Prospective Study of Sudden Cardiac Death Among Women in the United States

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Background—There are few data regarding the determinants of sudden cardiac death (SCD) in women, primarily because of their markedly lower rate of SCD compared with men. Nonetheless, existing data, although sparse, suggest possible gender differences in risk factors for SCD.

Methods and Results—In this prospective cohort of 121 701 women aged 30 to 55 years at baseline, SCD was defined as death within 1 hour of symptom onset. From 1976 to 1998, 244 SCDs were identified. Although the risk of SCD increased markedly with age, the percentage of cardiac deaths that were sudden decreased. Most (69%) women who suffered a SCD had no history of cardiac disease before their death. However, almost all of the women who died suddenly (94%) had reported at least 1 coronary heart disease risk factor. Smoking, hypertension, and diabetes conferred markedly elevated (2.5- to 4.0-fold) risk of SCD, similar to that conferred by a history of nonfatal myocardial infarction (relative risk, 4.1; 95% confidence interval, 2.9 to 6.7). Family history of myocardial infarction before age 60 years and obesity were associated with moderate (1.6-fold) elevations in risk. With regard to mechanism, 88% of SCDs were classified as arrhythmic. In 76% of these, the first rhythm documented was ventricular tachycardia or ventricular fibrillation.

Conclusions—These prospective data suggest that, as in men, coronary heart disease risk factors predict risk of SCD in women and that SCD is usually an arrhythmic death. Therefore, prevention of atherosclerosis or ventricular arrhythmias may reduce the incidence of SCD in women. (Circulation. 2003;107:2096-2101.)

Key Words: death, sudden ■ women ■ arrhythmia ■ coronary disease ■ risk factors

Sudden cardiac death (SCD) is more common in men than in women. As a result, women are underrepresented in studies of this health outcome, and the pathophysiology of SCD is much less certain in women. Although the underlying pathophysiology and risk factors for SCD in women are generally assumed to be similar to those in men, the limited amount of data available suggest that differences may exist. One study suggested that women who present with SCD are less likely to have a prior history of heart disease than men (37% versus 56%), and the prevalence of underlying coronary heart disease (CHD) may be lower than in men. In men, arrhythmic deaths account for most deaths that occur suddenly; however, there are no complementary data among women. Recent evidence suggests that women who suffer a cardiac arrest are less likely than men to have ventricular fibrillation (VF) as an initial rhythm. These sex differences are poorly understood and are based on limited data but do suggest that SCD may be a more heterogeneous disorder in women compared with men.

SCD is still an important public health problem in women. Even with a SCD rate 30% of that for men, 120 000 of the 400 000 SCDs in the United States each year will occur in women. Disturbingly, the decline in SCD rates among women has been markedly less than that observed for men. From 1989 to 1998, the rate of SCD actually increased by 21% among women aged 35 to 44 years in the United States compared with a 2.8% decline among men of the same age group. Differences in awareness, risk factors, underlying etiology, symptoms and signs, and outcomes may play some role in this trend.

These data underscore the importance of understanding SCD in women and examining predictors of risk separately by gender. We therefore characterized risk factors and additionally defined the syndrome of SCD in women in the ongoing Nurses’ Health Study (NHS), a cohort of 121 701 women who have been intensively followed up for >20 years.
Methods

The Nurses’ Health Study Cohort

The NHS began in 1976 when 121,701 female registered nurses, 30 to 55 years of age, completed a questionnaire about their medical history, CHD risk factors, menopausal status, and lifestyle factors. The cohort has been followed every 2 years with mailed questionnaires that update exposure information and inquire about newly diagnosed medical illnesses, including diagnoses of hypertension, hypercholesterolemia, and diabetes. In addition, they were asked to report their height, weight, smoking habits, and parental history of myocardial infarction (MI). In validation studies, information on CHD risk factors was very reliably and accurately reported in this cohort.7–10

Identification of Timing and Mechanism of Death

The timing and mechanism of cardiovascular deaths was ascertained in a two-step process. First, next of kin or postal authorities reported most deaths, and in addition, at the completion of each mailing cycle, the National Death Index was searched for names of nonrespondents to the questionnaire.11 Death certificates were obtained from state vital statistics departments to confirm all reported deaths. For all death certificates indicating possible cardiovascular disease, permission to obtain additional information from medical records or verbal reports was requested from family members. Deaths were then confirmed for a cardiovascular cause by physician review of medical records. The next of kin was interviewed regarding the circumstances surrounding the death if not adequately documented in the medical record.

Second, medical records and reports from next of kin of all cardiovascular deaths (excluding strokes) were reviewed by 2 cardiologists. In this second review, deaths were reclassified according to the length of symptoms preceding the terminal event. A death was considered sudden if the death or cardiac arrest that precipitated the terminal event occurred within 1 hour of symptom onset. Deaths occurring between 1 and 24 hours were classified as intermediate, and those occurring after 24 hours were considered nonsudden. Information from the death certificate was not used to determine timing of death.12

Because there are no studies linking SCD to arrhythmic death in women, we classified deaths as arrhythmic or nonarrhythmic based on the definition of Hinkle and Thaler.4 An arrhythmic death was defined as an abrupt spontaneous collapse of the circulation (pulse disappeared) without evidence of prior circulatory impairment (shock or congestive heart failure) or neurological dysfunction (change in mental status, loss of consciousness, or seizure). Deaths in which the pulse gradually disappeared or those preceded by circulatory impairment without evidence of prior circulatory impairment (as defined as an abrupt spontaneous collapse of the circulation (pulse disappeared) without evidence of prior circulatory impairment (shock or congestive heart failure) or neurological dysfunction (change in mental status, loss of consciousness, or seizure)).

Statistical Analysis

For each woman, person-months of follow-up were calculated from the date of return of the 1976 questionnaire to date of death or to June 1, 1998, whichever came first. The analysis is based on incidence rates, using person-months of follow-up as the denominator. We computed age- and multivariate-adjusted rate ratios with 95% confidence intervals (CIs). Cox proportional hazards models were then used to compute age- and multivariate-adjusted RRs for each CHD risk factor. The multivariate model simultaneously controlled for CHD risk factors, age, menopausal status, postmenopausal hormone use, and prior report of CHD. Information on these variables was updated every 2 years. If information was missing during a follow-up period, then person-time was assigned to a missing category for that time period. Tests for trend were performed by modeling smoking as a continuous variable (number of cigarettes smoked daily) and body mass index (BMI) as an ordinal variable in multivariate Cox proportional hazards models. To determine whether risk factors for SCD differed among younger versus older women, secondary analyses were performed after stratifying the population at age 60 years. To formally test for interactions with age, cross-product terms were entered into the full multivariate model individually. Statistical analysis was performed using SAS statistical software (SAS Institute Inc).

Results

Demographics of Sudden Deaths

From 1976 to 1998, 1110 cardiovascular deaths, excluding strokes, were confirmed by hospital records or next-of-kin reports. Of these deaths, 636 (57.3%) occurred out of the hospital or in the emergency room (out-of-hospital deaths). Information on symptoms preceding death was sufficient to make a determination on the timing of death in 850 (76.6%) of these deaths. For most of the deaths without sufficient information on timing, a witness could not be identified (81.2%). Of the deaths where timing could be determined, 244 (28.7%) occurred within 1 hour of the onset of symptoms, 157 (18.5%) occurred within 24 hours, and 449 (52.8%) occurred after 24 hours. Of the deaths that occurred within 1 hour of symptom onset, 89% occurred outside of the hospital or in the emergency room and 51% occurred at home before the arrival of emergency medical personnel. However, 33% of the out-of-hospital deaths occurred after >1 hour of symptoms.

With increasing age, the risk of SCD increased ($P$ trend <0.001, Figure 1). However, the percentage of deaths that were sudden declined ($P$ trend=0.01, Figure 2). Although SCD rates increased after menopause, after adjustment for age, the elevation in risk observed among postmenopausal women was markedly attenuated and no longer significant (RR, 1.31; 95% CI, 0.66 to 2.62).

Coronary Heart Disease and Sudden Cardiac Death

Of the women who died suddenly, 69% had no reported history of cardiac disease, and only 43% reported symptoms before death. Only 24 women (10%) had symptoms consistent with an acute coronary syndrome in the weeks preceding death, and 35 (14.4%) had definite evidence for an acute MI by ECG, cardiac enzymes, or autopsy at the time of death. However, a history of prior MI conferred a 4.4-fold risk of SCD (95% CI, 2.9 to 6.7).

We examined the impact of self-reported CHD risk factor status on risk of SCD. The overwhelming majority (94%) of women who died suddenly had reported at least 1 of the CHD risk factors outlined in Table 1, and 73% had reported at least 2 risk factors. Comparable percentages for the entire cohort were 87% and 55%, respectively ($P=0.001$). Table 1 outlines the age- and multivariate-adjusted risk of SCD associated with individual cardiac risk factors. All of the cardiac risk factors examined were associated with risk of SCD; however, smoking, diabetes, and hypertension had the strongest relations. Women who smoked 25 or more cigarettes per day were at a 4-fold (95% CI, 2.7 to 6.3) increased risk of SCD, similar to that conferred by a history of MI. Parental history of MI before age 60 years and obesity were associated with more modest, but statistically significant, elevations in risk of SCD. Compared with women with a BMI $<25$ kg/m$^2$, obese women (BMI $\geq 30$ kg/m$^2$) had a 1.6-fold increased risk of SCD; this risk was 2.5 (95% CI, 1.7 to 3.7) if diabetes and hypertension, potential biological mediators in the causal

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pathway, were not included as terms in the multivariate model. Self-reported hypercholesterolemia and a parental history of MI after age 60 years were not significantly associated with risk of SCD. The above results were not materially altered if women who reported a prior history of CHD were excluded from the analysis.

Because of prior reports suggesting that risk factors may differ in older versus younger women, we repeated the risk factor analysis after stratifying the population at 60 years of age (Table 2). Similar relationships were seen for most of the CHD risk factors in the younger and older women, except for parental history of MI. A parental history of MI before age 60 years seemed to be a risk factor only among women younger than age 60 years. The statistical test for an interaction between age 60 years and a parental history of MI before age 60 years was significant ($P<0.01$). None of the other interaction terms reached statistical significance; however, we had limited statistical power to detect such interactions.

**Mechanism of Sudden Cardiac Deaths**

In 570 of the cardiovascular deaths (52%), the death was witnessed with sufficient detail provided by witnesses or medical personnel to allow categorization of the mechanism of death. Of these, 154 occurred within 1 hour of symptom onset, and 135 of these deaths fulfilled the criteria for arrhythmic death as outlined by Hinkle and Thaler. Of the remaining deaths that occurred after >1 hour of symptoms ($n=390$) or where length of symptoms could not be accurately determined ($n=25$), 49 were classified as arrhythmic. Therefore, both the positive and negative predictive value of the 1-hour definition for arrhythmic death was 88% in this female population. The specificity of the 1-hour definition was 95%, and the sensitivity was 73%. Of the 135 sudden deaths that were classified as arrhythmic, a first cardiac rhythm near the time of the collapse was documented in 109 (81%). Of these deaths, 83 or 76% had ventricular tachycardia (VT) or VF documented near the time of collapse (Figure 3).
In this prospective cohort of 121,701 women aged 30 to 55 years at baseline, 244 SCDs were documented over 22 years of follow-up. Most of these deaths were out-of-hospital deaths (89%); however, an out-of-hospital death was not synonymous with a SCD. Thirty-three percent of all cardiac deaths occurring outside of the hospital occurred after 1 hour of symptoms. As expected, the risk of SCD increased markedly with age, especially after the age of 70 years. However, the percentage of cardiac deaths that were sudden declined. With regard to prior CHD, a history of nonfatal MI increased the risk of SCD in women by 4-fold, which is similar to that previously reported for women in the Framingham Heart Study but lower than the 11.7-fold increased risk of SCD observed among men in that cohort.1

As in Framingham1 and other cohorts,14 most women (69%) who suffered a SCD in our cohort had not had a CHD event documented before death, and very few (10%) had symptoms of acute coronary syndrome in the weeks preceding death. Therefore, most SCDs in women seem to be

<table>
<thead>
<tr>
<th>Cardiac Risk Factor</th>
<th>Person-Years of Follow-up (n=2,569,041)</th>
<th>Cases (n=244)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted</td>
<td>Multivariate*</td>
<td>(P)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>105,267</td>
<td>58</td>
<td>4.90 (3.63 to 6.61)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>635,970</td>
<td>152</td>
<td>3.17 (2.43 to 4.15)</td>
</tr>
<tr>
<td>Smoking</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>834,363</td>
<td>86</td>
<td>1.56 (1.13 to 2.15)</td>
</tr>
<tr>
<td>Current, 1 to 14 cigarettes/day</td>
<td>188,775</td>
<td>27</td>
<td>2.72 (1.74 to 4.26)</td>
</tr>
<tr>
<td>Current, 15 to 24 cigarettes/day</td>
<td>257,329</td>
<td>30</td>
<td>2.47 (1.60 to 3.82)</td>
</tr>
<tr>
<td>Current, (\geq) 25 cigarettes/day</td>
<td>165,468</td>
<td>33</td>
<td>4.61 (3.02 to 7.05)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>532,038</td>
<td>92</td>
<td>1.33 (1.00 to 1.77)</td>
</tr>
<tr>
<td>Parental history of MI before age 60 years</td>
<td>371,470</td>
<td>53</td>
<td>1.87 (1.37 to 2.57)</td>
</tr>
<tr>
<td>Parental history of MI, age (\geq) 60 years</td>
<td>336,900</td>
<td>47</td>
<td>1.36 (0.98 to 1.90)</td>
</tr>
<tr>
<td>BMI (&lt;25) kg/m(^2)</td>
<td>1,211,275</td>
<td>62</td>
<td>1.0</td>
</tr>
<tr>
<td>(25)–29.9 kg/m(^2)</td>
<td>577,026</td>
<td>46</td>
<td>1.26 (0.86 to 1.84)</td>
</tr>
<tr>
<td>(\geq30) kg/m(^2)</td>
<td>308,263</td>
<td>50</td>
<td>2.65 (1.82 to 3.85)</td>
</tr>
</tbody>
</table>

*Multivariate models controlled simultaneously for all the cardiac risk factors listed. In addition, models also controlled for age, menopausal status, postmenopausal hormone use, and prior report of coronary heart disease.

**Discussion**

In this prospective cohort of 121,701 women aged 30 to 55 years at baseline, 244 SCDs were documented over 22 years of follow-up. Most of these deaths were out-of-hospital deaths (89%); however, an out-of-hospital death was not synonymous with a SCD. Thirty-three percent of all cardiac deaths occurring outside of the hospital occurred after 1 hour of symptoms. As expected, the risk of SCD increased markedly with age, especially after the age of 70 years. However, the percentage of cardiac deaths that were sudden declined. With regard to prior CHD, a history of nonfatal MI increased the risk of SCD in women by 4-fold, which is similar to that previously reported for women in the Framingham Heart Study but lower than the 11.7-fold increased risk of SCD observed among men in that cohort.1

As in Framingham1 and other cohorts,14 most women (69%) who suffered a SCD in our cohort had not had a CHD event documented before death, and very few (10%) had symptoms of acute coronary syndrome in the weeks preceding death. Therefore, most SCDs in women seem to be

**TABLE 2. Age-Stratified Multivariate Risk of Sudden Cardiac Death by CHD Risk Factor Status**

<table>
<thead>
<tr>
<th>Cardiac Risk Factor</th>
<th>Relative Risk (95% CI) *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (\leq60) (98 cases)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.56 (1.42 to 4.62)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.94 (1.26 to 2.98)</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.30</td>
</tr>
<tr>
<td>Past</td>
<td>1.73 (1.01 to 2.97)</td>
</tr>
<tr>
<td>Current, 1 to 14 cigarettes/day</td>
<td>2.85 (1.41 to 5.75)</td>
</tr>
<tr>
<td>Current, 15–24 cigarettes/day</td>
<td>1.94 (0.96 to 3.93)</td>
</tr>
<tr>
<td>Current, (\geq25) cigarettes/day</td>
<td>4.86 (2.66 to 8.86)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.35 (0.83 to 2.22)</td>
</tr>
<tr>
<td>Parental history of MI before age 60 years</td>
<td>2.47 (1.60 to 3.82)</td>
</tr>
<tr>
<td>Parental History of MI age (\geq60) years</td>
<td>1.13 (0.61 to 2.08)</td>
</tr>
<tr>
<td>BMI (&lt;25) kg/m(^2)</td>
<td>1.0</td>
</tr>
<tr>
<td>(25)–29.9 kg/m(^2)</td>
<td>1.39 (0.79 to 2.43)</td>
</tr>
<tr>
<td>(\geq30) kg/m(^2)</td>
<td>1.31 (0.68 to 2.55)</td>
</tr>
</tbody>
</table>

*Multivariate models controlled simultaneously for all above cardiac risk factors, menopausal status, postmenopausal hormone use, and prior report of coronary heart disease.
unexpected. These data, in combination with the smaller declines in SCD rates among women, raise the concern that SCD may be more difficult to predict and, therefore, to prevent in women. This may be especially true for young women, where SCD comprises a larger proportion of cardiac mortality and SCD rates are increasing. One potential explanation for these findings, based on limited data from autopsy series and cardiac arrest survivors, is that the prevalence of CHD is lower in female SCD victims. Therefore, modification of CHD risk factors may not have as great an impact in reducing SCD risk in women.

In contrast, our data suggest that CHD risk factors do indeed predict SCD in women, and, therefore, CHD risk factor modification should favorably impact risk of SCD in women. Almost all of the women who died suddenly (94%) had reported at least 1 CHD risk factor, and modifiable risk factors such as smoking, hypertension, and diabetes conferred markedly elevated (2.5- to 4.0-fold) risks of SCD in this cohort. Heavy smoking was a particularly strong risk factor for SCD, especially among those younger than age 60 years. Smoking seems to predispose young women to acute coronary thrombosis in the setting of plaque erosions. Obesity was also associated with an increased risk of SCD, but to a lesser degree. However, the multivariate RR of 1.6 underestimates the true effect of obesity, because diabetes and hypertension, mediators in the causal pathway, were included in the model (removing them resulted in a RR of 2.5).

Parental history of MI before age 60 years was also a risk factor for SCD, but only among those younger than age 60 years (P-interaction = 0.01). This finding may imply that genetic factors or familial clustering of environmental factors play a larger role in younger women. Alternatively, the age of the parent at the time of the CHD event could be directly correlated with the age of the progeny at the time of SCD, as was found for SCD in the Paris Prospective Study. Because we did not ask about a parental history of SCD in this study, we cannot determine whether the association with parental history of MI is attributable to a general familial aggregation of CHD versus a specific aggregation of sudden CHD events.

Finally, a reported history of hypercholesterolemia was not a significant predictor of SCD risk in our cohort. In the Framingham Heart Study, total cholesterol was only related to SCD risk in women under age 65 years. Similarly, in our study, the relation between hypercholesterolemia and SCD appeared somewhat stronger in the women under age 60 years; however, the test for interaction with age was not significant (P = 0.16). Our power to detect such an interaction was limited, and these data may reflect the relative importance of plaque rupture in the pathogenesis of SCD in younger versus older women. An alternative and more likely explanation is that the null effect observed for hypercholesterolemia may be attributable to imprecise information on cholesterol levels or details of cholesterol-lowering therapy.

With regard to the mechanism of SCD, prior studies in men have suggested that an arrhythmic cause underlies most SCDs. Hinkle and Thaler, who investigated 142 deaths among 743 men, found that 91% of deaths occurring within 1 hour from the onset of symptoms were arrhythmic deaths. We used the same definition of arrhythmic death in our study of women and were able to classify 570 deaths. We found that 88% of deaths that occurred within 1 hour of symptoms were classified as arrhythmic. Therefore, the positive predictive value of the 1-hour definition for arrhythmic death seems to be similar in women and men.

When a rhythm was documented (81% of cases), VF or VT was observed in 76%. This percentage is similar to that reported in men by Hinkle and Thaler and among cardiac arrest victims associated with a sudden collapse. Thus, in contrast to a recent study of cardiac arrest victims, we did not find evidence to support a significant sex difference in the incidence of VF among SCD victims. These data on mechanism have implications for future studies on SCD. Because SCD may be predominantly an arrhythmic death in women as it is in men, genetic or environmental factors that directly affect myocardial vulnerability to arrhythmias may influence SCD risk in both sexes. These factors could alter the likelihood that the first presentation of ischemia will be a lethal ventricular arrhythmia.

Several limitations of the present study warrant consideration. First, information on CHD risk factors was ascertained by self-report, potentially leading to some misclassification. However, numerous validation studies have established that the nurses accurately report the CHD risk factors examined in this study. We cannot rule out the possibility of undiagnosed hypertension, diabetes, and hypercholesterolemia, although this is unlikely in this cohort of health professionals. Such random misclassification may have slightly biased our results toward the null. More likely, the female health professionals in our study were probably undergoing treatment for their hypertension, diabetes, and hypercholesterolemia, which might additionally attenuate the associations observed.

Because the purpose of our study is to identify risk factors for SCD, we used a rigorous definition of SCD requiring medical records or witnessed reports for confirmation. Therefore, we sacrificed sensitivity to maintain a high degree of specificity. As a result, some cases of true SCD will have been missed, either because the death was not witnessed or family members did not provide information on the circumstances surrounding the death. The factors that influence
whether a death is witnessed are not entirely random. Therefore, in an attempt to minimize bias, we included unwitnessed deaths if the participant had been seen within 1 hour of her death. Finally, as in any study involving free-living individuals, identification of the mechanism of death is difficult and, therefore, susceptible to error. We tried to minimize error by using a standard definition of arrhythmic death used in trials of antiarrhythmic therapy and requiring agreement between 2 cardiologists as to the mechanism of death.

In summary, although SCD is less common among women, it remains an important cause of mortality that requires more intensive primary preventive efforts. Because most SCDs occur among those without known cardiac disease, we must address this apparently healthy population to have a significant public health impact on SCD. These data suggest that many of these unheralded SCDs occur in the women with recognized CHD risk factors. However, as in men, no single CHD risk factor will predict with sufficient accuracy which women will die suddenly. Therefore, we must continue to search for new ways to more accurately identify and safely modify risk of SCD while encouraging risk factor reduction in apparently healthy populations.

Acknowledgments
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References
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