern of confounding by indication, we conducted sensitivity analyses by additionally adjusting for indications for tetracycline (history of periodontal disease in NHS/HPFS; severe teenage acne, adulthood severe acne, and rosacea in NHS2) or excluding those reporting these conditions. We examined whether UV exposure (ambient erythemal UV radiation, a measure of both UVA and UVB) or sun-sensitive phenotypes modified the associations between tetracycline use and skin cancer risk (Supplementary Information online). Stratified analyses were also conducted by body sites of melanoma/SCC and Breslow thickness of melanoma. Heterogeneity tests were conducted using Q statistics. We used random-effect meta-analysis models to get pooled HRs across the three cohorts.

Analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). All *P*-values were two tailed with the significance level set at $P<0.05$.

RESULTS

A total of 213 536 participants were included (Table 1). The mean (s.d.) age was 48.4 (7.2) years in NHS, 38.1 (47.1) years in NHS2, and 59.0 (9.5) years in HPFS at baseline. Tetracycline users tended to have more severe or blistering sunburns and had higher UV exposure.

Table 2. HRs (95% CIs) for the association between tetracycline use and risk of incident melanoma

	Person-years	Cases	Age-adjusted HR (95% CI)	Multivariate-adjusted HR[a] (95% CI)
NHS (1982–2012)				
Status				
No	2 285 831	887	1.00	1.00
Yes	120 389	51	1.14 (0.86–1.52)	1.10 (0.82–1.45)
Duration				
Never	2 285 831	887	1.00	1.00
<1 Year	82 319	31	1.01 (0.71–1.45)	0.96 (0.67–1.38)
1–2 Years	19 541	12	1.68 (0.95–2.98)	1.66 (0.94–2.95)
>2 Years	18 529	8	1.17 (0.58–2.35)	1.13 (0.56–2.26)
P for trend			0.18	0.26
NHS2 (1993–2011)				
Status				
No	832 323	210	1.00	1.00
Yes	680 527	200	1.16 (0.95–1.40)	1.10 (0.90–1.33)
Duration				
Never	832 323	210	1.00	1.00
<1 Year	551 838	161	1.14 (0.93–1.41)	1.10 (0.90–1.35)
1–2 Years	73 957	23	1.25 (0.81–1.92)	1.14 (0.74–1.75)
>2 Years	54 733	16	1.15 (0.69–1.90)	1.06 (0.63–1.76)
P for trend			0.29	0.52
HPFS (1992–2010)				
Status				
No	585 177	467	1.00	1.00
Yes	18 751	16	1.12 (0.68–1.84)	1.03 (0.62–1.69)
Duration				
Never	585 177	467	1.00	1.00
<1 Year	12 073	11	1.20 (0.66–2.18)	1.12 (0.62–2.05)
1–2 Years	2397	2	1.10 (0.27–4.42)	0.94 (0.23–3.79)
>2 Years	4281	3	0.90 (0.29–2.82)	0.81 (0.26–2.52)
P for trend			0.54	0.40
Meta-analysis				
Status				
No	3 703 331	1564	1.00	1.00
Yes	819 667	267	1.15 (0.99–1.34)	1.09 (0.94–1.27)
Duration				
Never	3 703 331	1564	1.00	1.00
<1 Year	646 230	203	1.12 (0.94–1.32)	1.07 (0.90–1.27)
1–2 Years	95 895	37	1.37 (0.98–1.92)	1.28 (0.92–1.79)
>2 Years	77 543	27	1.12 (0.76–1.65)	1.04 (0.71–1.54)
P for trend			0.22	0.47

Abbreviations: CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; NHS = Nurses' Health Study; NHS2 = Nurses' Health Study 2.
[a]Multivariate-adjusted analyses were performed stratifying by age and calendar time in each questionnaire cycle and adjusting for body mass index (<25, 25–29.9, or ⩾30 kg m^{-2}), smoking (never, past, or current smokers), alcohol intake (0, 0–4.9, 5–9.9, or ⩾10 g per day), childhood reaction to sun (practically none, some redness, burn, or painful burn/blisters), childhood tanning ability (practically none, little, average, or deep tan; NHS only), times of sunburns (0, 1–2, 3–5, 6–9, or ⩾10), mole count (0, 1–2, 3–5, 6–9, or ⩾10), hair colour (red, blonde, light brown, dark brown, or black), family history of melanoma (yes or no), citrus consumption (<2 times per week, ⩾2 to ⩽4 times per week, >4 times per week to <1 time per day, or ⩾1 time per day), average sun exposures (<1, 2–5, 6–10, or ⩾11 h), and erythemal UV radiation (in tertiles).

We identified 1831 melanoma cases during follow-up. We did not find significant associations between risk of incident melanoma and either ever tetracycline use (multivariate-adjusted pooled HR = 1.11, 95% CI = 0.95–1.29), or duration of use (*P*-trend = 0.33, Table 2).

A total of 3332 SCC and 36 377 BCC cases were documented during follow-up. Ever tetracycline use was significantly associated with modestly increased risk of BCC, with a pooled HR of 1.11 (95% CI = 1.02–1.21). The association appeared stronger in NHS (HR = 1.20, 95% CI = 1.13–1.28) than NHS2/HPFS and was not statistically significant in HPFS. There was a trend towards elevated BCC risk with increasing duration of use (*P*-trend = 0.05; Table 3). Although we did not find a significant association for SCC overall (HR = 1.04, 95% CI = 0.91–1.18), we observed positive interactions between tetracycline use and UV exposure in adulthood on SCC risk (pooled *P*-interaction = 0.05); the HR (95% CI) of SCC risk associated with tetracycline was 0.89 (0.73–1.10) for the lower half of UV exposure and 1.17 (0.99–1.40) for the upper half of UV exposure. We did not find significant modifications of SCC risk by sun-sensitive phenotypes, nor did we find any interactions for risk of BCC or melanoma. In stratified analyses, we did not find significant heterogeneity between tetracycline and melanoma risk by body sites or Breslow thickness of melanoma, or SCC risk by body sites (data not shown).

Sensitivity analyses did not materially change the findings (data not shown).

DISCUSSION

In our prospective study, tetracycline use was associated with modestly increased risk of BCC, but not with melanoma and SCC risk overall. Ambient UV radiation may interact with tetracycline use, increasing the risk of SCC.

Only limited studies have examined the associations between tetracycline use and risk of skin cancer. A Danish national register-based cohort study found a significant association between any short-term use of tetracycline and risk of melanoma (incidence rate ratio (IRR) = 1.1, 95% CI = 1.1–1.3), SCC (IRR = 1.5, 95% CI = 1.4–1.7), and BCC (IRR = 1.3, 95% CI = 1.3–1.4), but for long-term use of

Table 3. HRs (95% CIs) for the association between tetracycline use and risk of incident SCC and BCC

		SCC			BCC		
	Person-years	Cases	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)	Cases	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)
NHS							
Status							
No	2 010 837	1447	1.00	1.00	18 894	1.00	1.00
Yes	104 668	66	0.99 (0.77–1.27)	0.98 (0.76–1.25)	1049	1.23 (1.15–1.30)	1.20 (1.13–1.28)
Duration							
Never	2 010 837	1447	1.00	1.00	18 894	1.00	1.00
<1 Year	71 638	48	1.04 (0.78–1.39)	1.03 (0.77–1.38)	703	1.19 (1.10–1.28)	1.16 (1.08–1.25)
1–2 Years	16 954	9	0.87 (0.45–1.68)	0.84 (0.44–1.62)	173	1.32 (1.13–1.53)	1.27 (1.09–1.48)
>2 Years	16 076	9	0.88 (0.46–1.70)	0.88 (0.46–1.69)	173	1.32 (1.14–1.54)	1.29 (1.11–1.50)
P for trend			0.68	0.60		<0.0001	<0.0001
NHS2							
Status							
No	806 252	243	1.00	1.00	3478	1.00	1.00
Yes	656 732	220	1.08 (0.90–1.30)	1.04 (0.87–1.25)	3185	1.11 (1.06–1.17)	1.07 (1.02–1.12)
Duration							
Never	806 252	243	1.00	1.00	3478	1.00	1.00
<1 Year	532 730	182	1.09 (0.90–1.32)	1.05 (0.87–1.27)	2524	1.08 (1.03–1.14)	1.04 (0.99–1.10)
1–2 Years	71 371	23	1.14 (0.74–1.75)	1.09 (0.71–1.67)	384	1.28 (1.15–1.42)	1.20 (1.08–1.33)
>2 Years	52 631	15	0.93 (0.55–1.56)	0.89 (0.53–1.50)	277	1.20 (1.06–1.36)	1.14 (1.01–1.29)
P for trend			0.90	0.73		<0.0001	0.007
HPFS							
Status							
No	511 220	1310	1.00	1.00	9456	1.00	1.00
Yes	16 380	46	1.20 (0.90–1.61)	1.11 (0.83–1.49)	315	1.11 (0.99–1.24)	1.06 (0.95–1.19)
Duration							
Never	511 220	1310	1.00	1.00	9456	1.00	1.00
<1 Year	10 547	31	1.23 (0.86–1.75)	1.15 (0.80–1.64)	202	1.08 (0.94–1.24)	1.05 (0.91–1.20)
1–2 Years	2082	6	1.37 (0.61–3.06)	1.21 (0.54–2.71)	42	1.26 (0.93–1.71)	1.16 (0.85–1.56)
>2 Years	3752	9	1.05 (0.54–2.02)	0.95 (0.49–1.83)	71	1.13 (0.89–1.42)	1.06 (0.83–1.33)
P for trend			0.88	0.82		0.10	0.33
Meta							
Status							
No	3 328 309	3000	1.00	1.00	31 828	1.00	1.00
Yes	777 780	332	1.08 (0.94–1.23)	1.04 (0.91–1.18)	4549	1.15 (1.07–1.24)	1.11 (1.02–1.21)
Duration							
Never	3 328 309	3000	1.00	1.00	31 828	1.00	1.00
<1 Year	614 915	261	1.10 (0.95–1.27)	1.06 (0.92–1.23)	3429	1.12 (1.04–1.19)	1.09 (1.01–1.17)
1–2 Years	90 407	38	1.10 (0.79–1.53)	1.04 (0.75–1.44)	599	1.29 (1.19–1.40)	1.22 (1.12–1.32)
>2 Years	72 459	33	0.95 (0.67–1.34)	0.90 (0.64–1.28)	521	1.23 (1.13–1.34)	1.18 (1.06–1.31)
P for trend			0.88	0.58		0.02	0.05

Abbreviations: BCC = basal cell carcinoma; CI = confidence interval; HPFS = Health Professionals Follow-up Study; HR = hazard ratio; MV = multivariate; NHS = Nurses' Health Study; NHS2 = Nurses' Health Study 2; SCC = squamous cell carcinoma.
[a]Multivariate-adjusted analyses were performed adjusting for covariates as described in the footnote of Table 2.

tetracycline (additional five courses of treatment with tetracycline), the association remained significant only for BCC (Kaae *et al*, 2010). A case–control study reported an increased risk of BCC (OR = 1.8, 95% CI = 1.2–2.8), but not SCC (OR = 1.0, 95% CI = 0.6–1.7), associated with ever tetracycline use (Robinson *et al*, 2013).

Previously, we have reported heterogeneous associations between UV radiation and risks of different skin cancers (Li *et al*, 2016). In the current study, risk of SCC with tetracycline use increased among those with higher UV exposure, and this may support our hypothesis that tetracycline, as a photosensitising medication, acts as a co-carcinogen with UV radiation. However, we did not find similar interactions by UV radiation for BCC, nor did we find significant interaction between sun-sensitive phenotypes and tetracycline use on any skin cancer risk. Whether the observed modestly increased risk of BCC is directly due to tetracycline's phototoxic effects requires further investigation.

We observed much higher proportion of ever tetracycline users in NHS2 (45.0%) than NHS (4.9%) and HPFS (3.1%) (Table 1). Ever use of tetracycline was defined in NHS/HPFS as 'use for at least two months' and the majority of NHS/HPFS users may have used for acne or rosacea (Sutcliffe *et al*, 2007). Different from NHS/HPFS, NHS2 collected information on 'ever use of tetracycline' without specifying 'at least two months'. Tetracycline came into commercial use in 1978, when NHS (age 30–55 years at cohort inception in 1976) and HPFS (40–75 years at cohort inception in 1986) participants were far beyond the adolescence for teenage acne. In addition, because of secular changes, the use of tetracycline has greatly increased. These may explain the observed high proportion of ever users in NHS2 (age 25–42 years at cohort inception in 1989). We collected diagnoses of acne/rosacea in NHS2 and diagnosis of periodontal disease in NHS/HPFS, although we did not specifically ask the diseases that tetracycline was used to treat for each individual. In one prior analysis of NHS2, severe teenage acne was associated with increased melanoma risk and decreased SCC risk, but was not associated with BCC (Zhang *et al*, 2015). In another study, rosacea was associated with increased BCC risk (Li *et al*, 2015) but we lack sound biological plausibility for the associations. Sensitivity analyses to address concern of confounding by indication (acne and rosacea in

NHS2 and periodontal disease in NHS/HPFS) did not change our findings appreciably. Therefore, it is less likely that the observed associations can be directly explained by these diseases.

Our study has limitations. First, the cohorts did not assess use of other tetracycline class members. Therefore, we cannot assess use of other tetracycline family antibiotics, particularly doxycycline that has recognised photosensitising properties (Layton and Cunliffe, 1993; Drucker and Rosen, 2011). The above-mentioned Danish study reported significantly increased risk of melanoma, SCC, and BCC associated with doxycycline use (Kaae *et al*, 2010). However, a case–control study did not find significant associations with skin cancer (OR < 1) (de Vries *et al*, 2012). Another tetracycline class drug, minocycline, is not considered photosensitising (Drucker and Rosen, 2011). Second, tetracycline use was only asked once and not updated during follow-up. This may have biased our effect estimates towards the null, as further exposure to tetracycline was not accounted for. We cannot assess whether skin cancers developed more frequently in tetracycline users with ongoing or repeated exposure. The different way of data collection on ever tetracycline use in three cohorts (NHS2 *vs* NHS/HPFS) is also a limitation of our study. Third, we cannot rule out residual confounding by aesthetic-related concerns; participants taking tetracycline antibiotics to treat visible skin diseases may be more likely to seek UV exposure for tanning purposes that would increase their risk of skin cancer.

In conclusion, ever tetracycline users had a modestly increased risk of BCC. Tetracycline use and higher UV exposure may jointly increase SCC risk. Although the effect tends to be at most modest, considering the common use of tetracycline antibiotics in clinical practice, our study supports further investigation on the potential skin cancer risk associated with tetracycline, particularly for prolonged periods of use and in individuals with high levels of UV exposure.

ACKNOWLEDGEMENTS

We thank the participants and staff of the Nurses' Health Study and Health Professionals Follow-up Study for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. The authors assume full responsibility for analyses and interpretation of these data. The views presented in this manuscript do not necessarily represent the views of the Department of Veteran Affairs. The work was supported by the Research Career Development Award of Dermatology Foundation, Richard B. Salomon Faculty Research Award of Brown University, the National Institute of Health Grants for Nurses' Health Study (P01 CA87969 and UM1 CA186107), Nurses' Health Study II (UM1 CA176726), and Health Professionals Follow-up Study (UM1 CA167552). The funding sources had no role in study design and conduct; in the collection, management, analysis, and interpretation of data; in the preparation, review, or approval of the report; or in the decision to submit the article for publication.

CONFLICT OF INTEREST

AAQ is a consultant for Abbvie, Amgen, Centers for Disease Control and Prevention, Janssen, Merck, Novartis, and Pfizer. The other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

W-QL: study concept and design, statistical analysis, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content, AMD: analysis and interpretation of data and critical revision of the manuscript for important intellectual content, EC: critical revision of the manuscript for important intellectual content, FL and TV: acquisition of data and critical revision of the manuscript for important intellectual content, SL: statistical analysis and critical revision of the manuscript for important intellectual content, MAW: critical revision of the manuscript for important intellectual content, AAQ: study concept and design, acquisition of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, funding support, and study supervision.

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Supplementary Information accompanies this paper on British Journal of Cancer website (http://www.nature.com/bjc)