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Risk factors of long-term mortality in middle-aged women: a 27-year follow-up cohort

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ABSTRACT

Objective: This study aimed to evaluate the impact of different risk factors on long-term mortality in middle-aged women.

Methods: Women who received preventive health care control between 1990 and 1993 were recruited. Anamnesis and physical examination were recorded. Blood samples for the measurement of glycemia and lipids were taken. Data are reported as of December 2017.

Results: We studied 1197 women aged between 40 and 60 years. We observed 183 deaths (survival 84.0%; 95% confidence interval [CI], 81.7–86.1, Kaplan–Meier survival analysis). The main causes of death were cancer (39.9%; 95% CI, 32.7–47.1), cardiovascular disease (22.9%; 95% CI, 16.8–29.1), infectious disease (13.7%; 95% CI, 8.6–18.7), other causes (7.1%, 95% CI, 3.4–10.9), and unspecified cause (6.6%; 95% CI, 2.9–10.2). The final Cox regression model showed the following hazard ratios for mortality: diabetes mellitus 2.51 (95% CI, 1.40–4.51), history of fracture 2.47 (95% CI, 1.15–5.30), history of heart illness 2.06 (95% CI, 1.15–3.72), arterial hypertension 1.51 (95% CI, 1.08–2.11), age 1.07 (95% CI, 1.04–1.10), body mass index 1.06 (95% CI, 1.02–1.09), and sexual intercourse 0.94 (95% CI, 0.89–0.98). Lipid disorders did not reach statistical significance as a risk factor.

Conclusion: Diabetes, a history of fractures, and cardiovascular risk factors, except lipids, are markers of long-term mortality in middle-aged women. Physicians should pay special attention to these risk factors.

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Middle-aged women; mortality; risk factors; diabetes mellitus; fractures

Introduction

The ageing population has determined that physicians who care for women have had to modify their medical attention focus from the care of pregnant women toward the health care of older women[1,2]. In fact, some residency training programs in obstetrics/gynecology have for many years included primary care in the curriculum[3]. Physicians interested in women's health are in a privileged position to implement preventive medicine measures to mitigate the risk of chronic diseases.

Few studies have followed-up for decades a population of middle-aged women with baseline normal health. Most studies include women with chronic diseases or with risk factors and have included lifestyle interventions and/or drug administrations. In 1990 we initiated a cohort study, inserted in a health checkup program of working middle-aged women, in order to assess risk factors and to study their impact on chronic diseases and mortality without study intervention[4,5]. We intended to provide the physicians who attend women with specific information on health risks, which could allow them to implement preventive measures targeted at specific objectives. This publication presents the impact of risk factors, assessed in middle-aged woman, on mortality after 27 years of follow-up.

Methods and subjects

This study was carried out at South Metropolitan Health Service (Barros Luco Hospital, Santiago de Chile, Chile). Women who received preventive health care control during their annual checkup between October 1990 and March 1993 were invited to participate in this study.

Physical examination and questionnaire application were performed by a health professional with 10 years of experience. The following data were gathered in a precoded and pretested questionnaire: age, work activity, postmenopausal status (defined as amenorrhea greater than 12 months or the presence of follicle stimulating hormone concentrations greater than 30 mIU/ml), weight, height, diagnosis of diabetes mellitus (fasting blood glucose equal to or greater than 126 mg/dl at two separate moments, or glucose greater than 200 mg/dl in a glucose tolerance test and/or the use of glucose-lowering drugs)[6], presence of chronic arterial hypertension (systolic/diastolic arterial blood pressure equal to or

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greater than 140/90 mmHg, and/or the use of drugs intended to lower blood pressure), total smoked cigarettes (number of smoked cigarettes per day on average multiplied by the total time consumed), alcohol consumption, walks (hours per day), sexual activity (frequency of intercourse per month), personal history of fractures, myocardial ischemic disease, valvular heart disease and/or cardiac arrhythmia, surgical sterilization, frequency of hot flushes (number per day), family history of cancer (includes both parents), and family history of sudden death.

Blood samples were taken after 12 h of fasting. Total cholesterol and triglycerides were assessed using an enzymatic colorimetric method (Sigma, Sigma Chemical Co., St. Louis, MO, USA). The high-density lipoprotein cholesterol (HDL-C) subfraction was obtained from the cholesterol in the supernatant, after precipitation with Mg/Dextran sulfate (Sigma, Sigma Chemical Co.). The variation coefficients for normal ranges of total cholesterol, HDL-C, and triglycerides were 1.6, 3.9, and 3.9% intra-assay and 4.2, 4.6, and 3.9% inter-assay, respectively. The concentration of low-density lipoprotein cholesterol (LDL-C) was calculated with the Friedewald formula. Glycemia was measured with a colorimetric method (Hexokinase; Sigma Chemical Co.), with an intra-assay and inter-assay coefficient of variation of 0.7 and 1.2%, respectively.

In 2017, using the national identification number, the national death records were reviewed, consigning for each participating woman their vital status (alive or dead), date, and cause of death. Each woman's survival time was determined using this information.

Statistical analysis

The analysis was performed using the Stata program Stata/SE 15.0 for Windows. Results are presented as mean ± standard deviation or percentage with the corresponding 95% confidence interval (CI). Normality of distribution was evaluated with the Kolmogorov–Smirnov test, and homogeneity of variance with the Levene's test[7].

For the whole follow-up, the survival proportions for death events were described using Kaplan–Meier survival analysis[8]. The causes of death were described using proportions with their corresponding CIs. The observed variables were compared for deaths according to their nature and distribution.

Using the multivariable fractional polynomial (MFP) method allows adjusting the functional form of a given explanatory quantitative variable (counting and continuous predictors) of the Cox regression model; in addition, it allows determining whether that quantitative variable was important for the final selected Cox model. Thus, the MFP is useful when one wishes to preserve the quantitative nature of the covariates in a regression model, but suspects that some or all of the relationships may be non-linear[9].

The MFP method for the Cox regression model was performed using a stepwise backward selection approach for the following predictors: age, body mass index (BMI), postmenopausal status, diabetes mellitus, chronic arterial hypertension, total smoked cigarettes, alcohol consumption, walks, sexual intercourse, total cholesterol, HDL-C, LDL-C, triglycerides, personal history of fractures, heart illness, surgical sterilization, hot flushes, family history for cancer, and sudden death. The final Cox regression model for the whole period of follow-up of the cohort was established with predictors (variables of the final selected model) for which the hazard ratios (HRs) showed statistical significance ($p < 0.05$). In the final model, the log likelihood, Akaike Information Criterion, Bayesian Information Criterion, and HR were determined. In addition, for the final model, the adequate compliance was assessed for the following requirements: proportional risk, functional form, specification, calibration, and discrimination[7–9].

The compliance of proportional risk for the variables of the final model was assessed through log–log plots, the Therneau and Grambsch test[10], and testing for a cohort × time interaction. The correct functional form of the quantitative variables for the final model was checked for martingale residuals. The appropriate specification of the final model was studied with the Linktest (Stata program, Stata/SE 15.0 for Windows)[8].

The calibration aspect of the model refers to agreements between the predicted outcome and observed outcome. The final model was evaluated with graphical methods which included observed versus predicted values for probabilities and predictions and cumulative hazard of Cox–Snell residuals[9]. Also, a graphic evaluation for the deviance residuals versus the linear predictor of the final model was included. Additionally, for each variable, the comparison between survival predicted for Cox regression was performed in the final model and observed by the Kaplan–Meier survival model[11].

The discrimination of a prognostic model reflects its ability to distinguish between patient outcomes. We calculated Harrell's *C* discrimination index[12–14].

Ethical considerations

The study was approved by the local ethics committee (Southern Metropolitan Health Service, Santiago de Chile, Chile) and was in complete agreement with the Declaration of Helsinki. All patients provided written informed consent.

Results

A total of 1229 women were invited, and 1197 (97.4%) accepted to participate. The mean age was 48.5 ± 5.4 years, fluctuating between 40 and 60 years. Quantitative variables, except total smoked cigarettes and monthly sexual intercourse frequency, showed a symmetric distribution, so they are presented as mean and standard deviation. All quantitative variables showed $p < 0.01$ for the Kolmogorov–Smirnov test.

The working status of the participants was non-qualified workers ($n = 249$, 20.8%; 95% CI, 18.5–23.1), technical occupations ($n = 544$, 45.5%; 95% CI, 42.6–48.3), administrative officials ($n = 134$, 11.2%; 95% CI, 9.4–13.0), teachers ($n = 177$,

Table 1. Clinical features of the whole cohort and according to status (dead or alive) after the observed 27.2-year follow-up (1990 and 1993).

Variable	*Total* (n = *1197*)	*Alive* (n = *1014*)	*Dead* (n = *183*)	p-*Value*[a]
Age (years)	48.5 ± 5.4	48.0 ± 5.2	51.2 ± 5.9	<0.001[b]
BMI (kg/m^2)	25.9 ± 4.0	25.7 ± 3.8	27.2 ± 4.7	<0.001[b]
Postmenopausal status	278 (23.2%)	206 (20.3%)	72 (39.3%)	<0.001[c]
Diabetes mellitus	30 (2.5%)	18 (1.7%)	13 (7.1%)	<0.001[d]
Chronic arterial hypertension	203 (17.0%)	150 (14.8%)	53 (29.0%)	<0.001[c]
Total smoked cigarettes[g]	22,541 ± 55,698	21,670 ± 54,680	27,068 ± 60.671	0.217[f]
Ever alcohol consumption	190 (15.9%)	162(16.0%)	28 (15.3%)	0.818[c]
Walk (hours per day)	1.0 ± 0.8	1.0 ± 0.8	1.0 ± 0.7	0.464[b]
Sexual intercourse (per month)	2 (5)	2 (5)	0 (3)	<0.001[e]
Total cholesterol (mg/dl)	221.1 ± 44.3	220.5 ± 43.7	224.0 ± 47.3	0.162[f]
HDL cholesterol (mg/dl)	52.5 ± 13.0	52.4 ± 12.9	53.0 ± 13.6	0.284[f]
LDL cholesterol (mg/dl)	142.6 ± 40.0	142.5 ± 39.7	143.2 ± 41.7	0.827[f]
Triglycerides (mg/dl)	130.1 ± 65.2	128.3 ± 64.3	140.0 ± 69.5	0.013[f]
Personal history of fracture	18 (1.5%)	11 (1.1%)	7 (3.8%)	0.012[d]
Personal history of heart illness	40 (3.3%)	28 (2.8%)	12 (6.6%)	0.009[c]
Surgical sterilization	220 (18.4%)	182 (18.0%)	38 (20.8%)	0.365[c]
Hot flushes (number per day)	0.9 ± 2.2	0.9 ± 2.1	1.4 ± 2.9	0.021[b]
Family history of cancer	454 (37.9%)	390 (38.5%)	64 (35.0%)	0.371[c]
Family history of sudden death	8 (0.7%)	7 (0.7%)	1 (0.6%)	1[d]

Data are presented as mean ± standard deviation, frequency *n* (%), or median (interquartile range). BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
[a]*p*-Value as determined with: [b]Student's *t* test, one-tailed assuming unequal variance (variance ratio test $p < 0.05$); [c]Pearson's chi-squared test; [d]Fisher's exact test; [e]Mann–Whitney test; [f]Student's *t* test, one-tailed assuming equal variance (variance ratio test $p \geq 0.05$).
[g]Calculated as the number of smoked cigarettes per day for the total time consumed (i.e. 5 per day ×365 days [1 year] = 1825 cigarettes).

14.8%; 95% CI, 12.8–16.8), and qualified professionals ($n = 93$, 7.8%; 95% CI, 6.3–9.3).

The maximum observed time of follow-up was 27.2 years. Survival was 84.0% (95% CI, 81.7–86.1) as determined with Kaplan–Meier survival analysis. The causes of the 183 observed deaths included cancer ($n = 73$, 39. 9%; 95% CI, 32.7–47.1), cardiovascular disease ($n = 42$, 22.9%; 95% CI, 16.8–29.1), infectious disease ($n = 25$, 13.7%; 95% CI, 8.6–18.7), various causes ($n = 13$, 7.1%; 95% CI, 3.4–10.9), unspecified cause ($n = 12$, 6.6%; 95% CI, 2.9–10.2), gastrointestinal disease ($n = 9$, 4.9%; 95% CI, 1.8–8.1), and traumatism or intoxication ($n = 9$, 4.9%; 95% CI, 1.8–8.1).

The comparisons of each studied variable according to vital status (alive or dead) are presented in Table 1. The dummy variables for the whole cohort are also presented. The means for age, BMI, triglycerides, and frequency of hot flushes were significantly ($p < 0.05$) higher in the group of deceased women. Mean monthly sexual intercourse frequency was significantly higher ($p < 0.05$) in the group of surviving women. Diabetes mellitus, chronic arterial hypertension, postmenopausal status, personal history of fracture, and heart illness were significantly less frequent in the group of surviving women.

The MFP method was performed for the Cox regression model through stepwise backward selection. The final Cox regression model displayed the following values: log likelihood of −1.228, Akaike Information Criterion of 2.469, and Bayesian Information Criterion of 2.505. The dummy variables selected in the final model were diabetes mellitus, personal history of fracture, or heart illness. The quantitative variables chosen for the final model required power transformations of level 1. The following transformed variables were selected in the final model: age −48.5, BMI −45.4, and sexual intercourse −3.2.

The final Cox model showed the following HRs for mortality: diabetes mellitus 2.51 (95% CI, 1.40–4.51; $p = 0.002$), personal history of fracture 2.47 (95% CI, 1.15–5.30; $p = 0.020$), history of heart illness 2.06 (95% CI, 1.15–3.72; $p = 0.016$), chronic arterial hypertension 1.51 (95% CI, 1.08–2.11; $p = 0.015$), age 1.07 (95% CI, 1.04–1.10; $p = 0.001$), BMI 1.06 (95% CI, 1.02–1.09; $p = 0.001$), and sexual intercourse 0.94 (95% CI, 0.89–0.98; $p = 0.011$).

The log–log plots for ln(–ln[survival]) versus ln(time) using Kaplan–Meier estimates showed parallel log curves for the dummy variables considered in the final model. The Therneau and Grambsch test and testing for a cohort × time interaction in the final model were not significant.

The functional form for the quantitative variables was adequate according to martingale residuals. The link test showed a correct specification for the final model. The graphic evaluation of the model for the cumulative hazard of Cox–Snell residuals such as the deviance residuals versus the linear predictor showed an adequate goodness of fit. For 27.2 years, the comparison of predicted survival (according to the Cox model) versus observed survival (Kaplan–Meier survival analysis model) showed agreement. Harrell's *C* concordance coefficient was 68.73, indicating an appropriate discrimination of the proposed model.

Discussion

The leading cause of mortality in this cohort was cancer, almost double that from cardiovascular disease. This fact apparently does not correlate with Chilean mortality figures, indicating that cardiovascular diseases are responsible for 29.9% of all deaths in women and cancer would be responsible for 25.0%[15]. However, these figures can be understood when one analyzes cause and age of mortality in Santiago

de Chile. In 2015, mortality in women younger than 70 years of age was 41.6% for cancer and 22.8% for cardiovascular disease; however, in women older than 70 years the proportion was inverted, being 19.8% for cancer and 34.8% for cardiovascular disease. Therefore, as our cohort aged, cardiovascular mortality should have increased and surpassed cancer mortality, and hence resemble the official global statistics.

The main risk factor predictor of mortality was diabetes mellitus. This fact is easy to understand since diabetes is a disease that not only affects glucose metabolism but is also accompanied by diseases that can increase mortality. For example, the diabetic population has a higher risk of cancer, which would be related to various hormonal and metabolic disturbances; it has even been suggested that hyperglycemia itself enhances WNT/β-catenin signaling, which promotes cancer cell proliferation, migration, invasion, and immunological escape[16,17]. In addition to cancer, diabetes is associated with a higher prevalence of a number of comorbidities such as increased BMI, hypertension, and ischemic heart disease which increased risk of mortality in a 4-year follow-up study (HR 1.42)[18]. On the other hand, diabetes is especially ominous in women; the relative risk for fatal coronary heart disease associated with this disease is 50% higher in women as compared to men[19].

Other cardiovascular risk factors such as hypertension, obesity, older age, and history of heart illness were also predictors of a significantly higher risk of dying in our cohort. Hypertension is an important mortality risk factor, especially in women[20]. HR for hypertension as a cause of mortality in our cohort (HR 1.51) was similar to that found in a meta-analysis of hypertensive women aged 50–59 years (HR 1.33–1.85)[21]. Obesity is another independent risk factor of death. However, this risk decreases with age. A systematic review pointed out that the risk of mortality may range from HR 1.60 in obese women younger than 35 years of age to 1.11 in those older than 75 years, showing that obesity may play a more important role in the mortality risk in younger people than in older individuals[22]. Smoking did not appear as a risk factor predictor of death in our study; tobacco use was very low in our female cohort. The failure of the lipid profile to serve as a predictor of mortality in our cohort might be explained by the fact that the main cause of death was cancer; and second, its effect would be attenuated by the greater strength of other predictive factors that are also related to lipid profile alterations such as diabetes, hypertension, and history of heart disease. Previously, we had observed a null impact of LDL-C on coronary risk in women with acute coronary syndrome[23].

Our results also reveal that, in middle-aged women, the history of having a fracture is another risk factor that has an important impact on long-term mortality (HR 2.47). To the best of our knowledge, we have not found other studies showing this fact in women aged 40–60 years. But in one study that assessed the risk of mortality in women aged 55–81 years, followed-up by an average of 3.8 years, it was observed that the age-adjusted relative risk of dying following a clinical fracture was 2.15[24]. The relationship between bone fractures and the risk of mortality is also reflected in a study which demonstrated that the treatment of osteoporosis was associated with an 11% reduction in mortality[25]. The association of fracture with higher mortality could be explained by the paradigm of cellular senescence. Osteoporosis is associated with a series of chronic diseases, diabetes, cancer, atherosclerosis, and dementias, which all have their highest prevalence in older age[26]. Cellular aging is triggered by repeated cell divisions as well as other cellular stressors (reactive oxygen species) that activate tumor suppressor pathways which initiate senescence. These cells develop a machinery to secrete proinflammatory cytokines and proteases, which have systemic deleterious effects[27]. This paradigm, which considers aging to be a global condition, could be one of the explanations to understand the association of fractures with the highest risk of mortality.

Our study found sexual activity as a slight protective factor of mortality (HR 0.94). This should not be surprising as sexual activity is a reflection of good health. One study, assessing healthy Latin American women aged 40–59 years, found that a negative perception of their health status increased the risk of sexual failure[28]. In middle-aged women, sexual dysfunction was the main reason for sexual inactivity[29]. Perceived health is an independent predictor of mortality[30].

We can conclude by pointing out that diabetes, a history of fractures, and cardiovascular risk factors present in middle-aged women are markers of long-term mortality risk. Sexual activity, a reflection of good health, is a predictor of less mortality risk. Physicians who care for middle-aged women should give particular emphasis on the treatment of these risk factors. This behavior could increase life expectancy.

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