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Risks of Malignant and Non-Malignant Tumours in Tall Women Treated with High-Dose Oestrogen during Adolescence

Emelie Benyi[a] Helle Kieler[b] Marie Linder[b] Martin Ritzén[a] Jan Carlstedt-Duke[c] Torsten Tuvemo[d] Otto Westphal[e] Lars Sävendahl[a]

[a]Paediatric Endocrinology Unit, Department of Women's and Children's Health, [b]Center for Pharmacoepidemiology, Department of Medicine, [c]Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, [d]Department of Women's and Children's Health, Uppsala University, Uppsala, and [e]Göteborg Paediatric Growth Research Center, Institute of Clinical Sciences, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden

Key Words
Tall stature · Ethinyloestradiol · Growth reduction · Cancer · Malignant melanoma

Abstract
Background/Aim: High-dose oestrogen treatment has been used to reduce growth in tall adolescent girls. The long-term safety with regard to cancer has not been clarified. Our aim was to study if this growth reduction therapy affects cancer risk later in life. ***Methods:*** A cohort study of 369 (172 treated, 197 untreated) Swedish women who in 1973–1993 were assessed for tall adolescent stature was designed. Data were collected from university hospital records, patient questionnaires, and the Swedish Cancer Register. ***Results:*** Risks are presented as odds ratios (ORs) with 95% confidence intervals comparing treated to untreated subjects. In treated subjects, the overall OR for having a tumour (malignant or non-malignant) was 1.7 (0.8–3.8). The ORs were 2.3 (0.4–12.8) for breast tumours, 0.8 (0.2–2.6) for gynaecological tumours, and 6.1 (1.04–∞) for melanoma. When limiting to malignant tumours, the crude ORs were of similar magnitude. ***Conclusion:*** The OR for any melanoma was higher in treated than in untreated women, suggesting an increased risk of melanoma associated with high-dose oestrogen treatment during adolescence. Although the risk estimates were increased for overall tumours, breast tumours, malignant gynaecological tumours, and malignant melanoma, these associations were not statistically significant. Our results need to be verified in a larger cohort.

Introduction

Being tall is usually genetically determined and is associated with disease only in a minority of cases. Since the 1950s, oestrogens in combination with or without added progestins have been used to limit further growth by inducing premature growth plate closure in tall adolescent girls. Ethinyloestradiol, which is the oestrogen most frequently used in combined oral contraceptives (COCs), has been the preferred choice when treating tall girls. The doses used for growth limitation have been higher than

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E-Mail karger@karger.com
www.karger.com/hrp

Emelie Benyi
Paediatric Endocrinology, Lab Q2:08
Karolinska University Hospital
SE–171 76 Stockholm (Sweden)
E-Mail emelie.benyi@ki.se

those used for contraception. Although cancer is more common among tall women in general [1], the long-term cancer risk of high-dose oestrogen treatment has not been established in this patient group.

An increased risk of breast cancer has been reported in users of COCs, including in teenagers, although others have reported no increased risks [2, 3]. In a large meta-analysis of previous users of COCs, an increased risk of cervical cancer was found [4]. Although a role for oestrogen receptor-β in the development of malignant melanoma has been reported [5], so far no clear association between COC use and melanoma has been established [6, 7]. It is important to increase our knowledge about possible long-term risks involved when young adolescent girls are considered for oestrogen treatment.

Considering previous reports, it could be hypothesized that a high dose of oestrogen given to adolescent girls will increase the risk of cancer later in life. This led us to design the present cohort study, where we studied the association between exposure to high-dose ethinyloestradiol and overall tumour risk as well as specific risks for melanoma and breast and gynaecological tumours.

Subjects and Methods

Study Design

Tumour incidence in women who initiated high-dose oestrogen treatment for tall stature during their adolescence were compared with a control group of untreated women assessed for tall stature at the same centres during the same time period. The women were identified through hospital registers. Data on exposure were obtained from the medical records. Information on occurrence of tumours was obtained from national health registers and a health questionnaire sent to all subjects. Study subjects were followed up from the start of treatment (or an equivalent time point of inclusion for untreated) until December 31, 2010. The study protocol was approved by the Regional Ethics Board in Stockholm.

Subjects Studied

The original cohort included 390 Swedish women who were assessed for tall stature as young adolescents between 1973 and 1993 at four university hospitals in Sweden (fig. 1). A health questionnaire was sent out which a total of 220 (59.6%, 115 treated and 105 untreated) women filled out and returned. When receiving the questionnaire, the subjects were given the possibility to decline participation also in the register study by opt out. The opt-out procedure was based on the results from interviews with a random sample of women from the original cohort. For these women, active consent for participation in follow-up studies using register data was not crucial [8]. 21 individuals (6 treated and 15 untreated) denied participation and were therefore excluded. For the remaining 369 patients, register data were retrieved. Out of these, 172 (46.6%) were treated and 197 (53.4%) were untreated.

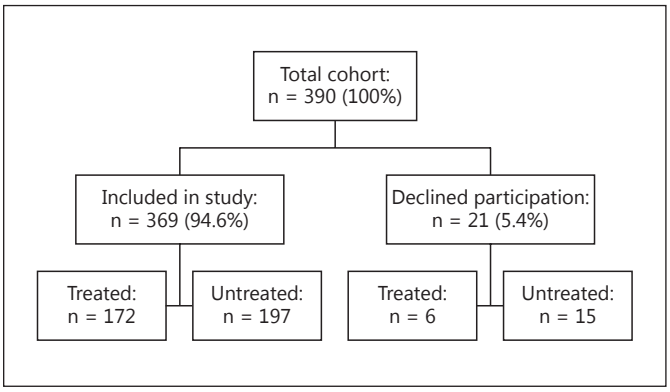

Fig. 1. A chart of the study cohort presenting included and excluded patients and how treatment status is distributed in these two groups.

Data Sources

Information on exposure to oestrogens, height at time of inclusion, and predicted height were retrieved from hospital medical records. Information on exposure was also collected from questionnaires, as well as adult height, education, and employment. Register data were obtained from three different health registers; the Swedish Cancer Register, the Swedish Cause of Death Register, and the Swedish Medical Birth Register [9].

The Swedish Cancer Register was used to study cancer occurrence in the cohort. This register contains information about clinical and morphological diagnosis and date of diagnosis. All malignant cancers should be reported and so should certain precancerous tumours, such as severe dysplasias, melanoma in situ, and non-malignant tumours in ovaries and other endocrine organs. The register is updated annually, and 99% of all cancers are confirmed morphologically [9]. All tumours reported to the Swedish Cancer Register during the study period 1973–2010 were included in our analysis. Basal cell carcinomas of the skin were not included because they were not reported to the Cancer Register before 2004 and because they lack the ability to become malignant and spread. A database of malignant tumours in the Swedish population extracted from the Swedish Cancer Register was also used. It is available for the public at the home page of The National Board of Health and Welfare [9].

The Swedish Cause of Death Register was used to study deaths and their relationship to cancer. This register contains dates and causes of death for all Swedish residents including deaths occurring outside of Sweden unless the individual has emigrated. It is also updated annually and the coverage is more than 99% [9].

The Swedish Medical Birth Register was used for information on adult height in those women in the cohort who had given birth. It contains information about maternal factors, pregnancy, delivery, and the neonatal period provided through antenatal, obstetrical, and neonatal records. Almost all births are reported to the register [9].

All the registers and the medical records include the unique personal identification number assigned to each resident in Sweden. The personal identification number allowed information to be linked between the data sources [10].

Table 1. Study cohort characteristics

Characteristic	Treated (n = 172)	Untreated (n = 197)
Age at inclusion, years	13.2 (12.3–14.0)	13.0 (12.2–14.0)
Height at inclusion, cm	176.0 (173.5–178.4)	175.0 (169.5–178.9)
Predicted adult height, cm	183.9 (180.7–186.0)	181.2 (179.0–183.8)
Achieved adult height, cm	181.0 (180.0–183.0)	181.0 (178.5–183.0)
Treatment duration, years	1.2 (0.95–1.6)	
Daily dose of ethinyloestradiol, μg	500 (250–1,000)	
Daily dose of MPA, mg	5 (5–5)	
Follow-up time, years	28.0 (25.7–32.4)	27.1 (24.8–32.1)

IQRs are shown in parentheses.

Exposures and Outcomes

During the study period, the doses of ethinyloestradiol used to diminish adult height decreased gradually from 1,000 μg/day (which at that time was used as symptomatic treatment of acromegaly) to 100 μg/day. Most of the oestrogen treatment was cyclic – 3 weeks on, 1 week off – with 1–2 weeks of medroxyprogesterone acetate (MPA) at the end of the oestrogen period. The MPA doses were fairly constant throughout the study period, normally 5 mg/day.

Breast tumours, gynaecological tumours, and melanomas were analysed specifically because they have previously been associated with oestrogen exposure. We also analysed associations between ethinyloestradiol exposure and all tumours reported to the Swedish Cancer Register, defined as 'any tumours' as well as malignant tumours separately.

The patients were given instructions for self-measuring their height [11]. Alternatively, in those patients where questionnaires were missing (n = 149), heights were collected from the Swedish Medical Birth Register for those women who had given birth and the rest were missing (n = 72).

Statistical Analyses

Summary statistics are presented as medians with interquartile ranges (IQRs). To test associations between exposure to ethinyloestradiol and tumours, we computed odds ratios (ORs) or exact ORs with 95% confidence intervals (CIs) within a logistic regression model. We used a 5% significance level, that is, p values <0.05 were considered statistically significant.

When looking for possible confounders the criteria are that they affect both the exposure and the outcome. Primarily, height was tested as a potential confounder. First we adjusted for adult height (n = 297). Second, we tested for predicted height before treatment (n = 252). Information on adult height was obtained from the questionnaires or from the Medical Birth Register; predicted height according to Bayley-Pinneau was obtained from hospital medical records [12]. Using information from the questionnaire, such as higher education and degree of employment (n = 220), difference in socioeconomic status was also tested as a confounder. Higher education was defined as further education after upper secondary school. No confounders were included in the final model, since they did not affect the estimates.

The treated and the untreated group were compared to the Swedish population with regard to occurrence of malignant cancer by using standardized incidence ratios (SIRs). The SIR is the sum of observed cases divided by the sum of expected cases. The population incidence rate was calculated for each year and age group. The expected number of cases for each year and age group was then calculated as the number of women under observation times the population rate.

The statistical software SAS® version 9.3 (SAS Institute, Cary, N.C., USA) was used for all analyses.

Results

Study Cohort

Baseline characteristics and treatment doses are presented in table 1. For 60% of all treated women, ethinyloestradiol was administered for 3 weeks followed by 1 week's break, and the cycle then repeated. The remaining 40% had a continuous administration of oestradiol. For 98% of all treated patients, the daily dose of MPA was 5 mg. MPA mostly was administered either for 5 days (44%) or for 14 days (32%). The remaining women received MPA for 6, 7, 8, or 12 days. Of the 172 treated patients, 9 were treated for less than 6 months and 5 of these for less than 3 months. One patient terminated therapy after only 2 weeks because of side effects (nausea, headache, swelling, and rash). Follow-up time is presented in table 1 and was calculated from start of treatment for treated individuals and the time of the last visit, when a final height prediction was made for untreated patients, which represented their time of inclusion.

Median predicted final heights at time of assessment for tall stature differed by 2.7 cm between the two groups (183.9 and 181.2 cm in treated and untreated, respectively). Adult height was missing for 72 (19.5%) women, but median adult height was identical in the two groups (181.0 cm). The proportion of women who had a higher education was 72% in the treated and 73% in the untreat-

Table 2. Tumour cases in the treated group

Patient ID	Tumour site	Age at start of treatment, years	Mean dose of oestradiol, μg	Treatment duration, years	Age at tumour diagnosis, years	Time to diagnosis[1], years
Malignant tumours						
1	cervix	13.5	500	0.5	29.8	16.3
2	ovary	12.5	250	1.3	17.2	4.7
3	breast	14.1	250	1.4	37.7	23.6
4	breast	11.9	500	0.9	38.4	26.5
5	breast	13.2	1,000	0.9	44.7	31.4
6	breast	13.7	525	1.3	45.4	31.7
7	thyroid skin[2]	13.2	1,000	0.9	16.7 46.9	3.5 33.5
8	haematopoietic[3] haematopoietic[4]	12.6	n/a	2.0	21.8 23.3	9.1 10.6
9	skin[2]	14.6	500	0.8	47.5	33.0
10	glottis[5]	11.7	500	0.4	40.2	28.4
Cancer in situ/benign tumours						
11	skin[6]	13.4	100	1.4	29.3	15.8
12	cervix	13.6	500	1.1	38.3	24.7
13	skin[7]	14.8	1,000	0.6	44.2	29.3
14	cervix	14.8	100	2.4	31.3	16.5
15	cervix	13.6	n/a	0.04	32.3	18.7
16	skin[6]	15.9	500	1.1	28.2	12.3

[1] Time from start of treatment to tumour diagnosis. [2] Malignant melanoma. [3] Leukaemia. [4] Hodgkin's disease. [5] Squamous cell carcinoma. [6] Melanoma in situ. [7] Actinic keratosis. Missing values are indicated as n/a.

Table 3. Tumour cases in the untreated group

Patient ID	Tumour site	Age at tumour diagnosis, years	Time from inclusion to diagnosis, years
Malignant tumours			
1	thyroid	42.6	27.1
2	breast	37.0	24.1
3	breast	45.6	32.9
4	cervix	34.1	19.3
Cancer in situ/benign tumours			
5	ovary	18.7	6.6
	cervix	32.3	21.1
6	haematopoietic[1]	36.1	25.8
7	cervix	25.8	12.0
8	cervix	30.2	16.6
9	cervix	31.7	17.4
10	cervix	33.5	17.9
11	cervix	41.0	27.2

[1] Myelodysplastic syndrome.

ed group. The proportion of women with full-time employment was 73% in the treated and 72% in the untreated group.

Two deaths occurred in the treated group, at 17 and 20 years of age, respectively. They were both due to accidents and not related to cancer. No deaths occurred in the untreated group.

Any Tumours (Malignant and Non-Malignant)

Out of 369 individuals who agreed to participate, 27 (16 treated and 11 untreated) developed tumours during the follow-up period (tables 2, 3). Six patients (4 treated and 2 untreated) developed a breast tumour. There were 2 cases of ovarian tumours (1 treated and 1 untreated) and 11 cases of cervical tumours (4 treated and 7 untreated). One untreated patient developed both an ovarian and a cervical tumour. There were 5 cases of skin tumours (all in the treated group), 4 melanomas and 1 non-melanoma. Haematological malignancy and thyroid cancer both occurred once in each group.

In treated patients, median age at tumour diagnosis was 35.0 (28.7–42.2) years and median time from start of

Table 4. Associations between exposure to ethinyloestradiol and tumours

Type of tumour	Number affected (%)		OR (95% CI)	p value
	treated (n = 172)	untreated (n = 197)		
Any tumours				
Overall tumours	16 (9.3)	11 (5.6)	1.73 (0.78–3.85)	0.18
Breast tumours	4 (2.3)	2 (1.0)	2.32 (0.42–12.83)	0.33
Gynaecological tumours	5 (2.9)	7 (3.6)	0.81 (0.25–2.61)	0.73
Melanoma	4 (2.3)	0 (0.0)	6.14 (1.04–∞)	0.046
Malignant tumours				
Overall tumours	10 (5.8)	4 (2.0)	2.98 (0.92–9.67)	0.07
Breast tumours	4 (2.3)	2 (1.0)	2.32 (0.42–12.83)	0.33
Gynaecological tumours	2 (1.1)	1 (0.5)	2.31 (0.21–25.65)	0.50
Melanoma	2 (1.1)	0 (0)	2.78 (0.33–∞)	0.22

The associations are presented as ORs for treated compared to untreated individuals.

treatment to diagnosis was 21.1 (14.1–29.0) years. In untreated patients, median age at tumour diagnosis was 34.1 (30.2–41.0) years and median time from inclusion to diagnosis was 19.3 (16.6–27.1) years.

The risks of developing tumours at least once during the follow-up period were calculated as ORs for treated compared to untreated individuals (table 4). For melanoma the OR was 6.1 (95% CI 1.04–∞) and this risk difference was statistically significant. For gynaecological tumours the OR was 0.8 (95% CI 0.2–2.6), for breast tumours 2.3 (95% CI 0.4–12.8), and for overall tumours it was 1.7 (95% CI 0.8–3.8). These risk differences were not statistically significant, however.

Malignant Tumours

Fourteen patients (10 treated and 4 untreated) developed a malignant tumour (tables 2, 3). Three of them developed two different types of malignant tumours. Three patients developed a malignant gynaecological tumour (2 treated and 1 untreated). All 6 cases of breast tumours and the 2 cases of thyroid tumours described above were malignant. One patient in the untreated group suffered from two different types of haematological malignancies. Two of the 4 cases of melanoma were classified as malignant.

Although not statistically significant, we found an OR of 3.0 (95% CI 0.9–9.7) for overall, 2.3 (95% CI 0.4–12.8) for breast, 2.3 (95% CI 0.2–25.6) for gynaecological cancer, and 2.8 (95 % CI 0.3–∞) for malignant melanoma (table 4).

Adjusted Values

Because neither adult nor predicted heights were found to be true confounders – that is, associated with both treatment and the tumours – heights were omitted from the analyses in the final model and therefore only crude ORs are presented.

Cancer Risk Compared to the General Population

The risks of developing cancer compared to the expected number of cases in the general population are presented as SIRs with 95% CIs in parenthesis. For the treated group, the SIR was 2.27 (1.09–4.17) for all cancers which is statistically significant (p = 0.015). For the untreated group it was 0.85 (0.23–2.18). With regard to specific cancer types, SIRs for the treated and untreated group, respectively, were 2.84 (0.76–7.28) and 1.39 (0.16–5.01) for breast cancer, 2.94 (0.33–10.62) and 1.36 (0.02–7.59) for gynaecological cancer, 3.42 (0.38–12.36) and not estimable due to no cases in the untreated group for malignant melanoma. The latter SIRs were not statistically significant.

Discussion

We report here significantly increased risk estimates for melanoma (malignant or in situ) in tall women treated with high-dose oestrogen during their adolescence. However, these results should be read with caution, since only small numbers of cancers were found. When restricting to those with malignant melanomas only, the OR

was still increased, although it was not statistically significant. An association between oestrogen treatment and melanomas might be explained, as previously suggested, by a mechanism involving the oestrogen receptor-β in melanocytes [5]. With the lower doses of oestrogen used for oral contraception or postmenopausal hormone replacement therapy, no association between oestrogens and melanoma was found [6, 7]. However, the doses of oestrogen and the age at administration differ. The first combined contraceptive pill introduced in 1960 contained 150 μg of mestranol which is equivalent to 100 μg of ethinyloestradiol. The doses of ethinyloestradiol in use have since then gradually decreased to 20–30 μg [13, 14]. A possible explanation to our results is, of course, that the difference in our study occurred by chance.

All six breast tumours were malignant and the OR of developing breast cancer in the treated group compared to the untreated was 2.3. This risk increase was not statistically significant at the 5% level, but it was in line with the increased risk reported in another Swedish study on breast cancer after the use of oral contraceptives at young age [2]. In that study, the use of oral contraceptives before a woman turned 20 generated a corresponding OR of 2.1, which is similar to what was found in our present study.

There were actually more cases of cervical and ovarian tumours in the untreated group, but the majority of them were non-malignant. Similarly, in a meta-analysis assessing cancer risk after exposure to sex hormones [4], no risk increase for ovarian cancer was found after use of COCs. Previous studies have actually shown a decreased risk of ovarian cancer after use of oral contraceptives [15]. For cervical cancer, a small risk increase was shown for present users. This excess risk declined after terminating the use of oral contraceptives. However, both the doses of oestrogen and the age of the women were different from our cohort.

The overall risk of developing a malignant tumour was increased three times in those tall women who were treated with oestrogens during their adolescence. It is important to point out, however, that this increase did not reach statistical significance. For overall tumour risk (malignant and non-malignant), the OR was lower at 1.7 (95% CI 0.8–3.8), which was still not significant.

When comparing the treated group to the Swedish population, the risk estimates were similar to those presented above. In this case, the increase in total risk of malignant tumours in the treated group was statistically significant, whereas the risks of malignant breast tumours, gynaecological tumours, and malignant melanoma were not. The untreated group had no increased risks of any malignant tumour, when compared with the Swedish population.

There is a unique opportunity in Sweden to study the long-term safety of different therapies, thanks to several national registers, including the Swedish Cancer Register. The completeness of the registers allowed us to reach a participation rate of about 95%, excluding only those study subjects declining to participate. The major limitation of our study is the limited statistical power to detect small risk increases. Although we included a majority of all women assessed for tall stature in Sweden between 1973 and 1993, and had the possibility of obtaining information on cancer for these women until 2010, we should acknowledge that the rarity of cancer at young ages would have required a larger population.

Most of the patients seen for tall stature were advised not to go on treatment if they had a family history of breast cancer or thrombosis because COCs have been linked to both thrombosis and breast cancer [2, 16]. This is an important confounder that partly might mask a true increased risk of cancer in the treated compared to the untreated group. Another possible confounder of the association between the treatment and the development of melanoma that we were not able to adjust for was cautiousness about one's appearance. It is possible that girls who chose treatment cared more about their appearance and consequently were more prone to expose themselves to sunlight or visiting tanning salons, which are both known risk factors for developing melanoma [17]. We compared the two groups with regard to socioeconomic factors but found the groups to be very similar in this aspect. Tall stature itself has been shown to increase the risk of certain cancer types [1]. Even though final height was very similar in treated and untreated individuals, it is likely that the treated group would have become taller if they had not received hormonal treatment [18]. The mechanism behind the known increased cancer risk in tall individuals is poorly understood, and it is not known whether it is the attained height, 'the genetic height', or levels of specific growth factors that explain this association. 'Genetic height' might be a confounding factor in the study because taller children are more prone to be treated and at higher risk of developing cancer. In our initial analyses we adjusted for predicted final height and attained adult height. We then found no major effect on our risk estimates.

Whether or not expected excessive tall stature should be reduced for psychosocial reasons is controversial. At present, a Swedish girl who is expected to suffer from very

tall stature might be considered eligible for growth-reducing therapy if the predicted final height exceeds 3 standard deviations above the mean, which corresponds to approximately 185 cm. Previously, girls with lower height predictions were accepted for treatment. Part of the change of policy might be explained by the secular trend in height, but changing attitudes to tall stature is probably more important. When oestrogen treatment of expected excessive tall stature was introduced, girls with a predicted adult height of even 175–180 cm were considered for treatment [19, 20].

When reducing growth in tall adolescents, one must carefully weigh the value of final height reduction against short- and long-term side effects of the treatment. Decreased fertility has been reported in tall women treated with high-dose oestrogen [21, 22]. The use of high-dose oestrogen treatment in tall girls has decreased in the last two decades, most likely because of increased acceptance of tall stature in the society and worries about adverse effects [23]. Today, there is also another treatment option; bilateral percutaneous epiphysiodesis, a surgical approach that effectively reduces the remaining growth in tall adolescents [24].

In summary, our data suggest that the risk of developing melanoma might be increased in tall women treated with high-dose oestrogen during adolescence. Breast tumours, malignant gynaecological tumours, and overall tumours (malignant and non-malignant) were also more common among treated women, although these differences did not reach the predefined significance level. Nevertheless, our findings raise concerns about the use of oestrogens in adolescent girls. If treated women are at an increased risk of developing cancer, this treatment method should be discontinued and specific screening programs should be designed for the women already treated. Before any such strategy is implemented, our data need to be verified in another cohort of women being treated with high doses of oestrogens during their adolescence.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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