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TOXICOLOGY INVESTIGATION

Proportionate Cancer Mortality in Methyl Methacrylate-Exposed Orthopedic Surgeons Compared to General Surgeons

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Abstract Methyl methacrylate (MMA), a volatile liquid used to make dentures, hearing aids, joint prostheses, and medical adhesives, has been associated with colorectal carcinomas in acrylic sheet manufacturing workers. A case–control proportionate cancer mortality investigation was conducted to determine cancer death differences in orthopedic surgeons performing total joint replacements (TJRs) (MMA-exposed cases) and general surgeons not performing TJRs (unexposed controls). The American Colleges of Orthopedic Surgeons and General Surgeons provided complete demographic information on 468 male orthopedic surgeons and 1,890 male general surgeons who died during 1991–2001. Decedent data was submitted to the National Death Index for matching with underlying causes of death on state death certificates. Proportionate differences in ages at death, deaths from cancer, and deaths from site-specific cancers were analyzed for statistically significant differences by unpaired, two-tailed t tests for continuous variables and by both proportionate cancer mortality ratios and Yates-corrected chi squares for categorical variables. Orthopedic surgeons died of cancer more often (χ^2=7.699, P=0.006) and at younger (t=5.53, P<0.001) ages (mean=69.4 years) than general surgeons (mean=79.2 years). For site-specific cancers, orthopedic surgeons died of esophageal cancer (χ^2=4.372, P=0.037) and myeloproliferative malignancies (χ^2=4.369, P=0.037) more often than general surgeons. Orthopedic surgeons are chronically exposed to MMA and are proportionately more likely to die from cancer, especially esophageal and myeloproliferative cancers, than general surgeons. MMA-exposed healthcare workers may be at increased risks of untimely deaths from site-specific malignancies.

Keywords Methyl methacrylate · Carcinogenicity · Toxicology · Industrial · Occupational · Healthcare industry exposures · Carcinogenic · Toxic

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Introduction

Methyl methacrylate (MMA), a colorless, volatile liquid with an acrid odor, is among the world's most commonly manufactured industrial chemicals with annual world production estimated at 3.2 million tons [1]. With widespread applications in the lighting, painting, paneling, plumbing, sealing, sheeting, and siding industries, and, especially, in the healthcare industry, there is an increasing annual demand for MMA as the world's population ages. The healthcare uses of MMA include dental amalgams and prostheses; orthopedic adhesives and coatings for prosthetic joints; vertebroplasty glues for injection into metastatic and pathologic bone fractures; hearing aids; eyeglass lenses and rims; and the very latest uses in rapidly hardening, acrylic jackets for chest wall reconstruction following radical surgical resections for cancer [2, 3]. The demand growth for MMA, 3.5% per year in 2005, is met by the world's largest producers, located in the USA, UK, and Europe [1].

Although ethyl acrylate ingestion has caused dose-dependent forestomach carcinomas in rodents and occupational MMA exposures during the 1940s have been associated with excess colorectal cancer mortality in acrylic sheet manufacturing workers, there have been relatively few studies on MMA carcinogenicity in animals or humans [4, 5]. Most MMA carcinogenicity studies in humans have

been combined retrospective cohort studies from the 1930s through the 1990s, or meta-analyses of the same and similar studies [4–10]. In addition, most of the negative cancer studies were authored by epidemiologists employed by major chemical manufacturers of MMA in the USA (American Cyanamid Company, Wayne, NJ; Rohm and Hass Co., Croydon, PA) and in the UK (Imperial Chemical Industries; Lucite International UK Ltd.) [6–8].

In light of prior investigations, the purpose of this proportionate cancer mortality study was to achieve the best experimental design, sample size, and statistical power required to identify any existing significant differences in the proportions of cancer deaths in well-matched cohorts of MMA-exposed orthopedic surgeons (n=468) and MMA-unexposed general surgeons (n=1,890). The objectives of this investigation were to compare the proportion of deaths during 1991–2001 from both organ system and site-specific cancers in deceased orthopedic surgeons exposed to MMA during joint replacements throughout their careers and in deceased general surgeons not performing joint replacements throughout their careers. Since our control or unexposed population of general surgeons all died before 2000, they were not exposed to the massive MMA releases during newly described MMA–mersilene mesh "sandwich" operations for chest wall reconstruction after radical surgical resections for invasive thoracic malignancies, as this procedure did not enter thoracic surgical practice until later in the twenty-first century [3].

The proportion of cancer deaths in the two comparison cohorts were assumed *a priori* to be the same, and other, uncontrolled, major behavioral confounders for cancer, including tobacco smoking, smokeless tobacco use, environmental tobacco smoke exposure, ethanol use, dietary saturated fat intake, sedentary lifestyle, activity levels, and lack of exercise, were assumed *a priori* to have distributed equally between the cohorts of surgeons with similar socioeconomic status and occupational stressors throughout their lifetime careers.

Methods

Following approval by the Institutional Review Board of the Louisiana State University Health Sciences Center in New Orleans, LA, this proportionate cancer mortality study commenced with requests made to professional association membership directors by officers of the respective associations, the American College of Surgeons (ACS) and the American College of Orthopedic Surgeons (ACOS). All study decedents during the period 1991–2001 were initially identified by their respective professional associations, the ACS and the ACOS, with their names, last addresses, dates of membership, periods of active practice, and dates and places of births and deaths. An initial study sample of 3,458 deceased surgeons, composed of 2,726 general surgeons and 732 orthopedic surgeons, was assembled from professional association membership registries. The subsequent confirmations of deaths by underlying causes were conducted by the National Death Index (NDI), a central, federally operated, computerized data repository of all US deaths; 1979 to the present. The investigators were blinded to the names of decedents confirmed as to underlying causes of death by the NDI.

Stringent exclusion criteria eliminated deaths outside of the US, joint professional association memberships, and several other potential death-related confounders (Table 1). All deaths were confirmed by linkages to state death certificates in states of death with underlying causes of death documented by four-digit ICD-9 codes. Additional exclusion criteria included surgeon deaths in 2000–2001 because all of these deaths had not all been forwarded to the NDI during this study, specifically all of the deaths in the State of New York following the September 11, 2001, terrorist attacks on New York City (Table 1). Female surgeon deaths were also excluded due to the small number of female surgeons dying during the study period, 1991–2001 (Table 1).

In this proportionate cancer mortality study, only the cancer deaths in professional registry-confirmed orthopedic surgeons were analyzed in comparison to the cancer deaths in professional registry-confirmed general surgeons. The cancer deaths in other operating room (OR) personnel, such as anesthesiologists, nurse anesthetists, and OR nurses, who may have been exposed to MMA vapor during assignments to total joint reconstruction cases were not included in this study.

Table 1 Exclusion criteria applied to the initial death cohort (N=3,458)

Study cohorts	General surgeons	Orthopedic surgeons	Totals
Initial sample sizes	2,726	732	3,458
Exclusion criteria			
All deaths in 2000 2001, except NY	431	167	598
Foreign deaths	153	11	164
New York deaths	171	37	208
Female deaths	4	0	4
Dual college memberships	1	1	2
Insufficient death information for NDI confirmation	836	49	885
Final NDI matched and confirmed sample sizes	1,890	468	2,358

NDI National Death Index

An *a priori* power and sample size analysis was conducted before the study subjects were assembled and directed a minimal sample size of 361 decedents in order to achieve 80% statistical power for correctly identifying significant differences in underlying causes of deaths. The final study sample size included 2,358 deceased surgeons, 1,890 general surgeons and 468 orthopedic surgeons, assumed to have been exposed to MMA vapor during prosthetic joint replacement operations during their professional lifetimes. Following the establishment of the final NDI-matched sample size of 2,358 study subjects, a *post hoc* power analysis at an alpha significance level of 0.05 demonstrated a statistical power of 98.7% for chi-square analyses to correctly identify statistically significant proportional differences in cancer deaths, if present.

Continuous variables, including mean ages at death from all causes and mean ages at death from cancer, were tested for statistically significant differences between the MMA-exposed orthopedic surgeons and the MMA-unexposed general surgeons by unpaired, two-tailed *t* tests. Categorical variables including the proportions of deaths from all causes, from organ system-specific cancers and from site-specific cancers, were tested for statistically significant differences at a significance level of 5% by Yates-corrected chi-square (χ^2) analyses. Statistically significant differences for both *t* tests and the chi squares were indicated by *P* values equal to or less than 0.05.

In addition to chi-square comparisons for proportional differences in deaths between the MMA-exposed orthopedic surgeons and the unexposed general surgeons, proportionate cancer mortality ratios (PCMR) were calculated for all cancer deaths, including all-cause cancer deaths, organ system-specific cancer deaths, and site-specific cancer deaths using the standard formula, a/a+c/b/b+d, i.e., the proportion of cancer deaths in the exposed study subjects divided by the proportion of cancer deaths in the unexposed control subjects. As the calculated PCMR approached 1.0, the proportions of cancer deaths in MMA-exposed orthopedic surgeons and unexposed general surgeons approached equality.

Results

Orthopedic surgeons died at significantly younger ages than general surgeons with mean ages at death of 70.0 years compared to 79.2 years during the study period (t=16.332, P<0.0001) (Table 2). Orthopedic surgeons died of all-cause cancer deaths at significantly younger ages than general surgeons with mean ages at death of 69.4 years compared to 75.2 years (t=5.530, P<0.001) (Table 2). Orthopedic surgeons died of all-cause cancer significantly more often than general surgeons (χ^2=7.699, P=0.006) and of all hematological malignancies significantly more often than general surgeons (χ^2=7.672, P=0.006) (Table 3). Orthopedic surgeons died of esophageal cancer (χ^2=4.372, P=0.037) and of myeloproliferative cancer including multiple myeloma (χ^2=4.369, P=0.037) significantly more often than general surgeons (Table 4). With the exception of esophageal cancer, there were no differences in the proportions of deaths from all other gastrointestinal malignancies in orthopedic surgeons compared to general surgeons including deaths from cancers of the colon, rectum, small intestine, liver, pancreas, and gall bladder (Table 4). Lastly, with the exception of esophageal cancer, there were no differences in deaths from cigarette smoking, smokeless tobacco, and environmental tobacco smoke exposure-associated malignancies between orthopedic surgeons and general surgeons including cancers of the tracheobronchial tree, lung, stomach, pancreas, colon, rectum, kidney, and bladder (Table 4).

Unlike the assumptions of prior investigations, most tobacco-associated malignancies occurred with equivalent proportions (i.e., proportionate cancer mortality ratios approaching 1.0) in both exposed-case and unexposed-control groups, with the exception of esophageal cancer, which has been associated with combined alcohol and tobacco use, reflux esophagitis, Barrett's esophagus, and an absence of *Helicobacter pylori* seropositivity (Table 4) [11]. Finding no statistically significant differences in most tobacco exposure-associated cancers between orthopedic surgeons and general surgeons confirmed the equivalent circulation of tobacco exposures as potential confounders between MMA-exposed orthopedic surgeons and MMA-unexposed general surgeons (Table 4).

Discussion

Acute and chronic systemic reactions to MMA vapors are relatively common among workers in the healthcare industry and in the acrylic product manufacturing industry. Among healthcare workers, operating room personnel, and dental laboratory technicians, especially those with pre-existing asthma, allergies, atopic dermatitis, or reactive airway diseases, appear to be predisposed to acute bronchospasm on new or repeat (Monday morning) MMA exposures [12–21]. These bronchospastic reactions may be accompanied by any combination of cough, oronasal mucosal erythema and edema, dyspnea, generalized erythroderma, and circulatory instability [12–21]. Liquids and pastes of all MMA monomers and polymers can penetrate all types of surgical gloves over time and have caused local dermatological reactions with later lichenification and fissuring in the fingertips of dental laboratory technicians, especially those who choose never to wear gloves at all when molding dental amalgams and dentures [17, 21].

Table 2 Mean ages of study cohorts at death (N=2,458)

Mean ages at death	General surgeons (n=1,890)	Orthopedic surgeons (n=468)	t test values[a] (unpaired, 2-tailed t tests)	P values*
Ages at death, all causes (years)	79.2	70.0	16.332	≤0.0001
Ages at death from cancer, underlying causes (years)	75.2	69.4	5.53	≤0.001

*P≤0.05, statistically significant

[a] Two-tailed, unpaired t tests

Chronic workplace exposures to MMA vapors have caused occupational asthma and chronic obstructive airways disease in industrial workers [15, 16]. The chronic neurotoxic effects of prolonged MMA exposures have been primarily confined to dental laboratory technicians and have included distal sensory peripheral neuropathy, generalized sensory peripheral neuropathy, olfactory dysfunction, and toxic dementia [17–20].

Unlike prior cancer mortality studies of chronic occupational MMA exposures, this investigation was a proportionate cancer mortality study that compared two groups of deceased surgeons assumed *a priori* to have equivalent all cancer and site-specific cancer mortality (Table 5). All other studies have been retrospective, descriptive, observational studies; standardized mortality rate (SMR) studies comparing observed to expected death rates; or meta-analyses, which have simply lumped prior studies for analysis, including ones by the same authors (Table 5) [4–8]. The design of this study permitted the exact confirmation of professional lifetime occupations and underlying causes of death.

The most important results of this study included the following: (1) Male orthopedic surgeons died from all causes at significantly younger ages than general surgeons. (2) Male orthopedic surgeons died at significantly younger ages from cancer than general surgeons. (3) Male orthopedic surgeons died from esophageal cancer significantly more often than general surgeons. Nevertheless, although the proportion of esophageal cancer deaths remained small in both groups, nine of 1,890 cancer deaths (0.48%) in general surgeons versus seven of 468 cancer deaths in orthopedic surgeons (1.5%), the difference was statistically significant (χ^2=4.372, P=0.037). (4) Male orthopedic surgeons died more often from all-cause hematological cancers and site-specific hematological cancers, including myeloproliferative disorders and multiple myeloma, than general surgeons.

Chronic occupational MMA exposures have now been associated with chronic gastritis, achlorohydria, and atrophic and erosive gastritis [22, 23]. Although this study was not designed to analyze the relationships among MMA-induced chronic gastritis, *H. pylori* seropositivity, and esophageal cancer, chronic occupational MMA exposures can cause chronic atrophic gastritis, and *H. pylori* infection or seropositivity is protective for esophageal cancer [10, 11, 22, 23]. Therefore, if chronic MMA exposures can destroy acid-producing gastric cells and cause achlorohydric atrophic gastritis, such exposures may also be bactericidal for *H. pylori*, predisposing MMA-exposed workers to esophageal cancer [10, 11, 22, 23]. Nevertheless, the relationships between *H. pylori* infection and gastric atrophy and esophageal cancer cannot be fully explained at this time [11, 22, 23]. Although most gastric carcinomas do indeed arise on a background of atrophic gastritis, there were no significant differences in the proportions of deaths from

Table 3 Proportionate cancer mortality for all cancer deaths and organ system cancer deaths (N=2,458)

Cancer deaths	General surgeons (n=1,890)	Orthopedic surgeons (n=468)	Proportionate mortality ratios	Chi-square values (Yates corrected)	P values
All cancers	472	147	1.3992	7.699	0.006*
All GI cancers	75	27	1.3540	2.521	0.112
Upper GI cancers (esophagus, stomach, SI)	30	10	1.2652	0.390	0.533
Colorectal and anal cancers	45	17	1.3961	1.832	0.176
GB, liver, and pancreatic cancers	41	13	1.2178	0.379	0.538
All GU cancers	123	31	1.0151	0.0001	0.989
All hematological cancers	128	50	1.4653	7.672	0.006*

GI gastrointestinal, *GB* gall bladder, *GU* genitourinary, *SI* small intestine

*P≤0.050, statistically significant

Table 4 Proportionate cancer mortality for all site-specific cancer deaths (N=2,458)

Site-specific cancers	General surgeons (n=1,890)	Orthopedic surgeons (n=468)	Proportionate mortality ratios	Chi-square values (Yates corrected)	P values
Esophageal	9	7	2.2232	4.372	0.037*
Stomach	19	3	0.9884	0.217	0.642
Small intestine	2	1	1.6808	0.019	0.890
Liver and GB	13	3	0.7622	0.042	0.838
Pancreas	28	10	1.3333	0.808	0.369
Colon	39	15	0.0546	1.704	0.192
Rectum and anus	6	2	1.2607	0.006	0.938
Trachea and lung	101	24	0.9658	0.005	0.943
Prostate	94	21	0.9162	0.101	0.751
Bladder	14	3	0.8887	0.006	0.939
Kidney	15	7	1.6128	1.313	0.252
Thyroid	4	1	1.0076	0.305	0.580
Lymphoma	64	25	1.4390	3.430	0.064
Leukemia	31	9	1.1364	0.050	0.822
Myeloproliferative and multiple myeloma	33	16	1.6655	4.369	0.037*

GB gall bladder

*$P \leq 0.050$, statistically significant

gastric carcinoma in MMA-exposed orthopedic surgeons and MMA-unexposed general surgeons, and the proportionate cancer mortality ratio of 0.9884 confirmed that the occurrences of gastric cancer were the same in both groups of surgeons (Table 4) [11, 23, 24].

In addition to the significant increase in deaths in orthopedic surgeons from esophageal cancer, the proportional increase in myeloproliferative cancers in orthopedic surgeons compared to general surgeons, also assumed *a priori* to be equivalent, cannot be fully explained. However, volatile organic solvents are often used to solubilize lyophilized MMA powders for coating and securing prosthetic joints and have been associated with hematological malignancies following chronic occupational exposures [24].

In addition to its well-established design for studying proportionate deaths from cancer, other strengths of this investigation included its (1) lack of financial sponsorship by major MMA manufacturers, many of whom supported earlier no-excess cancer cohort studies; (2) exact confirmation of death for all study decedents using both professional association and NDI registries; (3) use of four-digit, not three-digit, ICD-9 CPT codes with the highest confirmation (>80%), detection (>80%), and nosological (≥97%) match rates for determination of cancer as underlying causes of death based on histopathological diagnoses; and (5) control-to-case ratio of 4:1 using socioeconomically matched general surgeons as controls in similar occupations without MMA exposures and with assumed similar lifestyle cancer risks from alcohol use, diet, and smoking [25–27].

The weaknesses in this investigation that could not be controlled for included (1) all-male study decedents due to the small number of female surgeons (n=4) dying in 1991–2001; (2) no decedents from New York (NY) State due to unanticipated delays in filing NY State death certificates with the NDI after the September 11, 2001, attacks in New York City; (3) inability to measure the ambient air levels of MMA exposures in deceased orthopedic surgeons over their lifetime professional careers; (4) the relatively small cohort size (n=468) of deceased orthopedic surgeons compared to deceased general surgeons (n=1,860) that, nevertheless, reflected the current professional society membership ratio of approximately 4:1; and (5) an inability to account for the interrelationships of protective *H. pylori* infection or seropositivity, MMA-induced gastric atrophy, and esophageal cancer outcomes in orthopedic surgeons [11, 22, 23].

Conclusions

In conclusion, orthopedic surgeons performing total joint reconstructions and re-replacements with currently recommended MMA-cementing techniques died more often of cancer than a well-matched cohort of general surgeons [28–30]. The proportionately different cancer deaths in ortho-

Table 5 Prior epidemiological investigations of cancer risks from occupational methyl methacrylate exposures [5–10]

Cancer risks present (+) or absent (−)	Year published (ref. #)	Study sponsors	Study designs	Observation periods	Results and conclusions	Study limitations addressed by authors? Yes/no Specific study limitations
+	1991 (5)	Harvard University School of Public Health	Observed vs. expected deaths from colorectal cancer in 3 cohorts of male MMA-exposed workers	1933–1986	Workers in earliest cohort with highest MMA exposures had excess colorectal cancer mortality. There was a dose-dependent effect from MMA exposures on colorectal cancer mortality in male workers	Yes. The authors could not separate ethyl acrylate (EA) from MMA exposures during the manufacture of MMA in the EA/MMA polymerization process and could not account for specific proportions of EA and MMA in vapor mixtures
			Cohort #1=3,934 white males	1933 until death or 1986		
			Cohort # 2=6,548 white males	1946 until death of 1986		
			Cohort #3=3,381 white males	1943 until death or 1986		
	1996 (9)	Russian State Ministry of Health	Observed cancer mortality in workers exposed to 5 types of acrylates	1950s–1990s	There was a dose-dependent increase in cancer mortality only in MMA-exposed workers and not workers exposed to other acrylates	No. This was an observational study with no control group
−	2000 (10)	Russian State Ministry of Health	Observed 3,588 male and female workers exposed to increasing levels of MMA for cancer incidences	1950s–1990s	There was a dose-dependent increase in the incidence of lung cancer in males and genital cancers in females	No. This was an observational study with no control group
	1989 (6)	American Cyanamid Co. (USA)	Observed all causes of mortality in a cohort of 2,671 men, 1,561 of whom were exposed to MMA	1951–1983	Men exposed to the highest levels of MMA in acrylic sheet production had no greater cancer risks than unexposed workers. No dose–response effects were observed	No. This study aggregated all MMA-exposed workers and did not stratify by level or length of MMA exposures or by causes of non-cancer deaths. An all-cause mortality of only 67% in this study indicated incomplete ascertainment of both all cause and cancer deaths in the cohort
	2000 (7)	ICI (UK)	Observed mortality patterns among 4,324 male workers at 2 UK plants producing MMA sheets	1949–1988	There was reduced all-cause and colorectal cancer mortality, but a slight increase in all-cancer mortality in plant #1 workers compared to local and national population rates. There was reduced all-cause mortality, but an increase in all-cancer and colorectal cancer mortality in workers at plant #2 compared to local and national population rates. Study provided no clear evidence that MMA exposures affected mortality in workers	Yes. The authors could not calculate cumulative MMA exposures in plant #1 hired before 1949. The levels of MMA exposures could not be assessed at plant # 2

2005 (8)	ICI (UK)	Meta-analysis of all published (i.e., 2 cohort studies=references #5 and 9) and 1 unpublished study on the carcinogenicity of MMA exposures in acrylic manufacturing workers	NA	An excess of colorectal cancer mortality was restricted to men exposed to the highest MMA levels at 1 plant in the 1940s cannot be explained (see reference #5). All other excesses in all-cancer mortality likely "resulted from unexplained contributions of lifestyle exposures, such as cigarette smoking and diet"	No. This meta-analysis included a cohort study published by the same authors and an unpublished case–control study by the same authors nested in their cohort study

ICI Imperial Chemical Industries, UK

pedic surgeons compared to general surgeons were due to esophageal and myeloproliferative cancers and not to colorectal cancers as in earlier studies (Table 5) [5, 9, 10]. Further investigations will need to be conducted to assess the interrelationships of protective *H. pylori* infection (<40%), MMA-induced gastric atrophy, and esophageal cancer outcomes in orthopedic surgeons.

Since some orthopedic surgeons have now adopted self-contained breathing apparatus (SCBA)-equipped scrub suits for infection control purposes during high-risk intra-articular procedures; such personal protective equipment should also protect them from inhalational MMA exposures, in addition to specially ventilated operating rooms [30]. In the future, general and thoracic surgeons performing chest wall reconstructive procedures with MMA–mersilene mesh "sandwich" prostheses may be at increased risks of MMA exposures and cancer outcomes. Although not federally mandated by regulators in the USA, the periodic measurements of serum or urine methanol concentrations will provide reliable biomarkers for occupational MMA exposures and should be considered for all high-risk exposure groups [31].

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