Long-term Effect of Vasectomy on Coronary Heart Disease

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Abstract: We investigated the association between coronary heart disease (CHD) and vasectomy in a population of 10,632 men who were under surveillance for multiple CHD risk factors during participation in a university-based exercise testing program. We conducted a mail survey with telephone follow-up to determine the vasectomy status of individuals in the population. Responses were obtained from 6,159 individuals. The 4,944 males on whom information was complete enough to be included in the multivariate analysis comprised the study population. Among the 1,383 (28 per cent) vasectomized males in the study population, the interval from vasectomy to the time of the survey ranged from less than one year to 37 years with a mean duration of 15 years. Although increased relative risks for CHD were found to be associated with family history of CHD, high blood pressure and smoking in this population, the relative risk of CHD associated with vasectomy was not increased in general, nor was it increased when the vasectomized males were classified by time since vasectomy. Likewise, serum antisperm-antibody titers were not predictive of CHD among vasectomized men. These studies support the findings from previous investigations of populations with shorter average post-vasectomy experience in which vasectomy has been shown to be unassociated with altered risk of CHD in humans. (*Am J Public Health* 1984; 74:128–132.)

Introduction

Vasectomy is an effective and convenient means of sterilization, and has become increasingly popular as a birth-control technique in the United States and other countries during the past two decades.[1–4] It is estimated that approximately 500,000 vasectomies are currently being performed annually in the United States,[2] with over 6 million having been performed in the past ten years. Over 40 million vasectomies have been performed world-wide.[3] The overall prevalence of vasectomy in the United States is estimated at approximately 10 per cent of the adult White male population, with a high of 30 per cent in the western states.

Although vasectomy has been used as a contraceptive measure for over 40 years, little concern was expressed about the possible long-range health effects of the procedure until the early 1970s, when reports began appearing in the literature describing the development of antisperm antibodies in 50 to 70 per cent of men following a vasectomy operation.[5–7] Subsequently, Alexander and Clarkson reported that increased arterial plaque developed in vasectomized monkeys, as compared with non-vasectomized controls, after feeding either high fat diets[8] or regular monkey chow.[9] These observations formed the basis of an hypothesis[10] that antisperm antibodies form circulating immune complexes which collect in arterial walls and at bifurcations, contributing to the atherosclerotic process. This hypothesis remains to be substantiated, since no data to establish this mechanism are yet available.

A number of investigators have sought to evaluate the putative association between vasectomy and atherosclerosis, as manifested by coronary heart disease (CHD) and other symptoms, in humans.[11–21] No evidence of increased atherosclerotic disease among vasectomized men has thus far been reported. None of these studies, however, has investigated this relation in a large group of men with a substantially long interval following vasectomy. The length of the observation period subsequent to vasectomy is of particular importance because of the prolonged nature of the atherogenic process even in the presence of known or suspected CHD risk factors.[22] The present study was undertaken to evaluate the association between vasectomy and the development of CHD in a large population of men in which the average post-vasectomy interval was 15 years, a period of substantially greater duration than heretofore reported.

Methods

Population—The study population was drawn from 10,632 men who were under surveillance for CHD risk factors by virtue of their participation in the University of Washington Exercise Testing Registry (ETR). The ETR program[23] has been maintained on a continuing basis since 1975, and involves non-invasive examinations of registry participants for indicators of atherosclerotic heart disease, as well as other clinical and demographic factors which are obtained either at entry or during periodic exercise testing. Men enter the registry through one of two sources and then the registry population is made up of two major subpopulations: the industrial subpopulation (33 per cent of the registry population) comprises supervisors and executives of a large aerospace manufacturing firm who have company-provided annual physical examinations on a voluntary basis; the clinical subpopulation (67 per cent of the registry population) comprises a heterogeneous group of patients who have clinical examinations by over 50 private physicians located throughout the community for a variety of reasons, including self-motivation to ascertain health status. Men enter the registry at the time they have a clinical examination, including an electrocardiogram (ECG), perform a multistage treadmill test, and agree to permit follow-up evaluation. Data are entered directly into the ETR at the time the examination is performed by the examining physician via a terminal in his or her office.

As of June 1980, when the present study began, the registry comprised 9,413 eligible subjects. Twelve hundred and nineteen (1,219) additional men entered during the two-year study period. Subjects are predominantly white (95 per cent), with an average age of 48 years for the industrial

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subpopulation and 53 for the clinical group, range; 15 to 83 years. The two subpopulations were evaluated with respect to socioeconomic status (SES) by extrapolation of residential addresses of study subjects to census tracts classified according to specific SES criteria.[24]

ETR Data File—For each individual entering the ETR a clinical examination was performed, including a history, 12-lead electrocardiogram (ECG), and usually a chest X-ray. Smoking histories, family medical histories of heart disease and, frequently, serum cholesterol levels were also recorded. After providing informed consent for exercise testing and subsequent follow-up, all subjects voluntarily performed a multistage treadmill test of symptom-limited maximal exercise, as previously described.[25] Assessment of the first event of coronary heart disease (CHD) was determined on the basis of information obtained from the history, as well as from the physical and ECG examinations and the treadmill test. Clinical classification of the absence or presence of CHD was based, respectively, on the recognition of no disease in healthy persons, or by past or present coronary heart disease syndromes. The latter included typical angina pectoris (induced by exertion or emotion and relieved by rest or nitroglycerin), prior myocardial infarction (with typical history, enzyme responses and ECG changes), or history of prior cardiac arrest with resuscitation by ventricular defibrillation. Patients with a history of hypertension and with uncertain or other preliminary cardiovascular diagnoses were encouraged to enter the registry but were not diagnosed as having CHD.

All data acquired at examination—including age, sex, height, weight, risk factors, clinical appraisal and diagnosis of heart disease, treatment, heart size, resting heart rate, blood pressure and ECG findings, as well as heart rate, blood pressure, ECG responses and signs during and for the first five minutes after exercise testing—were recorded promptly and sent to the University of Washington Division of Cardiology for editing. Obvious disparities were verified by telephone calls to the involved physician. Data were then coded and filed in the ETR, which provided in retrospect the basis for the subsequent evaluation of CHD.

Vasectomy Status and Additional CHD Information

Information about the vasectomy status, including date of vasectomy and subsequent repair, if any, as well as information which was not complete or included in the ETR data file was requested of all eligible study subjects through mail questionnaire and subsequent telephone follow-up in 1980 or immediately subsequent to admission to the ETR for those admitted during the two-year period of the study. In addition to vasectomy status, information on occupational history, date of diagnosis of CHD if occurring prior to entry into the ETR, hospital admissions for any reason including CHD occurring subsequent to entry into the ETR, and additional information about CHD risk factors (smoking history, family history of CHD, and high blood presure) was solicited. Smoking history included questions about regular use of cigarettes, cigars or pipes, duration and quantity used, and date stopped, if appropriate. Questions on high blood pressure pertained to previous diagnosis of hypertension, and blood pressure level and treatments, if known. Subjects were also queried with respect to their willingness to give 10 ml of blood for immunological studies. These studies were conducted to examine the utility of antisperm-antibody levels following vasectomy in the prediction of CHD events.

Questionnaires were pretested on 100 randomly selected ETR participants before being sent to the entire ETR population. Cover letters explaining the purpose of the study and consent forms soliciting willingness to participate in the study accompanied the questionnaires. Initially, questionnaires were sent to the 9,413 men identified from the ETR file at the start of the study. Subsequently, questionnaires were sent to the additional 1,219 men who entered the registry during the course of the study, resulting in a total of 10,632 men from whom information was sought.

TABLE 1—Study Population: Long-term Effect of Vasectomy on CHD

Total ETR* Population	10,632	
Questionnaires returned as undeliverable	1,636	
Questionnaires not returned	2,132	
Total questionnaire respondents	6,568	
Subjects willing to participate		6,069(a)
Subjects unwilling to participate		499
Total confirmed deceased	296	
Questionnaire information provided by next of kin		90(b)
Unsuccessful follow-up		206
Total Study Respondents (a + b)	6,159	
Respondents with missing information	1,215	
Total Study Population	4,944	

*University of Washington Exercise Testing Registry (ETR)

For all non-respondents to the first mailing of the questionnaire, a second mailing was conducted two months later. We contacted by telephone those subjects who remained non-respondent for more than two months following the second mailing. These efforts were effective in acquiring useful information from about 25 per cent of the initially non-respondent segment of the study population. During the follow-up process, 296 deceased subjects were identified largely by surrogate respondents, usually the wife, who returned questionnaires either uncompleted or filled out on behalf of the deceased. For surrogates who did not provide complete information about the deceased, a revised version of the initial questionnaire along with a personal cover letter was sent asking for her/his description of the circumstances of the deceased person's death, as well as other pertinent information which had been requested directly of the living study participants.

As a result of all follow-up procedures, questionnaire responses were obtained from 6,159 men, 62 per cent of the total ETR population (Table 1). A major reason for non-response was that about 15 per cent of the total ETR population was not traceable through the postal service or the telephone company. Data on some of the variables of interest (age, smoking status, blood pressure, etc.) were incomplete or missing for 1,215 respondents. Hence, it was decided to include in the analysis only those 4,944 men for whom complete data were available, hereafter referred to as the study population. The rationale for excluding those for whom data on specific variables were incomplete is presented in the Results section.

Data Quality Control Procedures

Quality control procedures were established to verify the accuracy of the questionnaire data as entered into computer file. All questionnaire data were keyed into a computer file by experienced data entry personnel and verified by entering data twice into computer. Approximately 10 per cent of the respondent questionnaires were randomly selected, compared with those corresponding original individual computer files, and the errors corrected. A consistency rate of 99 per cent was observed prior to error

TABLE 2—Comparison of Characteristics of the Study Population According to Vasectomy Status and Source of Entry into the Exercise Testing Registry (ETR)

	Vasectomy Status		Study Population Total	Source of Entry into ETR	
	Vasectomy	Non-Vasectomy		Aerospace Industry	Clinical
Number of men in study	1383	3561	4944	1613	3331
Mean Age (years)	50	52	51	48	53
Vasectomy (%)	100	0	28	32	26
Coronary Heart Disease (%)	26	30	29	9	39
Smoking (%)	26	22	23	17	26
High Blood Pressure (%)	42	42	42	33	46
Family History (%)	41	39	39	34	42
Aerospace Industry (%)	37	31	33	100	0
Socioeconomic Status (%)					
Lowest	7.5	10.8	10.1	5.7	12.3
Low	21.6	18.9	19.8	18.7	20.5
Medium	35.0	30.2	32.1	28.9	33.5
High	35.8	40.0	38.0	46.7	33.7

correction. A general data editing program was instituted and, in cases of inconsistent or erroneous entries, corrections to the master file were made.

Statistical Methods

Two statistical techniques, a stratified Mantel-Haenszel analysis[26] and logistic regression analysis,[27] were applied, controlling for potential confounding effects caused by three classical risk factors (family history, high blood pressure and smoking) and two concomitant variables (age as of 1980 and source of entry into the ETR). Computations were performed using Biomedical Computer Programs (BMDP79)[28] Generalized Linear Interactive Modeling (GLIM3),[29] and Fortran programs on a DEC-10 computer system at the University of Washington.

Immunologic Analysis

As part of the overall investigation of the relationship between vasectomy and CHD, immunological studies were conducted to examine the predictive utility of antisperm-antibody titers in assessing the risk of CHD among vasectomized men. These studies were conducted as a test of the hypothesized association between circulating immune complexes formed from antisperm antibodies and the atherogenic process.[10] Two groups of vasectomized men, consisting of 81 with CHD and 81 without CHD were selected from members of the study population who had expressed a willingness to give blood for immunological studies. The 81 CHD cases consisted of all the vasectomized volunteers in the CHD group available at that point in the study. The 81 non-CHD cases were randomly selected from the non-CHD vasectomized population stratified to match the CHD volunteers with respect to present age (five-year age interval) and by time since vasectomy.

Blood collections, made by a registered public health nurse, were taken at the home or place of work of each subject. Blood samples (10 ml) were collected in non-heparinized serological vials and delivered on the same day as drawn to the University of Washington Serological Laboratory for separation of red cells from sera. Serum samples were then frozen and shipped to the Oregon Regional Primate Research Center for antisperm-antibody titer determinations. Vials were coded prior to shipment so that blind determinations would be made. A total of 134 samples (67 CHD and 67 non-CHD) were collected in this fashion.

Two antibody tests were performed on the 67 pairs of samples: the tray agglutination test (TAT)[30] and the sperm immobilization test (SIT).[31] In the tray agglutination test, the agglutination titer of sera to sperm is determined by placing three μl of each of fourfold serial dilutions of heat-inactivated sera to be tested under oil on the TAT plate. One μl of sperm suspension (27×10^6 sperm/ml Baker's Solution containing 25 per cent normal human serum) is added to each drop of serum. The plates are incubated two more hours at 37°C and assessment is made of sperm agglutination in each drop. For the SIT test, the serum was inactivated by heating at 56°C for 30 minutes and then analyzed for sperm immobilizing antibodies. The immobilizing activity was assessed at serum dilutions of 1:2, 1:4, and 1:16. Since sera of many controls typically exhibit agglutination when the TAT test is performed at less than 1:16 dilutions, only results of the analyses performed at 1:16 dilutions for both tests were used in these studies.

Results

Data Analysis

A comparison of the characteristics of the study population according to vasectomy status is presented in Table 2. The numbers of men in the study population with and without vasectomy were 1,383 and 3,561, respectively, resulting in a prevalence of vasectomy in the study population of 28 per cent. The proportion of coronary heart disease (CHD) cases among the vasectomized men uncontrolled for any concomitant variables was slightly lower than that among the non-vasectomized men, averaging 29 per cent for the whole study population. The vasectomized and non-vasectomized groups were roughly comparable with respect to mean age as well as in the proportion of classical CHD risk factors including smoking status, high blood pressure, and family history of CHD. The distribution of vasectomized and non-vasectomized men according to levels of socioeconomic status (SES) was also similar, although the proportion of non-vasectomized men in the extreme categories (lowest and high) was somewhat greater than for vasectomized men.

Table 2 also presents a comparison of the characteristics of the study population according to source of entry into the Exercise Testing Registry. The numbers of men in the study population who entered the ETR from the industrial and

TABLE 3—Distribution of Vasectomized Population by Time Since Vasectomy

Time Since Vasectomy (years)	Frequencies			Cumulative Frequency	Cumulative Per Cent
	CHD	Non-CHD	Total		
Over 25	95	111	206	206	14.9
21–25	68	129	197	403	29.2
16–20	59	141	200	603	43.7
11–15	57	193	250	853	61.8
6–10	59	254	313	1166	84.6
0–5	25	188	213	1379	100.0

Mean ± S.D.: 15.0 ± 9.1 (years)

clinical cohorts were 1,613 and 3,331, respectively. The industry group consisted of relatively younger and healthier men of somewhat higher socioeconomic status than the clinical group. Moreover, the proportion of CHD among the clinical group was over four times that seen in the industry cohort. The clinical group also showed a greater proportion of men with classical risk factors of CHD. These findings reflect the different method of recruitment of subjects from the two cohorts into the ETR, and identify the source of entry into the registry as a potentially important concomitant variable.

Table 3 presents the distribution of vasectomized men in the study population by time interval from the date of vasectomy to the date of the response to the mailed survey in this study (1980–1981), stratified by five-year intervals. The mean interval since vasectomy was 15.0 years, and the longest was 37 years. Time since vasectomy is correlated with age and possibly other CHD risk factors so that the increase in relative frequency of CHD with increasing time since vasectomy seen in this Table cannot be considered an effect of vasectomy.

Table 4 presents the estimated relative risks of fatal or non-fatal CHD associated with specific risk factors based on multivariate logistic regression analysis. The analysis has, in this case, controlled for the two important concomitant variables, age and source of entry into the ETR. Of the risk factors evaluated, all except vasectomy were associated with an estimated relative risk of CHD above unity. The 95 per cent confidence interval estimate of the relative risk of CHD associated with vasectomy was (0.84–1.17), whereas the interval estimate of the relative risks for family history, smoking history, and high blood pressure were (1.44–1.91), (1.21–1.67), and (1.18–1.56), respectively.

In conducting the analyses presented in Table 4, it was necessary to establish a convention regarding the handling of records in which information was missing on various potential confounding factors. Due to missing data on the age, family history and smoking history variables, 3 per cent of the survey respondent's were excluded from the analysis. Such an exclusion was deemed unlikely to lead to a biased estimate of relative risk. Since information regarding cholesterol levels was not provided for 38 per cent of total respondents, cholesterol level was not evaluated in these studies. We also found that a relatively large proportion (13 per cent) of respondents were uncertain with respect to previous diagnosis of hypertension. Thus, to examine if the exclusion of records with missing hypertension information would introduce a significant bias into the estimates of relative risk, the Mantel-Haenszel analysis was performed

TABLE 4—Estimated Relative Risks of Coronary Heart Disease Associated with the Specific Risk Factors

	Relative Risks*	95% Confidence Limits
Vasectomy	0.99	0.84–1.17
Family history	1.66	1.44–1.91
High blood pressure	1.36	1.18–1.56
Smoking history	1.43	1.21–1.67

*Relative risks are adjusted for age and source of entry into ETR (University of Washington Exercise Testing Registry).

only for the group for which information regarding blood pressure status was unknown, stratifying by age. This analysis indicated that the risk of CHD among vasectomized men relative to that of non-vasectomized men with unknown blood pressure was estimated to be 0.77. This estimate compared with 0.81 for the normal blood pressure group and 1.05 for the high blood pressure group. On the basis of these analyses, it was considered unlikely that the exclusion of those with missing information on blood pressure status would introduce a serious bias in the evaluation of relative risk. Therefore, family hisotry, smoking history, blood pressure, and age were evaluated as potential confounding variables with missing data excluded from the analyses. The number of cases in the analyses was 4,944 after exclusion of the missing data cases.

Table 5 presents the point and confidence interval estimates of relative risk of CHD in relation to time since vasectomy, adjusting for family history, blood pressure, smoking history, age, and source of entry into the ETR. The p value associated with the test of the linear effect of time since vasectomy on the occurrence of CHD when these factors are controlled is >.1 and, further, the 95 per cent confidence interval estimates of the relative risks of CHD include 1.0 in each time classification for the linear or non-restrictive model.

Antisperm-Antibody Analyses

The results of antisperm-antibody analyses showed that 51 per cent (69/134) of the samples had elevated tray agglutination titers (TAT) at a 1:16 dilution. A similar proportion, 47 per cent (62/133), had elevated sperm immobilization test (SIT) values. A comparison of the prevalence of

TABLE 5—Logistic Regression Estimates of the Relative Risks of Coronary Heart Disease in Relation to Time Since Vasectomy

Time Since Vasectomy (years)	Logistic Regression			
	Linear Model[a]		Non-Restrictive Model[b]	
	Relative Risks[c]	95% C.I.	Relative Risks[c]	95% C.I.
Over 25	0.95	0.59–1.54	0.95	0.54–1.66
21–25	0.97	0.63–1.48	0.96	0.53–1.76
16–20	0.99	0.68–1.44	1.10	0.69–2.37
11–15	1.01	0.72–1.41	0.98	0.55–1.84
6–10	1.03	0.75–1.41	1.17	0.80–2.61
0–5	1.05	0.77–1.43	0.73	0.25–1.27
No Vasectomy	1.00		1.00	

a) The linear model was fit to the mid-points of the intervals for time since vasectomy.
b) Time since vasectomy was stratified (or categorized) in the context of logistic regression analysis.
c) Relative risks are adjusted for family history, blood pressure, smoking history, age and source of entry into ETR (Exercise Testing Registry).

elevated antisperm-antibody titers for both tests among vasectomized men with and without CHD indicates that the prevalence of elevated antibody titer did not differ significantly among vasectomized men regardless of CHD status ($x_1^2 = 0.269$ for TAT and $x_1^2 = 0.007$ for SIT). Moreover, there was no evidence that antibody titer increases with time since vasectomy in men either with or without CHD. These results indicate that antisperm-antibody titers, as evaluated by the methods employed in these studies, do not have predictive utility with respect to the risk of CHD in humans following vasectomy.

Discussion

These results suggest that the risk of CHD does not differ substantially between vasectomized and non-vasectomized men, when controlled for known CHD risk factors, and does not vary substantially by time since vasectomy. These findings are consistent with those of Goldacre *et al*,[16] who reported no difference between vasectomized and control groups with respect to disease experience (including circulatory disease) during a 4.5 year follow-up period subsequent to vasectomy. That study, however, represented only the short-term experience of men who underwent vasectomy as hospital in-patients, and only utilized data on hospital morbidity and subsequent mortality experiences. Similarly, Walker, *et al*,[18] reported that the incidence of non-fatal myocardial infarction among 4,830 vasectomized men was, in fact, slightly lower (0.9 cases per 1,000 men) than that seen in 24,150 non-vasectomized men matched on the basis of calendar year of birth and duration of observation. Their finding cannot be compared directly with the present study results because of differences in both the means of diagnosis and selection of study subjects and in the methods of data analysis. However, the observation common to all studies, of no increased risk of CHD following vasectomy supports the conclusion that vasectomy does not predispose to atherosclerosis or subsequent coronary heart disease in humans as previously hypothesized.[7-10]

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