Published in final edited form as:

Cancer Causes Control. 2018 September ; 29(9): 855–862. doi:10.1007/s10552-018-1061-9.

C-reactive protein concentration and risk of selected obesity-related cancers in the Women's Health Initiative

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Abstract

Background—Obesity is a chronic inflammatory condition strongly associated with the risk of numerous cancers. We examined the association between circulating high-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation and strong correlate of obesity, and the risk of three understudied obesity-related cancers in postmenopausal women: ovarian cancer, kidney cancer, and multiple myeloma.

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Author contributions TMB, GCK, and TER conceived of and designed the analysis, interpreted the data, and revised the paper. TMB performed the analysis. SWS, GYFH, and WKN acquired the data, interpreted the data, and revised the paper. WEB, WKN, and MAB interpreted the data, and revised the paper. All authors gave final approval of the version to be published.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10552-018-1061-9>) contains supplementary material, which is available to authorized users.

Conflict of interest The authors have no competing interests to declare.

Methods—Participants were 24,205 postmenopausal women who had measurements of baseline serum hsCRP (mg/L) in the Women’s Health Initiative (WHI) CVD Biomarkers Cohort, a collection of four sub-studies within the WHI. Incident cancers were identified over 17.9 years of follow-up ($n = 153$ ovarian, $n = 110$ kidney, $n = 137$ multiple myeloma). hsCRP was categorized into study-specific quartiles. Adjusted Cox regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations of baseline hsCRP with the risk of these cancers.

Results—There was no clear association between baseline hsCRP concentration and the risk of ovarian cancer (quartile 4 vs. 1: HR 0.87, 95% CI 0.56–1.37), kidney cancer (HR 0.95, 95% CI 0.56–1.61), or multiple myeloma (HR 0.82, 95% CI 0.52–1.29). HRs for 1 mg/L increases in hsCRP also approximated the null value for each cancer.

Conclusions—The results of this study suggest that elevated CRP is not a major risk factor for these obesity-related cancers (ovarian or kidney cancers, or multiple myeloma) among postmenopausal women. Given the importance of elucidating the mechanisms underlying the association of obesity with cancer risk, further analysis with expanded biomarkers and in larger or pooled prospective cohorts is warranted.

Keywords

C-reactive protein; Obesity; Women’s health; Renal cell carcinoma; Multiple myeloma; Ovarian cancer

Introduction

Inflammation is hypothesized to play an important role in cancer development [1–4]. Indeed, a variety of inflammatory conditions or exposures are associated with increased risks of several cancers [3]. One important biomarker of systemic inflammation is C-reactive protein (CRP), an acute-phase reactant protein that is produced in the liver and found in the blood in response to inflammatory signaling [4]. CRP has been associated with systemic inflammation in a number of inflammatory conditions, as well as in cardiovascular disease and diabetes [4]. In addition, CRP is strongly associated with obesity, which itself is a chronic inflammatory state, in both sexes and in different populations [4, 5].

Prospective biomarker studies have reported positive associations of circulating CRP with risks of several common cancers [6, 7]. In a nested case-control study in Greece, Trichopoulos et al. [8], reported positive associations between plasma CRP and risks of cancers in the liver, lung, skin, bladder, and kidney. A recent meta-analysis of prospective studies reported a strong positive association between CRP and ovarian cancer risk [9].

The Women’s Health Initiative (WHI) is a prospective study that was designed to examine common causes of morbidity and mortality among postmenopausal women, including cancer [10]. Previous reports from the WHI have identified positive associations between circulating CRP and risks of breast [11], colorectal [12], and endometrial cancer [13]. Notably, obesity is a common risk factor for each of these diseases [14]. Herein, we examined the association of baseline high-sensitivity CRP (hsCRP) with the risk of three

less-common obesity-related cancers [14], ovarian, kidney, and multiple myeloma, which have not been previously studied in the WHI and for which the scientific evidence is limited.

Methods

Women's Health Initiative

The WHI consists of a clinical trial (CT) (Trial registration: [https://clinicaltrials.gov/identifier, NCT00000611](https://clinicaltrials.gov/identifier/NCT00000611)) and an observational study (OS). Detailed methods of the study are given elsewhere [10, 15, 16]. Briefly, 161,808 women, aged 50–79 years, were recruited at 40 US clinical centers between 1 September 1993 and 31 December 1998. The WHI CT included three overlapping components: two placebo-controlled hormone therapy trials [estrogen-alone ($n = 10,739$) and estrogen plus progestin ($n = 16,608$)]; a dietary modification compared to usual diet trial ($n = 48,836$); and a calcium/vitamin D supplementation placebo-controlled trial ($n = 36,282$) [17–19]. Participants in the OS were 93,676 women who were screened for participation in the CT but were ineligible or unwilling to participate, or who were directly recruited [20]. After the original WHI study ended in 2005, two WHI extension studies ending in 2010 and 2015, respectively, were carried out to collect additional follow-up data regarding new morbidity as well as mortality. Women provided written informed consent for participation in both the original and extension studies. Human Subjects Review Committees at all participating institutions approved the WHI study protocol.

Data collection

WHI participants attended baseline-screening visits, during which they completed self-administered questionnaires that elicited detailed information on demographics, medical, and reproductive history, family history of cancer, physical activity, and other risk factors. Height (cm) and weight (kg) were measured by clinic staff, and used to determine body mass index (BMI; kg/m^2).

The WHI CVD biomarkers cohort

Participants who had measurements of baseline CRP, fasting serum glucose and insulin, and other clinical parameters that were made in four sub-studies within WHI were assembled into the CVD Biomarkers Cohort ($n = 24,558$) to explore relationships between these biomarkers and CVD outcomes. Some sub-studies entailed selecting a random sample; others selected participants based on specific age and race/ethnicity criteria (Supplemental Fig. 1). As such, participants of the CVD Biomarkers Cohort were less likely to be white (47 vs. 82%), had fewer years of education (23.3 vs. 28.3% post-graduate education), were more likely to smoke (9.5 vs. 7.0%), and had a higher prevalence of diabetes (9.7 vs. 6.0%) than participants in the parent WHI OS + CT cohort. They were also less likely to use oral contraceptives (36.6 vs. 41.3%) or menopausal hormone therapy (39.4 vs. 56.0%). For the current study, $n = 353$ women were excluded due to missing hsCRP data, leaving $n = 24,205$ available for analysis. For analyses of ovarian cancer, we additionally excluded $n = 4,430$ women who reported bilateral oophorectomy and $n = 49$ who reported a prior diagnosis of ovarian cancer, leaving $n = 19,726$ for analysis. Data regarding prior history of kidney cancer or multiple myeloma at baseline were unavailable in the WHI.

Follow-up for cancer and censoring

Incident invasive cancer cases were self-reported annually in the OS; in the CT, they were reported semi-annually until 2005, and annually thereafter. Cases were confirmed by medical record review by physician adjudicators. After a median follow-up of 17.9 years, $n = 153$ invasive ovarian, $n = 110$ invasive kidney, and $n = 137$ multiple myelomas were identified within this sub-sample. Participants were right-censored from the analysis at the earliest of the following events: end of original follow-up for participants who were not enrolled in the WHI Extension Study, withdrawal from the study, death, loss of contact, or 31 December 2015, the last date of the WHI Extension study data adjudication.

Biospecimen collection and laboratory measures

Fasting blood samples were collected from WHI participants at their baseline-screening visit. Women were asked not to take hypoglycemic agents or non-steroidal anti-inflammatory drugs 48 h prior to the visit, except those taken regularly; and to abstain from smoking (< 1 h) or vigorous activity (< 12 h) prior to the visit. Blood was drawn with the participant in a seated position and processed locally according to standardized protocols for venipuncture [15]. Biospecimens were centrifuged, separated by layers, labeled, and stored at -70°C until shipped monthly on dry ice to the WHI central repository (McKesson BioServices, Rockville, MD), where samples are held for long-term storage at -80°C [15]. All laboratory measurements were made at the Advanced Research and Diagnostic Laboratory at the University of Minnesota. Blinded quality control samples of pooled blood from healthy women were run with each batch of study samples (5%; $n = 1,075$). Coefficients of variation ($\text{SD}/\bar{x}$) for all reported biomarkers were $\leq 3\%$. hsCRP (mg/L) was measured in serum by immunoassay on a Roche Modular P Chemistry analyzer using a latex particle-enhanced immunoturbidimetric assay kit (Roche Diagnostics; Indianapolis, IN) and read on the Roche Modular P Chemistry analyzer.

In addition to hsCRP, serum cholesterol and glucose were also measured. Serum high-density lipoprotein (HDL; mg/dL) cholesterol was measured using the HDLC plus 3rd generation direct method (Roche Diagnostics Corporation) on the Roche Modular P Chemistry analyzer. Serum triglycerides (mg/dL) were measured using the Triglyceride GB reagent (Roche Diagnostics Corporation) on the Roche Modular P Chemistry analyzer. Low-density lipoprotein (LDL; mg/dL) cholesterol was calculated in serum specimens with a triglyceride value < 400 mg/dL using the formula of Friedewald et al. [21]. For the vast majority of women ($n = 22,314$), fasting serum glucose was measured using the Gluco-quant Glucose/hexokinase reagent (Roche Diagnostics) on the Roche Modular P Chemistry analyzer. In the remaining women, glucose was determined by the hexokinase method on the Hitachi 747 (Boehringer Mannheim Diagnostics; Indianapolis, IN) [22].

Statistical analyses

hsCRP data were log-transformed for normality. All serum measures, including hsCRP, HDLC, LDLC, triglycerides, and glucose were categorized into study-specific quartiles in order to account for differences in the biomarkers' distributions in the sub-studies. For hsCRP, the lower bound of the upper quartile was 4.70–7.38 mg/L, depending on the WHI sub-study (Table 1). Overall quartiles were also considered, to address the possibility that

absolute hsCRP concentration is important. Frequencies and percentages of participants' baseline characteristics were compared by quartiles of baseline hsCRP using t tests and χ^2 tests as appropriate. Age-adjusted ratios for associations between participants' baseline characteristics and hsCRP were calculated using generalized linear regression models. Estimates are expressed as e^{β} which represents the ratio of the adjusted geometric mean for hsCRP in a given category of a variable relative to the referent category for that variable. Adjusted Cox proportional hazards (CPH) models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between baseline serum hsCRP and risk of ovarian cancer, kidney cancer, or multiple myeloma. Age-adjusted CPH models and multivariable-adjusted results are presented. A final multivariable model was determined by including characteristics that were associated with hsCRP and cancer status in bivariate analyses. Models were reduced using backward selection with $p < 0.05$ as the cutoff for retention, with the exception of age, which was retained in all models. Final multivariable models for each cancer are given in footnotes of Table 2. Cox regression models estimating associations for hsCRP as a continuous variable for overall (rather than study-specific) hsCRP quartiles are additionally adjusted for WHI sub-study. Schoenfeld residuals were used to verify that the proportionality assumption of CPH models was not violated [23]. A number of sensitivity analyses were performed: As CRP can be affected by acute infections, an analysis restricted to women with hsCRP < 10 mg/L was performed. We have previously observed artificially increased CRP among users of menopausal hormone therapy due to hepatic first-pass metabolism [11]. In a second sensitivity analysis, regression models were restricted to non-users of estrogen-alone therapy or use of non-steroidal anti-inflammatory drugs (NSAIDs). Third, we excluded women with a baseline history of any cancer from the analysis.

Results

Baseline participant characteristics were assessed across study-specific quartiles of serum hsCRP (Table 1). Consistent with the literature, BMI was strongly positively associated with hsCRP, with the proportions of class 1 and class 2 obesity increasing across increasing hsCRP quartiles. Relative to normal-weight women, class 1 and class 2 obese women had 2.66 (95% CI 2.56–2.76)- and 4.12 (3.96–4.29)-fold higher hsCRP. Associations between other baseline characteristics and hsCRP were weaker. Among them, increased parity, duration of estrogen therapy, cigarette smoking, prevalent diabetes, and increased categories of serum glucose and triglycerides were associated with increased hsCRP; whereas later age at menopause and higher levels of physical activity, alcohol consumption, or serum HDL cholesterol were each associated with lower hsCRP.

Associations between baseline serum hsCRP concentrations and risk of ovarian cancer, kidney cancer, and multiple myeloma are given in Table 3. We observed no evidence of an association with any of the three cancers. Contrasting the highest to the lowest study-specific quartile of hsCRP, HRs for ovarian cancer, kidney cancer, and multiple myeloma were 0.87 (95% CI 0.56–1.37), 0.95 (95% CI 0.56–1.61), and 0.82 (95% CI 0.52–1.29), respectively. Continuous HRs representing 1 mg/L increases in hsCRP also approximated the null value for each of the three cancers. Further adjustment for BMI had minimal effect on point estimates (Table 3). In sensitivity analyses, restriction of analyses to women with hsCRP $<$

10 mg/L, or non-users of estrogen therapy or NSAIDs, or women with no history of cancer at baseline also did not alter point estimates (data not shown). Associations remained null when overall—rather than study-specific—hsCRP quartiles were considered. Specifically, adjusted HRs for contrasts of hsCRP quartiles four to one were 0.97 (95% CI 0.63–1.50), 0.88 (95% CI 0.50–1.55), and 0.84 (95% CI 0.53–1.33), for ovarian cancer, kidney cancer, and multiple myeloma, respectively.

Discussion

In this prospective investigation among postmenopausal women, we found no evidence to support a positive association of serum hsCRP with the risk of three obesity-related cancers. For kidney cancer and multiple myeloma, in particular, our results add to a little-researched area.

Several prospective studies have examined associations between circulating CRP and ovarian cancer risk. In a recent meta-analysis of seven prospective studies including over 2,000 ovarian cancer cases, Zeng et al. [9], reported that women with the highest third of circulating hsCRP levels—approximately > 9.75 mg/L—had a 91% increased ovarian cancer risk relative to women with the lowest third (meta-RR 1.91, 95% CI 1.51–2.40). Our results are not wholly inconsistent with these findings. The cutpoints for the highest hsCRP quartiles in the WHI CVD biomarkers cohort sub-studies (i.e., 4.66–7.37 mg/L) were much lower than for the upper tertiles among studies included in the metaanalysis. Indeed, our finding of no association is consistent with respect to hsCRP distribution and results for the middle third of the biomarker in the meta-analysis (≈ 1 –10 mg/L; meta-RR 1.13, 95% CI 0.96–1.33) [9]. Taken together with prior reports, it may be that only higher levels of CRP are associated with ovarian cancer risk.

Studies examining associations of CRP with risks of kidney cancer [8] or multiple myeloma [24] are lacking. In a small Greek nested case-control study which focused on total cancer risk, a 1 SD (3.2 mg/L) increase in plasma CRP was associated with 48% increased kidney cancer risk (OR 1.48, 95% CI 1.11–1.96). The finding was based upon $n = 10$ kidney cancer cases. Our finding of no association, based upon $n = 110$ kidney cancer cases in postmenopausal women, contrasts strongly with this result. Our observation of no relation between hsCRP and multiple myeloma risk agrees with the only prior study on the topic. In 2012, Birmann et al. [24], reported no association between circulating CRP and multiple myeloma risk (n cases = 493; Quartile 4 vs. 1, OR 1.0, 95% CI 0.7–1.4), using data pooled as part of the Multiple Myeloma Cohort Consortium and which included 197 cases and 394 controls from the WHI ($n = 54$ cases and $n = 91$ non-cases overlapped with this study). When restricted to non-overlapping participants, findings were unchanged (continuous HR 1.03, 95% CI 0.84–1.27). Our findings suggest that alternative mechanisms beside obesity's effect on chronic inflammation may be important in the etiology of these two diseases among postmenopausal women.

This study has a number of strengths, including its prospective design and the high reliability of the biomarker assays. There are also limitations. Chief among them is the potential for measurement error, as hsCRP was measured at different dates in the

participating WHI sub-studies. We attempted to address this by examining sub-study-specific quartiles of exposure [25]. Similarly, CRP was measured at a single time point, which could also contribute to measurement error. Despite consistency with prior results, such error could nevertheless explain the null findings reported herein. Also, individuals regularly taking anti-inflammatory medications may have favored null associations. We are further limited in statistical power to detect modest associations, due to the relatively small number of incident cases of the three rare cancers examined within the cohort. Another limitation of our study is that the CVD Biomarkers Cohort sub-sample is not a random sample of the WHI. Women included in the sub-sample differed from the total WHI study population. However, while our results are not applicable to all of WHI, analyses conducted within the sub-sample should be valid.

The results of this study suggest that CRP is not a major factor in the etiologies of multiple myeloma, ovarian or kidney cancer among postmenopausal women. However, given the importance of elucidating the mechanisms underlying the association of obesity with cancer risk, further investigation evaluated in larger samples of women and interrogating additional inflammatory biomarkers as well as alternative pathways is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work is supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, and U.S. Department of Health and Human Services grants HHSN2682011000046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, and HHSN268201100004C. The funding source had no role in the collection of data, the analysis, interpretation, or writing of this report, or in the decision to submit the article for publication.

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Table 1
Distribution of hsCRP in the WHI CVD biomarkers cohort and its component studies

Study	High-sensitivity C-reactive protein (mg/L)				
	<i>n</i>	Quartile 1	Median	Quartile 3	IQR
WHI CVD Biomarkers Cohort	24,205	1.30	2.86	6.03	4.73
CVD Biomarkers for SNP Health Association Resource (SHARe)	11,963	1.57	3.50	7.38	5.81
CVD Biomarkers in Non-minority Hormone Therapy Participants	10,161	1.12	2.35	4.77	3.65
CVD Biomarkers in WHI Native Americans	588	1.63	3.74	6.25	4.62
Long Life Study-Phase III Biomarkers and GWAS	1,493	1.16	2.27	4.70	3.54

IQR interquartile range

Associations between participants' baseline characteristics and serum hsCRP in the Women's Health Initiative CVD biomarkers cohort, $n = 24,205$

Characteristics	Age-adjusted ratio (95% CI) ^a	Study-specific quartiles of serum high-sensitivity C-reactive protein (mg/L), n (%)				p Value ^b
		Quartile 1, $n = 6,053$	Quartile 2, $n = 6,057$	Quartile 3, $n = 6,043$	Quartile 4, $n = 6,052$	
Age, years [mean (SD)]	0.98 (0.98–0.99)	64.28 (7.41)	64.31 (7.40)	64.06 (7.20)	63.25 (7.07)	< 0.0001
Race						
White	1.00 referent	2,866 (47.35)	2,826 (46.66)	2,838 (46.96)	2,786 (46.03)	< 0.0001
Black	1.42 (1.37–1.47)	2,122 (35.06)	2,026 (33.45)	2,103 (34.80)	2,376 (39.26)	
Hispanic/Latina	1.26 (1.21–1.31)	918 (15.17)	1,058 (17.47)	954 (15.79)	744 (12.29)	
Native American	1.36 (1.24–1.49)	147 (2.43)	147 (2.43)	148 (2.45)	146 (2.41)	
WHI studies						
Clinical trials	1.00 Referent	4,437 (73.30)	4,569 (75.43)	4,569 (75.61)	4,544 (75.08)	0.01
Observational study	1.13 (1.10–1.17)	1,616 (26.70)	1,488 (24.57)	1,474 (24.39)	1,508 (24.92)	
Body Mass Index, kg/m ²						
< 25.0	1.00 Referent	2,772 (46.10)	1,443 (23.99)	863 (14.38)	543 (9.06)	< 0.0001
25.0–29.9	1.76 (1.70–1.82)	2,204 (36.65)	2,514 (41.79)	2,198 (36.62)	1,538 (25.67)	
30.0–34.9	2.66 (2.56–2.76)	782 (13.01)	1,434 (23.84)	1,789 (29.81)	1,826 (30.47)	
35.0	4.12 (3.96–4.29)	255 (4.24)	625 (10.39)	1,152 (19.19)	2,085 (34.80)	
Age at menarche, years						
10	1.00 Referent	350 (5.81)	386 (6.40)	448 (7.45)	544 (9.05)	< 0.0001
11–12	0.87 (0.82–0.92)	2,387 (39.64)	2,486 (41.24)	2,423 (40.27)	2,564 (42.63)	
13–14	0.81 (0.77–0.86)	2,575 (42.77)	2,497 (41.42)	2,468 (41.02)	2,258 (37.55)	
15	0.85 (0.80–0.91)	709 (11.78)	659 (10.93)	678 (11.27)	648 (10.77)	
Parity						
Nulliparous/nulligravida	1.00 Referent	738 (12.30)	655 (10.90)	621 (10.36)	611 (10.18)	< 0.0001
1	1.06 (1.00–1.12)	665 (11.08)	586 (9.75)	579 (9.55)	625 (10.42)	
2–4	1.04 (0.99–1.08)	3,556 (59.26)	3,562 (59.27)	3,545 (59.15)	3,473 (57.88)	
5	1.16 (1.10–1.22)	1,042 (17.36)	1,207 (20.08)	1,248 (20.82)	1,291 (21.52)	
Age at first birth, years						
Nulliparous/nulligravida	1.00 Referent	738 (14.11)	655 (12.39)	621 (11.99)	611 (11.67)	< 0.0001
< 20	1.23 (1.17–1.30)	887 (16.96)	1,117 (21.13)	1,119 (21.60)	1,307 (24.96)	

Characteristics	Age-adjusted ratio (95% CI) ^a	Study-specific quartiles of serum high-sensitivity C-reactive protein (mg/L), n (%)				p Value ^b
		Quartile 1, n = 6,053	Quartile 2, n = 6,057	Quartile 3, n = 6,043	Quartile 4, n = 6,052	
20–29	1.01 (0.96–1.06)	3,154 (60.29)	3,099 (58.63)	3,023 (58.35)	2,944 (56.22)	< 0.0001
30	0.98 (0.92–1.05)					
Age at menopause, years						
45	1.00 Referent	1,588 (28.90)	1,777 (32.51)	1,838 (33.86)	2,116 (38.90)	< 0.0001
46–50	0.82 (0.80–0.85)	1,863 (33.91)	1,787 (32.69)	1,740 (32.05)	1,629 (29.94)	
51	0.82 (0.79–0.85)	2,043 (37.19)	1,902 (34.80)	1,851 (34.09)	1,695 (31.16)	
Duration of estrogen therapy, years						
Non-user	1.00 Referent	4,517 (74.64)	4,352 (71.85)	4,192 (69.37)	4,026 (66.52)	< 0.0001
< 5	1.10 (1.05–1.14)	833 (13.76)	822 (13.57)	827 (13.69)	912 (15.07)	
5	1.32 (1.27–1.37)	702 (11.60)	883 (14.58)	1,024 (16.95)	1,114 (18.41)	
Duration estrogen + progestin therapy, years						
Non-user	1.00 Referent	5,224 (86.32)	5,278 (87.14)	5,295 (87.62)	5,447 (90.00)	< 0.0001
< 5	0.79 (0.75–0.83)	495 (8.18)	419 (6.92)	428 (7.08)	306 (5.06)	
5	0.94 (0.88–1.00)	333 (5.50)	360 (5.94)	320 (5.30)	299 (4.94)	
Physical activity, MET-h/week						
Inactive	1.00 Referent	1,103 (18.24)	1,380 (22.79)	1,484 (24.57)	1,855 (30.69)	< 0.0001
0.1–5.24	0.95 (0.91–0.98)	1,264 (20.90)	1,465 (24.20)	1,536 (25.43)	1,724 (28.52)	
5.25–14.49	0.79 (0.76–0.82)	1,709 (28.26)	1,557 (25.72)	1,570 (26.00)	1,415 (23.41)	
14.50	0.65 (0.62–0.67)	1,972 (32.61)	1,652 (27.29)	1,449 (23.99)	1,050 (17.37)	
Cigarette smoking, pack-years						
Non-smoker	1.00 Referent	3,237 (55.27)	3,234 (54.99)	3,081 (52.70)	2,906 (49.44)	< 0.0001
0.1–6.82	1.03 (0.99–1.07)	940 (16.05)	930 (15.81)	913 (15.62)	881 (14.99)	
6.83–21.38	1.06 (1.02–1.10)	917 (15.66)	923 (15.69)	921 (15.75)	937 (15.94)	
21.39	1.18 (1.14–1.23)	763 (13.03)	794 (13.50)	931 (15.93)	1,154 (19.63)	
Alcohol consumption, servings/week						
Non-drinker	1.00 Referent	2,804 (46.42)	3,057 (50.60)	3,210 (53.37)	3,545 (58.89)	< 0.0001
0.1–0.71	0.87 (0.83–0.90)	977 (16.17)	984 (16.29)	968 (16.09)	919 (15.27)	
0.72–3.15	0.79 (0.76–0.82)	1,012 (16.75)	908 (15.03)	906 (15.06)	791 (13.14)	
3.16	0.70 (0.67–0.72)	1,248 (20.66)	1,093 (18.09)	931 (15.48)	765 (12.71)	
Prevalent diabetes						< 0.0001

Characteristics	Age-adjusted ratio (95% CI) ^a	Study-specific quartiles of serum high-sensitivity C-reactive protein (mg/L), n (%)				p Value ^b
		Quartile 1, n = 6,053	Quartile 2, n = 6,057	Quartile 3, n = 6,043	Quartile 4, n = 6,052	
No	1.00 Referent	5,752 (95.11)	5,598 (92.48)	5,390 (89.28)	5,099 (84.38)	
Yes	1.77 (1.69–1.85)	296 (4.89)	455 (7.52)	647 (10.72)	944 (15.62)	
Serum glucose, mg/dL ²						< 0.0001
Quartile 1	1.00 Referent	2,286 (37.77)	1,778 (29.35)	1,525 (25.24)	1,234 (20.39)	
Quartile 2	1.11 (1.07–1.15)	1,593 (26.32)	1,491 (24.62)	1,327 (21.96)	1,082 (17.88)	
Quartile 3	1.33 (1.28–1.38)	1,428 (23.59)	1,599 (26.40)	1,584 (26.21)	1,496 (24.72)	
Quartile 4	2.00 (1.93–2.08)	746 (12.32)	1,189 (19.63)	1,607 (26.59)	2,240 (37.01)	
Serum triglycerides, mg/dL ²						< 0.0001
Quartile 1	1.00 Referent	2,416 (39.91)	1,510 (24.93)	1,145 (18.95)	1,044 (17.25)	
Quartile 2	1.43 (1.38–1.49)	1,594 (26.33)	1,535 (25.34)	1,480 (24.49)	1,479 (24.44)	
Quartile 3	1.67 (1.61–1.73)	1,187 (19.61)	1,552 (25.62)	1,630 (26.97)	1,624 (26.83)	
Quartile 4	1.94 (1.87–2.02)	856 (14.14)	1,460 (24.10)	1,788 (29.59)	1,905 (31.48)	
Serum HDL cholesterol, mg/dL ²						< 0.0001
Quartile 1	1.00 Referent	870 (14.38)	1,404 (23.18)	1,752 (28.99)	2,185 (36.10)	
Quartile 2	0.77 (0.74–0.80)	1,386 (22.90)	1,595 (26.33)	1,648 (27.27)	1,668 (27.56)	
Quartile 3	0.66 (0.63–0.68)	1,578 (26.07)	1,555 (25.67)	1,483 (24.54)	1,216 (20.09)	
Quartile 4	0.50 (0.49–0.53)	2,218 (36.65)	1,503 (24.81)	1,160 (19.20)	983 (16.24)	
Serum LDL cholesterol, mg/dL ²						< 0.0001
Quartile 1	1.00 Referent	1,716 (28.47)	1,442 (24.14)	1,416 (23.79)	1,609 (27.04)	
Quartile 2	1.01 (0.98–1.05)	1,547 (25.66)	1,444 (24.18)	1,494 (25.11)	1,433 (24.08)	
Quartile 3	1.03 (0.99–1.07)	1,457 (24.17)	1,538 (25.75)	1,449 (24.35)	1,443 (24.25)	
Quartile 4	1.10 (1.06–1.14)	1,308 (21.70)	1,549 (25.93)	1,592 (26.75)	1,465 (24.62)	

^aDerived from a generalized linear regression model of ln(hsCRP) as the outcome and adjusted for baseline age. Estimates are expressed as eβ, which represent the ratio of adjusted geometric means for hsCRP in a given characteristic category relative to the referent category

^bp Values derived from t tests (age) or χ^2 tests

Table 3

Associations of serum hsCRP with risk of ovarian cancer, kidney cancer, and multiple myeloma in the Women's Health Initiative CVD biomarkers cohort

	Ovary		Kidney		Multiple myeloma	
	n Cases	HR (95% CI)	n Cases	HR (95% CI)	n Cases	HR (95% CI)
<i>Age-adjusted models</i>						
Study-specific quartiles of hsCRP (mg/L)						
Quartile 1	45	1.00 Referent	26	1.00 Referent	44	1.00 Referent
Quartile 2	33	0.77 (0.49–1.20)	20	0.79 (0.44–1.41)	35	0.81 (0.52–1.27)
Quartile 3	39	0.96 (0.62–1.46)	30	1.20 (0.71–2.03)	24	0.57 (0.35–0.94)
Quartile 4	36	0.97 (0.62–1.48)	34	1.42 (0.85–2.37)	34	0.87 (0.55–1.35)
		<i>p</i> Trend = 0.96		<i>p</i> Trend = 0.08		<i>p</i> Trend = 0.27
Continuous ^a		1.02 (0.88–1.18)		1.17 (0.98–1.40)		0.99 (0.85–1.16)
<i>Multivariable-adjusted models</i>						
Study-specific quartiles hsCRP (mg/L)						
Quartile 1	45	1.00 Referent ^b	26	1.00 Referent ^c	44	1.00 Referent ^d
Quartile 2	33	0.72 (0.46–1.14)	20	0.65 (0.36–1.16)	35	0.79 (0.50–1.23)
Quartile 3	39	0.87 (0.56–1.35)	30	0.88 (0.52–1.51)	24	0.54 (0.33–0.90)
Quartile 4	36	0.87 (0.56–1.37)	34	0.95 (0.56–1.61)	34	0.82 (0.52–1.29)
		<i>p</i> Trend = 0.73		<i>p</i> Trend = 0.80		<i>p</i> Trend = 0.19
Continuous ^a		0.99 (0.85–1.15)		1.02 (0.85–1.23)		0.98 (0.83–1.15)
<i>Multivariable-adjusted models including body mass index</i>						
Study-specific quartiles of hsCRP (mg/L)						
Quartile 1	45	1.00 Referent ^e	26	1.00 Referent ^e	44	1.00 Referent ^e
Quartile 2	33	0.70 (0.44–1.10)	20	0.63 (0.35–1.14)	35	0.73 (0.47–1.15)
Quartile 3	39	0.80 (0.51–1.26)	30	0.85 (0.49–1.47)	24	0.48 (0.29–0.80)
Quartile 4	36	0.79 (0.49–1.29)	34	0.89 (0.51–1.57)	34	0.67 (0.41–1.10)
		<i>p</i> Trend = 0.46		<i>p</i> Trend = 0.97		<i>p</i> Trend = 0.05
Continuous ^a		0.96 (0.81–1.14)		1.00 (0.82–1.22)		0.93 (0.78–1.11)

^aContinuous measures additionally adjusted for WHI sub-study

^e Additionally adjusted for body mass index

^d Additionally adjusted for serum triglycerides

^c Additionally adjusted for physical activity, history of diabetes, and serum triglycerides

^b Additionally adjusted for WHI OS/CT participation and serum triglycerides

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