A population-based cohort study on sun habits and endometrial cancer

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BACKGROUND: No large cohort study has examined the risk of endometrial cancer in relation to sun exposure.

METHODS: A population-based cohort study of 29 508 women who answered a questionnaire in 1990–92, of whom 24 098 responded to a follow-up enquiry in 2000–02. They were followed for an average of 15.5 years.

RESULTS: Among the 17 822 postmenopausal women included, 166 cases of endometrial cancer were diagnosed. We used a multivariate Cox regression analysis adjusting for age and other selected demographic variables to determine the risk of endometrial cancer. Women using sun beds > 3 times per year reduced their hazard risk (HR) by 40% (0.6, 95% confidence interval (CI) 0.4–0.9) or by 50% when adjusting for body mass index or physical activity (HR 0.5, 95% CI 0.3–0.9), and those women who were sunbathing during summer reduced their risk by 20% (HR 0.8, 95% CI 0.5–1.5) compared with women who did not expose themselves to the sun or to artificial sun (i.e., sun beds).

CONCLUSION: Exposure to artificial sun by the use of sun beds > 3 times per year was associated with a 40% reduction in the risk of endometrial cancer, probably by improving the vitamin D levels during winter.

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Excess weight alone is estimated to cause around 50% of all endometrial cancer cases in Europe and the United States (Calle and Kaaks, 2004). Among the cohort studies of lifestyle factors and endometrial cancer, no large study has investigated the effect of UV exposure on risk. Sunlight is known to be the most important source of vitamin D. A Spanish study found an inverse correlation between endometrial cancer mortality and sun exposure (indirectly assessed by using latitude as an index of solar UVB levels) (Grant, 2007), whereas a recent meta-analysis adding the results of three case-control studies showed no correlation with dietary intake of vitamin D of which sunlight is the most important source (McCullough et al, 2008).

This prospective cohort study was carried out to assess the potential influence of sun and sun bed exposure on the risk of endometrial cancer. Of the women invited, 29 508 (74%) agreed to participate; those who had had a hysterectomy before recruitment were excluded. The initial survey was performed in 1990–92 and a follow-up, similar to the first, in 2000–02. Of the women answering the first questionnaire, 24 098 (82%) also completed the second questionnaire. The initial survey covered reproductive history, hormone use, family history of gynaecological cancer, constitutional factors, marital status, level of education, and lifestyle factors such as level of physical exercise, smoking habits, and sun exposure habits. The follow-up survey covered the past medical history, body mass index (BMI), and present regular exercise.

Low-potency oestrogen use and hormone treatment use were classified as previously described (Epstein et al, 2009). For simplicity, we choose not to present the effect of hormone-use duration in this paper. In our previous study, we found that the use of only combined hormone therapy was related to a decreased risk of endometrial cancer (odds ratio (OR) 0.3, 95% confidence interval (CI) 0.1–0.8), whereas the protective effect was found after 2 years, and increased with extended duration of use. In women using only high- or low-potency oestrogens, the overall risk was doubled (OR 2.3, 95% CI 1.5–3.7), being highest during the first 2 years, and dropping slightly thereafter (Epstein et al, 2009). Use of combined oral contraceptives (OCs) was dichotomised into those who had ever used and those who had never used OCs at the inception of the study. Women not answering the question were assumed to be never users. As information on menopause age was missing in quite some women, we decided not to analyse this demographic variable.
Parity was divided into null parity or parity (i.e., one or several children) as we found no difference in one, two, or multiparous. Smoking habits were recorded at the inception of the study, categorised as never smokers (reference) or ever smokers. The wording of the sun exposure questions at study inception was: (i) do you sunbathe during summer? (never, 1–14 times, 15–30 times, >30 times); (ii) do you go abroad on vacation to swim and sunbathe? (never, once every year or two, once a year, two or more times a year); (iii) do you use a sun bed? (never, 1–3 times, >4 times per year). The first two questions were dichotomised into yes or no in the final analysis.

The BMI (weight (kg) per length (m²)) was calculated on the basis of the present length and weight reported in the second questionnaire. Body mass index was classified into three groups (BMI <25, normal weight; BMI 25–29, over weight; or BMI >29, obese). The level of present physical exercise was also obtained at the second questionnaire, and it was divided into three categories: none, go for a walk one or more times a week, or strenuous exercise weekly.

By using the unique identification number assigned to all Swedish residents, all deaths and causes of death were established through the National Cause of Death Registry (NCD). Endometrial cancers were identified through the Swedish Cancer Registry (South Swedish Regional Tumour Registry and National Swedish Tumour Registry), using the ICD9 code numbers 179, 182, and the ICD 10 code number C54. Women with sarcoma of the uterus were excluded. Vital status and the diagnosis of endometrial cancer were determined up until 31 December 2007.

Statistics

Only postmenopausal women were included in this analysis, performed with Cox regression using 95% CIs (Cox, 1972). Endometrial cancer was used as a dependent variable and ‘time at risk’ as the time variable. The time at risk was calculated from the day of recruitment up until the date of cancer diagnosis, death, or last day of follow-up (31 December 2007), whichever came first. Age adjustment was performed in all analyses, as increasing age is a strong risk factor for endometrial cancer. We also made multivariate models adjusting for age, civil status, educational level, COCs use, hormone use, family history of gynaecological cancer, physical activity, and BMI. All calculations were performed using SPSS software (Statistical Package for Social Sciences (SPSS, Inc., Chicago IL, USA), version 10.0.1) and P-values <0.05 were considered significant.

RESULTS

At the end of the follow-up in December 2007, 166 of the 17 822 postmenopausal women had developed endometrial cancer, and demographic characteristics in relation to their risks are presented in Table 1. Decreased risk was found in women ever using COCs. Ever use of any combined hormone replacement therapy decreased the risk, whereas ever use of low- or high-potency oestrogen only doubled the risk. Ever smokers had a decreased risk of endometrial cancer (hazard ratio (HR) 0.7, 95% CI 0.5–0.99). An increased risk was found in women overweight (BMI 25–<30) or obese.

Table 1 Demographic characteristics of postmenopausal women with and without endometrial cancer

| Data from inception of the study | Women with cancer (n = 17656) | Women without cancer (n = 166) | Hazard ratio | 95% CI  |
|---------------------------------|-------------------------------|-------------------------------|--------------|--------|
| **Education**                   |                               |                               |              |        |
| <9 years                        | 4232                          | 47                            | 1.1          | 0.7–1.6|
| 9 years                         | 2393                          | 22                            | 0.9          | 0.5–1.5|
| 10–12 years                     | 3126                          | 26                            | 1.0          | 0.6–1.6|
| >12 years                       | 5384                          | 49                            | 1.0          | Reference |
| Other                           | 2521                          | 22                            | 0.9          | 0.5–1.5|
| **Marital status**              |                               |                               |              |        |
| Unmarried                       | 898                           | 4                             | 0.5          | 0.2–1.4|
| Married                         | 13 762                        | 126                           | 1.0          | Reference |
| Divorced                        | 1914                          | 16                            | 0.9          | 0.5–1.5|
| Widow                           | 1082                          | 20                            | 1.8          | 1.1–2.9|
| **Smoker**                      |                               |                               |              |        |
| Never smoker                    | 7491                          | 87                            | 1.0          | Reference |
| Ever smoker                     | 10 041                        | 77                            | 0.7          | 0.5–1.0|
| **Parity**                      |                               |                               |              |        |
| 0                               | 1 990                         | 15                            | 1.3          | 0.8–2.2|
| ≥ 1                             | 15 666                        | 151                           | 1.0          | Reference |
| **Used combined oral contraceptives** |                       |                               |              |        |
| Never                           | 8 525                         | 105                           | 1.0          | Reference |
| Ever                            | 9 131                         | 61                            | 0.5          | 0.4–0.7|
| **Use of hormone therapya**     |                               |                               |              |        |
| Never use                       | 11 431                        | 100                           | 1.0          | Reference |
| Ever use combined HT            | 3 388                         | 19                            | 0.7          | 0.4–1.1|
| Ever use oestrogen only         | 2 484                         | 42                            | 1.9          | 1.3–2.7|
| **Family history of gynaecological cancer** |               |                               |              |        |
| No                              | 17 067                        | 153                           | 1.0          | Reference |
| Yes                             | 589                           | 13                            | 2.5          | 1.4–4.4|
| **Data from the second survey** |                               |                               |              |        |
| **BMI**                         |                               |                               |              |        |
| <25                             | 7 278                         | 45                            | 1.0          | Reference |
| 25–29                           | 4 992                         | 41                            | 1.4          | 0.9–2.2|
| >29                             | 1 540                         | 36                            | 3.5          | 2.2–5.4|
| Missing information             | 4 446                         | 44                            | 1.7          | 1.1–2.5|

BMI = body mass index; CI = confidence interval; TH = hormone therapy. aUse of hormones was gathered at both questionnaires and the combined result is presented. Cox regression analysis with age adjustment was used throughout.
There is indirect evidence that UV exposure might affect the risk of endometrial cancer, women living at higher latitudes having a lower risk than those at lower latitudes (Grant, 2007; Mohr et al., 2007). In our study, we found that sunbathing abroad or in Sweden during the summer had little or no effect on the risk, whereas sun bed users had a significantly reduced risk. The major source of vitamin D is sunlight, which penetrates the skin and converts 7-dehydrocholesterol to 25-hydroxicholecalciferol vitamin D3 (25-OHvitD) through pre-vitamin D3 (Holick, 2007). Vitamin D deficiency has also been associated with 30–50% increased risk of colon, prostate, and breast cancer, along with an increased mortality in these cancers (Holick, 2007). It has been suggested that if a cell become malignant, 1,25-dihydroxy Vitamin D can induce apoptosis and prevent angiogenesis, thereby reducing the potential for the malignant cell to survive (Holick, 2006). However, a recent meta-analysis of three case–control studies showed no relation between dietary vitamin D intake and endometrial cancer (McCullough et al., 2008). This can probably be explained by sunlight being the most important source of vitamin D, most diets being low in Vitamin D. In this meta-analysis, the highest intake category was 244 to 476 IU per day (McCullough et al., 2008), which is much less than the recommended 2000 IU per day (Garland et al., 2007). An ecological...
study produced an estimated overall reduction in cancer mortality of 20% for Western European women living below the 59th latitude and of 9% for women in the United States if they were all given a daily dose of 1000 IU vitamin D (Grant et al, 2007). The disadvantage of using sun beds to reduce the risk of endometrial cancer is the reportedly increased risk of melanoma (OR 1.8, 95% CI 1.2–2.7) in regular sun bed users (Westerdahl et al, 1994). Another alternative to reduce the risk of endometrial cancer and other vitamin D-related malignancies would be to provide adequate (2000 IU per day) vitamin D supplement in countries such as Sweden where people are at risk of developing seasonal vitamin D deficiency. We would welcome new prospective randomised studies on the health benefits of vitamin D supplement in populations at risk of vitamin D deficiency.

The positive effect of artificial sun exposure through sun bed use also continued when adjusting for potential confounding lifestyle factors such as BMI and physical activity. Overall, physical activity reduced the risk of endometrial cancer by half. Other cohort studies have shown differing results; most have continued when adjusting for potential confounding lifestyle factors such as BMI and physical activity.

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Thune, 2003; Schouten et al, 2004; Friberg et al, 2006), whereas others showed no association (Colbert et al, 2003). Hypothesised mechanisms include changes in obesity and/or fat mass as well as a reduced exposure to endogenous oestrogens (McTiernan et al, 1998). As information on present physical activity was obtained at the second survey and was lacking in a substantial number, the related findings must be interpreted with caution.

In our study, smoking women had a decreased risk of endometrial cancer, which is in agreement with other prospective cohort studies (Terry et al, 2002; Viswanathan et al, 2005; Al-Zoughool et al, 2007; Loerbroks et al, 2007). We found that sun bed users were at lower risk of endometrial cancer and there may be an association between vitamin D deficiency and endometrial cancer.

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