Dietary Cadmium Intake and Risk of Breast, Endometrial and Ovarian Cancer in Danish Postmenopausal Women: A Prospective Cohort Study

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Abstract

Purpose: Cadmium is a human lung carcinogen and possesses estrogen-like activity. This combination of carcinogenic and estrogenic activity makes cadmium a contaminant of high concern for hormone-related cancers. Diet and smoking are the main sources of cadmium exposure. The aim of this study was to investigate the association between dietary cadmium intake and risk of breast, endometrial and ovarian cancer in Danish postmenopausal women.

Methods: We estimated dietary cadmium intake in the Diet, Cancer and Health cohort at enrolment 1993-97. The estimates were based on food frequency questionnaires and cadmium contents in all foods. Among 23,815 postmenopausal women we identified 1390 breast, 192 endometrial, and 146 ovarian cancer cases from enrolment through December 31, 2010 using the Danish Cancer Registry. Cox regression was used to analyse the association between dietary cadmium intake and cancer risk.

Results: Mean dietary cadmium intake was 14 μg/day. Cadmium was not associated with breast cancer, incidence rate ratio (IRR) = 0.99, 95% confidence interval (CI): 0.87–1.13 per 10 μg higher dietary cadmium intake/day; endometrial cancer, IRR = 1.08, 95% CI: 0.76–1.53; or ovarian cancer, IRR = 1.15, 95% CI: 0.78–1.70. We found a positive association between cadmium and endometrial cancer for the women with BMI <25 (IRR = 1.50, 95% CI: 0.94–2.39), whereas an inverse association was seen for the women with BMI ≥25 (IRR = 0.69, 95% CI: 0.42–1.12); p value for interaction = 0.02.

Conclusions: Our study does not indicate that our estimated dietary cadmium intake is associated with hormone-related cancers in women.

Introduction

Breast cancer is the most frequently diagnosed cancer among women in Denmark and endometrial and ovarian cancer are the most commonly diagnosed gynaecological cancers. These three cancers are the most frequent hormone-related cancers among women, collectively accounting for about 6000 new cases of cancer in Denmark each year [1].

Established risk factors of these female cancers are related to cumulative exposure to estrogens and reproductive life such as early age at menarche, nulliparity, late age at first pregnancy, short lactation and late menopause [2]. Use of hormone replacement therapy (HRT), higher BMI, lower physical activity, and a family history of the disease are also recognized risk factors for these cancers [2–3]. In addition, breast cancer is also related to higher alcohol consumption, radiation exposure, higher educational level, and a higher socioeconomic status [2–3]. However, one study has shown that four of the most well-established risk factors for breast cancer (later age at first birth, nulliparity, higher family income, and first-degree family history of breast cancer) still may explain less than half of the breast cancer cases in the United States [4].

Cadmium is an IARC classified group 1 proven human carcinogen of the lung based on mechanistic and epidemiologic evidence from high-exposure occupational settings [5]. Proposed mechanisms of cadmium carcinogenesis include oxidative stress, DNA damage, altered DNA repair, and enhanced proliferation and/or depressed apoptosis [6–7]. More recently, both in vitro and in vivo studies have demonstrated that cadmium also exerts estrogenic activities, such as proliferation of breast cancer cells [8–10], activation and increased expression of estrogen regulated genes [9,11] and activation of the estrogen receptor (ER)-α [9–10,12–13]. Animal experiments have shown that environmentally relevant doses of cadmium induce estrogenic responses in female rats, including increased uterine weight and hypertrophy of the...
endometrial lining with these responses blocked by anti-estrogen
[14]. This combination of carcinogenic and estrogenic activities
makes cadmium a contaminant of particularly high concern for
hormone-dependent cancers. Further, cadmium has been shown to
induce progesterone receptor (PGR) levels in breast cancer cells,
the induction being blocked by anti-estrogen [9]. Mechanistic and
epidemiologic evidence suggest that estrogen-mimicking contam-
inants, including the environmental and dietary pollutant cadmi-
um, may contribute to development of hormone-related cancers
[14].

Diet is a main source of human exposure to cadmium in the
non-occupationally exposed population. Cereal products and
vegetables are important dietary exposure sources [15–16], as
plants absorb cadmium from phosphate fertilizer and fallout due
to fossil fuel and waste combustion and due to the high
consumption of these dietary items. Smoking is also an important
source of cadmium exposure, since cadmium easily accumulates in
the tobacco plant and cadmium in tobacco smoke is effectively
absorbed in the lungs. The average cadmium intake from food
generally varies from 8–25 µg/day [17] and daily cadmium
exposures can double in smokers [18].

Three prospective cohort studies have assessed the association
between dietary cadmium intake and risk of breast cancer, of
which one study indicated an association [19], whereas two did not
report any associations [20–21]. The authors of the former study
also investigated dietary cadmium exposure in relation to
endometrial cancer, showing a significant positive association
[22], whereas they did not find an association for ovarian cancer
[23].

The present study aimed to investigate whether dietary
cadmium exposure is associated with hormone-related cancer of
the breast, endometrium and ovary assessed in a large population-
based prospective cohort in Denmark.

Materials and Methods

Ethics Statement

This study was approved by the regional research ethic
committee for Copenhagen and Frederiksberg. Written informed
consent was obtained from all study participants. The study was
carried out without contact to the cohort members or their
families. Anonymity of participants was retained by strict data
management.

Study Population

From December 1, 1993, through May 31, 1997, a total of
57,053 individuals (29,875 women and 27,178 men), who were
aged 50–65 years, born in Denmark, and had no previous cancer
diagnosis, were enrolled in the prospective Diet, Cancer and
Health cohort [24]. At enrolment, each participant completed a
self-administered, interviewer-checked 192 item semi-quantitative
food frequency questionnaire and a questionnaire covering lifestyle
habits including information on present and previous smoking,
physical activity, reproductive history, health status and social
factors. In total 56,999 persons filled in the detailed dietary
questionnaires.

We used the Danish Cancer Registry to identify incident cases
of invasive breast cancer, endometrial cancer and ovarian cancer
among cohort members. Information on ER status, PGR status
and histology type was obtained from The Danish Breast Cancer
Cooperative Group (DBCG) [25]. To limit the impact of
endogenous estrogens and thereby to avoid masking the potential
estrogenic influence of cadmium, we restricted our study to
women postmenopausal at baseline. Data on potential confound-
ers were obtained from the detailed questionnaires administered at
enrolment. 23,815 postmenopausal women (1390 breast cancer
cases, 192 endometrial cancer cases and 146 ovarian cancer cases)
had complete covariate information and were used for statistical
analyses. Mean follow-up time was 13 years for the cohort.

Assessment of Dietary Cadmium Exposure

We estimated dietary cadmium intake per day for each person
in the prospective DCH cohort based on the 192 item semi-
quantitative food frequency questionnaire filled in at enrolment.
For the calculations we used food monitoring data from The
Danish Food Monitoring Programme for Nutrients and Contam-
inants, 1993–97 [26]. The Danish Food Monitoring Programme
was initiated in 1983 and monitoring cycles run for 5-year periods
to allow for a comparison of trace element contents (including
cadmium) over time in food items sold in Denmark and to assess
the potential health concerns of the dietary intake of the trace
elements investigated. The samples of each food item were
analysed individually, giving detailed information on the variation
of trace elements in food items sold on the Danish market. The
number of samples analysed of each specific food item was decided
on the basis of earlier experience concerning the variation in
contents of trace elements in that specific food item. For our study,
dietary cadmium measurements from the 5-year monitoring
period 1993–97 were used, since this period matches with the
period of completion of the food frequency questionnaire in the
DCH cohort. The contents of more than 80 different foods were
monitored from 1993–97. For food items where data were not
available during this period, we used data from the monitoring
period 1998–2003, and data from unspecified years. The obtained
cadmium concentration for each food item was added to the food
table using the FoodCalc program [27] and we obtained an
estimate of dietary cadmium intake per day (µg cadmium per day)
for each participant in the DCH cohort.

Statistical Analyses

We used Cox proportional hazard models with age as the
underlying time scale [28]. This ensured comparison of individuals
of the same age. We used left truncation at age of enrolment, so
that people were considered at risk from enrolment into the
cohort, and right censoring at the age of cancer under study
(event), death, emigration, any other cancer diagnosis (except non-
melanoma skin cancer), or end of follow-up (December 31, 2010),
whichever came first.

We estimated crude and adjusted incidence rate ratios (IRRs)
using the estimate of dietary cadmium intake as a linear variable.
The adjusted models were carried out with a priori defined
potential confounders: Educational level (<3 y; 8–10 y; >10 y) as
a measure of socioeconomic status, smoking status (never; former;
current), as smoking is a major source of cadmium and never
smokers are at lower risk of endometrial and ovarian cancer, and
the following known risk factors: number of births (0; 1–2; 3–8);
age at first birth (years, continuous), HRT status (never; former;
current), HRT use (years, continuous), age at menarche (years,
continuous), BMI (continuous), height (cm, continuous), physical
activity (MET score, continuous), and alcohol intake (g/day,
continuous). Linearity was evaluated with use of linear splines with
three boundaries for dietary cadmium intake, age at first birth,
HRT use, age at menarche, BMI, height, physical activity and
alcohol intake and there was no deviation from linearity. Also, we
estimated crude and adjusted IRRs for tertiles of daily dietary
cadmium intake, based on distribution among all cohort members.
Only participants with complete covariate information were
included. Only adjusted IRRs are reported here, as crude and adjusted IRRs were similar in all analyses.

Further, we evaluated \textit{a priori} specified individual characteristics as potential effect modifiers (for breast and endometrial cancer): Educational level (<8, 8–10 y, >10 y), smoking status (never, former, present), HRT use (never, former, present), BMI (<25, ≥25), dietary zinc intake (<median, ≥median), and dietary iron intake (<median, ≥median).

In order to minimize the potential effect of exposure to endogenously produced adipose tissue estrogen, obtained hormones from medical treatment and/or to smoking-derived cadmium, we also restricted analyses to participants who: 1) were never smokers and had BMI <25, and 2) were never smokers and never HRT users, 3) had BMI <25 and were never HRT users, and 4) were never smokers, had BMI <25 and were never HRT users. This was only analysed for breast cancer due to the relatively small number of endometrial and ovarian cancer cases.

Also, we calculated IRRs for different subgroups of breast cancer classifications: Estrogen receptor status (ER+ and ER-), progesterone receptor status (PGR+ and PGR-) and the two most frequent histology types (ductal and lobular).

The procedure PHREG in SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) was used for the statistical analyses.

Results

Among the 29,875 women of the Diet, Cancer and Health cohort, we excluded 338 with a cancer diagnosis before baseline, 1 with unknown month of cancer diagnosis, 5,295 not being defined as postmenopausal at baseline, and 401 with incomplete covariate data. This

\begin{table}
\centering
\caption{Baseline characteristics by tertiles of dietary cadmium intake in the cohort (N = 23,815) of the Diet, Cancer and Health Study, 1993–97.}
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Tertiles of dietary cadmium intake} & <11.9 μg/day & 11.9–15.3 μg/day & >15.3 μg/day \\
\hline
\textbf{Age (years)} & 57 (57) & 57 (57) & 57 (57) \\
\hline
\textbf{Education (years), %} & & & \\
Low (<8) & 39 & 33 & 29 \\
Medium (8–10) & 49 & 50 & 48 \\
High (>10) & 12 & 17 & 23 \\
\hline
\textbf{Smoking, %} & & & \\
Never & 37 & 43 & 47 \\
Former & 21 & 24 & 26 \\
Current & 42 & 33 & 27 \\
\hline
\textbf{Hormone replacement therapy (HRT) status, %} & & & \\
Never & 50 & 50 & 48 \\
Former & 34 & 34 & 36 \\
Current & 16 & 16 & 16 \\
\hline
\textbf{Number of births, %} & & & \\
0 & 12 & 12 & 13 \\
1–2 & 60 & 60 & 59 \\
3–8 & 28 & 28 & 28 \\
\hline
\textbf{Age at first birth*} & 23 (23) & 24 (23) & 24 (24) \\
\hline
\textbf{Years of HRT use*} & 6 (4) & 6 (4) & 6 (4) \\
\hline
\textbf{BMI (kg/m²)} & 14 (14) & 14 (14) & 14 (14) \\
\hline
\textbf{Height (cm)} & 163 (163) & 164 (164) & 165 (165) \\
\hline
\textbf{Physical activity (MET h/week)} & 62 (53) & 68 (59) & 75 (66) \\
\hline
\textbf{Energy intake (kcal/day)} & 1,650 (1,636) & 2,047 (2,022) & 2,533 (2,468) \\
\hline
\textbf{Alcohol (g/day)c} & 15 (10) & 14 (10) & 13 (9) \\
\hline
\textbf{Zinc intake (mg/day)d} & 14 (12) & 17 (14) & 20 (18) \\
\hline
\textbf{Iron intake (mg/day)d} & 14 (10) & 16 (13) & 19 (16) \\
\hline
\textbf{Whole grain intake (g/day)} & 128 (118) & 179 (168) & 256 (237) \\
\hline
\textbf{Vegetable intake (g/day)} & & & \\
\hline
\hline
\textsuperscript{*Among those having given birth.} \\
\textsuperscript{+Among all users (those reporting use for at least one year).} \\
\textsuperscript{cAmong drinkers.} \\
\textsuperscript{dSum of intake from diet and supplement.} \\
\textsuperscript{Mean (median) values are given if not otherwise specified.} \\
\end{tabular}
\end{table}
investigated hormone-related cancers (Table 2), neither in linear nor categorical analyses. For ovarian cancer there seemed to be a tendency towards a positive association, but confidence intervals were wide due to the relatively low number of cases, and estimates were not statistically significant.

Table 3 shows risk estimates for potential effect modifiers for breast cancer and endometrial cancer. We did not complete these analyses for ovarian cancer due to the relatively low number of cases that would be included in each stratum. BMI seemed to modify the association between cadmium intake and endometrial cancer as we found a positive association for the group with BMI ≥25, whereas an inverse association was observed for the group of BMI <25, with a P value for interactions = 0.02. However, none of the risk estimates in each individual stratum in the analysis was significant. We did not find any statistically significant interactions for the remaining potential effect modifiers.

Table 4 shows the risk estimates for breast cancer among a priori defined subgroups. We did not establish any significant associations between dietary cadmium intake and breast cancer for any of the subgroups.

For breast cancer, risk analyses were also carried out for estrogen receptor classification (ER+ and ER−); progesterone receptor classification (PGR+ and PGR−) and for the two most frequent histology types (ductal and lobular) (Table 5). No significant associations were found, but a tendency towards a positive association with dietary cadmium intake was seen for lobular breast cancer.

**Discussion**

In this study, we did not find significant associations between dietary cadmium intake and risk of hormone-related cancers in postmenopausal women. In line with our results, the large American prospective VITAL cohort study did not find any evidence of an association between dietary cadmium intake and
Table 3. Modification of associations between dietary cadmium intake and breast and endometrial cancer by relevant stratification factors.

| Stratification factors | Breast cancer | Endometrial cancer |
|------------------------|---------------|-------------------|
|                        | N cases      | IRR* | 95% CI | p<sup>b</sup> | IRR* | 95% CI | p<sup>b</sup> |
| Education              |              |      |        |            |      |        |            |
| Low (≤8 y)             | 422          | 0.92 | (0.72, 1.17) | 0.77 | 1.02 | (0.55, 1.87) | 0.68 |
| Medium (8–10 y)        | 687          | 1.01 | (0.84, 1.21) | 1.14 | 0.77 | (0.70, 1.86) | 1.10 |
| High (>10 y)           | 281          | 1.03 | (0.79, 1.35) | 0.77 | 0.77 | (0.37, 1.61) | 0.77 |
| Smoking                |              |      |        |            |      |        |            |
| Never                  | 587          | 1.11 | (0.92, 1.35) | 0.98 | 0.98 | (0.62, 1.53) | 0.95 |
| Former                 | 335          | 0.85 | (0.66, 1.11) | 1.00 | 0.98 | (0.47, 2.14) | 0.98 |
| Current                | 468          | 0.95 | (0.77, 1.19) | 1.11 | 0.99 | (0.55, 2.24) | 0.99 |
| HRT users              |              |      |        |            |      |        |            |
| Never                  | 522          | 1.00 | (0.81, 1.22) | 0.82 | 0.98 | (0.62, 1.77) | 0.82 |
| Former                 | 174          | 1.14 | (0.81, 1.60) | 1.35 | 1.04 | (0.62, 2.14) | 1.04 |
| Present                | 694          | 0.95 | (0.79, 1.14) | 1.04 | 1.04 | (0.55, 2.24) | 1.04 |
| BMI                    |              |      |        |            |      |        |            |
| ≤25                    | 719          | 1.08 | (0.91, 1.28) | 1.50 | 1.04 | (0.55, 1.77) | 1.04 |
| ≥25                    | 671          | 0.89 | (0.73, 1.07) | 0.69 | 0.98 | (0.42, 1.12) | 0.98 |
| Total zinc intake      |              |      |        |            |      |        |            |
| < median               | 677          | 1.00 | (0.81, 1.24) | 0.85 | 0.98 | (0.46, 1.55) | 0.98 |
| ≥ median               | 713          | 0.98 | (0.82, 1.15) | 1.04 | 1.04 | (0.46, 1.55) | 1.04 |
| Total iron intake      |              |      |        |            |      |        |            |
| < median               | 667          | 1.00 | (0.78, 1.26) | 0.68 | 0.99 | (0.84, 1.17) | 0.99 |
| ≥ median               | 723          | 0.99 | (0.82, 1.17) | 1.10 | 0.99 | (0.71, 1.69) | 0.99 |

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

*Adjusted for educational level (≤8 y; 8–10 y; >10 y), smoking status (never; former; current), number of births (0; 1–2; 3–8), age at first birth (years, continuous), HRT status (never; former; current), HRT use (years, continuous), age at menarche (years, continuous), BMI (continuous), height (cm; continuous), physical activity (MET score, continuous) and alcohol intake (yes/no and g/day, continuous). BMI (continuous) was not included in the stratification analyses on BMI.

<sup>b</sup>p values for interaction.

Incidence rate ratios are per 10 μg dietary cadmium intake/day. Adjusted models results are shown.

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postmenopausal breast cancer risk [20]. Similarly, a prospective Japanese study did not find an association between dietary cadmium intake and breast and endometrial cancer [21] and a Japanese case-control study did not find a significant association between dietary cadmium intake and risk of breast cancer [29]. In contrast to these and to our results, prospective studies of postmenopausal women in the Swedish Mammography Cohort (SMC) reported positive associations with postmenopausal endometrial cancer [22] and breast cancer [19], but did not find an association for ovarian cancer [23]. In spite of the fact that these studies (19–22, 29) and our study are relatively similar in exposure assessment and in study design, they represent four somewhat different countries with differences in dietary habits, quality of cadmium monitoring data, pollution levels of cadmium, etc., which could have impacted these studies differently. Still there is consistency in findings (except for SMC’s positive association for endometrial and breast cancer). The above described studies included a wide range of dietary cadmium exposure with mean values ranging from 10.9 μg/d in the American study [20] to 26.4 μg/d in the Japanese study [29], whereas in Sweden similar values were found as in our study [22]. That is, based on the present literature, dietary cadmium intake does not overall seem to be associated with risk of hormone-related cancers in postmenopausal women, regardless of exposure levels. Whether this picture reflects a true lack of association with hormone-related cancers or whether the results reflect non-differential exposure measurement error in the estimation of dietary cadmium intake concealing a true association is unclear.

Two American retrospective breast cancer case-control studies found significant trends for increased odds ratios across quartiles of urinary cadmium levels [30–31]. Urinary cadmium level is considered the standard biomarker for lifetime cadmium body burden in the general population and this procedural contrast to our study may to some extent clarify the discrepancy in results. However, a limitation of the case-control studies is that urine samples were collected after diagnosis, introducing the possibility of disease- or treatment-related alterations of the urine cadmium measure, leading to a non-causal association between urinary cadmium measurement and cancer risk.

The clinical, pathologic, and molecular characteristics of breast cancer differ by their ER and/or PGR expression profile and the effects of risk factors of breast cancer, such as reproduction related exposures, also differ by ER/PGR status [32]. Cadmium has been shown to bind the nuclear ER and appears to interact with its hormone-binding domain [12]. Recently, cadmium was shown to activate membrane-bound ERs [33], indicating an alternative mode of action even in the absence of nuclear ER. Examining the association between cadmium exposure and ER as well as PGR

![Table 4](image)

### Table 4. Incidence rate ratios of breast cancer (per 10 μg dietary cadmium intake/day) for relevant subgroups.

| Subgroups | N cases | IRR* | 95% CI |
|-----------|---------|------|--------|
| Never-smokers and BMI<25 | 282 | 1.23 | (0.94, 1.60) |
| Never-smokers and never HRT users | 237 | 0.95 | (0.70, 1.30) |
| BMI<25 and never HRT users | 224 | 1.11 | (0.82, 1.47) |
| Never-smokers, BMI<25 and never HRT users | 92 | 1.08 | (0.69, 1.71) |

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

*Adjusted for educational level (<8 y; 8–10 y; >10 y), smoking status (never; former; current), number of births (0; 1–2; 3–8), age at first birth (years, continuous), HRT status (never; former; current), HRT use (years, continuous), age at menarche (years, continuous), BMI (continuous), height (cm, continuous), physical activity (MET score, continuous) and alcohol intake (yes/no and g/day, continuous).

Adjusted model results are shown.

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![Table 5](image)

### Table 5. Incidence rate ratios of breast cancer classifications (per 10 μg dietary cadmium intake/day).

| Breast cancer classification | N cases* | IRRb | 95% CI |
|-----------------------------|---------|------|--------|
| Estrogen receptor | | | |
| Positive | 981 | 1.00 | (0.85, 1.15) |
| Negative | 228 | 0.88 | (0.62, 1.22) |
| Progesteron receptor | | | |
| Positive | 405 | 0.85 | (0.67, 1.09) |
| Negative | 266 | 1.12 | (0.84, 1.49) |
| Histology | | | |
| Ductal | 1,026 | 0.98 | (0.89, 1.13) |
| Lobular | 172 | 1.12 | (0.78, 1.59) |

Abbreviations: IRR, incidence rate ratio; CI, confidence interval.

*In each analyses, we excluded those with no information on the classification under study (ER status, PGR status or histology). For the histology analyses we also excluded those being characterised with other histology types than ductal and lobular.

bAdjusted for educational level (<8 y; 8–10 y; >10 y), smoking status (never; former; current), number of births (0; 1–2; 3–8), age at first birth (years, continuous), HRT status (never; former; current), HRT use (years, continuous), age at menarche (years, continuous), BMI (continuous), height (cm, continuous), physical activity (MET score, continuous) and alcohol intake (yes/no and g/day, continuous).

Adjusted model results are shown.

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subtypes may provide further insights into possible hormone disrupting properties of cadmium. In this study, we investigated whether the association between cadmium and breast cancer risk differed between ER and PGR expression and histology. A previous study found significant positive association among ER+ and PGR- patients [29], but we could not confirm these findings in our study. Our results showed a relatively stronger association for the lobular breast cancer subtype compared with the ductal subtype, though none of the results were significant. Dietary cadmium intake has to the best of our knowledge not been investigated as a risk factor for histological subtypes before and for PGR status previously only in one case-control study [29].

After menopause, women with higher BMI have a slightly increased risk of breast cancer compared with leaner women. This may be explained by the fact that estrogen after menopause is formed mainly in the adipose tissue. Obese postmenopausal women have plasma levels of endogenous estrogens nearly twice as high as lean women [2]. We conducted analyses stratified by BMI and expected a priori to obtain a higher estimate for women with lower BMI due to the reduced influence of adipose tissue-derived estrogen exposure. We found an interaction for endometrial cancer and to a lesser extent for breast cancer. This tendency was also seen in other [19,22], but not all [20,29] studies. Since tobacco smoking is a source of cadmium intake, it has often been assumed that the lack of positive findings for tobacco on breast cancer indicates that cadmium is not a risk factor [34], although smoking also has some anti-estrogenic properties [35] perhaps masking a cadmium effect. In support of the anti-estrogenic effect, smoking has been associated with decreased risk of endometrial cancer. In order to minimize the potential effect of exposure to endogenously produced adipose tissue estrogen, obtained hormones from medical treatment and/or to smoking-derived cadmium, we performed analyses stratified by BMI, HRT and smoking. We investigated all combinations of being never smokers, having BMI<25 and being never HRT users, but did not find statistically significant associations.

Cadmium shares some structural similarities with the mineral zinc and there is some mechanistic evidence that zinc increases the sequestering of cadmium by inducing metal-binding metallothioneins, as well as directly reducing cadmium absorption [36–37]. The iron-cadmium ratio also seems to be important since low body iron stores seem to be linked to increased intestinal absorption of cadmium [38]. Therefore, we would expect the strength of a possible association between dietary cadmium intake and cancer to be most prominent among women with low levels of zinc intake or iron intake. However, neither zinc nor iron seemed to modify the association between cadmium intake and cancer risk. These null results were also found in the American study on dietary cadmium and breast cancer risk, which did not find evidence for interactions between cadmium and breast cancer risk factors, smoking habits, iron or zinc intake [20]. However, mechanistic evidence of interplay suggests the role of cadmium versus zinc and iron to be investigated further in epidemiologic studies of hormone-related cancers.

The major strength of this study is the prospective design that was based on a well-defined cohort with data on potential confounders. Furthermore, virtually complete nationwide registries provided information on vital status and cancer status. Further, disease status could not have biased exposure assessment because questionnaire data was obtained before cancer diagnosis.

Non-differential exposure measurement error in the estimation of dietary cadmium intake may be a factor concealing a true association between cadmium and the investigated cancers. That is, a limitation of this study includes our ability to accurately assess dietary cadmium intake, which may have moderated our estimates. Participants of the Diet, Cancer and Health cohort were asked to report their average dietary habits within the year prior to enrolment, and these answers may reflect long-term dietary pattern and long-term exposure to dietary cadmium. However, their dietary pattern may have changed during the follow up period. Also, some deviation in the content of cadmium in specific food items could be another important source of measurement error. Future studies are needed including use of urinary levels as marker for cadmium exposure in relation to hormone-related cancer in large prospective studies.

In conclusion, the results of the present study do not support the hypothesis that cadmium contamination of food is a risk factor for postmenopausal hormone-related cancers in women.

Author Contributions
Conceived and designed the experiments: KTE ORN MS JRM JAM. Performed the experiments: JH KTE. Analyzed the data: JH KTE. Contributed reagents/materials/analysis tools: AT JH. Wrote the paper: KTE ORN MS JRM JAM AT JH.

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