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Acknowledgements—Supported by the BioMed 2 Program (contract BMH4-CT96-0754), and in France by the INSERM-CNAMTS (convention No 3AM078), the Ligue Nationale contre le Cancer and the Fondation de France and in Switzerland by the Federal Office of Public Health.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S44–S45, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00108-7

IV.2 Does Risk of Endometrial Cancer Increase with Longer Duration of Tamoxifen Use?

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The effects of tamoxifen duration and dosage on the risk of endometrial cancer have not yet been examined extensively. In the six studies that examined the effect of duration of treatment, a significantly positive trend was found in four, a non-significant positive trend in one and a non-significant negative trend in one. © **1998 Elsevier Science Ltd. All rights reserved.**

OVER THE past decade conclusive evidence has emerged that tamoxifen treatment is associated with moderately increased risk of endometrial cancer [1]. Table 1 gives an overview of the most important studies examining the risk of endometrial cancer in relation to tamoxifen use [2–9]. There are four reports on randomised controlled trials, four case–control studies and one cohort study. In these studies, the risk of endometrial cancer among tamoxifen-treated women is 2- to 7-fold increased as compared to the risk in non-users. A more precise estimate of the risk is not yet available. The large variation in risks presented in Table 1 is likely to be partly related to the instability of the estimates, due to the relatively small numbers of endometrial cancers included in individual studies. This variation may also reflect, however, differences in the daily dosage and duration of tamoxifen between the various patient populations.

The effects of tamoxifen duration and dosage on the risk of endometrial cancer have not been examined extensively. In most clinical trials, it is not possible to study these effects since duration and dosage vary little among the patients included in individual studies [3–5]. A comparison of the trial reports (Table 1) suggests that dosage is not a major risk factor; roughly similar risk increases of endometrial cancer have been observed after daily tamoxifen dosages of 20 and 40 mg [2, 5, 7]. In a combined analysis of three Scandinavian trials, the relative risk of endometrial cancer in tamoxifen-

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Table 1. Endometrial cancer risk after tamoxifen

Author	No. of breast cancers	No. of endometrial cancers (*n* in TAM-users)	Dosage (mg)	Duration	Relative risk (95% CI) TAM versus no TAM, unless stated otherwise	Trend in RR with longer TAM use
Fornander and associates* clinical trial [2]	1,846	15 (13†)	40	2–5 years	6.4 (1.4–28)	+
Andersson and associates* clinical trial [3]	1,710	9 (7)	30	48 wks	3.3 (0.6–32.4)	n.r.
van Leeuwen and associates case–control [4]	n.a.	98 (23)	20–40	Varied	Ever use: 1.3 (0.7–2.4) ≥ 2 years: 2.3 (0.9–5.9) (P = 0.049 for trend)	+
Fisher and associates clinical trial [5]	2,843	17 (15†)	20	Planned: ≥ 5 years Median: 41 months	7.5 (1.7–32.7) 2.2‡ (not given) 2.3§ (not given)	n.r.
Cook and associates case–control [6]	n.a.	34 (9)	Mostly 20	Varied (mostly: < 2 years)	0.6 (0.2–1.9)	(–)
Rutqvist and associates clinical trial [7]	4,914	42 (34)	30–40	48 wks–5 years	4.1 (1.9–8.9)	(+)
Curtis and associates cohort [8]	87 323	457 (73)	Unknown	Unknown	2.0 (1.6–2.6)† 1.2 (1.1–1.4)¶	n.r.
Sasco and associates case–control [9]	n.a.	43 (29)	Mostly 20	Varied	Ever use: 1.4 (0.6–3.5) ≥ 5 years: 3.5 (0.9–12.7) (P = 0.02 for trend)	+
Bergman and associates unpublished case–control	n.a.	297 (106)	20–40	Varied	Ever use: 1.5 (1.1–1.9) ≥ 5 years: 6.8 (2.4–19.4)	+

n.a., not applicable; TAM, tamoxifen; CI, confidence interval; RR, relative risk. *Data also included in Rutqvist [7]. †In tamoxifen-allocated women. ‡Compared to general population. §Compared to NSABP (B-06) trial. ¶No TAM-group compared to general population. +, significantly positive; (+), non-significantly positive; (–), non-significantly negative; n.r., not reported.

treated patients appeared to be higher in the Stockholm trial (RR, 5.6; 95% CI 1.9–16.3) than in the Danish and South-Swedish studies (RRs 2.0 and 3.3, respectively) [7]. One explanation for this finding is the longer duration and/or higher daily dose of tamoxifen therapy in the Stockholm trial (40 mg daily for 2 or 5 years) compared to that in the other two trials (30 mg daily for 1 year). The case–control studies are particularly well suited to investigate effects of duration and dosage since most of them were population-based, ensuring large variation in treatment strategies. In the Dutch study, a significant increase in risk emerged with increasing duration of use and also with increasing cumulative dose [4]. The duration-response trends were similar with daily doses of 40 mg or 20 mg and less. However, this observation was based on small numbers. The study was recently expanded and now includes 297 cases and 854 control subjects. The first analyses show a strong trend of increasing risk of endometrial cancer with duration of tamoxifen use ($P < 0.001$). For women who had used tamoxifen for 2–5 years, or ≥ 5 years, (RR, 2.0, 95% CI 1.2–3.2) and (RR, 6.8, 95% CI 2.4–19.4), respectively, compared to never users. Dose intensity did not affect the risk. In the French study, the risk also increased significantly with duration of use, but the risk increase per year of use may have been overestimated since the percentage of controls with unknown duration of tamoxifen treatment was larger than that of the cases [9]. In the only cohort study, which examined risk of endometrial cancer in breast cancer patients reported to the Surveillance Epidemiology, and End Results (SEER) programme in the USA, information of duration and dosage of tamoxifen was not available [8]. However, the difference in endometrial cancer risk between tamoxifen-users and non-users was more pronounced in 5-year survivors of breast cancer, suggesting an increasing risk of endometrial cancer with duration of use. In conclusion, in the 6 studies that examined the effect of duration of treatment, a significantly positive trend was found in four [2, 4, 9], a nonsignificant positive trend in one [7], and nonsignificant negative trend in one [6]. Larger studies are needed to assess the separate and combined effects of tamoxifen duration and dosage on the risk of endometrial cancer.

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