Original Contribution

Urinary Cadmium and Risk of Invasive Breast Cancer in the Women’s Health Initiative

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Cadmium is a widespread heavy metal pollutant that may act as an exogenous estrogenic hormone. Environmental cadmium exposure has been associated with risk of breast cancer in retrospective studies. We prospectively assessed the relationship between cadmium exposure, evaluated by creatinine-normalized urinary cadmium concentration, and invasive breast cancer among 12,701 postmenopausal women aged ≥50 years in a Women’s Health Initiative study of bone mineral density. After a median of 13.2 years of follow-up (1993–2010), 508 cases of invasive breast cancer and 1,050 comparison women were identified for a case-cohort analysis. Multivariable Cox regression was used to calculate hazard ratios and 95% confidence intervals. Risk of breast cancer was not associated with urinary cadmium parameterized either in quartiles (comparing highest quartile with lowest, hazard ratio = 0.80, 95% confidence interval: 0.56, 1.14; P for trend = 0.20) or as a log-transformed continuous variable (per 2-fold higher urinary cadmium concentration, hazard ratio = 0.94, 95% confidence interval: 0.86, 1.03). We did not observe an association between urinary cadmium and breast cancer risk in any subgroup examined, including never smokers and women with body mass index (weight (kg)/height (m)²) less than 25. Results were consistent in both estrogen receptor–positive and estrogen receptor–negative tumors. Our results do not support the hypothesis that environmental cadmium exposure is associated with risk of postmenopausal breast cancer.

breast cancer; cadmium; case-cohort studies; environmental carcinogens; postmenopause; women’s health

Abbreviations: CI, confidence interval; Cd, cadmium; Cr, creatinine; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor; U-Cd, creatinine-normalized urinary cadmium concentration; WHI, Women’s Health Initiative.

Cadmium is a heavy metal that is a widespread environmental contaminant with no known physiological function in humans (1). Outside of occupational settings, the general population is believed to be primarily exposed to cadmium through tobacco, grains, and some vegetables that take up cadmium from contaminated agricultural soils (2–5).

Cadmium has linked to multiple carcinogenic pathways, including oxidative stress and inflammation (6, 7), interference with DNA repair (8, 9), and alterations in DNA methylation (10). More relevant to hormone-related cancers is evidence that cadmium may act on estrogenic signaling pathways (11, 12), stimulates proliferation of breast cancer cells in vitro (13), and increases uterus and mammary gland weight in rats (14). Long-term exposure to low concentrations of cadmium has been shown to malignantly transform breast cells in vitro, although the effect appears to be independent of estrogen receptor α (15).

Cadmium is a known human carcinogen (16), and epidemiologic evidence supports a link between cadmium and increased risk of lung cancer (17–19), but these occupational studies have left unaddressed hormone-driven cancers in women. Investigators from 5 nonoccupational case-control studies (20–24) have reported associations between urinary cadmium, a measure of cumulative exposure to cadmium over decades (25–31), and breast cancer risk in a variety of populations and over a wide range of exposures. In prospective studies in Sweden, researchers have observed an association between estimated dietary cadmium intake and endometrial...
cancer (32) and postmenopausal breast cancer (33) but not ovarian cancer (34). In contrast, prospective studies from the United States (35, 36) and Japan (37) have not found associations of dietary cadmium with postmenopausal breast cancer risk. Prospective studies of urinary cadmium have supported a positive association between urinary cadmium and total cancer mortality, but not breast cancer mortality (38–40).

To evaluate the association between cadmium exposure and breast cancer risk, we conducted a prospective study of urinary cadmium concentration and risk of postmenopausal breast cancer in the Women’s Health Initiative (WHI).

METHODS

WHI population and case-cohort study sample

Study participants were selected from the WHI, a large longitudinal study of postmenopausal women aged 50–79 years, comprising 2 arms: an observational study and 3 randomized clinical trials. The study design and recruitment have been extensively described in detail elsewhere (41–43). Participants were recruited between October 1, 1993, and December 31, 1998, at 40 clinical centers across the United States. A total of 161,808 women were enrolled in the WHI.

Data and specimen collection

All women completed self-administered questionnaires at baseline screening and enrollment. Questionnaires collected detailed information on demographic characteristics, dietary habits, reproductive history (including use of menopausal hormone therapy for 3 months or longer (estrogen or estrogen plus progesterone; pills or patches)), medical history, and lifestyle factors, including tobacco use, alcohol use, and physical activity (41). Anthropometric measurements were taken at baseline clinic visits using a standardized protocol, and body mass index was calculated as weight divided by height squared. The present study included only women enrolled at sites in the WHI study of bone mineral density (Birmingham, Alabama; Phoenix/Tucson, Arizona; and Pittsburgh, Pennsylvania (n = 12,701)), because those sites were the only WHI sites at which urine samples were routinely collected.

For the present study, we implemented a case-cohort design (44, 45). First, among women enrolled at the WHI bone mineral density study sites, we identified all invasive breast cancer cases (n = 573). Cases with a history of breast cancer prior to WHI enrollment (n = 23), with breast cancer reported on the death certificate only (n = 2), without a urine sample in the repository (n = 36), or with unknown smoking status (n = 4) were excluded, leaving 508 cases for analysis. Of these, 505 cases were confirmed by histological analysis of the primary tumor, 1 had only positive cytological results available, 1 was histologically confirmed via metastasis only, and 1 was confirmed with diagnostic imaging only.

Next, we randomly selected 1,050 women in 5-year age groups frequency-matched to the ages of breast cancer cases at enrollment. To be eligible for the subcohort, women had to be without a personal history of breast cancer at enrollment (n = 234 excluded), have at least 1.0 mL of urine in the WHI sample repository (n = 2,414 excluded), 1,246 of whom gave no sample), and have complete information on smoking history (n = 148 excluded). After these exclusions, 9,905 women were eligible for sampling into the present study. Subcohort members were selected without regard to future incidence of breast cancer; therefore, by chance, 50 women later diagnosed with invasive breast cancer (i.e., cases) were also included in the subcohort for the present analyses (44–46).

Follow-up for cancer and censoring

Participants reported medical events annually (WHI Observational Study) or semiannually (WHI Clinical Trials) through mailed self-administered or telephone-administered questionnaires. Breast cancers reported by participants were adjudicated by WHI Clinical Coordinating Center staff and via physician review of medical records (41, 47). Data on estrogen receptor (ER) and progesterone receptor (PR) status were available for 88% of breast cancers in WHI and 91% of cases in the present study. Women were followed until the earliest of incidence of invasive breast cancer, death, or final contact. The original WHI study period ended on March 31, 2005, with additional active follow-up (WHI Extension 1) for consenting women. For this report, follow-up ended on September 30, 2010, the end of WHI Extension 1; median follow-up time was 13.2 years. Death was ascertained through clinical center follow-up of family reports and routine checks with the National Death Index (47).

Urinary cadmium and creatinine concentrations

Women in the WHI bone mineral density study provided a first-void morning urine sample, recorded the time of void on the sample collection vial, and refrigerated the sample until they attended the baseline clinical visit. Upon receipt at the clinic, the sample was logged, centrifuged, aliquoted into cryovials, and frozen for shipment and storage at −70°C in the WHI repository.

Urine samples of women selected for the present study were obtained from the WHI biorepository and shipped frozen to the Ultra-trace Elements and Metals Testing Facility at the Trace Elements Laboratory, Wisconsin State Laboratory of Hygiene (Madison, Wisconsin; http://www.slh.wisc.edu/environmental/trace/) for measurement of cadmium and creatinine levels. The laboratory staff was blinded with respect to participant disease status, and urine samples for cases and noncases were processed in random order. All laboratory procedures were completed in 2012.

Urinary cadmium concentration was measured using sector field inductively coupled plasma mass spectrometry on a Thermo-Finnigan Element 2 mass spectrometer (Thermo Scientific, Waltham, Massachusetts), following procedures similar to those previously described (20, 48–50). Urine samples were diluted 1 + 5.6 and 1 + 9 with 2% (v/v) high-purity 16M nitric acid containing 3 internal standards for analysis. The formation of the isobaric interference molybdenum oxide was monitored throughout the analytical sequence, and where appropriate, a run position empirical correction was applied to the cadmium data (51). Molybdenum oxide formation was also evaluated with stable molybdenum isotope spikes in selected participant samples. Molybdenum oxide
formation fractions were in the range 0.0015–0.0025, and molybdenum oxide correction at the median urinary cadmium concentration was 20%, consistent with published results from other populations (51, 52).

Mass spectrometry assay batches included participant samples, standard reference material aliquots, and multiple quality control samples (duplicates, spikes, check standards, and blanks). Duplicate participant samples resulted in a mean intraassay coefficient of variation for urinary cadmium of 2.7%. Several externally certified reference standards for metals in urine were used (US National Institute of Standards and Technology 2670a (both high and low levels) (National Institute of Standards and Technology, Gaithersburg, Maryland), Seronorm 210705 (SERO AS, Billingstad, Norway), and UTAK 12111 Normal Range (UTAK Laboratories, Valencia, California)), and recoveries ranged from 90.8% to 102.8%. Reference materials compared between analysis batches resulted in a mean interassay coefficient of variation of 8.7%. The median cadmium concentration in sample blanks was less than 0.01% of the median participant urinary cadmium concentration.

Total urinary cadmium (Cd) concentration was calculated based on the isotope $^{111}$Cd (12.8% fractional abundance). Total urinary cadmium values below the lowest level of quantification (0.0035 µg/L; n = 12, including 5 cases) were substituted with 0.0025 µg/L (level of quantification divided by $\sqrt{2}$).

Urinary creatinine (Cr) was measured via the enzymatic colorimetric method in 96-well plate format with an M5e automated plate reader (Molecular Devices, Inc., Sunnyvale, California) and a BioAssay Systems QuantiChrom Creatinine Assay Kit (BioAssay Systems LLC, Hayward, California). Duplicate samples produced a mean relative percent difference of 1.8%. All samples returned values above the assay limit of quantification.

### Missing information

Women with missing information on adjustment variable(s) were included in the analysis in a separate category for adjustment. No single variable had data missing for more than 10% of participants. In sensitivity analyses, we repeated our analysis including only women with complete information on all variables.

### Statistical analysis

Creatinine-normalized urinary cadmium concentration (U-Cd) was calculated for each woman by dividing urinary cadmium concentration by urinary creatinine concentration, and was measured in µg of cadmium per g of creatinine (µg/g-Cr). U-Cd was parameterized into quartiles, with quartile cut-offs based on U-Cd in the comparison subcohort women. Multivariable Cox proportional hazards regression with time from WHI enrollment (in days) as the time variable was applied to estimate adjusted hazard ratios with 95% confidence intervals by quartile of U-Cd. For the age-stratified case-cohort design, we applied methods previously described using pseudolikelihood estimators and robust variance estimates (46). Trends were examined by assigning to each quartile the ordinal value of that quartile and treating it as a continuous variable; $P$ for trend was estimated from a Wald test of this coefficient compared with zero. In additional separate analyses, we treated U-Cd as a continuous log-transformed variable (base 2) or a linear (untransformed) continuous variable.

We selected confounders on the basis of knowledge about risk factors for breast cancer and sources of cadmium exposure. Results from multivariable models were stratified by age at enrollment (50–54, 55–59, 60–64, 65–69, 70–74, or 75–79 years) and adjusted for WHI component (Observational Study or Clinical Trials), race/ethnicity (non-Hispanic white, other), education (high school diploma or less, some college or postsecondary education, college degree or more), body mass index (<25, 25–29.9, or ≥30), alcohol consumption at baseline (never drinker, past drinker, or consumer of <1 drink/month, <1 drink/week, 1–7 drinks/week, or >7 drinks/week), use of any formulation of hormone therapy at baseline (never use, ever use), assignment to hormone therapy use during the WHI Hormone Therapy Trial (not randomized, estrogen-alone placebo, estrogen-alone intervention, estrogen + progesterin placebo, or estrogen + progesterin intervention), age at first birth (nulliparous, <20 years, 20–29 years, or ≥30 years), age at menopause (<45, 45–49, 50–54, or ≥55 years), family history of breast cancer (first-degree relatives only; yes/no), cigarette smoking status (never, former, or current smoker), and pack-years of smoking among smokers (<5, 5–19, or ≥19 pack-years). Subsequently, additional adjustment for mammography within 2 years prior to baseline (yes/no), physical activity, and age at menarche were investigated. We also examined an alternative model with urinary cadmium and urinary creatinine entered as separate terms (rather than normalizing each woman’s urinary cadmium values) (53).

We applied the same methods for each outcome of interest to several subgroups of women: never users of hormone therapy at enrollment who participated in the WHI Observational Study or were assigned to one of the placebo arms of the WHI Hormone Therapy Trial; women with body mass index less than 25; never smokers; and women in the WHI Observational Study.

In further analyses, we examined risk of breast cancer according to ER and PR status. For analyses restricted to a specific tumor hormone receptor expression subtype (e.g., ER-positive), only cases with the phenotype of interest were included in the data set, and Cox regression was repeated as described. In a sensitivity analysis, we excluded cases diagnosed within 1 year of enrollment ($n = 41$). The proportional hazards assumption was tested by calculation of Schoenfeld residuals (54). No violations were observed for urinary cadmium parameterized in quartiles or continuously, in the study sample as a whole or within each age stratum.

With 500 incident cases, we estimated that in a cohort study we would have 80% power to detect ($\alpha = 0.05$) an association with a hazard ratio of 1.28 or greater. All tests of statistical significance were 2-sided. All statistical analyses were completed in Stata statistical software, releases 13 and 14 (StataCorp LP, College Station, Texas).

### Ethical conduct of research

All WHI participants provided written informed consent. Human subjects review committees at all participating sites...
approved the WHI study protocols. The study described here was reviewed and approved by the Fred Hutchinson Cancer Research Center (Seattle, Washington) Institutional Review Board as an ancillary study to WHI.

RESULTS

Compared with the age-matched comparison subcohort, women diagnosed with breast cancer were more likely to be non-Hispanic white and had a higher body mass index. Cases also reported a later age at menopause, previous cigarette smoking, and higher educational attainment (Table 1).

The distribution of U-Cd in the comparison cohort women was positively skewed (mean = 0.63 (standard deviation, 0.50) µg/g-Cr; median, 0.51 (interquartile range, 0.33–0.77) µg/g-Cr). The median U-Cd concentration was similar in cases (median, 0.50 (interquartile range, 0.32–0.71) µg/g-Cr), although the mean U-Cd concentration was slightly lower in cases (0.58 (standard deviation, 0.36) µg/g-Cr) than in the subcohort (P = 0.03 for difference). In the comparison cohort, median U-Cd was notably higher in older women, smokers, lean women (body mass index <25), and women who consumed more than 7 alcoholic beverages per week (Table 1).

We did not observe an association of breast cancer risk with U-Cd parameterized in quartiles (comparing highest quartile with lowest quartile, hazard ratio (HR) = 0.80, 95% confidence interval (CI): 0.56, 1.14; P for trend = 0.20) or as a continuous variable (per 2-fold higher U-Cd concentration, Table 1.)
HR = 0.94, 95% CI: 0.86, 1.03) (Table 2). As an untransformed linear variable, U-Cd was inversely associated with breast cancer risk (per 1 µg/g-Cr, HR = 0.72, 95% CI: 0.55, 0.94). In addition, we did not observe an association between quartiles of U-Cd and increased risk of breast cancer in any subgroup of women examined, including never smokers, women with body mass index less than 25, and never users of hormone therapy.

We repeated our analysis after restricting the data to ER-positive tumors, ER-positive/PR-positive tumors, and ER-negative/PR-negative tumors. The association between U-Cd and breast cancer risk did not vary markedly between breast cancer subtypes (Table 2).

Results of sensitivity analyses restricting the data to women with complete information or excluding cases diagnosed within 1 year of enrollment were not substantively different. Additional adjustment for preenrollment mammography, physical activity, or age at menarche did not meaningfully change results. Results from models that included urinary cadmium and creatinine as separate terms were nearly identical to results presented here.

DISCUSSION

In this report, we have described the results of a prospective study of the association between cadmium exposure, assessed by measurement of urinary cadmium concentration, and invasive breast cancer risk in a large cohort of postmenopausal US women. Despite a range of urinary cadmium levels comparable to those of previous retrospective studies...
of US and European populations (20, 22, 23), our results did not provide evidence that cadmium exposure was linked to increased risk of breast cancer in this population.

Several previous retrospective case-control studies have found a positive association between urinary cadmium level and breast cancer risk (20–24). Because these studies collected urine after breast cancer diagnosis, the results may have been subject to “reverse causation,” although the mechanism for elevation of urinary cadmium following diagnosis remains unclear. Alternatively, the case-control studies may have been subject to unidentified selection biases. By design, our study was much less likely to be subject to these limitations. Notably, 2 earlier prospective studies with a small number of breast cancer cases also did not observe elevated breast cancer mortality associated with urinary cadmium (38, 39). In a recent prospective study that relied on geographic information to estimate airborne cadmium exposure, Liu et al. (55) observed a possible positive association between cadmium exposure and hormone receptor–negative breast cancer.

Cadmium is inefficiently excreted and persists in the human body for decades following absorption, accumulating primarily in the kidneys and liver (56, 57). Urinary cadmium is widely regarded as reflective of long-term, cumulative exposure, albeit a complex mixture of recent and previous exposures (26–31). The relationship between renal cadmium levels, measured from autopsy and living donor samples, and urinary cadmium concentrations may be weaker in older adults than in younger adults, partly because cadmium in both matrices has been suggested to plateau at approximately age 50 years (28, 58, 59). Although the women in our study may have changed their diets or smoking habits since enrollment in the WHI and collection of urine samples, this is unlikely to have strongly influenced our classification of long-term exposure based on urinary cadmium. Therefore, we believe our measure of cadmium exposure is the most appropriate for studies of this design.

With the high quality of case identification and adjudication provided by the WHI, we were able to examine risk of breast cancer according to ER and PR status for over 90% of the

### Table 2. Hazard Ratios for Invasive Breast Cancer According to Creatinine-Normalized Urinary Cadmium Concentration Among Selected Participants in the Women’s Health Initiative, 1993–2010

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases</th>
<th>HRb</th>
<th>95% CI</th>
<th>HRc</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile of U-Cd³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>129</td>
<td>1</td>
<td>Referent</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>2</td>
<td>135</td>
<td>0.98</td>
<td>0.72, 1.32</td>
<td>0.99</td>
<td>0.72, 1.36</td>
</tr>
<tr>
<td>3</td>
<td>134</td>
<td>1.01</td>
<td>0.75, 1.36</td>
<td>0.89</td>
<td>0.64, 1.25</td>
</tr>
<tr>
<td>4</td>
<td>110</td>
<td>0.88</td>
<td>0.64, 1.20</td>
<td>0.80</td>
<td>0.56, 1.14</td>
</tr>
<tr>
<td><em>P</em> for trend</td>
<td></td>
<td>0.48</td>
<td></td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Per 2-fold increase in U-Cd</td>
<td>508</td>
<td>0.96</td>
<td>0.88, 1.04</td>
<td>0.94</td>
<td>0.86, 1.03</td>
</tr>
<tr>
<td>Per 1 µg/g-Cr</td>
<td>508</td>
<td>0.81</td>
<td>0.65, 1.01</td>
<td>0.72</td>
<td>0.55, 0.94</td>
</tr>
<tr>
<td><strong>Subgroups</strong>⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>255</td>
<td>0.91</td>
<td>0.79, 1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index &lt;25</td>
<td>150</td>
<td>0.90</td>
<td>0.73, 1.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone therapy nonuser²</td>
<td>218</td>
<td>0.86</td>
<td>0.74, 1.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observational Study women only</td>
<td>281</td>
<td>0.90</td>
<td>0.79, 1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-positive cases only</td>
<td>374</td>
<td>0.98</td>
<td>0.89, 1.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-positive/PR-positive cases only</td>
<td>312</td>
<td>0.97</td>
<td>0.87, 1.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-negative/PR-negative cases only</td>
<td>81</td>
<td>0.88</td>
<td>0.70, 1.11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Cd, cadmium; CI, confidence interval; Cr, creatinine; ER, estrogen receptor; HR, hazard ratio; PR, progesterone receptor; U-Cd, creatinine-normalized urinary cadmium concentration; WHI, Women’s Health Initiative.

* Expressed as µg of cadmium per g of creatinine (µg/g-Cr).
  b Results were stratified by age group (50–54, 55–59, 60–64, 65–69, 70–74, or ≥75 years).
  c Results were stratified by age group and adjusted for WHI study component (Observational Study or Clinical Trials), age at first birth, age at menopause, family history of breast cancer, smoking status, pack-years of smoking, body mass index, education, alcohol consumption, WHI Hormone Therapy Trial arm, and hormone therapy use.
  d Quartile 1, <0.325 µg/g-Cr; quartile 2, 0.325–0.502 µg/g-Cr; quartile 3, 0.503–0.748 µg/g-Cr; quartile 4, >0.748 µg/g-Cr.
  e Estimated risk per 2-fold increase in U-Cd.
  f Weight (kg)/height (m)².
  g For women enrolled in the WHI Observational Study, women who had never used hormone therapy at baseline; for women enrolled in the WHI Clinical Trials, women who were never users at baseline and were assigned to the placebo group in the WHI Hormone Therapy Trial or not randomized into the WHI Hormone Therapy Trial.
cases, a design characteristic motivated by earlier reports that cadmium acts as a “metallohormone” (60) through estrogen receptor α to induce proliferation in breast cancer cell lines (13) and in vivo (14). Our results did not support this idea.

Some limitations should be considered in interpreting our results. Although statistical power in the primary analysis was adequate to observe associations consistent with those of previously published case-control studies (20–24), the sizes of some subgroups, such as the ER- and PR-negative cases, were limited. In contrast to most of the earlier studies of urinary cadmium and breast cancer risk, our study included only postmenopausal women; however, the majority of cases and controls in earlier studies were postmenopausal. Thus, the possibility that cadmium is associated only with premenopausal breast cancer seems an unlikely explanation for our findings. The WHI urine samples were first morning voids collected by participants at home, following standard urine collection protocols. Analysis of cadmium concentrations was not planned at the time of urine collection, and environmental contamination was possible. This appears to have been a minimal limitation in our study: We obtained and tested cryovials used by WHI and found no evidence of contamination; ambient environmental cadmium levels in air are generally very low; our measured urinary cadmium levels were similar to those from previous studies of similar populations that followed stricter collection protocols (61–63); and we observed expected trends in urinary cadmium with age and smoking.

Finally, the use of a single spot urine sample, as in our analysis, is common in epidemiologic studies, primarily because collecting a large number of 24-hour urine samples or multiple spot urine samples is unfeasible, and spot urine samples have been shown to be a valid matrix for assessing metal exposures. Nonetheless, spot urine samples potentially introduce measurement error (64). Specifically, variation in the collection times of spot samples may influence excretion of cadmium (64); however, 84% of our participants collected urine prior to 8 AM. Thus, we cannot rule out the possibility that our sample collection protocol may have contributed to nondifferential measurement error and could have biased our results towards the null, but we would expect that any influence was small, particularly in comparison with other measures of cadmium exposure, such as dietary estimates (36).

In conclusion, in this prospective study of urinary cadmium concentrations and breast cancer risk, we did not find evidence to support the hypothesis that cadmium exposure is a cause of invasive breast cancer.

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