Cataract Extraction and Coronary Heart Disease Risk

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Oxidative damage to proteins in the human lens is believed to be important in the etiology of age-related cataract. Because free radical-mediated oxidative damage to lipoproteins may accelerate atherosclerosis, the authors hypothesized that the development of cataract might be a marker for such damage and therefore might be associated with future risk of coronary heart disease (CHD). The authors followed 60,657 women aged 45–63 years and without known coronary disease, stroke, or cancer in 1984. During 10 years of follow-up (674,283 person-years), the authors documented 887 incident cases of CHD and 2,322 deaths. After adjustment for age, smoking, and other coronary risk factors, cataract extraction was significantly associated with higher risk of CHD (relative risk (RR) = 1.88, 95% confidence interval (CI): 1.41, 2.50) for total CHD, 2.44 (95% CI: 1.54, 3.89) for fatal CHD, and 1.63 (95% CI: 1.14, 2.34) for nonfatal myocardial infarction). The positive association between cataract extraction and total CHD was stronger among women with a history of diabetes (RR = 2.80, 95% CI: 1.77, 4.42) than among those without reported diabetes (RR = 1.51, 95 percent CI: 1.04, 2.18). In multivariate analyses, cataract extraction was associated with significantly increased overall mortality (RR = 1.37, 95 percent CI: 1.13, 1.66), which was entirely explained by the increased mortality from cardiovascular disease (RR = 1.84, 95% CI: 1.29, 2.64). These findings are compatible with current hypotheses relating oxidative damage and tissue aging to the development of cataract and CHD. Am J Epidemiol 2001;153:875–81.

antioxidants; cataract; coronary disease; diabetes mellitus; prospective studies; women

Oxidative damage to proteins and lipids in the human lens is believed to be important in the etiology of age-related cataract (1, 2). In epidemiologic studies, intakes of antioxidants from diet and supplements have been associated with lower risk of cataract (3, 4), lending support to the oxidation hypothesis. Thus, cataract may be considered as a directly observable marker for overall balance between oxidative stress and antioxidant defense. Because free radical-mediated oxidative damage to lipoproteins is also thought to be an important risk factor for atherosclerosis (5), the authors hypothesized that the development of cataract would be positively associated with future risk of coronary heart disease (CHD). Increased glycosylation of tissue proteins associated with glucose intolerance may be another potential mechanism underlying this positive association (6).

To test the hypothesis that cataract is a marker of CHD, the authors examined the relation of cataract extraction to incidence of CHD and overall mortality during 10 years of follow-up among women enrolled in the Nurses’ Health Study.

MATERIALS AND METHODS

Subjects

The Nurses’ Health Study cohort was established in 1976, when 121,700 female registered nurses aged 30–55 years and residing in 11 large US states completed a mailed questionnaire on their medical history and lifestyle. Every 2 years, follow-up questionnaires have been sent to update information on general health factors and to identify newly diagnosed cases of coronary disease and other diseases. Since 1980, validated food frequency questionnaires have been used to assess dietary intakes every 2–4 years (7). For this analysis, the authors used 1984 as the baseline, since this was when cataract extraction was first assessed. After exclusion of women who reported diagnosed cancer or cardiovascular disease at baseline, the population for analysis included 60,657 women aged 45–63 years in 1984. Women
less than age 45 years were excluded from the analysis because cataracts occurring at a younger age are probably due to a congenital causes or to chronic steroid use, ocular trauma, or previous intraocular surgery. Women were added to the analysis after 1984 as they reached age 45 years. Nevertheless, alternative analyses including all women yielded similar results.

**Ascertainment of cataract extraction**

In 1984, 1986, 1988, 1990, and 1992, participants were asked whether they had had a cataract extraction since the last questionnaire. When a woman reported an extraction, the authors requested permission to review medical records and then wrote or telephoned the ophthalmologist to confirm the extraction and to obtain additional details regarding the cataract. Of 805 participants who reported a first cataract extraction by 1988, 769 women (96 percent) permitted us to contact the ophthalmologist; 687 ophthalmologists responded and all confirmed the extraction (8). The confirmation rate also reached 100 percent for self-reported cataract extractions that occurred between 1988 and 1992. Because of the accuracy of self-reported cataract extractions, they were used as the exposure variable in the analyses. Only the first extraction was used as the exposure.

**Assessment of diabetes**

On the baseline and all subsequent biennial questionnaires, the participants were asked whether they had ever been diagnosed with diabetes. Self-reported diabetes was validated by a supplementary questionnaire about symptoms, diagnostic tests, and hypoglycemic treatment of diabetes and was confirmed by medical record review in a sample (9). Medical records were requested from a random sample of 84 participants who reported a diagnosis of diabetes. Of these 84 women, 71 provided permission for medical record review; medical records could be obtained for 62. An endocrinologist who was blinded to the information and then wrote or telephoned the ophthalmologist to confirm the extraction and to obtain additional details regarding the cataract. Of 805 participants who reported a first cataract extraction by 1988, 769 women (96 percent) permitted us to contact the ophthalmologist; 687 ophthalmologists responded and all confirmed the extraction (8). The confirmation rate also reached 100 percent for self-reported cataract extractions that occurred between 1988 and 1992. Because of the accuracy of self-reported cataract extractions, they were used as the exposure variable in the analyses. Only the first extraction was used as the exposure.

**Endpoints**

Study physicians with no knowledge of the self-reported risk factor status reviewed the records. Nonfatal myocardial infarction (MI) was confirmed if data in the record met the criteria of the World Health Organization of symptoms and signs of myocardial infarction or an elevation of cardiac enzyme levels (11). Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable (17 percent). The authors included all confirmed and probable cases in the analyses because results were the same after exclusion of probable cases.

Deaths were reported by next of kin and the postal system or were ascertained through the National Death Index. Follow-up for the deaths was more than 98 percent complete (12). The authors obtained copies of death certificates and medical records, when available, and determined causes of death (classified according to the categories of the International Classification of Diseases, Eighth Revision).

Fatal CHD was confirmed by hospital records or autopsy or if CHD was listed as the cause of death on the death certificate and evidence of previous CHD was available. The authors designated as presumed fatal CHD cases in which CHD was the underlying cause on the death certificate, but no records were available. These cases constituted about 15 percent of fatal CHD cases. Analyses limited to confirmed cases yielded very similar results, although with less precision.

**Data analysis**

For CHD analyses, person-time for each participant was calculated from the date of return of the 1984 questionnaire to the date of confirmed CHD, death from any cause, or June 1, 1994, whichever came first. Incidence rates of CHD were calculated for women who reported an extraction by dividing the number of incident cases by the number of person-years of follow-up. The relative risk of CHD was computed as the rate among women with extractions divided by the rate among women without extractions, with adjustment for 5-year age categories. For the analysis of overall mortality, person-time was calculated from the date of the 1984 questionnaire to the date of death from any cause or June 1, 1994. The relative risk was computed as the mortality rate among women with extractions divided by the corresponding rate among women without extractions.

The pooled logistic regression across the five 2-year intervals (13), which is asymptotically equivalent to Cox regression with time-varying covariates, was used to adjust simultaneously for potential confounding variables. Most covariates were updated biannually, including age (5-year categories); body mass index (<21, 21–22.9, 23–24.9, 25–28.9, and ≥29 kg/m²); cigarette smoking (never and pack-year categories); menopausal status (premenopausal, postmenopausal with no hormone replacement, postmenopausal with hormone replacement, and postmenopausal with current hormone replacement); multivitamin and vitamin E supplement use (yes/no); alcohol consumption (0, 0.1–4, 5–14, and ≥15 g/day); and history of hypertension (yes/no), diabetes (yes/no), and hypercholesterolemia (yes/no). Aspirin use (nonuser, 1–6 times per week, and ≥7 times per week, and dose unknown) was assessed in 1982, 1984, and 1988. Physical activity (metabolic equivalent score per week) was assessed in 1986, 1988, and 1992. Parental history of MI was assessed in 1984. In the main analyses, the authors controlled for pack-years of smoking as a previous study suggested that the number of pack-years of smoking (calculated by multiplying the number of packs smoked per day (one pack = 20 cigarettes) by the number of years over which that amount was smoked) was a stronger predictor of cataract than current number of cigarettes smoked per day (8). In our analysis, adjustment for...
current number of cigarettes smoked per day yielded similar results. In additional analyses, the authors adjusted for dietary intakes of antioxidants, which have been inversely associated with risk of cataract in the Nurses’ Health Study (4). To obtain this score, we categorized dietary intakes for carotene, vitamins C and E, and riboflavin into quintiles, and for each participant, the quintile value for each nutrient was summed, and the sum was recategorized into quintiles.

RESULTS

At baseline in 1984, 520 women reported cataract extractions. By 1992, a total of 2,336 women reported cataract extractions. Women with cataract extractions were somewhat older and heavier, and they were more likely to have hypertension and diabetes and to smoke cigarettes than were those without extraction (table 1). Dietary intakes were similar between women with and those without extractions.

During 10 years of follow-up (674,283 person-years), 887 incident cases of CHD (652 nonfatal MI and 235 fatal CHD) and 2,322 deaths were documented, of which 462 were from cardiovascular disease, 1,255 were from cancer, and 605 were from other causes. In age-adjusted analyses, cataract extraction was significantly associated with increased risk of total CHD (relative risk (RR) = 2.57, 95 percent confidence interval (CI): 1.94, 3.40), fatal CHD (RR = 3.48, 95 percent CI: 2.20, 5.51), and nonfatal MI (RR = 2.19, 95 percent CI: 1.53, 3.13) (table 2). These relative risks were attenuated, but remained statistically significant after further adjustment for pack-years of smoking, history of diabetes, and other covariates (RR = 1.88, 95 percent CI: 1.41, 2.50 for total CHD; RR = 2.44, 95 percent CI: 1.54, 3.89 for fatal CHD; and RR = 1.63, 95 percent CI: 1.14, 2.34 for nonfatal MI). Pack-years of smoking was strongly associated with risk of CHD (compared with never smokers, RRs were 0.85 for <10 pack-years, 1.27 for 10–24 pack-years, 2.42 for 25–44 pack-years, and 3.84 for ≥45 pack-years). The association for cataract extraction remained virtually unchanged after the exclusion of women whose cataracts were due to congenital causes, steroid use, trauma, or surgery (205 subjects). Additional adjustment for the dietary antioxidant score slightly attenuated the association for cataract extraction (RR of total CHD = 1.74, 95 percent CI: 1.38, 2.21). In this model, the relative risks of CHD across quintiles of the antioxidant score were 1.0, 1.08, 0.82, 0.91, and 0.91 (95 percent CI: 0.75, 1.12).

The positive association between cataract extraction and total CHD was stronger among women with a history of diabetes (multivariate RR = 2.80, 95 percent CI: 1.77, 4.42) than among those without (RR = 1.51, 95 percent CI: 1.04, 2.18), but the confidence intervals overlap (p for interaction = 0.14) (table 3). Among women with a history of diabetes, the increased risk with cataract extraction was more pronounced for fatal CHD (RR = 4.45, 95 percent CI: 2.21, 8.97) than for nonfatal MI (RR = 2.13, 95 percent CI: 1.17, 3.89). Additional adjustment for duration of diabetes did not alter the results, although the risk of CHD increased significantly with increasing duration of diabetes in this cohort. In stratified analyses according to smoking status, the multivariate RRs of total CHD associated with cataract extraction were 2.52 (95 percent CI: 1.57, 4.07) for never smokers and 1.64 (95 percent CI: 1.15, 2.34) for ever smokers. Among smokers, the RR was 1.29 (95 percent CI: 0.82, 2.03) for women without a history of diabetes and 2.63 (95 percent CI: 1.44, 4.79) for women with such a history.

After adjustment for age, cataract extraction was significantly associated with increased risk of overall mortality (RR = 1.70, 95 percent CI: 1.40, 2.06) (table 4). This relative risk was somewhat attenuated but remained statistically significant after further adjustment for smoking, history of diabetes, and other covariates (RR = 1.37, 95 percent CI: 1.13, 1.66). This association appeared to be stronger for women with a history of diabetes (RR = 1.76, 95 percent CI: 1.19, 2.60) than for those without such a history (RR = 1.27, 95 percent CI: 1.02, 1.60) (p for interaction = 0.25). The increase in mortality was virtually entirely explained by the increased risk of fatal cardiovascular disease (multivariate RR = 1.84, 95 percent CI: 1.29, 2.64). Cataract extraction was not significantly associated with mortality from cancer (RR = 0.95, 95 percent CI: 0.69, 1.30).

TABLE 1. Age-standardized characteristics at baseline (1984) by status of cataract extraction, in 1992,* The Nurses’ Health Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of women (n = 58,321)</th>
<th>Yes (n = 2,336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
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</tr>
<tr>
<td>History of diabetes</td>
<td>3.2%</td>
<td>8.0%</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>24.4%</td>
<td>31.5%</td>
</tr>
<tr>
<td>History of high cholesterol</td>
<td>9.3%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Current smoking</td>
<td>24.4%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Parental history of MI† before age 60 years</td>
<td>13.7%</td>
<td>15.7%</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>43.4%</td>
<td>45.7%</td>
</tr>
<tr>
<td>Multivitamin supplement use</td>
<td>37.7%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Vitamin E supplement use</td>
<td>18.6%</td>
<td>17.3%</td>
</tr>
<tr>
<td>Mean</td>
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<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>53.3</td>
<td>56.5</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1</td>
<td>26.2</td>
</tr>
<tr>
<td>METs score per week‡</td>
<td>14.1</td>
<td>11.8</td>
</tr>
<tr>
<td>Alcohol use (g/day)</td>
<td>7.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Saturated fat (g/day)</td>
<td>21.9</td>
<td>22.1</td>
</tr>
<tr>
<td>Polyunsaturated fat (g/day)</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Trans fat (g/day)</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Dietary antioxidant score§</td>
<td>8.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Vegetables (servings/day)</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Fruits (servings/day)</td>
<td>2.2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* Women less than age 45 years at baseline were excluded from the analysis.
† MI, myocardial infarction.
‡ Assessed in 1986. Derived as average time per week spent in each of eight activities multiplied by the metabolic equivalent (MET) value of each activity. The MET value is the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram of body weight per hour at rest.
§ To create this score, dietary intakes for carotene, vitamins C and E, and riboflavin were categorized into quintiles and for each participant, the quintile value for each nutrient was summed.
DISCUSSION

In this large prospective study, the authors found a significant positive association between cataract extraction and 10-year incidence of CHD among women. There was also a significant positive association between cataract extraction and overall mortality. The increased risk was primarily due to deaths from cardiovascular disease.

This study has several strengths. The prospective design eliminates potential biases due to selection of the sample and recall of the exposure that can frequently occur in retrospective studies. The high rate of follow-up minimizes potential bias due to loss to follow-up. The large size provides the opportunity to examine the associations among diabetics and within strata of other important covariates.

Potential limitations of this study must also be considered. Although detailed information on a multitude of potential confounders was collected and adjusted for, the authors cannot rule out the possibility that unmeasured confounders may explain the observed association. In addition, physician-diagnosed diabetes was reported by the participants, but with high accuracy according to additional information obtained from supplemental questionnaires asking about symptoms and treatment and a validation study using medical record review. Some diabetics may have been undiagnosed and the rate of misclassification may increase with age, but the overall proportion of undiagnosed diabetes would be relatively small compared with that in the general population because of the nurses’ relative greater access to medical care.

Cataract extraction was self-reported by the nurses, but its confirmation rate was 100 percent based on ophthalmologists’ reports. Because repeated standardized eye examination of persons in this large cohort was not possible, the procedure of cataract extraction was used to define the occurrence of cataract. Thus, women with untreated cataracts were in the nonexposed group. This kind of misclassification would tend to attenuate any positive association between cataract and CHD, although the magnitude of such misclassification is likely to be small, since the untreated cases would represent only a small fraction of the total noncases. The use of cataract extraction rather than cataract not yet requiring surgery as the exposure decreases the chance for variation in the thresholds for diagnosis of disease. Because all of the participants were registered nurses, access to medical care and their threshold for surgery are likely to be more uniform than in the general population.

Epidemiologic data on cataract and risk of CHD are sparse. In a prospective study of male physicians (14), subjects with self-reported cataract had a relative risk of 1.15 (95 percent CI: 0.87, 1.53) for total cardiovascular events and 1.34 (95 percent CI: 0.78, 2.32) for fatal cardiovascular events during 5 years of follow-up. The study did not examine diabetics and nondiabetics separately. In the Framingham Eye Study, Podgor et al. (15) found a positive association.
TABLE 3. Relative risks of coronary heart disease according to history of cataract extraction by diabetes status, the Nurses' Health Study, 1984–1994

<table>
<thead>
<tr>
<th>Cataract extraction</th>
<th>No</th>
<th>Yes</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR*</td>
</tr>
</tbody>
</table>

**Women without a history of diabetes**

- Total CHD* (no. of cases) 671 30
- Person-years 635,882 10,127
- Age-adjusted
  - Cataract extraction
    - Yes 1.88 1.29, 2.72
    - No 1.00 1.00
- Multivariate†
  - Cataract extraction
    - Yes 1.51 1.04, 2.18
    - No 1.00 1.00

**Women with a history of diabetes**

- Total CHD (no. of cases) 162 24
- Person-years 26,996 1,278
- Age-adjusted
  - Cataract extraction
    - Yes 2.83 1.80, 4.44
    - No 1.00 1.00
- Multivariate†
  - Cataract extraction
    - Yes 2.00 1.77, 4.42
    - No 1.00 1.00

**p value**

- 0.0009
- 0.01
- 0.0001
- <0.0001
- 0.01
- 0.01

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* RR, relative risk; CI, confidence interval; CHD, coronary heart disease; MI, myocardial infarction.
† Adjusted for age (5-year categories); time period (five periods); body mass index (<21, 21–22.9, 23–24.9, 25–28.9, and ≥ 29 kg/m²); pack-years of smoking (never smoked, 1–9, 10–24, 25–44, and ≥45 pack-years); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); parental history of myocardial infarction before age 60 years; multivitamin supplement use (yes/no), vitamin E supplement use (yes/no); alcohol consumption (0, 0.1–4, 5–14, and ≥15 g/day); history of hypertension (yes/no); history of high cholesterol (yes/no); aspirin use (nonuser, 1–6/week and ≥7/week); and metabolic equivalent score per week (quintiles).

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between lens changes and incidence of cardiovascular events among diabetics (RR = 1.8, p = 0.07). There were only 57 cases of cardiovascular disease in this study.

The increased mortality associated with cataract extraction among women with a history of diabetes observed in this study is consistent with previous studies. Podgor et al. (16) reported a direct relation between lens changes and mortality among diabetics. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (17), diabetic retinopathy, cataract, glaucoma, and visual impairment were significant predictors of mortality among persons with either type 1 or type 2 diabetes. Although these data suggest a positive relation of cataract to overall mortality among diabetics, the association in persons without diabetes has been less clear. The Framingham Study found a nonsignificant increased risk of overall mortality among nondiabetics (RR = 1.17, p = 0.29) (16). However, Thompson et al. (6) reported a significant association between nuclear cataract and mortality in a cohort of 473 elderly nondiabetic subjects in England during 6 and 8 years of follow-up (RR = 1.49, 95 percent CI: 1.13, 1.97 after adjustment for age, sex, and ever smoking). In a study conducted in rural India, where type 2 diabetes is uncommon, Minassian et al. (18) found a significant association between cataract and mortality (age- and sex-adjusted RR = 2.2, 95 percent CI: 1.3, 3.9). It should be pointed out that in the Framingham Study (16), lens changes were broadly defined, including mild lens changes, clinically significant cataract, and cataract extraction. Therefore, participants in our study and two previous studies (6, 18) probably had more severe lens changes than did the Framingham participants.

The positive association between cataract and risk of CHD or mortality from all causes should not be interpreted as a direct cause-effect relation. Most likely, cataract formation reflects more generalized tissue damage associated with oxidative stress, which has been characterized as part of the aging process (19). The ocular lens, which is exposed to light and ambient oxygen, is particularly sensitive to photooxidative damage (2). Extensive oxidation of protein and other components in the lens has been observed in human cataracts.
Thus, cataract may be considered as a directly observable marker for the overall balance between oxidative stress and antioxidant defense. Previous findings of lower risk of cataract with higher intake of antioxidants (3, 4) provide support for the oxidation hypothesis. In addition, there is strong evidence that free radical-mediated oxidative damage to low density lipoproteins may be an important risk factor for atherosclerosis (5). Oxidized low density lipoprotein is atherogenic in the vessel wall, probably because it is taken up more readily by macrophages to create cholesterol-laden form cells found in atherosclerotic lesions, which stimulate smooth muscle cell proliferation. The positive association between cataract extraction and incident CHD observed in our study lend indirect support to the general hypothesis of oxidative stress in the pathogenesis of CHD.

Another potential mechanism for this positive association may be related to glycosylation of tissue protein associated with glucose intolerance. In this study, the positive association between cataract extraction and CHD observed in our study lend indirect support to the general hypothesis of oxidative stress in the pathogenesis of CHD.

In summary, these data indicate a significant positive association between cataract extraction and risk of CHD in women. These findings are compatible with current hypotheses relating oxidative damage and tissue aging to the development of CHD. Clinically, cataract may be considered as a marker of future risk of CHD.

ACKNOWLEDGMENTS

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REFERENCES

10. National Diabetes Data Group. Classification and diagnosis of

<table>
<thead>
<tr>
<th>TABLE 4. Relative risks of overall mortality according to history of cataract extraction by diabetes status, the Nurses’ Health Study, 1984–1994</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract extraction</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>All subjects</td>
</tr>
<tr>
<td>No. of cases</td>
</tr>
<tr>
<td>Age-adjusted</td>
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<tr>
<td>Multivariate†</td>
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<tr>
<td>Women without a history of diabetes</td>
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<tr>
<td>No. of cases</td>
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<tr>
<td>Age-adjusted</td>
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<td>Multivariate‡</td>
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<tr>
<td>Women with a history of diabetes</td>
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<tr>
<td>Age-adjusted</td>
</tr>
<tr>
<td>Multivariate‡</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Models included age (5-year categories); time period (six periods); body mass index (<21, 21–22.9, 23–24.9, 25–28.9, and ≥29 kg/m²); pack-years of smoking (never smoked, 1–9, 10–24, 25–44, and ≥45 pack-years); menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, and postmenopausal with current hormone replacement); parental history of myocardial infarction before age 60 years; family history of breast cancer; alcohol consumption (0, 0.1–4, 5–14, and ≥15 g/day); history of hypertension (yes/no); history of diabetes (yes/no); history of high cholesterol (yes/no); and metabolic equivalent score per week (quintiles).


