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Association Between Documented Family History of Cancer and Screening for Breast and Colorectal Cancer

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Abstract

Purpose—To examine whether patients with a documented family history of breast or colorectal cancer, either positive or negative, were more likely to receive breast or colorectal cancer screening services than those with no documentation.

Methods—Medical record reviews were conducted on 3,433 patients aged 55 and older from four primary care practices in two rural Oregon communities. Data collected included patient demographic and risk information and receipt of screening mammography and/or one of four modalities to screen for colorectal cancer.

Results—Mammography and colorectal cancer screening rates were low in these rural communities, with 50% of average risk women being up-to-date for mammography and 37% of women and 38% of men being up-to-date for colorectal cancer screening according to their risk level. A positive family breast cancer history was associated with an increased likelihood of being up-to-date for mammography screening (OR 2.09, 95% CI 1.45-3.00 relative to a recorded negative history). A positive family history for colorectal cancer was associated with an increased likelihood of being up-to-date with colorectal cancer screening according to U.S. Preventive Services Task Force (USPSTF) low risk guidelines for males (OR 2.89, 95% CI 1.15-7.29) and females (OR 2.47, 95% CI 1.32-4.64) relative to a recorded negative family history. Forty-four percent of the charts of female patients and 56% of the charts of male patients contained no documentation of a family cancer history having been taken. The absence of any recorded family cancer history was associated with a decreased likelihood of being up-to-date for mammography screening (OR 0.70, 95% CI 0.56-0.88 relative to recorded negative history) or for colorectal cancer screening OR 0.75, 95% CI 0.60-0.96 in females, 0.68, 95% CI 0.53-0.88 in males relative to recorded negative history).

Conclusion—Recording family history of cancer was associated with up-to-date cancer screening, even if the family history was negative. Establishing clinical routines to obtain family history could improve appropriate use of cancer screening.

Introduction

Cancer is the second leading cause of death in the U.S. (1), with colorectal and breast cancers ranking as the second and third most common causes of cancer deaths, respectively (2). In addition, the economic burden from cancer related morbidity and mortality is high with medical care expenditures alone estimated at 26 billion dollars in 2006 for these two cancers alone (3). Screening for breast and colorectal cancer has been shown to reduce mortality (4-7) and to be cost effective (8-10), thus making it a clinical priority as noted by the US Preventive Services Task Force (USPSTF) (11, 12). This is especially true among patients with a family history of both these cancers, as risk for both is subsequently increased (13).

Assessing family history may be the most important step a primary care clinician can take in identifying those who will most benefit from screening. However, while several studies show physicians often report that they collect family history information (14, 15) and value its contribution (16), other studies using actual encounter data suggest that family history is either not obtained or is underutilized in risk assessments (17-20). The collection of family history information allows physicians to tailor screening services to the individual. However, there is a paucity of literature about how family history information is captured in primary care offices and whether this affects either provider recommendation or actual use of cancer screening services. One study conducted by Felson, et al (21) found that having a personal or family history of colorectal cancer increased the odds of being up-to-date for colorectal cancer screening. This study focused only on colorectal cancer screening and the study focused on an urban population. Research in rural areas is especially lacking.

We conducted an in-depth assessment of the relationships between family history of breast and/or colorectal cancer and being up-to-date with appropriate screening tests in rural primary care settings and specifically examined whether patients with a documented positive family history of these diseases in their medical record were more likely to receive screening services. The results of this study will inform primary care clinicians about the effects that recording family history may have on activating physician behavior toward targeted screening.

Methods

Study Population

Data for the study were obtained by abstraction of medical records from four primary care clinics in two rural Oregon communities. Two of the clinics were private practices and two were federally qualified health centers (FQHC's); one of each type was represented in each community. Patient-level eligibility criteria included being aged 55 or older and having at least one clinic visit within the prior two years. This was done to ensure both eligibility of screening tests under study and opportunity to receive either the test or recommendations from their clinician to be screened.

Oregon Health & Science University's Institutional Review Board approved all study activities. No identifiers were collected during the medical record review; thus a HIPAA waiver was obtained for collection of personal health information without consent. In three of the four practices, all charts of patients aged 55 and older in the practice were reviewed and abstracted. In one practice, 1,000 patients were selected at random for review. This was done because this practice was very well established and had significant numbers of patients in the age range under study.

Medical Record Review

The medical record review instrument was adapted from one used by members of the research team in another study (22) and was pre-tested in two non-study clinics, one using paper charts and one using electronic medical records to simulate the varying health record formats used in the study clinics. We collected data on receipt of breast and colorectal cancer screening tests, including dates tests were received for up to 10 years. Breast cancer screening included mammography, and colorectal cancer screening included fecal occult blood test (FOBT), colonoscopy, flexible sigmoidoscopy, and double contrast barium enema (DCBE).

Patient information was also collected to characterize demographic and risk factors of the study sample. These data included age, race/ethnicity, body mass index, marital status, occupation, health behaviors, such as smoking status and alcohol use, insurance status and type, total number of visits in the previous 5 years, number of health maintenance visits, comorbidities, and family history. Family history of cancer was defined as having an affected first-degree relative (mother, father, sister, brother, son, or daughter), which was categorized according to type of cancer (breast, colorectal, or other). Because we were interested in determining if the presence of a positive family history correlated with increased screening

rates, we categorized family history as No Documented Family History Information, Notation of a Negative Family History and notation of a 1st Degree Relative with the specific cancer under study (breast or colorectal).

Two specially trained medical record reviewers abstracted the data and 10% of the records were re-reviewed for reliability by a third independent reviewer. The kappas for agreement between reviewers were 0.75 for family history of CRC or BC, 0.56 for FOBT within 1 year, 0.87 for flexible sigmoidoscopy within 5 years and 0.80 for colonoscopy within 10 years. A total of 3,593 patients aged 55 and older were eligible using our visit history criteria, and their records were abstracted for this analysis. The chart reviews were conducted between October 2008 and August 2009.

Statistical Analysis

The final analysis set consisted of 3,433 patients (1,870 women and 1,563 men). Out of 3,593 patients whose medical records were reviewed, 160 patients were excluded from the final analysis set due to prior diagnosis of cancer or missing age information: 9 ovarian cancer survivors, 100 breast cancer survivors, 38 colorectal cancer survivors, 1 survivor of both ovarian and breast cancer, 1 survivor of ovarian and colon cancer, 5 survivors of breast and colon cancer, 1 survivor of breast, ovarian and colon cancer, and 5 subjects for whom age was missing, resulting in a total of 3433 patients included in the analysis. Analysis of up to date status for mammography excluded an additional 2,918 women, including 18 women with bilateral mastectomies or recent abnormal mammograms, which might indicate that mammograms were follow-up rather than screening; 11 women who were not eligible for mammography screening (4 women with a history of having a bilateral mastectomy, 6 women with recent abnormal screening results, and 1 woman who was transgendered male to female). USPSTF guidelines in effect during the time period covered by the chart audits (e.g., 10/2008-08/2009) were used for determination of up-to-date status for mammography and colorectal cancer screening according to the patient's risk level. Subjects were classified as up-to-date on colorectal screening if any FOBT, flexible sigmoidoscopy, DCBE or colonoscopy screen was within the risk status specific guideline for that test. Subjects were classified as high risk if they had a positive family history of colon cancer or a history of abnormal colon cancer screening tests. Because current USPSTF guidelines exclude patients 75 and older, a sensitivity analysis was performed excluding patients in this age range to test the effect of the exclusion on the strength of the observed associations.

All statistical analyses were performed using Statistical Analysis System (SAS) version 9.3. Random effect logistic regression models were used to assess the effect of documented family history of cancer on up-to-date cancer screening status, adjusted for potential confounding variables. Because of possible correlation of screening rates within patients in the same clinic, clinics were treated as a random effect in logistic regression models. Odds ratios and 95% confidence intervals were estimated for each family history category, adjusted for a set of pre-selected confounders. To maintain uniform adjustment for confounders, a single set of demographic variables was selected for adjustment on the basis of a statistically significant association with up-to-date screening status for any cancer prior to the addition of comorbidity and family history to the models. The selected confounders

were age (category), ethnicity, smoking status, BMI class, length of contact with the clinic, total number of patient visits, and insurance status.

Co-morbidity adjustment included variables significantly associated with the cancer specific screening status in models that included demographic variables but excluded family history. Specifically, analyses of up-to-date status for breast cancer screening were adjusted for asthma and cardiovascular disease co-morbidity, while analyses of up-to-date status for colorectal cancer screening were adjusted for cardiovascular and digestive disease and performed for men and women separately.

Results

Distributions of social, demographics, clinic visits and health characteristics, such as number of co-morbid conditions were fairly similar between men and women represented in this study (Table 1). Eighteen hundred and fifty-nine women were included in the analysis of mammography screening according to family history (Table 2). Of the 1,859, 44% had no documented information regarding their family history, 45% had documented negative family history and 11% had a first-degree relative with breast cancer. Fifty-three percent of women with a family history of breast cancer were up-to-date for mammography screening within the last year and another 16% were up-to-date for screening within 1-2 years. Forty percent of women with a documented negative family history were up-to-date for mammography screening within the past year and an additional 14% were up-to-date for screening within 1-2 years. Twenty-nine percent of women with no information about family history were up-to-date for mammography screening within the past year with 11% more up-to-date for screening within 1-2 years. Compared to women with a negative family history, women with a positive family history were significantly more likely to be up-to-date. And women with documentation of a negative family history were significantly more likely to be up-to-date than those with no documentation of family history (Table 2).

All 1,563 men were included in the descriptive analyses of the type of colorectal cancer received according to family history and receipt of colorectal cancer screening (Table 3). Fifty one percent of male patients and 52% of female patients had no record of any colorectal screening of any kind in their charts. This included 7 of the 29 male patients and 18 of the 64 female with a positive family history for colorectal cancer. Fifty-six percent of the males had no information about family history, 43% had a documented negative family history, and 2% (n=29) had a documented family history of colorectal cancer. Among women, all 1,870 were included in the analyses and 44% of them had no information about family history of colorectal cancer in the chart, 53% had a documented negative family history and 3% (n=64) had a documented positive family history. Of those with a positive family history whose last colorectal cancer screening test was colonoscopy, 52% were up-to-date (data not shown).

Table 4 outlines the odds of being up-to-date for any colorectal cancer screening test according to family history. The analysis of the association of up to date status with family history excluded 8 men and 31 women with test orders recorded in their charts within the screening guidelines with no record of the tests having been performed 6 months or more

after the orders were written. Of those men with a positive family history, 16 (55%) were up-to-date according to USPSTF high-risk guidelines. Of those 16 who were up-to-date, 37% were up-to-date with FOBT in the past year and 63% were up-to-date with colonoscopy within 5 years (median 2.5 years (data not shown)). For men, those with a documented positive family history are more likely to be up-to-date for either the low risk (OR 2.89, 95% CI 1.157-2.9) or high risk (OR 2.55, 95% CI 1.10-5.89) screening guidelines compared to men with a negative family history. Compared to men with a negative family history, men with no family history noted in the chart were likely to be up-to-date for colorectal cancer screening (OR 0.68, 95% CI 0.55-0.91 for low risk, 0.70, 95% CI 0.55-0.91 for high risk). Among women, having a documented family history of colorectal cancer resulted in them being more likely to be up-to-date for colorectal cancer screening of any type using the low risk guidelines (OR 1.8, 95% CI 1.01-3.19) or the low risk guidelines (OR 1.94, 95% CI 1.08-3.48 compared to women with a documented negative family history (referent group)). Being up-to-date using the high-risk guidelines was not significant for women with a positive family history. Like men, women with no documentation regarding family history were least likely to be up-to-date.

Discussion

This study is important because it demonstrates that patients with any record of family history, either positive or negative, are more likely to be up-to-date for breast and colorectal cancer screening compared to those with no record of family history. Perhaps some clinicians have a system in place to document family history, while others do not. We also found that patients with a documented positive family history of either cancer were more likely to be up-to-date for screening for both cancers compared to patients with a documented negative family history. This finding was most dramatic for men with a family history of colorectal cancer and being up-to-date for the related colorectal cancer screening tests. Because risk of this disease is higher among men than women, this finding suggests that primary care physicians in rural areas may be aware of the risk posed by both male gender and having a family history and act on this information and as a result these patients are more likely to be screened.

Of concern is the substantial number of patients (44% and 56% of men and women) for whom no risk information was noted. Studies on the collection, value and use of family history in primary care settings are contradictory (14-20). However, with advancements in genetics and familial cancers, it is becoming increasingly important to record family history, the self-report of which is fairly sensitive and specific (23). A very recent editorial (24) discussed the importance of collecting standardized information on family history of cancer and then updating it consistently every 5-10 years for patients between the ages of 30 and 60 (25).

In our study, it may be that rural primary care practices lack a systematic approach to routinely collecting and documenting family history and thus it was often missing. But because of this, we do not know the risk status of a large number of patients in these practices. We did examine Oregon Behavioral Risk Factor Surveillance System (BRFSS) data from 2009 (26), which indicated 30.2% of Oregon women report having a close blood

relative (dead or alive), including parent, brother, sister, or child who has been diagnosed with breast cancer and 23.3% with a positive family history of colorectal cancer. Our study showed only 11% of women had a documented family history of breast cancer and 2% and 3% had a documented family history of colorectal cancer among men and women respectively, which is far lower than has been reported in BRFSS data. This suggests that important family history information is not being documented in rural primary care practice. A recent study comparing documentation of basic health measures, including problem list, past medical history, smoking status, alcohol and family history found no differences between practices using an electronic health record and those using paper records (27). The lack of family history documentation reflects the need to change the behavior of busy primary care clinicians.

If resources are limited, or practices are chaotic, then perceptions of the need to collect family history may be less than other perceived needs of the patients or practices. Regardless, it makes sense to target cancer-screening activities to those at greatest risk. By considering family history of cancer a “vital sign”, clinicians can act on the information quickly. Overall, we found screening rates were low, as we report in detail elsewhere (27). Unfortunately, disparities in breast and colorectal cancer screening exist among several underserved populations, including those residing in rural areas (28, 29). People living in rural areas face many barriers to health care. They generally have lower household incomes, are less likely to be insured, and more likely to live in designated health professional shortage areas (30). Barriers to preventive care are also amplified in this population because access to healthcare providers and many screening services, especially those that cannot be done in the primary care office, are less available than in urban areas. Litaker, et al (31) found lower breast cancer screening rates associated with fewer primary care providers per capita, as well as absence of a usual source of medical care in rural versus urban settings. Clearly, more research is needed in rural primary care settings.

The strengths of our study include the detailed information we were able to obtain from rural primary care practices on a large number of well-established patients. Weaknesses include the retrospective nature of a chart review, which did not allow us to determine with great accuracy when family history was recorded in the chart, whether the providers knew about patients’ family history but did not document it, and how assessment of family history, which may change over time, is monitored.

In conclusion, we found that about one-half of patients in our study had a family history of cancer documented in the medical record. If the family history was recorded, the patient was more likely to be up-to-date for breast cancer screening in women, and colorectal cancer screening in men, compared to those without recorded family history. Establishing routines where this is done regularly could improve cancer screening in these complex settings.

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Table 1
Social, Demographic and Clinical Characteristics of Patients

Patient Characteristics	Females (n=1,870)	Males (n=1,563)	Total (n=3,433)
Age			
Mean (SD)	65.6 (9.7)	64.8 (9.0)	65.2 (9.4)
Median (range)	62.6 (50-100)	62.4 (51-97)	62.5 (50-100)
Aged 75 and older	335 (18%)	222 (14%)	557 (16%)
BMI			
Mean (SD)	29.3 (6.8)	29.3 (5.3)	29.3 (6.2)
Median (range)	28.2 (14-60)	28.7 (16-55)	28.4 (14-60)
% Missing	26%	30%	28%
Hispanic			
Hispanic	13%	12%	12%
Not Hispanic	34%	28%	31%
Unknown	53%	60%	57%
Race			
White	61%	57%	59%
Other	3%	3%	3%
Unknown	37%	40%	38%
Marital Status			
Partnered	57%	69%	62%
Solo	35%	31%	29%
Unknown	9%	9%	9%
Occupation			
Private Company	26%	30%	28%
Self Employed	6%	4%	5%
Government	5%	13%	9%
Retired	29%	33%	31%
Not working for pay	14%	9%	12%
Unknown	20%	11%	16%
Smoking History			
Current smoker	12%	17%	14%
Former Smoker	20%	31%	25%
Never smoked	63%	46%	55%
Not noted	5%	6%	6%
Alcohol Use			
Current	36%	49%	42%
Former	4%	11%	7%

Patient Characteristics	Females (n=1,870)	Males (n=1,563)	Total (n=3,433)
Never	51%	32%	42%
Unknown	9%	8%	9%
Health Care Visits in last 2 years - Median (range)	11 (1-236)	10 (1-407)	10 (1-407)
Comorbid Conditions¹ Median (Range)	2 (0-8)	2 (0-8)	2 (0-8)
Length of Contact with Clinic Median (25%, 75%)	9.6 (4.2, 19.3)	10.3 (3.5, 20.4)	9.9 (4.0-19.8)

¹ Comorbid condition types surveyed: asthma, arthritis, cardiovascular disease, digestive disease, diabetes, hypertension, low back pain.

Table 2

Mammography Screening According to Patient Risk Factors

	Timing of Last Screening Mammography n (%)				Odds Ratio for Receiving Mammography Screening (95% Confidence Interval)		
	n (Col%)	Not Up-to-date	Up-to-date	1-2 years	<1 year	Within 2 Years (Up-to-date) ²	Within 1 Year ²
All women	1859	634 (34%)	305 (16%)	238 (13%)	682 (37%)		
Age less than 75	1528	483 (32%)	244 (16%)	206 (13%)	595 (39%)		
Family History of Breast Cancer							
Family history not documented	817 (44%)	349 (43%)	147 (18%)	86 (11%)	235 (29%)	0.70 ³ (0.56-0.88)	0.69 ⁵ (0.54 – 0.87)
Negative family history	843 (45%)	249 (30%)	133 (16%)	120 (14%)	341 (40%)	1.0	1.0
1 st degree relative with breast cancer	199 (11%)	36 (18%)	25 (13%)	32 (16%)	106 (53%)	2.09 ⁴ (1.45-3.00)	1.76 ⁶ (1.27 – 2.45)

¹ Excludes 1 transgendered male to female, 4 women with bilateral mastectomy, and 6 women with recent abnormal screening results.

² Odds ratios were determined using random effects logistic regression models that included clinics as a random effect and adjusted for age, ethnicity, smoking status, length of contact with clinic, last recorded insurance type, BMI category, number of clinic visits, and asthma and cardiovascular disease co-morbidity.

³ Odds ratio when the analysis was limited to women under age 75: 0.72 (95%CI 0.56-0.94)

⁴ Odds ratio when the analysis was limited to women under age 75: 2.31 (95%CI 1.54-3.47)

⁵ Odds ratio when the analysis was limited to women under age 75: 0.75 (95%CI 0.57-0.97)

⁶ Odds ratio when the analysis was limited to women under age 75: 1.79 (95%CI 1.25-2.56)

Table 3

Type of Most Recent Colorectal Screening

	N Patients (Col %)		FOBT		Flex Sig		DCBE		Colonoscopy		No CRC Screening Records
	N Patients (Row%)	Years since last screen /	N Patients	Years since last screen /	N Patients (Row%)	Years since last screen /	N Patients (Row%)	Years since last screen /	N Patients (Row%)	Years since last screen /	
Men	1,563										
Most Recent CRC Screening	370 (24%)	1.4 (0.3, 3.6)	57 (4%)	2.7 (1.4, 3.9)	8 (1%)	4.1 (1.5, 6.3)	333 (21%)	2.2 (0.8, 4.1)	795 (51%)		
Up-to-date²											
Based on Low Risk Guidelines	622 (40%)	240 (65%)	51 (89%)		6 (75%)		325 (98%)		0		
Based on High Risk Guidelines	505 (22%)	182 (49%)	51 (89%)		5 (63%)		267 (80%)		0		
Based on Personal Risk Level	599 (38%)	233 (63%)	51 (89%)		6 (75%)		309 (93%)		0		
Family History of CRC CA											
No Family hx info	868 (56%)	197 (23%)	24 (3%)	3.1 (1.4, 4.3)	2 (0.2%)	5.6 (3.5, 7.7)	134 (15%)	1.8 (0.6, 3.9)	511 (59%)		
Negative Family hx	666 (43%)	165 (25%)	33 (5%)	2.5 (1.4, 3.3)	6 (1%)	3.2 (1.4, 6.1)	185 (28%)	2.4 (1.0, 4.4)	277 (42%)		
1 st Degree Relative	29 (2%)	8 (28%)	0 (0%)	--	0 (0%)	--	14 (48%)	2.0 (0.3, 3.5)	7 (24%)		
Women	1,870										
Most Recent CRC Screening	401 (21%)	1.7 (0.6, 3.9)	27 (1%)	3.3 (1.5, 7.3)	15 (1%)	3.9 (1.0, 5.3)	461 (25%)	2.5 (0.9, 4.6)	966 (52%)		
Up-to-date²											
Based on Low Risk	711 (38%)	248 (62%)	18 (67%)		11 (73%)		434 (94%)		0		
Based on High Risk	551 (29%)	172 (36%)	18 (67%)		10 (67%)		351 (76%)		0		

	N Patients (Col %)		FOBT		Flex Sig		DCBE		Colonoscopy		No CRC Screening Records
	N Patients (Row%)	Years since last screen	N Patients	Years since last screen	N Patients (Row%)	Years since last screen	N Patients (Row%)	Years since last screen	N Patients (Row%)	Years since last screen	
Based on Personal Risk	694 (37%)	239 (60%)	18 (67%)		11 (73%)		426 (92%)				0
Family History of CRC CA											
No Family hx info	820 (44%)	163 (20%)	4 (0.5%)	1.8 (0.6, 5.1)	4 (0.5%)	8.2 (5.3, 8.9)	4 (0.5%)	2.4 (0.9, 4.2)	154 (19%)	2.7 (0.9, 4.1)	495 (60%)
Negative Family hx	986 (53%)	227 (23%)	21 (2%)	1.7 (0.6, 3.5)	21 (2%)	3.1, (1.4, 4.6)	11 (1%)	4.2 (1.6, 5.9)	274 (28%)	2.2 (0.9, 5.0)	453 (46%)
1 st Degree Relative	64 (3%)	11 (17%)	2 (3%)	2.6 (0.5, 3.6)	2 (3%)	(4.4, 8.2)	0 (0%)	--	33 (52%)	2.5 (0.7, 4.7)	18 (28%)

¹ Years since last screen for patients whose last or most current CRC screen was in category. Median, (25th%, 75th%).

² Up to date by any CRC screen type based on the guidelines for the test type. Patients with test orders within screening guidelines for the test but which were over 6 months old with no record of testing were not considered up to date (N=8 men, 31 women).

Table 4

Colorectal Screening Status According to Family History

	N	Up-to-date for Low Risk Guidelines		Up-to-date for High Risk Guidelines	
		N (%) Up-to-date	Odds Ratio ² (95% CI)	N (%) Up-to-date	Odds Ratio ² (95% CI)
Men	1,555	622 (40%)		505 (32%)	
Age less than 75	1333	534 (40%)		437 (33%)	
Family History of CRC Cancer					
No Family history information	867 (56%)	280 (32%)	0.68 (0.53 - 0.88)	181 (21%)	0.70 (0.55-0.91) ³
Negative Family history	659 (42%)	321 (49%)	1.0	217 (33%)	1.0
1 st Degree Relative with CRC	29 (2%)	21 (72%)	2.89 (1.15-7.29)	16 (55%)	2.55 (1.10 - 5.89) ⁴
Women	1,839	711 (39%)		551 (29%)	
Age less than 75	1508	585 (39%)		464 (30%)	
Family History of CRC Cancer					
No Family history information	813 (44%)	245 (30%)	0.76 (0.60 - 0.96)	197 (24%)	0.87 (0.68 - 1.11) ⁵
Negative Family history	966 (53%)	429 (44%)	1.0	326 (34%)	1.0
1 st Degree Relative with CRC cancer	60 (3%)	37 (62%)	2.47 (1.32-4.64)	28 (47%)	1.94 (1.08-3.48) ⁶

¹ Patients with test orders within guidelines but no record of test being done 6 months after order were excluded from the analysis (N=8 men, 31 women).

² Odds ratios were determined using random effects logistic regression models that included clinics as a random effect and adjusted for age, ethnicity, smoking status, length of contact with clinic, last recorded insurance type, BMI category, number of clinic visits, and digestive and cardiovascular disease co-morbidity.

³ Odds ratio in analysis restricted to age less than 75: 0.82 (0.63-1.08).

⁴ Odds ratio in analysis restricted to age less than 75: 3.34 (1.53-7.25).

⁵ Odds ratio in analysis restricted to age less than 75: 0.85 (0.64-1.12).

⁶ Odds ratio in analysis restricted to age less than 75: 1.96 (1.01-3.82).