Schätzung von Tumorrisiken anhand aus der Berufsbiografie abgeleiteten Expositionsvariablen

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1 Einleitung

Krebshäufigkeiten unterscheiden sich nach Alter, Geschlecht, ethnischer Zugehörigkeit, geografischer Lage, Zeitperiode und sozialem Status (Jemal et al. 2008). Diese Attribute sind auch mit dem Begriff Arbeit und Zugang zu Arbeit verknüpft.

Arbeit, wie auch der Arbeitsbegriff, verändern sich. Berufliche Tätigkeiten werden automatisiert und rationalisiert (Seidler et al. 2008). Arbeit ist eine Notwendigkeit zum Lebensunterhalt und gleichzeitig wird durch Arbeit Ungleichheit in den Bereichen der Gesundheit und des Sozialen erzeugt. Arbeit bestimmt den Platz, der in der Gesellschaft eingenommen wird sowie die Lebensbedingungen und -möglichkeiten: die häusliche Umgebung, die Erholungsmöglichkeiten und die Gesundheitsvorsorge einschließlich des Zugangs zum Gesundheitswesen (Costa 2005, Thebaud-Mony 2004).

Im Schweiße deines Angesichts sollst du dein Brot essen. Dieses Bibelwort für belastende Arbeit, lässt sich, wie in neueren Veröffentlichungen gezeigt wird, nicht nur mit Risiken für physische sondern auch für psychische Beeinträchtigungen heranziehen, die vielfältig und abhängig von mehreren Einflussfaktoren sind (Seidler et al. 2008).

Durch die Genese von Tumoren durch Chemikalien im Tierversuch konnte gezeigt werden, dass Krebs eine expositionsbedingte Ursache haben kann. Die Zuweisung von Einflüssen auf die Entstehung von Krankheiten ist ein Betätigungsfeld der Epidemiologie. Die Arbeitsepidemiologie ist dabei ein wichtiges Gebiet der Krebsforschung. Berufsbedingte Expositionen gegenüber krebsauslösenden Substanzen zu ermitteln stellt eine besondere Herausforderung dar. Die Arbeitsepidemiologie erlaubt, den Anstieg von Tumoren in spezifischen Berufsgruppen im Vergleich zur Bevölkerung oder anderen Berufsgruppen zu messen. Dabei können Berufsverlauf und spezifische Berufseinflüsse in den Analysen berücksichtigt werden (Thebaud-Mony 2004). Der Frage, welche exogenen Ursachen für die Krebsentstehung mitverantwortlich sind, wird in zahlreichen epidemiologischen Studien nachgegangen. Neben der Bestimmung eines Basisrisikos in einer Bevölkerung ist die Erkennung von Mustern mit veränderten Erkrankungshäufigkeiten, wie die Nähe zu Kernkraftwerken, Mülldeponien und toxischen Substanzen in der Arbeits- und Umweltumgebung eine zentrale Aufgabe der Epidemiologie (Clapp et al. 2005).

Epidemiologie ist das Studium von Verteilungen und Determinanten gesundheitsrelevanter Zustände oder Ereignisse in spezifischen Bevölkerungsgruppen und die Übertragung der

Ergebnisse zur Kontrolle und Eindämmung von Gesundheitsproblemen. Das Ziel ist die Unterstützung, der Schutz und Erhalt der Gesundheit (WHO 2004). Speziell die Arbeitsepidemiologie fragt nach Ursachen und der Verbreitung von Krankheiten im berufsspezifischen Kontext, um Gefahren zu identifizieren, auf Richtlinien und Grenzwerte Einfluss zu nehmen und damit zu einer Arbeitsumwelt beizutragen, die die Gesundheit weniger belastet.

Es konnte eine Anzahl von Stoffen, die in unterschiedlichen Arbeitsbereichen eingesetzt werden, mit der Genese von Krebs in Zusammenhang gebracht werden (IARC 2010). In den letzten Jahren werden verstärkt berufliche Einflussfaktoren auf die Entstehung von Krebserkrankungen untersucht, dabei spielen zeitliche Aspekte und verhaltensbedingte Einflüsse eine zentrale Rolle. Die Identifizierung von Risikoberufen für Tumore ist ein effektives Werkzeug, um krebsverdächtige Chemikalien zu identifizieren (Boffetta et al. 1995, Siemiatycki et al. 1991). Nach Angaben der USEPA sind für die USA nur etwa 4% der Krebs-Todesfälle auf Expositionen am Arbeitsplatz und weniger als 1% auf Industrieprodukte zurückzuführen (Bahadir et al. 2000). Die Angabe der Anzahl der beruflich bedingten Krebs-Todesfälle kann in diesen Statistiken je nach Fokus und Zählweise variieren, da Ursachen von Krebserkrankungen selten auf Einzelstoffe zurückzuführen sind und variable Umwelteinflüsse einen Effekt maskieren oder verstärken können (Boffetta et al. 1995).

Veränderungen von Produktionsbedingungen und damit verbundener Umstellung von Chemikalien und Arbeitsverfahren spielen eine Rolle beim Erkennen von Einflüssen auf die Gesundheit. Die Frage nach dem Karzinogen umfasst ein weites Spektrum von Stoffen. So sind zu Anfang des Jahres 2010 nach Beilstein etwa 9,8 Millionen chemische Verbindungen und 10 Millionen chemische Reaktionen bekannt (PRNewswire 2010). Die IARC in Lyon hat seit 1971 bis heute etwa 900 Chemikalien bewertet und daraus eine Liste von etwa 400 Chemikalien mit nachgewiesenem oder verdächtigt kanzerogenem Potenzial zusammengestellt (IARC 2010).

Es werden verschiedene, von unterschiedlichen Typen von Zellen ausgehende Krankheiten unter dem Begriff Krebs zusammengefasst. Der Krebsprozess ist mehrstufig, oft örtlich beschränkt und geht mit Veränderungen von Wachstum, Differenzierung und Tod von Zellen einher. Krebszellen sind den Wachstum regulierenden Einflüssen des Organismus ganz oder teilweise entzogen (Schulte-Hermann & Parzefall 2010). Krebs wird in der Regel bei älteren Menschen beobachtet. Dafür kommen als Gründe in Frage, dass mit steigendem Alter in Zellen Änderungen induziert werden, die neoplastische Übergänge erlauben oder begünstigen, das altersabhängig die Suszeptibilität gegenüber einer neoplastischen Transformation erhöht ist und bei Exposition eine kumulierte Wirkung von Kanzerogenen vorliegen kann (Schulte-Hermann & Parzefall 2010).

Berufe mit erhöhtem Krebsrisiko für jeweilige Krebslokalisationen zeigen häufig ein unterschiedliches Spektrum an Tätigkeiten mit einem weit gefächerten Expositionsalltag auf. Eindeutige Beziehungen zwischen stofflicher Exposition und Krebserkrankung verbleiben meist auf der Beobachtungsebene wie die Ergebnisse von Krain (1972) sowie von Malker et al. (1986) für Tumoren der extra-hepatischen Gallengänge, von van den Eeden et al. (1991), Knight et al. (1996) und Pearce et al. (1987) für Hodentumoren und Shangina et al. (2006), Marchand et al. (2000) und Boffetta et al. (2003) für Lokalisationen von Tumoren der oberen Luft- und Speisewege (UADT) beispielsweise zeigen.

Epidemiologie ist eine quantitative Wissenschaft die auf Grundlage einer Anzahl von Beobachtungen basiert. Expositionseinstufungen werden in den unter Abschnitt 1.4.1 bis 1.4.3 vorgestellten Fall-Kontrollstudien auf der Basis von Interviews vorgenommen, in denen die Studienteilnehmer konkret zu verschiedenen Tätigkeiten, Prozessen und Materialen während ihrer Berufstätigkeit befragt wurden.

Um aussagefähige Auswertungen durchzuführen, müssen Daten nach einheitlichen Kriterien erfasst werden und in einer Form vorliegen, die eine eindeutige Zuordnung der vorliegenden Parameter ermöglicht und gleichzeitig eine höchstmögliche Trennschärfe gewährleistet. Damit stellt sich das Problem des Optimums zwischen Quantität und Qualität der Daten. Ein Interview muss in einem vertretbaren Zeitrahmen ablaufen und sollte möglichst alle relevanten Bereiche abdecken, die helfen, eine Forschungsfrage zu beantworten und gegebenenfalls neue Hypothesen zu generieren. Die Datenerhebung muss sich somit der Herausforderung stellen, dass Fragen zugleich Fragmentierung bedeutet.

Die Datengrundlage, mit deren Hilfe eine Expositionseinstufung vorgenommen wird, bestimmt die Aussagefähigkeit einer Studie (Pearce et al. 1989a, Pearce et al. 1989b). Dies gilt insbesondere für Fall-Kontrollstudien, bei denen die Expositionseinstufung in der Regel ohne objektive Daten vorgenommen wird und den Aussagen des Studienteilnehmers vertraut werden muss. Da gute Auswertungskonzepte eine schwache Datenqualität nicht ausgleichen können, ist die sich an das Interview anschließende Expositionseinstufung im

Vorfeld zu bedenken und von elementarer Bedeutung, um valide und reliable Ergebnisse zu erhalten.

1.1 Soziale Schicht

Verschiedene Erkrankungen, gerade auch Krebserkrankungen, verteilen sich nach beruflichen Tätigkeiten und beruflichen Stellungen unterschiedlich. Dies konnte an einigen Tumorlokalisationen, wie etwa Brustkrebs (Webster et al. 2008, Yost et al. 2001), Prostatakrebs (Coker et al. 2006, Sanderson et al. 2006, Faggiano et al. 1994) und Tumoren des Bauchraums (Faggiano et al. 1994, Chow et al. 1993) gezeigt werden.

Aktuelle Forschungsfragen beschäftigen sich damit, ob es diesen Gradienten auch bei Hodentumoren gibt (Marsa et al. 2008, Möller & Skakkebaek 1996). Damit stellt die aus der beruflichen Stellung resultierende soziale Schicht eine Dimension beruflicher Exposition dar. Der Einfluss des sozialen Hintergrunds wird anhand von verschiedenen Klassifikationsmodellen anhand jeweils einer Fall-Kontrollstudie zu Hodentumoren und Tumoren der oberen Luft- und Speisewege (upper aerodigestive tract: UADT) untersucht.

Die Berufsangabe wird in vielen Studien benutzt, um den sozialen Status zu messen (Avendano et al. 2005, Griffin et al. 2002, Smith et al. 1997). Die Begriffe „Sozial“ und „Status“ sind Konstrukte aus der sozialwissenschaftlichen Theorie, die in beobachtbare Merkmale umgesetzt werden müssen. Dabei werden nur wenige der möglichen Inhalte des theoretischen Konstrukts in die operationalisierte Variable umgesetzt. Merkmal und Variable unterscheiden sich dadurch, dass das Merkmal theoretisch, die Variable aber beobachtbar ist, und sich in einer Population feststellen lässt (Schendera 2004). Das Konstrukt „Sozialer Status“ lässt sich in unterschiedlicher Tiefe bestimmen, es kann als Haushaltseinkommen pro Kopf, Wohnlage, Beruf aber auch Attributen wie Sprachgewandtheit usw. definiert werden. Dabei ist die in den Daten messbar vorhandene Variable abhängig von der Definition (Schendera 2004). Häufig sind aus den verschiedenen Skalen, die den sozialen Status anhand des Berufs messen, keine eindeutigen Beziehungen abzuleiten, da sich Indikatoren für soziale Klasse selbst auf komplexe Weise zusammensetzen (Lahelma et al. 1990). Wie sozialer Status gemessen werden kann, hängt ab von der Population. So wurde in einer Population mit niedrigem Volkseinkommen das Vorhandensein eines Fernsehers als Indikator für hohen sozialen Status herangezogen (Islami et al. 2009).

Der Vergleich von sozialem Status ist innerhalb von Gesellschaften zulässig, in denen gleiche Normen gelten, da mit dieser Maßeinheit die Lage innerhalb einer Sozialstruktur charakterisiert wird. Ein Vergleich zwischen Gruppen, in denen unterschiedliche Normen und Werte vorhanden sind kann als nicht sinnvoll betrachtet werden, solange kein verbindendes Element zur Verfügung steht.

Die Variable *Standard International Occupational Prestige Scale* (SIOPS), die das soziale Prestige misst, ermöglicht es als verbindendes Element das Ansehen von Berufen unabhängig vom kulturellen Hintergrund zu bewerten (Treiman 1977). Ein Vergleich über die Variable SIOPS kann dann stattfinden, wenn Berufstitel und Berufsbezeichnungen nach dem International Standard Code of Occupations (ISCO) (ILO 1968) klassifiziert sind. Die Werte der SIOPS-Skala sind aus Ländern unterschiedlichster sozialer Lage, wie beispielsweise den USA, Indien, England und der damaligen UdSSR, ermittelt. Die Abstände der relativen Werte für die jeweilige Berufsgruppe sind im Vergleich der einzelnen Länder untereinander, mit minimalen Abweichungen, gering (Treiman 1977). Die Überführung in den international standardisierten Prestigewert stellt eine Nivellierung von nationalen Abständen dar. Vergleiche zwischen agrarwirtschaftlich und industriell geprägten Ländern sowie zwischen Ländern unterschiedlicher politischer Ausrichtung sind somit möglich. Damit eignet sich die Variable zur Analyse von Daten aus internationalen Studien, wie im Manuskript Kapitel 2.4 verwendet.

Eine der SIOPS verwandte Variable ist der *International Socio-Economic Index of Occupational Status* (ISEI) (Ganzeboom & Treiman 1996). Beides sind kontinuierliche Variablen des beruflichen Status die miteinander hoch korrelieren (Wolf 1995). Der Unterschied zwischen SIOPS und ISEI ist, das Erstere eine Zuordnungsskala beruhend auf Bewertungen aus Umfragen ist, während die zweite Variable als Maßzahl Bildung, berufliche Tätigkeit und Einkommen aus Daten aus 16 Ländern (u.a. den USA, Brasilien, den Niederlanden, Japan, Australien und Irland) in Beziehung setzt. Im Artikel „Social factors and risk of testicular cancer“ (Kapitel 2.3) wird neben dem ISEI das hierarchisch geprägte Erikson-Goldthorpe-Portocarero-Klassenschema (EGP) (Erikson et al. 1983), das in vielen epidemiologischen Studien Anwendung findet, als Klassifikation der sozialen Schicht eingesetzt.

1.2 Pestizide

Die zweite in dieser Dissertation verfolgte Dimension von möglichen Einflussfaktoren auf die Entstehung von Hodentumoren bzw. Tumoren der extrahepatischen Gallenwege ist der berufliche Kontakt gegenüber Pestiziden. Einen Fokus auf Pestizide als Krebs bedingenden Faktor zu legen begründet sich darin, dass Pestizide ein hohes schädigendes Potenzial besitzen, sich durch eine Vielzahl von chemischen Wirkungen auszeichnen und Zellfunktionen in nachhaltiger Weise beeinflussen (Maroni & Fait 1993). Viele synthetisch hergestellte Pestizide werden durch das Einführen von Halogenen in die chemische Struktur stabilisiert. Dadurch werden sie gegenüber physikalischen und chemischen Einflüssen haltbar (Stolz et al. 1995). Diese chemische Strukturstabilisierung hat Auswirkungen auf physiologische Prozesse, wenn die Pestizide in den Organismus gelangen. Expositionen gegenüber Pestiziden können wegen ihrer hohen biologischen Aktivität, und unter Umständen wegen ihrer langen Verweildauer in Umwelt und menschlichen Körper zu kurz- und langfristigen Gesundheitsbeeinträchtigungen führen (Maroni & Fait 1993).

Pestizide können das Krebsrisiko durch verschiedene Mechanismen erhöhen (Acquavella et al. 2003, Dich et al. 1997). Pestizidexpositionen werden in erster Linie mit Erkrankungen des zentralen Nervensystems, der Leber und der Blutbildenden Organe assoziiert (McDuffie et al. 2001, Anttila et al. 1995).

Eine Anzahl von chemischen Verbindungen, darunter Pestizide wie Benzolhexachlorid (BHC), Chloraz und Dichlordiphenyldichlorethen (DDE) sind potentiell geeignet, hormonelle Signalwirkungen zu beeinflussen, und werden daher als endokrine Disruptoren bezeichnet. Deformationen des Urogenitaltrakts sowie einige Krebserkrankungen, u.a. Hodentumore, Brustkrebs und Gebärmutterkrebs werden mit Expositionen gegenüber endokrinen Disruptoren in Verbindung gebracht (Lottrup et al 2006, Swan et al. 2006, Damstra et al. 2002).

Studien, die einen Zusammenhang von beruflichen Pestizidexpositionen und Hodentumoren untersuchen, kommen zu kontroversen Ergebnissen, und nur wenige zeigen ein erhöhtes Hodentumorrisiko unter Pestizidexponierten (Guo et al. 2005, Fleming et al. 1999, Wiklund et al. 1989). Eine schwedische Fall-Kontrollstudie ergab ein erhöhtes Risiko für Hodentumoren für die Exposition gegenüber Insektiziden, von denen ein großer Teil den Wirkstoff N,N-diethyl-m-toluamid (DEET) enthielt (Hardell et al. 1998). In einer weiteren Studie, in der prädiagnostische Seren von 754 Fällen und 928 Kontrollen ausgewertet wurden, wurde bei erhöhten Serumkonzentrationen der organochlorinen Pestizidwirkstoffe cis-nonachlor und trans-nonachlor sowie DDE ein signifikant erhöhtes Risiko für Hodentumoren festgestellt (McGlynn et al. 2008). Eine andere Studie konnte diese Ergebnisse an 49 Fällen und 51 Kontrollen wiederholen (Purdue et al. 2009), verweist jedoch auch auf eine Studie, die keine derartige Assoziation feststellen konnte (Biggs et al. 2008).

Berufliche Expositionen als potentielle Risikofaktoren für extrahepatische Gallenblasen- und Gallenwegstumore (GBT/GWT) bei Männern werden aufgrund der Seltenheit der Erkrankung wenig untersucht. Nur wenige dieser Studien untersuchen die mögliche Assoziation von Pestizidexpositionen und GBT/GWT. Erhöhte Konzentrationen der Pestizide BHC, Dichlordiphenyltrichlorethan (DDT) sowie Aldrin und Endosulfan wurden in der Gallenflüssigkeit von GBT/GWT-Patienten gemessen (Shukla et al. 2001). Ein erhöhtes Risiko für Leber- und Gallenblasentumoren wurde ebenfalls unter Arbeitern einer pestizidproduzierenden Fabrik aufgedeckt (Amoateng-Adjepong et al. 1995).

Als Risikofaktoren für GBT/GWT werden jedoch fast ausschließlich medizinische Ursachen wie Gallensteine genannt. Frauen haben ein zwei- bis sechsmal höheres Risiko an Tumoren der Gallenblase zu erkranken als Männer. Das Risiko für Frauen an diesem Tumor zu erkranken steigt mit Übergewicht und der Anzahl der Kinder an (Donohue et al. 1998, Cubertafond et al. 1994) und lässt darauf schließen, dass möglicherweise durch Genvarianten modulierte hormonabhängige Ursachen vorliegen (Park et al. 2009). Dadurch wird die Hypothese, dass Pestizide ein möglicher Risikofaktor für GBT/GWT sind, unterstrichen.

1.3 Methoden

Jeder Einzelarbeit liegt eine Fall-Kontrollstudie zugrunde. Fall-Kontrollstudien sind für die Erforschung von Krankheitsursachen ein effektives Werkzeug, wenn der Erkrankung eine lange Induktionsphase vorausgeht und die Erkrankung selten auftritt (Breslow 2005, Breslow & Day 1980). Eine weitere Stärke dieser Studienform ist, dass Hypothesen in Bezug auf Assoziationen zwischen mehreren Risikofaktoren und einer Erkrankung gezielt untersucht werden können ohne das Studienprotokoll zu überfrachten.

Die retrospektive Erfassung macht gleichzeitig eine der wesentlichen Schwächen der Fall-Kontrollstudie aus. Eine hauptsächliche Begrenzung besteht darin, dass Expositionen nicht vollständig oder eventuell verzerrt erinnert werden können, und es damit zu verschiedenen Formen von Fehleinschätzungen und Fehlklassifikationen kommen kann. In dieser Studienform besteht im Allgemeinen eine hohe Anfälligkeit gegenüber sämtlichen Formen von Verzerrungen (Breslow & Day 1980), wobei nicht-differentielle Fehlklassifikationen der Exposition die Risikoschätzer in Richtung Nullrisiko verzerren, während differentielle Fehlklassifikationen eine Verzerrung in jegliche Richtung zur Folge haben kann (Pearce et al. 2007).

1.4 Hintergrund der Studien

Die Datenbasis für dieses Promotionsvorhaben setzt sich aus drei verschiedenen Fall-Kontrollstudien zusammen. Es handelt sich um die Studien ARCAGE: **A**lcohol-**R**elated **C**ancers **A**nd **G**enetic susceptibility in **E**urope, HTS: **H**oden-**T**umor-**S**tudie, RARECAN: Risk factors for **RAR**e **CAN**cers of unknown aetiology, deren deutscher Teil mit dem Akronym EVA für **E**uropäische **V**erbundstudie zu Expositionen am **A**rbeitsplatz bezeichnet wird. EVA war konzipiert als spezieller deutscher Teil der europäischen RARECAN-Studie der gegenüber dem internationalen Studienprotokoll auf die Untersuchung von Hodentumoren ausgedehnt wurde. Damit konnte auf die schon entwickelten und eingesetzten Instrumente zurückgegriffen werden, was eine effiziente Ausnutzung der Ressourcen darstellte.

1.4.1 Europäische Verbundstudie zu Expositionen am Arbeitsplatz/ Risk factors for RARe CANcers of unknown aetiology (EVA/ RARECAN)[1]

Zwischen 1995 und 1997 wurde die Datenerhebung für die Studie RARECAN durchgeführt, um mögliche durch Lebensstil oder Arbeit bedingte Ursachen für verschiedene seltene maligne Neubildungen zu erforschen. Es wurden maligne Neubildungen des Auges, des Thymus, der Knochen, des Dünndarms, der Brust und der Gallenblase und –wege bei Männern in die populationsbasierte Studie aufgenommen. Für alle Krebsfälle wurde eine populationsbasierte Kontrollgruppe so angelegt, dass für jede Fallgruppe mindestens ein 1:4 Matching erreicht wurde. Die Studie wurde in den Ländern Schweden, Lettland, Großbritannien, Frankreich, Italien, Spanien, Portugal, Deutschland und Dänemark durchgeführt, wobei in die Analyse zu Tumoren der Gallenblase und -wege sechs Länder die erforderliche Anzahl von mindestens 10 männlichen Fällen einbringen konnten (Frankreich, Deutschland, Italien, Schweden, Dänemark und Spanien). Es stand

[1] Quelle soweit nicht anders angegeben: Abschlussbericht der Rarecan/EVA Studie

die Untersuchung möglicher unbekannter krebsauslösender Expositionen im Fokus dieser Studie. Die ausgewählten Krebslokalisationen sollten als „Signaltumoren“ für mögliche Karzinogene Substanzen fungieren.

Um in dem Zeitrahmen von 1995 bis 1997 eine ausreichende Anzahl von neu erkrankten Krebspatienten für die Studie gewinnen zu können, wurde in Deutschland ein multizentrisches Studiendesign mit Erhebungszentren im Saarland (Saarbrücken), in Essen, in Bremen und in Hamburg gewählt. Damit wurde eine Gesamtbevölkerung von 3,8 Millionen Einwohnern abgedeckt (Lynge et al. 2005). Die Einbeziehung der bevölkerungsbezogenen Krebsregister des Saarlandes und Hamburgs leistete einen Beitrag zur Qualitätssicherung, da hierdurch sowohl die Abschätzung der erwarteten Erkrankungsfälle als auch die Überprüfung der Vollständigkeit der Studieninzidenz zur Minimierung eventueller Selektionseffekte sichergestellt werden konnten.

Als spezieller deutscher Teil wurden Patienten die an einem Hoden-/Keimzelltumor neu erkrankt waren, in die Studie aufgenommen. Zu diesen Fällen wurden die gleichen Kontrollen nach Altersgruppe und Studienzentrum zugematcht, die daraus resultierende Fall-Kontrollstudie (EVA) setzt sich aus 269 Fällen und 797 Kontrollen zusammen.

1.4.2 Alcohol-Related Cancers And Genetic susceptibility in Europe (ARCAGE)

Der Hintergrund der von der International Agency for Research on Cancer (IARC) koordinierten Studie war die Untersuchung der Empfänglichkeit für eine genetische Schädigung am Metabolismus von Alkohol und Tabak beteiligten Gene, sowie bekannter lebensstilbedingter Risikofaktoren wie Rauchen, Alkoholkonsum und Ernährung auf die Entstehung von Tumoren der oberen Luft und Speisewege. Die Studie war auch darauf ausgerichtet, die Risiken bei unterschiedlichen Konsummustern der mit der Entstehung dieser Tumoren assoziierten Risikofaktoren zu ermitteln.

Die Studie wurde als internationale multizentrische Fall-Kontrollstudie konzipiert, um eine ausreichende Anzahl von Fällen bereitzustellen, die eine Analyse von Untergruppen ermöglicht. Daten wurden von 15 Studienzentren in 10 europäischen Ländern (Prag (Tschechische Republik), Bremen (Deutschland), Athen (Griechenland), Aviano, Padova, Turin (Italien), Dublin (Irland), Oslo (Norwegen), Edinburgh, Manchester, Newcastle (Großbritanien), Paris (Frankreich), Tartu (Estland), Zagreb (Kroatien) und Barcelona (Spanien)) erhoben und umfassten 2338 Fälle und 2227 Kontrollen, die die Einschlusskriterien erfüllten. Der Erhebungszeitraum war zwischen 2002 und 2005. Bis auf die britischen Studienzentren wurden in allen Studienzentren krankenhausbasierte Kontrollen rekrutiert. In die Studie wurden Frauen und Männer eingeschlossen. Proxy-Interviews waren nicht zugelassen.

Die Daten des französischen Teils der Studie wurden nach Abschluss der ARCAGE-Datenerhebung implementiert. Die Datenerhebung in Frankreich/Paris war zwischen 1987 und 1992. Der Einschluss der Daten aus Paris war möglich, da ein ähnliches Studienprotokoll angewendet wurde.

1.4.3 Hoden Tumor Studie (HTS)

Die Studie wurde im Anschluss an eine Inzidenz-Studie im Jahr 2000 und eine Inzidenz-Validierungsstudie im Jahr 2005 durchgeführt. Beide Studien wiesen eine erhöhte Anzahl von Hodentumorneuerkrankungen im Zeitraum 1989 bis 2000 in Werken eines deutschen Fahrzeugherstellers nach.

Um mögliche Ursachen für dieses Cluster zu identifizieren wurde eine Fall-Kontrollstudie initiiert, die aktuelle und ehemalige Mitarbeiter des Fahrzeugherstellers einschließt. Nur die sechs westdeutschen Standorte des Fahrzeugherstellers wurden in die Fall-Kontrollstudie eingeschlossen. Die Erhebungsinstrumente dieser Studie waren in Teilen aus früheren Fall-Kontrollstudien zu Expositionen am Arbeitsplatz (EVA) vorhanden, wurden jedoch für die aktuelle Fragestellung modifiziert und erweitert. Speziell für den Bereich Fahrzeugbau wurde der Fragebogen in Zusammenarbeit mit Mitarbeitern des Fahrzeugherstellers und Spezialisten aus dem Bereich Arbeitsschutz/Werksschutz erweitert und an die Fragestellung angepasst.

Der Erhebungszeitraum war von Dezember 2006 bis Juni 2008. Es wurden Computer gestützte persönliche Interviews (CAPI) durchgeführt. Es wurden 205 Fälle und 1091 Kontrollpersonen interviewt. Die Kontrollen wurden den Fällen im Verfahren eines Incidence-Density-Samplings zugeordnet. Bei diesem Design kann jeder Studienteilnehmer als Kontrolle einen Fall zugeordnet werden, wenn dieser Studienteilnehmer zum Zeitpunkt der Diagnose des Falles nicht selbst an einem Keimzelltumor erkrankt war und die weiteren Einschlusskriterien erfüllt sind. Um einem Fall zugeordnet zu werden musste das Geburtsjahr der Kontrolle dem des Tumorpatienten ±2 Jahre entsprechen. Berufspezifische Expositionen wurden in dieser Studie nur bei Indexpersonen erfragt, da von Proxy-Interviews keine detaillierten Angaben erwartet wurden.

1.5 Grundlage der Expositions- bzw. Sozialschichteinstufungen

Mit Ausnahme der ARCAGE-Fragebögen enthalten alle Fragebögen eine Liste der möglichen ausgeübten Berufe mit berufsspezifischen Fragebögen, die über diese Liste ausgewählt werden und gezielt Expositionen und Umstände der Exposition in einem Berufsfeld erfragen. Die durch Interviews gewonnenen Angaben umfassen in den ausgewerteten Studien die gesamte Berufsbiografie, d.h. Angaben zu allen haupt- und nebenberuflichen Tätigkeiten, genauen Beschreibungen der Tätigkeit, der hergestellten Produkte sowie der Branche in der der beschäftigende Betrieb angesiedelt ist (Abb. 1.1), von - nach Studienprotokoll - mindestens einem halben Jahr Dauer bis zum Zeitpunkt der Erkrankung bei Fällen und zugematchten Kontrollen (nur Manuskript Kapitel 2.2), bzw. Zeitpunkt des Interviews für Kontrollen.

Die Interviewer, die für die Befragung der Studienteilnehmer eingesetzt wurden, wurden regelmäßig geschult, um die Qualität der Interviews auf einem hohen Niveau zu halten und den Einsatz der berufsspezifischen Fragebögen zu optimieren. Der für die Auswertung der sozialen Faktoren notwendige Schritt der Umsetzung der Berufsangaben in einen einheitlichen Kode (Beruf nach *International Standard Classification of Occupations*, Version von 1968 [ISCO-68] wurde von erfahrenen Kodierern ausgeführt. Für jeden Studienteilnehmer resultieren im Hinblick auf den Beruf die kalendarischen Informationen Jahr und Alter bei Beginn und Ende einer Berufstätigkeit sowie der ISCO-68 Kode für die ausgeführte Berufstätigkeit.

Ziel der Erstellung der Berufsbiographie ist die lückenlose Aufnahme aller Aktivitäten, die mit der Aufnahme der ersten beruflichen oder für einen Beruf qualifizierenden Tätigkeit ausgeführt wurden (Abb. 1.1). Dies umfasst auch ökonomisch inaktive Phasen wie z.B. Krankheit, Rente und Arbeitslosigkeit ab einem halben Jahr Dauer.

Die durch die Berufsliste ausgewählten Zusatzfragebögen zu Tätigkeiten in spezifischen Berufsfeldern gaben die Möglichkeit Expositionen, die während der Tätigkeiten auftraten, genauer zu erfragen. Die Einstufung der Exposition gegenüber Pestiziden erfolgt in den Manuskripten dieses Themenbereichs (Kapitel 2.1 und 2.2) aus in Interviews gezielt diese Exposition betreffende Fragen. Die Fragen umfassen den Zeitpunkt und die Dauer der Exposition, die verwendeten Hauptklassen der Pestizide sowie die Verwendung von Schutzmaßnahmen (Abb. 1.2) innerhalb einer Berufsphase und für verschiedene angebaute Pflanzen bzw. gehaltene Tiere. Die Fragenkataloge, die in beiden Studien den Einsatz und die Umstände der Pestizidexposition erfassen, sind ähnlich. Aufgrund der niedrigen Anzahl Exponierter in der Hodentumorstudie „HTS“ (Kapitel 2.2) wurde das Thema „Pestizidexposition“ auf Tätigkeiten in der Land- und Forstwirtschaft sowie Tätigkeiten in der Holzverarbeitung ausgeweitet.

Abbildung 1.1: Auszug aus dem Hauptfragebogen (RARECAN-Studie) in dem die Berufsbiografie für Beruf Nr. 1 aus der Berufsbiografie und Tätigkeiten erfragt wurden mit Feldern für die einzutragenden Kodierungen für Beruf (ISCO) und Branche (NACE) aus den gegebenen Antworten.

Job number 1 ☐☐ | Starting year: 19 ☐☐ | Ending year: 19 ☐☐

1. From 19… to 19… you worked at … (company name) or as … (occupation).
What exactly was made or done at this workplace? ______________________

1.a Main products/activities and production processes involving the subject ______________________

1.b Other products/activities and production processes involving the subject ______________________

2. Please describe what you mainly did and how you did it:
If you performed several tasks or jobs during this job period, please start with the task you on average spent most time at. Describe afterwards other tasks or jobs.

2.a Main task ______________________

2.b Other tasks ______________________

3. What materials or chemicals did you work with or were you exposed to? ______________________

4. Did you use any machines?
☐ Yes ☐ No ☐ Don´t know
If you used machines, please describe them: ______________________

5. Were you regulary involved with the maintenance of these machines? ☐ Yes ☐ No
If yes, please describe how you did it: ______________________

6. Were there persons performing jobs different to yours, who were working in the same room or near to you?
☐ Yes ☐ No ☐ Don´t know
If yes, please describe the production and occupation of the persons working in the same room as you or near to you
____

7. How many hours per week did you on average on your job?
Average hours per week: ☐☐

8. Was this a seasonal job?
☐ Yes ☐ No ☐ Don´t know

9. Were there any significant changes in your work during this job? Did you change job title, work tasks, products or processes?
☐ Yes ☐ No ☐ Don´t know
If yes, specify: ______________________

Coding of industry and occupation[†]:

10. Main industry of study subject:	☐☐☐☐☐	(NACE)		
11. Main occupation of study subject:	☐☐☐☐☐	(ISCO)		
12. Other industries of study subject:	☐☐☐☐☐	and	☐☐☐☐☐	(NACE)
13. Other occupations of study subject:	☐☐☐☐☐	and	☐☐☐☐☐	(ISCO)
14. Industry of nearby workers:	☐☐☐☐☐	(NACE)		
15. Occupation of nearby workers:	☐☐☐☐☐	(ISCO)		

[†]Der Kodierer/die Kodiererin hatte im Anschluss an das Interview die Aufgabe, anhand der Angaben zu den Fragen 1 bis 9 die ISCO und NACE Kodes (10 bis 15 im Fragebogen) zu ermitteln.

Abbildung 1.2: Auszug aus dem berufsspezifischen Fragebogen „Farming, Market Gardeners Parks, Florists and Greenhouse workers“ (FB5) der die Abfrage der Exposition gegenüber Pestiziden, sowie die Ausbringungsmethode und die Verwendung von Schutzmaßnahmen beinhaltet.

(for each crop fill in one extra page)‡

Crop: Hectares From 19 To 19

4. Were herbicides, insecticides or fungicides (pesticides) used on the farm/garden?

	Herbicides	Insecticides	Fungicides
4.a In which year were the treatments first applied?	19	19	19
4.b In which year were the treatments last applied?	19	19	19
4.c How many years in total?	years	years	years
4.d How many days per year on average?	days	days	days
4.e Did you personally usually apply or assist in the treatments?	Yes No	Yes No	Yes No
4.f How many hours daily did you spend on average on the pesticide treatments?	h/d	h/d	h/d
4.g Did you prepare the mixture?	Yes No	Yes No	Yes No
5 How were the treatments applied?			
5.a With backpack or hand sprayer?	Yes No	Yes No	Yes No
5.b Tractor mounted sprayer?	Yes No	Yes No	Yes No
5.c Aerial application?	Yes No	Yes No	Yes No
5.d Other	Yes No	Yes No	Yes No

If yes, please specifiy:

Insecticides: ____________________

Herbicides: ____________________

Fungicides: ____________________

6. Did you apply fumigants?

Yes No Don´t know

7. Did you use the following protective equipment when applying pesticides:

Overall	Yes	No	Don´t know
Working clothes	Yes	No	Don´t know
Leather/Rubber gloves	Yes	No	Don´t know
Handkerchief over mouth	Yes	No	Don´t know
Filter mask	Yes	No	Don´t know
Cabin on tractor	Yes	No	Don´t know
Other	Yes	No	Don´t know

If yes, please specify: ____________________

8. Did you clean the equipment, or the tools used for the pesticide treatments?

Yes No Don´t know

‡Interviewanweisung.

Abbildung 1.3: Auszug aus dem Hauptfragebogen der Studie RARECAN in dem die Exposition gegenüber Pestiziden behandelt wird.

1.a Have you ever worked with pesticides?	☐ Yes	☐ No	☐ Don´t know
1.b Have you ever worked on a farm, marked garden, or greenhouse? (If yes, secure that the supplementary questionnaire on farming (No. 5) has been filled out)	☐ Yes	☐ No	☐ Don´t know
1.c Have you worked as a gardener?	☐ Yes	☐ No	☐ Don´t know
1.d Have you worked in parks?	☐ Yes	☐ No	☐ Don´t know
1.e Have you worked as a florist?	☐ Yes	☐ No	☐ Don´t know
1.f Have you worked on a highway, railway, utility or as a right-of-way mainteinance crew?	☐ Yes	☐ No	☐ Don´t know
1.g Have you worked with pesticides in any other non-farm job?	☐ Yes	☐ No	☐ Don´t know

If yes, please specify: ______________________

2.a Did you use	Yes	No	Don´t know	2.b Year starting	2.c Year ending	2.d How many days per year?
Herbicides	☐	☐	☐	19	19	
Insecticides	☐	☐	☐	19	19	
Fungicides	☐	☐	☐	19	19	

3.a Did you usually use protective equipment? ☐ Yes ☐ No ☐ Don´t know

If yes, Please specify the type of protective equipment: ______________________

4. How did you apply the pesticides? ______________________

Durch die Angaben zur Berufsbiographie und die vorhandenen berufsspezifischen Fragebögen besteht in den hier ausgewerteten Studien zu Pestizidexpositionen (Kapitel 2.1 und 2.2) die Möglichkeit, die Plausibilität der Expositionsangaben zu überprüfen und nötigenfalls zu korrigieren. Diese Möglichkeit besteht in der Studie RARECAN für Pestizide schon innerhalb des einleitenden Hauptfragebogens, da ausgewählte Expositionen, zu denen Pestizide zählen, dort gesondert abgefragt wurden (Abb. 1.3).

Tätigkeiten, die eine mögliche Expositionsquelle für Pestizide darstellen, ohne die Angabe einer Pestizidexposition zu berücksichtigen, wie Tierhaltung oder Anbau von Früchten oder Beschäftigung in der holzbe- und verarbeitenden Industrie wurden ebenfalls als Indikator-Variable ausgewertet. Als Expositionsmerkmale wurden in den Manuskripten bestimmt:

- Exposition gegenüber Pestiziden (gesamt) und Hauptklassen von Pestiziden
- Berufsfeld in dem Pestizideinsatz erfolgte
- Tätigkeit bei der Pestizidexposition stattfand
- Benutzung von persönlichen Schutzmaßnahmen
- Prozess, technisches Gerät bei Pestizideinsatz
- Anbaufrucht
- gehaltene Tiere
- Dauer der Exposition (Jahre)
- Erste Exposition (Jahr, Alter)
- Letzte Exposition (Jahr, Alter)

In der Hodentumorstudie (Kapitel 2.2) konnte die Auswertung der Pestizidexpositionen aufgrund der niedrigen Anzahl Exponierter nur anhand einer Einstufung in jemals und niemals Exponierte erfolgen.

1.6 Ziel und Struktur der Arbeit

Diese Arbeit vereinigt zwei Themenbereiche anhand vier verschiedener Fall-Kontrollpopulationen: die Untersuchung von stofflichen Expositionen und der beruflich-sozialen Position. Das Oberthema dieser Arbeit ist die Expositionseinstufung in retrospektiven Studien. Alle Expositionseinstufungen wurden anhand von Eigenangaben der Studienteilnehmer durchgeführt. In jeden der vier Publikationsmanuskripte wird eine andere Methode der Expositionseinstufung angewandt. In den Manuskripten werden Krebsrisiken aufgrund der beruflichen Expositionen gegenüber Pestiziden (Kapitel 2.1 und 2.2) und der sozialen Schicht anhand der Berufbiografie (Kapitel 2.3 und 2.4) untersucht. Die Selbstangaben werden in der Arbeit Kapitel 2.1 zudem genutzt, um einen in der Literatur beschriebenen Algorithmus einzusetzen, der die mögliche Intensität der Exposition anhand von verschiedenen Merkmalen der Anwendung einstuft (Dosemeci et al. 2002).

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2 Vorstellung der Manuskripte

In den in diesem Kapitel vorgestellten Manuskripten „Risk factors for extra hepatic bile tract carcinoma in men: Occupational exposure to pesticides. Results from an European multi-centre case-control study“ (Kapitel 2.1) und „Local cluster of germ cell cancer not explained by previous or concurrent activities and exposures in farming and forestry in a cohort of male automotive workers in Germany“ (Kapitel 2.2) werden Angaben hauptsächlich aus berufsspezifischen Fragebögen verwendet um Expositionen gegenüber Pestiziden zu quantifizieren und statistisch zu analysieren.

Das Thema soziale Faktoren/soziale Schicht wird in „Social factors and risk of testicular cancer“ (Kapitel 2.3) und „Life course social mobility and risk of upper aerodigestive tract cancer in men“ (Kapitel 2.4) untersucht. Als Grundlage für die Einstufung des sozioökonomischen Status bzw. des sozialen Prestiges dienen in beiden Manuskripten die Angaben zur Berufsbiografie.

2.1 Occupational exposure to pesticides and bile tract carcinoma in men: results from a European multicenter case-control study.

Schmeisser N, Kaerlev L, Bourdon-Raverdy N et al.: Cancer Causes Control. 2010; 21:1493-502.

Abstract

Objectives: To estimate the associations between occupational exposure to pesticides and extrahepatic biliary tract carcinoma in men a population based case control study was carried out.

Methods: Cases (N=104), aged 35-70 years, diagnosed in 1995-1997, were sampled by active reporting systems from hospitals. Controls (N=1401) were a random sample of the general male population. Information on occupation and confounding factors were obtained by questionnaires. Exposures were quantified with respect to time, application methods and use of personal protective equipment. Intensity was evaluated by using a published algorithm which weighted the exposure assigned according to the use of personal protective equipment and mode of application. Logistic regression analyses were conducted adjusted for gallstones, age and country.

Results: Being ever exposed to pesticides resulted in an odds ratio (OR) of 1.0 [95%-Confidence Interval (CI) 0.6-1.6]. A modestly elevated risk was found for backpack mounted sprayers OR=1.4 [95%-CI 0.7-2.6] and vine farmers OR=2.5 [95%-CI 0.9-7.2]. Using time periods and exposure frequency as intensity measure, no elevated risks were found. The only exception was year of maximum exposure which yielded an OR of 1.6 [95%-CI 0.7-3.5]. However, no clear trend was observed in this analysis.

Conclusions: This study does not rule out that pesticide exposure represents an occupational risk factor for extrahepatic biliary tract carcinoma, but no indication of a strong association was observed. Some modes of exposure were weakly, albeit not significantly associated with carcinoma risk. The observed estimates of effects may be influenced by a lack of precise exposure assessment. Different chemical compositions of pesticides were utilised during a long time span of pesticide exposure and it should be considered that the exposure is assessed with substantial uncertainty that could non-differential and bias results towards the null.

KEY WORDS: gallbladder cancer; bile tract cancer; environment; agriculture

Introduction

Gallbladder and extrahepatic bile tract cancers (GBC/BTC) are rare in most parts of the world but represent a public health problem in some regions, particularly Latin America and South Asia (1).

Gallstones are the most well-established risk indicator for all entities of GBC/BTC (2-4). Other established medical causes of GBC/BTC are endoparasital infestations and bacterial infections in some geographical regions (5-7). The incidence increases with age and women are affected 2 to 6 times more often by GBC than men, while BTC is more frequent in men in most areas of the world (8).

The aetiology of GBC/BTC is not studied much in men. The rareness of GBC/BTC with an annual incidence of 0.1-2.5/100,000 in men in Western Europe (9) renders collection of a sufficient number of cases difficult and impedes determination of risk factors for this fatal disease with a 5-year survival rate of roughly 10% (10, 11).

No link between occupational risk factors and the development of GBC/BTC has been well established. Possible interactions of exposures which may promote growth of GBC/BTC have not been extensively studied to date (2, 12).

Workers in different industries such as chemistry or aircraft construction as well as in woodworking plants have had an increased mortality rate for BTC. Workers in the metal-processing and textile industries were affected more frequently by GBC. Persons employed in the automobile or rubber industry showed increased risks for both cancer localizations (13, 14).

With respect to pesticide exposure, inconsistent results for associations with GBC/BTC have been reported. Pesticide-exposed male farmers and farming employees were found to have no increased risk for GBC/BTC in several register-based studies (15-18). In contrast, Shukla and co-workers (19) measured significantly increased concentrations of the pesticides benzenhexachloride (BHC) and dichlor-diphenyl-trichlorethane (DDT) and non-significantly increased concentrations of Aldrin and Endosulfan in the bile of GBC-patients with intensive pesticide exposure. An aggravation of risk for GBC/BTC in DDT-exposed subjects was also observed in another study. But due to the high DDT exposure levels in the general population these results have to be interpreted with caution (20). In a further study, exposure to Aldrin, dibromochloropropane, Dieldrin and Endrin were associated with an elevated standardised mortality rate for carcinoma of the liver and the gallbladder (21). A significant increase of liver and gallbladder cancer was also observed in a cohort of workers of a chemical plant that produced a number of pesticides (e.g. Aldrin, Dieldrin, Azodrin, Vapona). But this increase was only observed among men of European descent and was dependent on time and conditions of employment (22).

In the present multicentre case-control study the association of GBC/BTC and occupational pesticide exposure was examined.

Population and Methods

The analyses are based on the European multi-centre case control study "Occupational Risk Factors for Rare Cancers of Unknown Aetiology". Methods and objectives of the study have been described before (23).

Data collection took place between January 1995 and June 1997 in ten European countries. Eligible cases were men, registered in Denmark, France, Germany, Italy and Sweden, aged 70 years or younger with a newly diagnosed carcinoma of the gallbladder (ICD-9: 156.0), carcinoma of the extrahepatic bile tract (ICD-9: 156.1), Ampulla of Vater (ICD-9: 156.2) or a carcinoma with unspecified localisation of the extrahepatic bile tract (ICD-9: 156.9). Morphology codes included M8000 - M8570, restricted to malignant neoplasms according to the ICD-O (24). Due to poor prognosis and short survival time of the GBC/BTC cases an active reporting system was established to recruit incident cases in time. Only patients with a pathological diagnosis confirmed by reference pathology as either definite or possible were included in the present analyses.

Population controls were identified and drawn randomly from resident registries in Denmark, France, Germany, Italy and Sweden. Since the Rare Cancer Study included several cancer entities (cancers of the small intestine, male gallbladder and bile ducts, thymus, bone, male breast, eye melanoma, and mycosis fungoides), four controls per case based on the most frequent cancer site expected in each participating centre were selected.

For the present analyses GBC/BTC case and control populations from five countries with ten or more male cases were included. Only interviews with the index person were considered eligible for this analysis which is based on reports of specific agent exposures.

Questionnaire

All potential participants were informed with the letter of invitation that the study was related to ‘‘occupation and health’’, but were not informed of any specific hypothesis associated to a particular occupation, chemical or product. The cases and controls identified to the study had to fill-in and return a self-administered questionnaire together with their consent. This list was used as a starting point for the interview undertaken either face-to-face or by telephone. All participants were administered the same questionnaire. Each subject was interviewed by trained interviewers which were not informed about case-controls status. The main questionnaire (MQ) included personal characteristics, physical constitution and medical conditions, as well as alcohol and tobacco consumption. Occupational history was a central part of the MQ. For each job held by the subject for 6 months or longer during lifetime starting and ending year, together with working hours/week, activities, work tasks, job title, materials handled, and selected exposures such as organic solvents and pesticides and circumstances of these exposures as well as use of protection equipment was solicited. In addition, 27 job specific questionnaires (JSQ) of which seven addressed exposure to pesticides were applied.

Occupational Pesticide Exposure Assessment

To quantify pesticide exposures, different possibilities of temporal and intensity patterns of use, based on information from the MQ and JSQs, were applied. Information was obtained for major type of pesticide (fungicide, herbicide, insecticide) applied, personal protective equipment (PPE) use (leather/rubber gloves, filter mask, boots, overall), technical equipment for applying pesticides (backpack, tractor with/without cabin, other form of application), year of beginning and end of pesticide application, as well as average days per year one of the three majors type of pesticides was applied.

Duration of exposure was used to estimate dose. Risk estimates based on duration were calculated for cumulative years and cumulative days. As a surrogate for peak pesticide exposure the year with the highest number of reported exposure days was analysed. In addition, year and age of first and last exposure were examined.

Based on the JSQs and MQ, an overall individual intensity score of pesticide exposure was derived using an algorithm proposed by Dosemeci and colleagues (25). The different application methods were analysed as a further surrogate of exposure intensity:

Exposure intensity= (mixing status+ application method + equipment repair status) * use of personal protective equipment

For pesticide handling the following exposure categories were used: assuming that mixing took less than 50% of exposure time, mixing status was weighted with 0 for never and with 3 for ever mixing. Application on crops was weighted 1 for distributing tablets, 2 for in-furrow applications and 3 for boom spray applications, 8 for backpack spraying and 9 for hand spraying. Pesticide application on animals was weighted 1 for application on ear tags, 5 for dipping the animal, 6 for spraying the animal, 7 for pouring pesticides on the animal and 9 for using a powder duster. Cleaning the equipment after application was weighted with 2.

Four groups of PPE categories were constructed: never using any protection (0%), wearing face shields, leather/rubber gloves or boots (20%), using a cartridge respirator or gas mask (30%), wearing a chemically resistant overall (40%). These percentages were multiplied with the summed pesticide handling factor (applying, repairing, mixing). Maximum protection therefore leads to a reduction of exposure by 90%. In the case of no protection the summed exposure weights are not reduced.

Subjects exposed to pesticide-applying or pesticide-handling tasks of other workers were defined as bystanders. Since there was no model available for estimating bystander exposure, exposure intensity of bystanders was calculated in the same way as for applicators, reduced by 90%.

Statistical Analysis

Risk estimates were calculated by unconditional logistic regression models applying exact methods. Results are presented as odds ratios (OR) with 95% confidence intervals [95%-CI]. Logistic regression model 1 (OR_1) included country and age (as a continuous variable). Logistic regression model 2 (OR_2) includes additionally medical history of gallstones (confirmed or treated by a physician). Body mass index was computed as weight (kg) divided by height squared (m^2) and categorized according to the World Health Organisation's standard ranges: mild thinness and normal body weight (≥17.0-≤25.0), overweight (≥25-<30.0) and obesity (≥30) (26). To calculate BMI, the last available weight at least 1 year prior to the interview was used (range 1 to 5 years). All analyses were performed with SAS (Version 8.2).

Results

A total of 104 cases and 1401 controls were included in the study. Among cases, 27 (26.0%) were diagnosed as gallbladder carcinoma, 36 (34.6%) as carcinoma of the bile tract, 37 (35.6%) as carcinoma of the Ampulla of Vater and 4 (3.9%) as overlapping carcinomas. On average cases were six years older than controls and reached less likely a professional degree. No consistent association was observed with GBC/BTC for the BMI based on the weight one to five years before diagnosis (cases) or interview (controls). Cases were more likely to have had gallstones (Table 1).

Table 1: Demographic distribution, age and BMI characteristics of study sample.

	Cases		Controls		$p^{•}$
	N	%	N	%	
Total	104		1401		
Country					
Denmark	29	27.9	192	13.7	
Sweden	17	16.4	139	9.9	
France	32	30.8	313	22.3	
Germany	16	15.4	554	39.5	
Italy	10	9.6	203	14.5	
BMI# [kg/m^2]					
17.0 -25.0)	39	37.5	607	43.3	
[27.0-30.0)	50	48.1	642	45.8	
[30.0+]	13	12.5	133	9.5	0.6
Missing	2	1.9	19	1.4	
Educational level					
Left school until age 15†	41	39.4	342	24.4	
Left school age 16/17†	6	5.8	68	4.9	
Left school after age 17†	5	4.8	101	7.2	
Manual profession	28	26.9	472	33.7	
Non-manual profession	22	21.2	414	29.6	0.01
Missing	2	1.9	4	0.3	
Gallstones	23	22.1	79	5.6	<0.0001
Age mean [min-max]	59 [35-70]		54 [35-70]		<0.0001
Cancer sub-site					
Gallbladder cancer (156.0‡)	27	26.0			
Bile tract cancer (156.1‡)	36	34.6			
Ampulla of Vater (156.2‡)	37	35.6			
Site unspecified (156.9‡)	4	3.9			

#Body mass index (BMI=weight [kg]/height [m^2]) was calculated on the basis of using information on self reported body height and weight (one to five years before diagnosis (cases) or interview (controls)). †No further education/training, ‡According to ICD-8, •*p*-values were derived from Pearson´s χ^2 tests for categorical variables and from Student's t-test for age.

Risk estimates for occupational pesticide exposure stratified by country are shown in Table 2. A non-significantly increased risk for exposure to pesticides was observed only for the Italian subpopulation (OR_2=3.1 [95%-CI 0.8-11.4]). No risk increase was observed for occupational exposure to pesticides in the pooled study population (OR_2=1.0 [95%-CI 0.6-1.6]).

Table 2: Distribution of cases and controls and odds ratios (OR) within 95%-CI to occupational exposure to pesticides by country.

Country	Case		Pesticide [yes]		Control		Pesticide [yes]		OR_{1x}[95%-CI]	OR_{2x}[95%-CI]
	N	%	N	%	N	%	N	%		
Denmark	29	27.9	5	17.2	192	13.7	45	23.4	0.7 [0.3-1.8]	0.7 [0.3-1.8]
France	32	30.8	6	18.8	313	22.3	66	21.1	0.8 [0.3-2.0]	0.9 [0.3-2.1]
Germany	16	15.4	2	12.5	554	39.5	34	6.1	1.7 [0.4-7.3]	1.7 [0.4-7.7]
Italy	10	9.6	4	40.0	203	14.5	24	11.8	2.9 [0.8-10.7]	3.1 [0.8-11.4]
Sweden	17	16.4	2	11.8	139	9.9	20	14.4	0.7 [0.2-3.1]	0.8 [0.2-3.6]
Total‡	104	100	19	18.3	1401	100	189	13.5	0.9 [0.6-1.6]	1.0 [0.6-1.6]

OR_{1x} adjusted for age, OR_{2x} adjusted for age and medical confirmed gallstones. ‡OR_{1x} and OR_{2x} additionally adjusted for country.

Among pesticide exposed subjects who were employed as crop, vegetable or fruit farmers (OR_2=1.1 [95%-CI 0.6-2.0]), as well as in other agricultural and related occupations that included work with farm animals (OR_2=0.6 [95%-CI 0.3-1.4]) no increased risks were seen (Table 3).

Table 3: Odds ratios (OR) of possible pesticide exposure according to reported activity in job specific questionnaire (JSQ).

	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
	N	%#	N	%#		
Farming	13	46.4	122	43.1	1.0 [0.6-1.8]	1.1 [0.6-2.0]
Working with animals	7	43.8	81	51.6	0.6 [0.3-1.4]	0.6 [0.3-1.4]
Forestry	-		12	27.9	-	-
Farming/Forestry total	15	65.2	152	63.3	0.9 [0.5-1.5]	0.9 [0.5-1.6]
Slaughtering animals or processing meat	1	20.0	2	9.1	3.5 [0.5-25.3]	4.3 [0.6-30.9]
Railway working	-	-	-	-	-	-
Paint manufacture	-	-	3	25.0	-	-
Chemical industry‡	-	-	1	2.9	-	-
Total	16	55.2	157	53.2	0.9 [0.5-1.6]	1.0 [0.6-1.7]

#Percent of all men reported activities within this job specific questionnaire. The reference for calculating odds ratios included all participants not exposed in the specific job task category. ‡After controlling for performed tasks, the participant with occupational contact to pesticides working in a control room of a chemical plant was classified as a bystander in all following analyses. OR_1: adjusted for age (continuous) and country. OR_2: adjusted for age (continuous), country and medically confirmed gallstones.

No increased risks were observed for applying pesticides in the barn and for applying pesticides on animals in livestock (OR_2=1.2 [95%-CI 0.4-4.0] and OR_2=0.7 [95%-CI 0.3-1.5], respectively). Pesticide exposure analysed by different types of crop did not lead to an elevated risk for GBC/BTC. The only elevated risk for pesticide exposure was observed for 4 cases and 24 controls which applied pesticides as winegrowers (OR_2=2.5 [95%-CI 0.9-7.2]) (results not shown).

Table 4: Odds ratios (OR) and 95% CI for GBC/BTC and pesticide exposure by major type of pesticide and total number of pesticides[†].

	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
Type of pesticide	N	%	N	%		
Fungicides	4	3.9	66	4.7	0.5 [0.2-1.5]	0.6 [0.2-1.6]
Herbicides	12	11.5	114	8.2	0.9 [0.5-1.7]	1.0 [0.5-1.8]
Insecticides	13	12.5	149	10.7	0.8 [0.4-1.4]	0.8 [0.4-1.5]
Number of pesticide types						
1	11	10.6	95	6.8	1.2 [0.6-2.2]	1.2 [0.6-2.2]
2	3	2.9	41	2.9	0.6 [0.2-2.1]	0.7 [0.2-2.1]
3	4	3.9	50	3.6	0.7 [0.2-1.8]	0.7 [0.3-2.0]

[†]One case and three controls are excluded because of missing values in pesticide use. OR_1: adjusted for age (continuous) and country. OR_2: adjusted for age (continuous), country and medically confirmed gallstones.

Information on major type of pesticide used was available for all but one case and three controls (Table 4). No increased risks after exposure to a certain major type of pesticide were found for GBC/BTC. Neither was there an increased risk for the number of pesticides applied. After mutual adjustment for number of applied pesticide types elevated risk estimates for herbicide exposure (OR_2=2.5 [95%-CI 0.8-8.2]), but not for insecticides (OR_2=0.6 [95%-CI 0.2-1.9]) were found (results not shown). For fungicides this adjustment was not possible since all cases exposed to fungicides were simultaneously exposed to insecticides and herbicides.

The analyses of start year and duration of occupational pesticide exposure did not reveal any significantly elevated risk. An increased, but statistically non-significant risk was observed for the analysis of year with maximum days of exposure as a proxy for intensity (OR_2=1.6 [95%-CI 0.7-3.5]), but no dose-response relationship for cumulative number of exposed days during a subject's lifetime was seen (Table 5).

ORs for the method of applying pesticides and the use of protective equipment are also shown in Table 5. A moderately elevated risk was observed for pesticide application using a backpack with a spray pistol or spray rod (OR_2=1.4 [95%-CI 0.8-2.5]). For applying pesticides using a tractor without cabin (OR_2=1.2 [95%-CI 0.4-3.9]) and for coating and brushing pesticides on animals only slightly elevated risk estimates (OR_2=1.2 [95%-CI 0.4-3.4]) were observed. Applying the algorithm by Dosemeci (25) did not reveal a positive dose-response relationship between exposure intensity and GBC/BTC. Intensity weighted by exposure days could not be quantified because there were too many missing values.

Table 5: Odds ratios (OR) for time periods, duration of exposure in years and exposure frequency in days as proxies for intensity of exposure and for pesticide exposure according to tasks performed and estimated exposure intensity (Reference=unexposed subjects i.e. 89 cases and 1212 controls).

	Cases		Controls			
Start Year	N	%	N	%	OR_1 [95%-CI]	OR_2 [95%-CI]
1932-1952	9	8.7	65	4.6	1.1 [0.6-2.3]	1.1 [0.5-2.3]
1953-1963	5	4.8	62	4.4	0.7 [0.3-1.8]	0.8 [0.3-2.1]
1964-1993	5	4.8	62	4.4	0.9 [0.4-2.3]	1.0 [0.4-2.4]
Year last exposure						
1942-1964	8	7.7	63	4.5	1.2 [0.6-2.4]	1.2 [0.6-2.5]
1965-1991	5	4.8	64	4.6	0.9 [0.3-2.1]	1.0 [0.4-2.4]
1992-1997	6	5.8	62	4.4	0.8 [0.4-1.9]	0.8 [0.4-1.9]
Age first exposure						
≤15	7	6.7	73	5.2	1.0 [0.5-2.2]	1.0 [0.5-2.2]
16-22	5	4.8	52	3.7	1.0 [0.4-2.5]	1.1 [0.5-2.8]
≥23	7	6.7	64	4.6	0.9 [0.4-1.9]	0.9 [0.4-2.0]
Age last exposure						
15-23	6	5.8	63	4.5	1.0 [0.4-2.4]	1.1 [0.5-2.5]
24-45	4	3.8	64	4.6	0.8 [0.3-2.1]	0.8 [0.3-2.2]
46-70	9	8.7	62	4.4	1.0 [0.5-2.0]	1.0 [0.5-2.1]
Duration of exposure [years]						
0.5-6	7	6.7	64	4.6	1.2 [0.5-2.6]	1.2 [0.5-2.5]
7-22	4	3.8	63	4.5	0.7 [0.2-1.8]	0.7 [0.3-2.0]
23-53	8	7.7	62	4.4	1.0 [0.5-2.1]	1.0 [0.5-2.1]
Maximum days per year[1]						
≥1 - ≤4	5	4.8	54	3.9	0.8 [0.3-2.0]	0.7 [0.3-1.8]
>4 - ≤12	2	1.9	53	3.8	0.4 [0.1-1.4]	0.4 [0.1-1.5]
≥13	7	6.7	53	3.8	1.4 [0.6-3.0]	1.6 [0.7-3.5]
Days total[1]						
≤53	3	2.9	54	3.9	0.6 [0.2-1.8]	0.5 [0.2-1.6]
>53-≤263	7	6.7	53	3.8	1.2 [0.6-2.7]	1.4 [0.6-3.0]
≥264	4	3.8	53	3.8	0.7 [0.3-1.9]	0.7 [0.3-2.0]
Exposure as:						
Bystander/Applicator	4	3.8	36	2.6	0.9 [0.3-2.6]	1.0 [0.4-2.7]
Bystander only	3	2.9	35	2.5	0.8 [0.2-2.4]	0.8 [0.2-2.4]
Applicator only	12	11.5	117	8.4	1.0 [0.6-1.9]	1.1 [0.6-2.0]
Mixing ever	8	7.7	110	7.9	0.7 [0.3-1.4]	0.7 [0.3-1.5]
Mixing never	11	10.6	78	5.6	1.3 [0.7-2.5]	1.4 [0.7-2.6]
Exposure by:						
Tractor applicator	7	6.7	63	4.5	1.0 [0.4-2.1]	1.1 [0.5-2.4]
Tractor with cabin†	4	4.3	38	3.0	0.9 [0.3-2.6]	1.0 [0.4-2.8]
Tractor without cabin†	3	3.3	25	2.0	1.0 [0.3-3.3]	1.2 [0.4-3.9]
Tractor bystander	1	1.0	10	0.7	0.8 [0.1-5.5]	0.9 [0.1-6.8]
Never used tractor	10	9.6	115	8.2	1.0 [0.5-1.8]	0.9 [0.5-1.8]

Table 5: continued

Exposure by:						
Backpack applicator	14	13.5	104	7.4	1.2 [0.7-2.2]	1.4 [0.8-2.5]
Backpack applicator ever[†]	12	11.9	92	7.1	1.3 [0.7-2.3]	1.4 [0.7-2.6]
Backpack Bystander only[†]	2	2.2	12	1.0	1.1 [0.3-4.4]	1.4 [0.3-5.6]
Never backpack applicator	5	4.8	84	6.0	0.6 [0.2-1.4]	0.6 [0.2-1.4]
Exposure by:						
Other forms of application	5	4.8	41	2.9	1.1 [0.4-2.6]	1.0 [0.4-2.5]
Coating, brushing applicator[†]	4	4.3	30	2.4	1.1 [0.4-3.1]	1.2 [0.4-3.4]
No other application forms	14	12.5	147	10.5	0.9 [0.5-1.6]	1.0 [0.5-1.7]
Use of PPE[#]						
No/low protection	5	4.8	47	3.4	1.1 [0.4-2.8]	1.2 [0.5-3.0]
Medium/high protection	2	1.9	44	3.1	0.4 [0.1-1.7]	0.5 [0.1-1.9]
Full protection	11	10.6	95	6.8	1.0 [0.5-1.9]	1.0 [0.5-1.9]
Intensity score[2]						
Low	5	4.8	55	3.9	1.0 [0.4-2.4]	0.9 [0.4-2.2]
Medium	7	6.7	56	4.0	1.0 [0.5-2.2]	1.0 [0.5-2.4]
High	5	4.8	54	3.9	0.9 [0.4-2.2]	1.0 [0.4-2.5]

[1]Five cases and 29 controls have been excluded from the analysis because of missing values in cumulative days of pesticide use. Percent include subjects with known exposure status. OR_1: adjusted for age (continuous) and country. OR_2: adjusted for age (continuous), country and medically confirmed gallstones. Percent include subjects with known exposure status. [#]PPE: Personal protective equipment. Calculated median of subjects´ protective equipment use for all tasks in percent according the proposed algorithm (25): No/low=10-60%, medium/high=70-80%, full protection=100%. [2]Calculated intensity of pesticide exposure by proposed algorithm (25): Low=1.0-6.4, medium=6.5-9.0, high=9.1-14.0. [†]Inserted risk estimates of tasks and exposures marked italic based on monovariate analyses.

Discussion

There are only few studies in low risk populations on risk of GBC/BTC among agricultural workers or among farmers handling pesticides (17, 27). One industrial cohort in a pesticide manufacturing plant reported a higher risk of gallbladder and liver carcinoma (21).

Overall, the results of this population-based study did not support the hypothesis that occupational pesticide exposure leads to elevated risks for GBC/BTC in men. The observed increased risks based on few study subjects, did not reach statistical significance and were limited by low power. Given the observed prevalence of exposure by 14% in controls, the chance to detect a real OR of 1.5 is 40%. Vice versa, for the given prevalence an OR of 2.8 has to be detected by the sample size of this study to have a power of 80%.

In this study only occupational pesticide exposure obtained in personal interviews with the index subjects was considered as relevant, which increases the accuracy of information on pesticide usage as compared to information from proxy interviews (28). To minimize differential misclassification cases and controls were administered the same questionnaire by trained interviewers.

The study was controlled for age, country and medical history of gallstones as potential confounders. Since adjusting for BMI and educational level as potential confounders did change the risk estimates by less than 10% these two variables were not included in the final logistic regression models.

Information collected in this study provided a longitudinal view of exposure histories in five countries, for which an industrial hygiene analysis was not feasible. In addition, pesticide application was observed to depend on geographical, ecological and meteorological factors (29), which can hardly incorporated in an industrial hygiene analyses. However, risk estimates based on self reports are susceptible to reporting-bias. Most likely misclassification of exposure will be non-differential with respect to case-control status since it can be assumed that subjects were not aware of a potential association between GBC/BTC and pesticide exposure in particular since the study hypothesis were only given in broader terms, so it can be assumed that exposures were reported reliable. Fryzek and co-workers (30) found in their case-control study on pesticides and pancreatic cancer that pesticide exposure was not over-emphasized by study subjects. Furthermore, pesticide use has been shown to be well remembered and reported by pesticide applicators (31, 32).

Most of the pesticide exposed participants in this study did not report frequent exposure. Applying pesticides in agrarian branches is dependent on season so there are months in which the body burden is low. Lack of information on the average days exposed to pesticides per task may have also affected accuracy of exposure assignment since changes in exposure over time could not be incorporated. The resulting misclassification of exposure would be most likely non-differential. Non-differential misclassification may have reduced power, particularly for specific pesticides, exposure frequency and pesticides used long before or for a short period.

Occupational activities that were investigated in this study included not only agrarian professions, but also diverse activities such as handling of animals, processing of meat products and work in the chemical industry and exposure to pesticides differ probably widely in these occupations.

In this study non-occupational exposure to pesticides were not considered. Potential sources of non-occupational pesticide exposure include domestic applications of pesticides (e.g. in the garden or on pets), consumption of agricultural products and exposure from carpets treated with pesticides (33).

It was not possible in this study to analyse specific chemical groups of pesticides because specific chemical groups were not solicited in the questionnaire since it can not be expected, that participants remember exposures with this level of details. The study covers a time span of 65 years of occupational pesticide exposure. In this period a number of different chemical classes of pesticides were used. Because not all exposed subjects used the same specific chemical group of a pesticide at a particular point in time, an association between pesticide exposure and GBC/BTC could have been masked. Furthermore, detailed analyses of occupational exposure to different chemical classes of pesticides would probably be hampered by low statistical power because of only a few exposed cases.

Although no elevated risks for occupational pesticide usage were observed in the present study, an effect of pesticide exposure on GBC/BTC cannot be ruled out. One case-control study observed significant higher levels of pesticides and pesticide metabolites in the bile of gallbladder and bile tract cancer cases as compared to control subjects with a diagnosis of gallstones in a geographical region with high environmental levels of pesticides and other pollutants (19).

Furthermore, pesticides may increase the risk of cancer through various mechanisms. Some pesticides are genotoxic themselves and may cause gene mutations or DNA rearrangements. Organophosphates, rapidly transferred via kidneys, may form DNA-binding alkyl-groups (34). Organophosphates were also found to inhibit the cytochrom-p450 system which slows down metabolism of pesticides in human liver microsoms and may lead to accumulation of these chemicals in the body (35, 36). Organochlorine pesticides like DDT and Chlordane are known as tumour promoters in animals and/or possess hormonal properties (37, 38) and may therefore stimulate the growth of cells in hormone sensitive tissues (39). A causal effect of pesticides on the carcinogenesis of liver and bile tract cancer is also possible since some pesticides are metabolised in the liver and excreted with the bile. In animal models, continuously given doses of DDT and parathion led to inflammation and necrosis of the bile tract (40).

Summarizing, the findings of the present study add support to cohort and register based studies that pesticides do not play a major role in GBC/BTC in low risk populations. In future studies it appears to be important to disentangle the effects of different chemical groups of pesticides or groups of pesticides and genetic variants and the risk of GBC/BTC. For this purpose more research is needed in larger studies bringing together questionnaire based data, documentation of the complete personal pesticide exposure biography and the assessment of genetic polymorphisms related to pesticide metabolism.

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2.2 Local cluster of germ cell cancer in a cohort of male automotive workers in Germany not explained by previous or concurrent activities and exposures in farming and forestry.

Schmeisser N, Behrens T, Mester B et al. Cancer Epidemiol. 2011;35:73-7

Abstract

OBJECTIVE: To examine whether exposures or activities in farming, forestry and related occupations explain the excess incidence of germ cell cancer observed among male employees in one of six car manufacturing plants that is located in a geographic area where farming is frequent.

METHODS: A cohort based case-control study was conducted among workers in six car manufacturing plants located in areas with different industrial structure. The study involved 188 cases of germ cell cancer identified through active retrieval in 38 hospitals and 1000 controls, drawn from administrative accounting files, individually matched by year of birth (±2 years). Information regarding tasks and exposures and potential confounding variables were obtained by face-to-face or telephone interviews. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using a conditional logistic regression model adjusted for cryptorchidism and other potential confounders.

RESULTS: In this case-control study 5.3% of cases and 6.3% of controls ever worked in agriculture or livestock farming. No increased risks were observed working in agriculture (OR=0.8 95%-CI: 0.4-1.6), livestock farming (OR=0.8 95%-CI: 0.4-1.6) or for exposure to pesticides (OR=0.7 95%-CI: 0.3-1.7), fertilizers (OR=0.8 95%-CI: 0.4-1.8) and disinfectants (OR=1.0 95%-CI: 0.3-2.8). There were no statistically significant increases in risk associated with ever exposure to salt based wood protection agents (OR=2.3 95%-CI: 0.6-9.1), working with plywood (OR=1.4 95%-CI: 0.6-3.2), coated wood (OR=1.4 95%-CI: 0.5-3.9) or working in forestry (OR=1.7 95%-CI: 0.5-6.4). Lagging of exposures did not alter the results.

CONCLUSIONS: The observed excess incidence in the cohort of automotive workers can be hardly explained by previous or concurrent work in farming or forestry. Because of the small numbers of subjects ever employed in farming the statistical power in assessing associations between agricultural work and agricultural exposures was limited, and does not allow final conclusions about the association of farming related exposures and GCC risk.

Keywords: testicular cancer, agriculture, pesticides, fertilizer

Introduction

With this analysis the question whether agricultural work might be an explanation for the excess incidence of germ cell cancer (GCC) seen in rural car manufacture workers was addressed. A company physician observed an excess of GCC cases in a car-manufacturing plant located in rural area with intensive agriculture and livestock farming. An incidence study was initiated to evaluate whether the suspected excess is real. The standardized incidence rate of GCC between 1989 and 2000 in this plant was SIR=2.3 (95%-CI: 1.7-3.1). For this plant the standardized incidence was 25.9 while for the entire cohort the standardized incidence was 14.0 compared with an incidence rate of 10.6 in the reference population [1]. In the whole cohort about 70 men more than would be expected contracted GCC. Information was given by the company that many workers, especially in the plant where the highest excess was observed, have worked in farming or forestry before or even during their employment. A cohort based case-control study was needed to assess a detailed exposure history for each individual to examine occupational exposures which could cause the excess incidence.

For work in agriculture or related activities an elevated risk was reported in several studies [2-5]. Studies examining the association between testicular cancer and agricultural jobs and exposures are inconsistent. An increased risk for testicular cancer regarding farming and for contact with farm animals was observed in a case-control study assuming that contact to farm animals might be an explanation [6]. Wiklund and co-workers [7] observed an increased risk of testicular cancer in agriculture in a register based study which was higher for pesticide applicators than for agricultural workers. A significantly elevated risk for exposure to insecticides was also observed in a case-control study [6]. Again, McDowall and co-workers [8] and Kelleher and co-workers [9] found an elevated risk for workers in agriculture, but not for farmers. Exposure to fertilizers was also assumed to be associated with testicular cancer [10,11].

Tasks and exposures in forestry, farming and related occupations were examined in this case-control study of occupational exposures in the car manufacturing industry to find out, whether exposures in farming or forestry may play a role for the observed excess incidence. Since pesticides and wood protection agents are among the exposures of interest, the analysis was expanded to other occupational areas where such exposures may occur, namely woodworking, slaughtering and leather production.

Material and Methods

Case and Control Recruitment

This study was designed as a case-control study of GCC in a cohort of nearly 202,000 male car manufacturing workers of one company in Germany to examine associations with several environmental and occupational exposures in accordance with the requirement of the local Institutional Review Board. Case subjects had a new diagnosis of GCC (ICD-10: C48 (GCC of the retroperitoneum), C62 (GCC of the testicles), C76 (malignant neoplasm not particularly specified) and C80 (malignant neoplasm of unspecified site); ICD-O [12]: 9060-9104). Before diagnosis they had to have worked between 1989 and 2006 in one of the six plants of one company in West Germany for a cumulative period of at least 6 months. The plants are located in areas differing in population density, land use patterns and industrial structure. One of the plants where the excess of cases was particularly high is located in a rural area mainly characterized by extensive agriculture and livestock farming, while four of the other plants are located in densely populated areas characterised by intensive agriculture and metal industry and one plant located in an area characterised by metal industry and power engineering.

Field work for case ascertainment was started in March 2004. A three-level case ascertainment was accomplished to avoid under-coverage. In a first step, the companys´ health insurance data were reviewed for hospital admission mentioning GCC. In a second step, cases reported by the company health insurance were validated by manual re-examination of patients´ records in 38 hospitals. Simultaneously for additional cases not reported by the health insurance was searched in the same hospitals. In a third step all outpatient care units of cancer patients were contacted to identify further cancer patients. A validation with Cancer Registry data in 2009 proved that the coverage of underlying GCC patients in this study is 94.1% (N=18 cases were not identified during case ascertainment). Cancer diagnosis was actively ascertained on-site by comprehensive screening of all patients' files. Each patient was contacted directly by the federal state industrial medical officer for recruitment into the study. Copies of the cases´ medical records and pathology reports were reviewed to confirm eligibility. A reference pathologist reviewed tumour material and pathology reports to confirm the diagnosis during the course of the study. Identified cases in medical record were matched to the study cohort by manual data linkage.

Controls were ascertained from company accounting files of the participating plants. A follow-up for vital status among compulsory registries of residence for all workers who quit their job or who were retired was accomplished with support by the company for controls. All eligible subjects were contacted regardless if they had moved outside the study area or not. At least two and up to ten controls were randomly selected from the risk set of a given case individually matched by year of birth (±2 years). Controls were required to have worked for at least 6 months before the diagnosis of the matched case in one of the study plants between 1989 and 2006 and had to be alive and free of GCC at date of diagnosis of the matched case.

Out of 291 eligible cases that were initially identified 215 (73.9%) were interviewed. A total of 4.7% were excluded from analysis because their physician's report did not confirm a diagnosis of GCC or they did not fulfil criteria of job tenure. Among controls, 50% of those initially contacted and eligible for inclusion in the study completed the interview. Most non-responders refused participation without giving a reason (42.5% of cases, 40.9% of controls). Time constraints were stated by 8.8% of controls. Other reasons were mentioned by 13.7% of cases and 13.7% of controls. No contact was possible for 33.5% of cases and 21.8% of controls because they were neither reached by phone nor they did reply to letters and for 0.7% cases and 2.8% controls no contact information was obtained. Overall, 205 patients and 1097 control subjects were included in the final analysis. Next-of-kin were interviewed for 17 cases and 10 controls which were deceased or medically incapable of participating in an interview. Because job specific questionnaires (JSQs) were not part of the surrogate interviews next-of-kin subjects were excluded, leaving 188 cases and 1000 control subjects for analysis. All study subjects gave written consent to participate.

Data Collection and Exposure Assessment

Face-to-face or telephone interviews were conducted by trained interviewers who were not aware of the case-control status of participants.

The questionnaire solicited information about physical conditions, medical history, family history, education, nutrition and smoking. The questionnaire also solicited a detailed occupational history. A person was permitted to report one main occupation and one avocation at the same time. Job specific questionnaires (JSQs) were employed to solicit detailed information on exposures, related activities and duration of exposure for every job held for at least six months. Up to six of 37 different JSQs could be applied per interview to keep interviews to a reasonable length. The following JSQs were analysed: ‘farming, market gardeners, parks and greenhouse workers’, ‘working with animals’, ‘forestry’, ‘wood working’, ‘tanneries and leather production’, ‘slaughtering animals or processing meat’.

Information was collected on the lifetime history of working on a farm, forestry or wood working branch and occupations processing agricultural goods. Specific tasks as well as exposure to biocides (disinfectants, pesticides, wood protection agents) and fertilizers in these jobs were considered. For the subjects who were exposed to pesticides, personal handling and bystander exposure was distinguished. The duration of activity to agriculture and livestock farming as well as forestry and wood working was obtained by summing up the activities of the non-overlapping periods. The resulting variables were classified with respect to the median duration of activity of controls as: never exposed (reference), duration lower than median and duration equal or longer than median.

Occupational exposures that occurred in the year prior to diagnosis of the matched case were not considered. Subjects never exposed to a given agent or who never performed a given task constituted the reference group. All statistical analyses were run with SAS 8.2 software (SAS Institute, Cary, NC). The odds ratios (ORs) and 95% confidence intervals (95% CIs) for GCC according to exposure to biocides, fertilizers and job specific tasks were calculated using the conditional logistic regression model (OR_1) and were adjusted for a history of cryptorchidism (OR_2). ORs were not reported if a given category included less than three cases. The size of the study sample was sufficient to evidence ORs of 4.2, 2.4 and 2.0 for exposure prevalence of 1, 5 and 10% with a power of 0.8 and an alpha error of 5% (two-sided).

Results

Participants did not differ from non-participants in respect to manual/non-manual classification according the administrative accounting files. Among participating cases 86.3% were blue collar workers (non-participating: 84.2%) and among participating controls 86.3% were blue collar workers (non-participating: 86.5%). No difference in birth year was observed for participants and non-participants. Participants as well as non-participants were born between 1931 and 1977 (median 1964).

Among participants 51.6% of cases and 47.3% of controls had less than 10 years of school attendance or had no school degree. The attainment of a secondary school degree was similar in both groups (27.1% in cases and 27.7% in controls), and 21.3% of cases and 25.0% of controls reached a higher school degree, i.e. 12 or more years of school education. Mean age at time of diagnosis was 34.8 years for cases and controls. A family history of cancer was more frequent among cases (25.5%) as compared to controls (20.5%) (OR_1=1.4 95%-CI 0.9-2.0). A family history of testicular cancer was also more frequent among cases (2.1%) as compared to controls (1.2%) (OR_1=2.0 95%-CI 0.6-6.3). A higher proportion of medically confirmed cryptorchidism was reported by cases (11.7%) than by controls (4.7%) (OR=2.7 95%-CI 1.6-4.6).

In this case-control study 5.3% of cases ever worked in an agricultural context, as compared to 6.3% of controls. Among cases the frequency of the three most requested and completed JSQs in this study, were 80%, 80% and 79% for agriculture, livestock and wood working, respectively. Among controls these frequencies were higher (90%, 98% and 96%). There was only a minor difference between cases and controls requesting six or more JSQs (cases 10.1%, controls 12.2%). The average number of JSQs per interview was 3.4 in cases and 3.2 in controls (data not shown).

As shown in Table 1, there were no associations between GCC risk and farming or animal husbandry. Risk estimates of particular tasks of livestock farming as well as processing farm goods are based on very low exposure prevalence. An excess risk was observed for forestry, however, based on only three cases. For subjects ever employed in the wood working industry no increased risk was observed. In addition, no increased risk was observed for working in one of the working areas and for working duration in agriculture and/or livestock farming and in woodworking and/or forestry.

Most of the examined occupations started before the late 1970s for cases and controls. No increased GCC risk was found for number of years exposed in agriculture and livestock farming or forestry and woodworking. Varying time lags for exposure up to 20 years before diagnosis did not alter the ever-never associations substantially (Table 1).

Table 1: Distribution of cases and controls and ORs with 95% CIs for germ cell cancer associated with reported activity by JSQ (ever versus never).

	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
	N	%	N	%		
JSQ: Agriculture	8	4.3	60	6.0	0.7 [0.3-1.5]	0.8 [0.4-1.6]
Exposure lag 5 years	8	4.3	53	5.3	0.8 [0.4-1.7]	0.9 [0.4-1.8]
Exposure lag 15 years	7	3.7	43	4.3	0.9 [0.4-2.0]	1.0 [0.4-2.2]
Exposure lag 20 years	5	2.7	28	2.8	1.0 [0.4-2.7]	1.1 [0.4-2.9]
Crops cultivated:						
Grain *(Gramineae)*	8	4.3	50	5.0	0.9 [0.4-1.9]	0.9 [0.4-2.0]
Potatoes and tomatoes (*Solanaceae*)	7	3.7	31	3.1	1.3 [0.5-2.9]	1.4 [0.6-3.2]
Beet (*Beta*)	5	2.7	28	2.8	1.0 [0.4-2.6]	1.0 [0.4-2.7]
All other	3	1.6	20	2.0	0.8 [0.2-2.8]	0.9 [0.3-3.2]
JSQ: Livestock$^{\alpha}$	8	4.3	58	5.8	0.8 [0.4-1.6]	0.8 [0.4-1.6]
Exposure lag 5 years	8	4.3	53	5.3	0.8 [0.4-1.8]	0.8 [0.4-1.8]
Exposure lag 15 years	7	3.7	43	4.3	0.9 [0.4-2.0]	0.9 [0.4-2.0]
Exposure lag 20 years	4	2.1	33	3.3	0.7 [0.2-1.9]	0.6 [0.2-1.9]
Keeping of:						
Cattle	6	3.2	41	4.1	0.8 [0.3-1.9]	0.8 [0.3-1.9]
Pigs	6	3.2	38	3.8	0.9 [0.4-2.1]	0.9 [0.4-2.1]
Fowls	2	1.1	17	1.7	-	-
Horses	3	1.6	14	1.4	1.2 [0.3-4.1]	1.1 [0.3-3.9]
Other	2	1.1	6	0.6	-	-
Slaughtering animals on the farm	5	2.7	25	2.5	1.1 [0.4-3.0]	1.1 [0.4-3.0]
Epidemics on animals	1	0.5	1	0.1	-	-
Working duration [years] in Agriculture or Livestock						
1-11	5		34		0.8 [0.3-2.0]	0.8 [0.3-2.0]
12-41	7		35		1.1 [0.5-2.6]	1.2 [0.5-2.8]
JSQ: Slaughtering animals or processing meat$^{\beta}$	3	1.6	15	1.5	1.1 [0.3-3.8]	1.1 [0.3-3.7]
Exposure lag 5 years	3	1.6	15	1.5	1.1 [0.3-3.8]	1.1 [0.3-3.7]
Exposure lag 15 years	2	1.1	9	0.9	-	-
Exposure lag 20 years	2	1.1	6	0.6	-	-
Slaughtering mammals	3	1.6	12	1.2	1.3 [0.4-4.7]	1.3 [0.4-4.6]
Slaughtering fowls	1	0.5	2	0.2	-	-
Handling animals	0	0	4	0.4	-	-
Kill and gut	2	1.1	12	1.2	-	-
Meat processing	2	1.1	15	1.5	-	-
Salting	2	1.1	9	0.9	-	-
Curing meat	2	1.1	12	1.2	-	-
JSQ: Tanning and leather production	1	0.5	1	0.1	-	-
JSQ: Forestry	3	1.6	10	1.0	1.6 [0.4-5.7]	1.7 [0.5-6.4]
Exposure lag 5 years	3	1.6	10	1.0	1.6 [0.4-5.7]	1.7 [0.5-6.4]
Exposure lag 15 years	2	1.1	5	0.5	-	-
Exposure lag 20 years	2	1.1	4	0.4	-	-
JSQ: Wood working$^{\delta}$	11	5.9	53	5.3	1.1 [0.6-2.2]	1.1 [0.5-2.1]
Exposure lag 5 years	11	5.9	50	5.0	1.2 [0.6-2.3]	1.1 [0.6-2.2]
Exposure lag 15 years	9	4.8	36	3.6	1.4 [0.6-2.9]	1.3 [0.6-2.7]
Exposure lag 20 years	6	3.2	18	1.8	1.8 [0.7-4.8]	1.7 [0.6-4.4]
Working in a sawmill	1	0.5	6	0.6	-	-
Plywood fabrication	1	0.5	1	0.1	-	-
Carpentry	2	1.1	6	0.6	-	-
Joiner	5	2.7	23	2.3	1.2 [0.4-3.1]	1.1 [0.4-3.0]
Cabinetmaker	2	1.1	20	2.0	-	-
Window and door fabrication	1	0.5	4	0.4	-	-
Parquet recliner	0		3	0.3	-	-
Other	3	1.6	18	1.8	0.9 [0.3-3.1]	0.9 [0.3-3.0]
Working materials						
Hardwood	3	1.6	33	3.3	0.5 [0.1-1.6]	0.4 [0.1-1.4]
Softwood	10	5.4	41	4.1	1.3 [0.6-2.6]	1.2 [0.6-2.5]
Plywood	8	4.3	29	2.9	1.5 [0.7-3.4]	1.4 [0.6-3.2]
Coated wood	5	2.7	18	1.8	1.6 [0.6-4.4]	1.4 [0.5-3.9]
Other	1	0.5	12	1.2	-	-

Table 1: continued.

Working duration [years] in Forestry or Wood working						
1-4	8		31		1.4 [0.6-3.0]	1.3 [0.6-2.9]
5-41	6		29		1.1 [0.4-2.8]	1.1 [0.4-2.8]

$^{\alpha}$Two controls have been excluded because of missing data of occupational period. $^{\beta}$One control has been excluded because of missing data of occupational period. Analyses did not include livestock working. $^{\delta}$One case and two controls were excluded because of missing time period information. Five controls were disclosed because of excluded case in the risk set. Risk estimates stratified for matching variable age (OR_1). Risk estimates additionally adjusted for medical confirmed cryptorchidism (OR_2).

Table 2: Distribution of cases and controls and ORs with 95% CIs for GCC for exposure (ever vs. never exposed) to pesticides, disinfectants, wood protective agents and fertilizers reported by JSQ.

	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
Exposure to fertilizers	N	%	N	%		
Agriculture (total)	7	3.7	48	4.8	0.8 [0.4-1.8]	0.9 [0.4-1.9]
Crops handled with chemical fertilizer	6	3.2	36	3.6	0.9 [0.4-2.2]	1.0 [0.4-2.4]
Potassium salts	6	3.2	27	2.7	1.2 [0.5-3.0]	1.3 [0.5-3.2]
Phosphorous compounds	4	2.1	26	2.6	0.9 [0.3-2.5]	0.9 [0.3-2.6]
Nitrogenous compounds	5	2.7	28	2.8	1.0 [0.4-2.6]	1.1 [0.4-2.8]
Forestry	0		3	0.3	-	-
Fertilizers total	7	3.7	50	5.0	0.8 [0.3-1.7]	0.8 [0.4-1.8]
Exposure to disinfectants						
Livestock farming	3	1.6	15	1.5	1.1 [0.3-3.8]	1.0 [0.3-3.6]
Slaughtering	1	0.5	8	0.8	-	-
Tanning	0		0		-	-
Disinfectants total	4	2.1	22	2.2	1.0 [0.3-2.9]	1.0 [0.3-2.8]
Exposure to Pesticides						
Agriculture	4	2.1	38	3.8	0.6 [0.2-1.6]	0.6 [0.2-1.7]
Livestock	1	0.5	7	0.7	-	-
Slaughtering	0		0		-	-
Forestry	0		1	0.1	-	-
Tanning	0		0		-	-
Pesticides total[1]	5	2.7	42	4.2	0.6 [0.3-1.6]	0.7 [0.3-1.7]
Agriculture (self applied)	2	1.1	11	1.1	-	-
Livestock (self applied)	1	0.5	4	0.4	-	-
Pesticides self applied total	3	1.6	14	1.4	1.3 [0.4-4.5]	1.2 [0.3-4.4]
Exposure to wood protection agents						
Forestry	0		0		-	-
Woodworking (total)	4	2.1	27	2.7	0.8 [0.3-2.3]	0.7 [0.3-2.1]
Tar based wood protection agents	1	0.5	11	1.1	-	-
Solvent based wood protection agents	2	1.1	20	2.0	-	-
Salt based wood protection agents	3	1.6	7	0.7	2.5 [0.7-9.8]	2.3 [0.6-9.1]
Wood protection agents (total)	4	2.1	27	2.7	0.8 [0.3-2.3]	0.7 [0.3-2.1]

[1]One control was exposed by railway working and additional included in this analysis. Risk estimates stratified for matching variable age (OR_1). Risk estimates additionally adjusted for medical confirmed cryptorchidism (OR_2).

Ever-never exposure quantification of exposure to biocides or fertilizers in any of the JSQs considered is listed in Table 2. Low exposure prevalence was observed for all single agents and detailed analyses were not feasible. No exposure to one of the farming related exposures revealed an excess risk, but the number of exposed subjects was very small. However, exposure to wood protection agents based on chromium, arsenic or copper salts revealed an elevated risk, though statistically non-significant.

Discussion

A number of studies observed an increased testicular cancer risk for employment in farming [4,13-16], while others [17-19], did not observe such an increased risk. Based on information given by the company´ physicians the rationale behind this study was that previous or concurrent agricultural work and agriculture related exposures was responsible for the observed excess incidence of GCC in workers of a car manufacturing plant in rural area. This hypothesis was not confirmed.

As this study was not matched for study plant, risk estimates were also adjusted for this variable. However, adjustment for plant location did not change the risk estimates, neither did adjustment for a family history of testicular cancer, education and ethnic (German/non-German) origin.

This study has limitations. The participation rate in this study was lower among controls than among cases and raises concerns about possible selection bias. On the one hand, participants and non-participants did not differ in respect of their occupational class (blue collar/white collar) and participating control subjects in this study did not differ substantially in educational level than participating cases, which may rule out an underestimation of exposure in controls. On the other hand, the frequency of the three most requested and completed JSQs in this study, were different for cases and controls. One reason for this difference might be the restriction to a maximum of six JSQs per interview suspending more potentially exposed cases than controls from analyses. However, this observed difference between cases and controls is unsuitable to explain potential biasing effects.

This study is the first attempt to evaluate causative agents and tasks in this cohort based case-control study more specifically to explain the excess incidence. The observed cluster is hardly explained by agriculture, but this does not mean that there is no risk associated with agriculture, because the statistical power to assess risks in agriculture was very low. However, the study has sufficient power to assess whether the observed cluster is explained by agriculture. The statistical power is sufficient to detect a twofold risk, if the exposure of interest was 5% among controls. Taking the observed prevalence of 6.3% of controls in the case-control study having worked in agriculture the relative risk would have to have fourfold, i.e. about 25% of the cases would had to have worked in an agricultural context in this study to explain the excess of GCC in the cohort.

This study was not designed to assess, whether exposure in farming by themselves are associated with GCC. Not only the low statistical power but also differences in study design and study subjects make it difficult to examine how the results relate to previous findings for occupational exposures in agriculture.

Moderately, but statistically non-significantly increased risks were observed for forestry, handling with plywood and coated wood and exposure to salt based wood protection agents, while no evidence was found that the observed GCC excess in the cohort of car manufacturing workers can be explained by previous or simultaneous work in farming or forestry. The finding of an elevated risk for salt based wood protection agents requires verification in a larger study.

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2.3 Social Factors and Risk of Testicular Cancer

Schmeisser N, Conway DI, Stang A et al.: (unpublished)

Abstract:

Background: Incidence rates for testicular cancer have risen over the last few decades. Findings of an association between the risk of testicular cancer and social factors are controversial. The association of testicular cancer and different indicators of social factors were examined in this study.

Methods: The study included 797 control subjects and 269 subjects newly diagnosed with testicular cancer of which 170 cases were classified as seminoma and 99 as nonseminoma. The age of study subjects ranged from 15 to 69 years. Social factors were based on the achieved educational level, post educational training, occupational sectors according to Erikson-Goldthorpe-Portocarrero (EGP) and the socioeconomic status (SES) on the basis of the International Socio-Economic Index of occupational status (ISEI). Odds ratios [ORs] and corresponding 95% confidence intervals [95%-CIs] were calculated for the whole study sample and for seminoma and nonseminoma separately.

Results: An increased testicular cancer risk was observed for subjects with an apprenticeship (OR=1.5 [95%-CI: 0.9-2.5]) or an university degree (OR=1.5 [95%-CI: 0.9-2.6]) relative to those whose education was limited to school. Analysis of occupational sectors revealed an excess risk for farmers and farm related occupations. No clear trend was observed for the analyses according the ISEI-scale.

Conclusions: Social factors based on occupational measures were not a risk factor for testicular cancer in this study. The elevated risk in farmers and farm related occupations warrants further research including analysis of occupational exposures.

Keywords: Germ cell cancer; Socioeconomic Status; Case control study; Occupational risk factors

Introduction

Subjects affected most by testicular cancer are men between 15 and 40 years of age. For men older than 40 years of age the risk of testicular cancer decreases continuously (1, 2). The age distribution of testicular cancer is in sharp contrast to other neoplasms for which incidence rises with increasing age. Established risk factors for testicular cancer include a family history of testicular cancer and a history of an undescended testis (3, 4). Exposure to endocrine disrupting chemicals in an occupational context or *in utero*, has been suggested as a factor in cancer development (5). The incidence rates of testicular cancer have risen continuously in Western Europe and other industrialized countries, which may be due to changed environmental and life circumstances in these countries. In particular, in Germany the average numbers of testicular cancer per year in the 1980s and 1990s were 3196 and 3836. The corresponding age-standardised incidence rates were 7.7 and 8.9 per 100,000 (6). However, study results on the association of social factors and testicular cancer have been conflicting. Excess risks for higher levels of education or occupations related to higher social class, like administrators and managers and other professionals were observed in some studies (7-10). Other studies did not observe an association between social status and testicular cancer (11-17) or even observed an inverse association (18, 19). In one study the association of testicular cancer and socioeconomic status (SES) differed by histological type (20). A register based study in Finland observed a decrease of testicular cancer incidence rates among subjects of higher social classes and an increase of incidence rates in the lower social classes between 1971 and 1995, leading to a levelling off of the social gradient (21).

In this study, in addition to educational attainment at school and level of professional training as defined in a previous study (22) further social factors based on job histories were considered. In detail, socioeconomic status (SES) based on the International Socio-Economic Index (ISEI) (23) and social class based on the Erikson-Goldthorpe-Portocarrero (EGP) (24) classification was explored. Both the International Socio-Economic Index (ISEI) of occupation, which is a vertical grouping approach, and the Erikson-Goldthorpe-Portocarrero (EGP) classification of occupations which adopts a class schema, claim that employment relations are basic social characteristics of western society.

Study subjects and Methods

All participants were registered residents of the city states Bremen and Hamburg, the Saarland region and the city Essen. Study subjects randomly drawn from registration offices had to live in the study regions between July 1995 and December 1997. Incident cases, diagnosed between July 1995 and December 1997, were reported by an active registration system via hospitals and pathologists. In Hamburg cases were also identified via the state cancer registry.

Eligible cases had to have a diagnosis of tumour of the testis (ICD-10: C62.0-C62.9), epididymis (C63.0), spermatic cord (C63.1) or extragonadal germ cell tumours (C38.3; C48.0; C71.0-C71.9; ICD-O: M9060-9102).

Copies of pathology reports and histological material were obtained from hospitals. Pathology reports were reviewed centrally and compared with histological material when available by a reference pathologist to determine the histological type of tumour. Tumours were classified as seminomas (N=170, 63.2%) or nonseminomas (N=99, 36.8%) according to Parkin and co-workers (25). The latter group also included extra-gonadal germ cell tumours. More detailed descriptions and demographic characteristics of the participants were published elsewhere (22, 26-28).

Cases and controls had to be between 15 and 69 years of age. An n:m-matching for 5-year age strata and study region was chosen. To obtain sufficient power in this study, a matching ratio of 1:4 was realised for the age group 35-69, while for the age strata 15-34 a matching ratio of 1:2 was considered to be sufficient since most cases were expected in this age group. Inclusion criteria were fulfilled by 269 cases and 918 controls. Cases and controls were recruited in parallel. For this purpose controls were selected prospectively according to the expected case distribution. This left 121 controls for which no matching case interview was obtained.

Participants were interviewed face-to-face (N=984, 92.3%) or by telephone (N=82, 7.7%). Almost all interviews were performed with an index person (N=978, 91.7%). For deceased subjects or subjects to ill to answer the questions, a next-of-kin interview was solicited. The interview entailed questions about medical conditions since childhood, chemical and physical exposures and an occupational biography for every job held 6 months or longer.

For each employment period, the job title and industry and a brief summary of the job tasks were assessed. Each job was assigned a five-digit *International Standard Code of Occupations* (ISCO) (29) and a five-digit industry code (NACE) (30).

Assessment of Social Factors

Measures of social factors in this study were level of educational attainment at school, level of professional training, occupational sector based on EGP and SES based on ISEI.

Job title codes (ISCO) were linked to the *International Socio-Economic Index of Occupational Status* (ISEI) (23). The ISEI assigns values between 10 and 90 to job titles with respect to education and income. Judges, lawyers and physicians achieve the highest values, while unskilled labourers in agriculture and housekeepers the lowest values. In this scale a continuous hierarchical approach the distinctions of work related tasks and social patterns disappear in favour of a single parameter. The ISEI score provides a mechanism for ranking occupations related to both the level of education required and the income earned (23). ISEI-Scores for the maximum ever achieved, the longest held and the last job were used to quantify the possible effect of socioeconomic status on testicular cancer risk. ISEI values were grouped into five categories employing the best possible equal distribution of controls.

For the present analyses, ISCO codes were aggregated according to occupational sector and training required (EGP) assuming that internal homogeneity within a category is great and that a definable external social heterogeneity to members of other categories exists (24). The EGP is based on occupational group, required training, self support/independence, social mobility and leadership. Each reported job was classified into one of the following ten occupational categories: (I) higher service (includes mostly professionals, large enterprise employers and higher managers (>10 subordinates)); (II) lower service (includes mostly associate professionals, lower managers (1-10 subordinates), higher sales); (III) routine clericals/sales (includes routine clerical and sales workers); (IV) small employers (includes small entrepreneurs (1-10 subordinates); (V) self-employed (own account workers, no employees, artists); (VI) manual foremen (manual workers with supervisory status (>1 subordinate)); (VII) skilled manual (mostly craft workers, some skilled service, skilled machine operators, also gardeners); (VIII) semi-unskilled manual (mostly machine operators, elementary sales services and state work creation scheme); (IX) farm workers (employed farm workers, irrespective of skill level; also family farm workers); (X) farmers/farm managers (self-employed and supervisory farm workers, irrespective of skill level). Categories I and II, III, IV and V, VI and VII, IX and X were collapsed into for analysis.

Occupational histories excluded jobs starting within one year before the case diagnosis or before the first mailing to controls. For analysis of first job, last job, longest held job, job highest ranked and job lowest ranked the highest category formed the reference. Subjects which had never worked were excluded from analysis, except for the ever/never analysis of

EGP. For this analyses, those subjects who did not work in the specific field under consideration were used as reference group in the ever/never analysis.

Educational level according to the German school system was classified into four levels (≤9 [no school degree, Sonderschulabschluss, Hauptschulabschluss], 10 [mittlere Reife], 12 [Fachabitur] and 13 [Abitur] years of school education). In addition, the highest professional post school level (none, apprenticeship, university or college degree, others) was analysed.

Statistical Analysis

Odds Ratios (OR) and 95%-confidence intervals [95%-CI] were calculated stratified for the five year age strata and study centres. All analyses were carried out for the whole study and by the two main histological subgroups. Odds ratios and corresponding confidence intervals were estimated by the maximum likelihood method using the procedure PHREG for conditional logistic regression analysis. The level of statistical significance was defined as $p<0.05$ (two-sided). All analyses were carried out using SAS 8.2. ORs were not reported if a given category included less than three cases.

Results

The proportion of medically confirmed cryptorchidism was higher in cases (4.8%) than in controls (1.0%). Among seminoma cases the proportion of medically confirmed cryptorchidism was 4.7% and 1.1% among the controls. In nonseminoma cases the prevalence of medical confirmed cryptorchidism was 5.1% while in the controls the prevalence was 1.0%. Overall, nonseminoma cases were on average 5 years younger than seminoma cases (nonseminoma: 31.1±8.4; seminoma: 36.9±8.8; controls: 38.0±11.7 [mean±sd]) (data not shown).

The distribution of number of occupations for cases and controls is shown in Table 1. Seven cases (six nonseminoma cases; one seminoma case) and 20 controls were still attending school or were students with no job history at the time of diagnosis (case) or first mailing (controls). Job histories of nonseminoma cases lasted 14.6±8.6 years, of seminoma cases 21.5±12.6 and of controls 21.0±12.9 years [mean±sd]. Except for the nonseminoma cases the number of occupational periods did not differ between cases and controls.

Table 1: Frequency of economically active periods for cases and controls for whole study and separated for analyses of age groups and histology.

Frequency	Cases N=269		Controls N=797	
Complete Study	N	%	N	%
0	7	2.6	20	2.5
1-2	108	40.2	324	40.7
3-4	98	36.4	281	35.3
5+	56	20.8	172	21.6
Seminoma	Cases N=170		Controls N=725	
0	1	0.6	13	1.8
1-2	43	25.3	192	26.5
3-4	74	43.5	299	41.2
5+	52	30.6	221	30.5
Nonseminoma	Cases N=99		Controls N=682	
0	6	6.1	20	2.9
1-2	37	37.4	193	28.3
3-4	40	40.4	274	40.2
5+	16	16.2	195	28.6

Stratification by educational level and professional degree is shown in Table 2. Risk estimates were not elevated for higher educational levels in the complete study group or in the histological subgroups. Subjects with professional degrees (i.e. apprenticeship, technical colleges, study at university and university for applied sciences) in the whole study group and in the analysis of seminoma cases as compared to subjects without professional training were at higher risk. For nonseminoma cases and their matched controls no increased risk was observed for professional training. No risk was observed for being employed before the age of 18 (OR=1.0; 95%-CI 0.7-1.4) (data not shown).

Table 2: Distribution of cases and controls by educational level and professional degrees and corresponding Odds Ratios with 95% confidence intervals

	Cases		Controls		
	N	%	N	%	
Complete Study	(269)		(797)		OR (95%-CI)
Years at school					
≤9	89	33.1	304	38.1	1.0†
10	61	22.7	192	24.1	0.8 (0.6-1.3)
12	25	9.3	78	9.8	0.9 (0.5-1.5)
13	94	34.9	222	27.9	1.0 (0.7-1.5)
Unknown	0	0.0	1	0.1	
Professional training					
None	24	8.9	95	11.9	1.0†
Apprenticeship	164	61.0	485	60.9	1.5 (0.9-2.5)
University degree	62	23.1	154	19.3	1.5 (0.9-2.6)
Other	19	7.1	63	7.9	0.9 (0.4-1.9)
Seminoma	(170)		(725)		
Years at school					
≤9	60	35,3	267	36,8	1.0†
10	39	22,9	180	24,8	0.8 (0.5-1.4)
12	17	10,0	75	10,3	0.9 (0.5-1.6)
13	54	31,8	202	27,9	1.0 (0.6-1.6)
Unknown	0	0,0	1	0,1	
Professional training					
None	12	7,1	88	12,1	1.0†
Apprenticeship	111	65,3	446	61,5	2.2 (1.1-4.3)
University degree	40	23,5	142	19,6	1.8 (0.9-3.7)
Other	7	4,1	49	6,8	1.6 (0.5-5.1)
Nonseminoma	(99)		(682)		
Years at school					
≤9	29	29,3	225	33,2	1.0†
10	22	22,2	172	25,4	0.8 (0.4-1.5)
12	8	8,1	73	10,8	0.8 (0.3-1.9)
13	40	40,4	206	30,4	1.1 (0.6-1.9)
Unknown	0	0,0	1	0,1	
Professional training					
None	12	12,1	80	11,7	1.0†
Apprenticeship	53	53,5	400	58,7	0.9 (0.5-1.9)
University degree	22	22,2	140	20,5	1.1 (0.5-2.5)
Other	12	12,1	62	9,1	0.5 (0.2-1.4)

†Reference.

No difference between cases and controls was observed (cases: mean score 42.8, median score 39; controls: mean score 42.4, median score 39) (data not shown). Risk estimates by ISEI-scores are presented in Table 3. Analyses of the maximum ISEI score reached during the lifetime showed no increased risks. A modest increased risk was observed for seminoma cases where the risk increase was restricted to the lowest category (OR=1.4; 95%-CI 0.8-2.4). For nonseminoma study sample no increased risk was observed as compared to the reference category. The analyses by ISEI of the job held longest and the last job held revealed no clear trends.

Table 3: Distribution and frequency for achieved maximum ISEI scores and ISEI scores for the longest and last held job for whole study population and for histologic subgroups and corresponding Odds Ratios.

Complete Study	**Cases**		**Controls**		
Maximum	**N**	**%**	**N**	**%**	**OR (95%-CI)**
[16-37)	59	22.5	156	19.6	1.1 [0.7-1.8]
[37-44)	48	18.3	172	21.6	0.9 [0.5-1.4]
[44-55)	51	19.5	151	19.0	1.0 [0.6-1.6]
[55-66)	51	19.5	151	19.0	0.9 [0.6-1.5]
[66-88]	53	20.2	147	18.4	1†
Missing	7		20		
Last held job					
[16-37)	96	35.7	264	33.3	0.9 [0.6-1.4]
[37-44)	36	13.8	132	16.6	0.8 [0.5-1.3]
[44-55)	39	14.1	145	18.2	0.7 [0.4-1.1]
[55-66)	44	16.4	117	14.7	0.9 [0.6-1.5]
[66-88]	47	17.5	119	14.9	1†
Missing	7		20		
Longest held job					
[16-37)	104	38.7	277	34.9	0.9 [0.6-1.5]
[37-44)	41	15.2	150	18.8	0.8 [0.5-1.3]
[44-55)	33	12.3	144	18.1	0.6 [0.3-1.0]
[55-66)	43	16.0	106	13.3	1.0 [0.6-1.7]
[66-88]	41	15.2	100	12.6	1†
Missing	7	2.6	20	2.4	
SEMINOMA	Cases		Controls		
Maximum	N	%	N	%	
[16-37)	37	21.9	141	19.9	1.4 [0.8-2.4]
[37-44)	32	18.9	159	22.3	0.9 [0.5-1.6]
[44-55)	32	18.9	137	19.2	0.9 [0.5-1.6]
[55-66)	32	18.9	141	19.8	0.9 [0.5-1.6]
[66-88]	36	21.3	134	18.8	1†
Missing	1		13		
Last held job					
[16-37)	59	34.9	240	33.8	0.9 [0.6-1.6]
[37-44)	24	14.2	123	17.3	0.8 [0.5-1.5]
[44-55)	25	14.8	133	18.7	0.7 [0.4-1.3]
[55-66)	29	17.2	109	15.3	0.9 [0.5-1.6]
[66-88]	32	18.9	107	15.0	1†
Longest held job					
[16-37)	64	37.7	259	35.9	0.9 [0.5-1.5]
[37-44)	29	17.1	133	18.3	0.9 [0.5-1.5]
[44-55)	21	12.4	128	17.7	0.5 [0.3-1.0]
[55-66)	25	14.7	101	13.9	0.8 [0.4-1.5]
[66-88]	30	17.7	91	12.6	1†
Missing	1		12		
NONSEMINOMA	Cases		Controls		
Maximum	N	%	N	%	
[16-37)	22	23.7	128	19.5	0.9 [0.4-1.9]
[37-44)	16	17.2	148	22.3	0.7 [0.3-1.5]
[44-55)	19	20.4	129	19.5	0.9 [0.5-1.9]
[55-66)	19	20.4	133	20.1	1.0 [0.5-1.9]
[66-88]	17	18.3	124	18.7	1†
Missing	6				
Last held job					
[16-37)	37	39.8	223	33.8	0.9 [0.4-1.7]
[37-44)	12	14.0	110	16.6	0.7 [0.3-1.6]
[44-55)	14	14.0	126	19.0	0.7 [0.3-1.5]
[55-66)	15	16.1	103	15.5	0.9 [0.4-2.0]
[66-88]	15	16.1	100	15.1	1†

Table 3: continued

Longest held job					
[16-37)	40	40.4	230	33.9	1.1 [0.5-2.2]
[37-44)	12	12.1	130	19.1	0.7 [0.3-1.7]
[44-55)	12	12.1	128	18.8	0.6 [0.3-1.5]
[55-66)	18	18.2	91	13.3	1.4 [0.6-3.3]
[66-88]	11	11.1	83	12.2	1[†]
Missing	6	6.1	19	2.8	

[†]Reference.

ORs by occupational sectors (EGP) are shown in table 4. An increased risk for testicular cancer was observed for ever held an agriculture related job (OR=2.2 95%-CI 1.1-4.2). For seminoma cases the effect was of the same strength (OR=2.4 95%-CI 1.1-5.0), while for nonseminoma cases the OR estimate was smaller (OR=1.6 95%-CI 0.5-4.8). For all other classes no increased risk was observed. This pattern was replicated for almost all analysis presented in table 4. Compared with subjects in the highest EGP quintiles, increased risks were observed for category IX-X for first, last and occupation with highest category ever.

Table 4: Stratification and Odds Ratios with 95%-CI of occupational sectors according to Erikson, Goldthorpe and Protocarero for complete study group and histologic subgroups

	Complete Study					Seminoma					Nonseminoma[#]				
Category[1]	**Cases**		**Controls**			**Cases**		**Controls**			**Cases**		**Controls**		
	N	**%**	**N**	**%**	**OR [95%-CI]**	**N**	**%**	**N**	**%**	**OR [95%-CI]**	**N**	**%**	**N**	**%**	**OR [95%-CI]**
First held job															
I-II	25	9.5	69	8.9	1	15	8.9	63	8.8	1	10	10.8	60	9.1	1
III-V	40	15.3	140	18.0	0.9 [0.5-1.5]	24	14.2	126	17.7	0.9 [0.4-1.8]	16	17.2	126	19.1	0.8 [0.3-1.9]
VI-VII	134	51.1	404	52.0	1.1 [0.7-1.9]	90	53.3	372	52.2	1.3 [0.7-2.4]	44	47.3	335	50.8	0.9 [0.4-1.9]
VIII	56	21.4	148	19.0	1.1 [0.8-1.4]	34	20.1	138	19.4	1.1 [0.8-1.6]	22	23.7	128	19.4	1.0 [0.6-1.5]
IX-X	7	2.7	16	2.1	1.6 [0.5-4.6]	6	3.6	13	1.8	2.1 [0.6-6.7]	1	1.1	11	1.7	-
Last held job															
I-II	70	26.7	172	22.1	1	45	26.6	155	21.8	1	25	26.9	150	22.7	1
III-V	53	20.2	192	24.7	0.7 [0.4-1.0]	34	20.1	180	25.3	0.7 [0.4-1.2]	19	20.4	162	24.5	0.6 [0.3-1.1]
VI-VII	82	31.3	243	31.3	0.9 [0.6-1.3]	55	32.5	223	31.3	1.0 [0.6-1.6]	27	29.0	205	31.1	0.7 [0.4-1.3]
VIII	52	19.8	165	21.2	0.9 [0.7-1.1]	31	18.3	151	21.2	0.9 [0.7-1.2]	21	22.6	138	20.9	0.9 [0.6-1.2]
IX-X	5	1.9	5	0.6	3.0 [0.8-11.7]	4	2.4	3	0.4	4.3 [0.9-20.8]	1	1.1	5	0.8	-
Longest held job															
I-II	54	20.6	145	18.7	1	37	21.9	133	18.7	1	17	18.3	125	18.9	1
III-V	46	17.6	166	21.4	0.8 [0.5-1.2]	27	16.0	154	21.6	0.7 [0.4-1.2]	19	20.4	139	21.1	0.8 [0.4-1.6]
VI-VII	101	38.5	287	36.9	1.1 [0.7-1.6]	70	41.4	261	36.7	1.2 [0.8-2.0]	31	33.3	242	36.7	0.8 [0.4-1.5]
VIII	56	21.4	171	22.0	0.9 [0.8-1.2]	32	18.9	156	21.9	0.9 [0.7-1.2]	24	25.8	146	22.1	1.0 [0.7-1.4]
IX-X	5	1.9	8	1.0	1.3 [0.4-4.1]	3	1.8	8	1.1	1.0 [0.2-4.1]	2	2.2	8	1.2	-
Lowest category ever															
I-II	18	6.9	42	5.4	1	10	5.9	38	5.3	1	8	8.6	37	5.6	1
III-V	28	10.7	101	13.0	0.7 [0.3-1.4]	18	10.7	89	12.5	0.8 [0.3-2.0]	10	10.8	90	13.6	0.5 [0.2-1.5]
VI-VII	85	32.4	241	31.0	1.0 [0.5-1.8]	54	32.0	222	31.2	1.1 [0.5-2.5]	31	33.3	200	30.3	0.8 [0.3-1.8]
VIII	130	49.6	392	50.5	0.9 [0.7-1.3]	86	50.9	362	50.8	1.0 [0.7-1.5]	44	47.3	332	50.3	0.8 [0.5-1.3]
IX-X	1	0.4	1	0.1	-	1	0.6	1	0.1	-	0	0.0	1	0.2	-
Highest category ever															
I-II	86	32.8	231	29.7	1	58	34.3	211	29.6	1	28	30.1	201	30.5	1
III-V	58	22.1	194	25.0	0.8 [0.5-1.2]	35	20.7	183	25.7	0.7 [0.5-1.2]	23	24.7	167	25.3	0.8 [0.4-1.5]
VI-VII	105	40.1	307	39.5	1.1 [0.7-1.5]	71	42.0	276	38.8	1.2 [0.8-1.8]	34	36.6	257	38.9	0.9 [0.5-1.5]
VIII	10	3.8	40	5.1	0.8 [0.5-1.2]	2	1.2	38	5.3	0.5 [0.3-1.0]	8	8.6	31	4.7	1.0 [0.6-1.6]
IX-X	3	1.1	5	0.6	2.2 [0.5-10.4]	3	1.8	4	0.6	3.5 [0.7-17.7]	0	0.0	4	0.6	-

Table 4: continued.

Ever held job															
I-II	86	32.0	231	29.0	1.1 [0.8-1.5]	58	34.1	211	29.1	1.1 [0.7-1.5]	28	28.3	201	29.5	1.2 [0.7-1.9]
III-V	92	34.2	308	38.6	0.7 [0.5-1.0]	58	34.1	286	39.4	0.6 [0.4-0.9]	34	34.3	268	39.3	0.9 [0.5-1.4]
VI-VII	166	61.7	494	62.0	1.2 [0.9-1.6]	110	64.7	453	62.5	1.2 [0.8-1.7]	56	56.6	413	60.6	1.1 [0.7-1.7]
VIII	130	48.3	392	49.2	1.0 [0.7-1.3]	86	50.6	362	49.9	1.0 [0.7-1.4]	44	44.4	333	48.8	1.0 [0.6-1.5]
IX-X	17	6.3	30	3.8	2.2 [1.1-4.2]	13	7.6	23	3.2	2.4 [1.1-5.0]	4	4.0	22	3.2	1.6 [0.5-4.8]

[1]Categories were assigned as follows: I=Higher service (includes mostly professionals, large enterprise employers and higher managers (>10 subordinates)); II=Lower service (Includes mostly associate professionals, Lower managers (1-10 subordinates), higher Sales); III=Routine clericales/sales (Includes routine clerical and sales workers); IV=Small employers (Includes small entrepreneurs (1-10 subordinates); V=Independent (Own account workers, no employees, artists); VI=Manual foremen (Manual workers with supervisory status (>1 subordinate)); VII=Skilled manual (Mostly craft workers, some skilled service, skilled machine operators, also gardeners); VIII=Semi-unskilled manual (Mostly machine operators, elementary sales services and state work creation scheme); XI=Farm workers‡ (Employed farm workers, irrespective of skill level; also family farm workers); X=Farmers/Farm managers (Self-employed and supervisory farm workers, irrespective of skill level). Frequencies and calculations for social status ever held. ‡: only Farm workers and forestry workers.

Discussion

Different methods of assigning social position may produce different results in terms of trends in health and inequality (31, 32). Four indicators of social groupings were analysed in this study. School education was not observed to have an impact on testicular cancer risk. The elevated risk observed for professional training as compared to no training was restricted to the seminoma subgroup. Overall, there was no hint in this study that examined social factors are associated with testicular cancer. This result is in line with other newer studies (11, 17).

Elevated risks in association with EGP other than agriculture were not observed in this study. An excess risk in agriculture and related occupations was also observed in several studies (9, 33-35). Increased risks in agriculture and related occupations are not explained by social factors but rather with exposures such as pesticides (33, 35), fertilizers (36, 37) or contact with farm animals and zoonotic infections (33) which were not in the scope of this study.

No increased risks were observed for non-agricultural occupational sectors based on the EGP which is in line with other studies (14, 21, 38). Also, no evidence was found that socioeconomic status (ISEI) is associated with testicular cancer. This indicates that factors other than occupation as a mediating variable between income and education may be responsible for testicular cancer risk.

Neither EGP categories nor continuous hierarchy by ISEI were a risk factor for testicular cancer in this study. If a social gradient for testicular cancer in Germany existed in the past and exposures were associated with this gradient, this gradient was attenuated by omnipresent exposures that do not differ by social circumstances. The rising trends of testicular cancer in industrialised countries may be an indirect indication for alignment of social dependent exposures.

This study has several limitations. First, the study suffered from low response (cases 76%, controls 57%). For the study region of Hamburg participation was lower among controls with lower education which might have resulted in an overestimation of the risk in the lower SES status groups. Hence, it is possible that a participation bias might have biased the effect estimates. Sensitivity analysis by leaving out Hamburg revealed similar findings, which could also be explained by specifics of the population structure of Hamburg.

Second, misclassification of social status is likely to have occurred. As the assessment of the social status is not based on a dichotomous variable, the direction of bias due to non-differential misclassification cannot be predicted.

Third, periods of unemployment and illness cannot be ranked by both scales utilised in this study. Non-consideration of such periods may lead to an underestimation of any social difference (39).

The strength of this study is to measure occupational social factors on the basis of full detailed life history of occupations. This information was obtained by in-person interviews. Population based controls were used in this study, which permits full examination of social differences. Study subjects were not aware of this study hypothesis, and occupational biography is an unprejudiced variable, so reporting bias is not likely to occur. Different possible confounding variables were considered by adjusting for post-educational degree or medical confirmed undescended testis and job frequency. However, the results were stable in all analyses.

Conclusion

The absence of an effect was not specific to the ISEI score, as another occupational scaling method, the EGP, was not related to testicular cancer, except farming and farm related working. It is unclear how this negative finding for occupation can be explained, but it may point to different social indicators telling different things about groups differing in age or other characteristics. The findings support the hypothesis that social inequalities in testicular cancer are not be based upon differences in occupational sectors or derived SES. More information is needed on the specific social correlates (e.g. work characteristics, living areas), since education and occupation are not only indicators of access to material properties, but also correlates with psychosocial properties.

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2.4 Life course social mobility and risk of upper aerodigestive tract cancer in men

Schmeisser N, Conway DI, McKinney PA et al.: Eur J Epidemiol. 2010; 25:173-82.

Abstract

Background: The aim of this study was to explore associations between social mobility and tumours of the upper aero-digestive tract (UADT), focussing on life-course transitions in social prestige (SP) based on occupational history.

Methods: 1796 cases diagnosed between 1993 and 2005 in ten European countries were compared with 1585 controls. SP was classified by the Standard International Occupational Prestige Scale (SIOPS) based on job histories. SIOPS was categorised in high (H), medium (M) and low (L). Time weighted average achieved and transitions between SP with nine trajectories: H→H, H→M, H→L, M→H, M→M, M→L, L→H, L→M and L→L were analysed. Odds ratios (ORs) and 95%-confidence intervals [95%-CIs] were estimated with logistic regression models including age, consumption of fruits/vegetables, study centre, smoking and alcohol consumption.

Results: The adjusted OR for the lowest versus the highest of three categories (time weighted average of SP) was 1.28 [1.04−1.56]. The distance of SP widened between cases and controls during working life. The downward trajectory H→L gave an OR of 1.71 [0.75−3.87] as compared to H→H. Subjects with M→M and L→L trajectories ORs were also elevated relative to subjects with H→H trajectories.

Conclusions: The association between SP and UADT is not fully explained by confounding factors. Downward social trajectory during the life course may be an independent risk factor for UADT cancers.

Keywords: laryngeal cancer, pharyngeal cancer, oral cancer, oesophageal cancer, case-control study, socioeconomic status

Introduction

Tumours of the oral cavity, larynx, oropharynx, hypopharynx and oesophagus are designated as upper aero-digestive tract tumours (UADT). Approximately 100,000 men are diagnosed with UADT per year in the European Union [1,2]. The multifactorial origin of these tumours is well-known. The most important risk factors are consumption of alcohol and tobacco, and the combined exposure leads to a multiplicative risk for these tumour sites [3]. High intake of fruit and vegetables has a protective effect [4-6].

Some epidemiological studies show that employment in several industries with occupational exposures to asbestos, acid mists or solvents are associated with an increased risk of UADT [7]. Occupational characteristics may not only have an effect on cancer outcome via exposures but also by influencing opportunities for social and economic participation and affecting circumstances. In addition, occupation may be a basic variable for lifestyle and psychosocial determinants of health related behaviour [8-10].

Associations between socioeconomic status (SES) and UADT have been observed in several studies, and low SES has been linked to an increased risk of different sites of UADT, independent from other risk factors for this cancer [11-16].

Social status is usually measured by education, income or occupation. An additional dimension is the degree of desirability of a given occupation, which is an expression of its social prestige (SP). The *Standard International Occupational Prestige Scale* (SIOPS) [17] assigns occupational roles to an occupational prestige hierarchy expressed in scores. The SIOPS is based on a large set of data from studies in 59 countries. It showed to be invariant over time and comparable between countries [17,18]. The ranks of the SIOPS range from 78 points for physicians and some other occupations with higher education like university teachers to 14 points for unskilled workers in the agricultural sector. How social hierarchy affects health outcome is not fully understood. Modifiable lifestyle factors may explain the effect [19,20].

The aim of this study was to explore associations between social mobility and UADT, focussing on life-course transitions in SP and to asses the role of known risk factors of UADT on this association. This analysis is restricted to men because occupational biographies of women tend to be affected by economically inactive periods [21].

Population and Methods

In accordance with the requirements of the local Institutional Review Boards in 14 centres of 10 European countries (Czech Republic, Germany, Greece, Italy, Ireland, Norway, United Kingdom, Spain, Croatia and France) incident cases of UADT were contacted personally through weekly monitoring of the included hospitals. Cases included in this study had a histology confirmed diagnosis of different entities of UADT (Oral cavity (ICD-10: C00.3-C09.9; ICD14.0-ICD14.9), Larynx (ICD-10: C32.0-C32.9), Oropharynx (ICD-10: C10.0-C10.9), Hypopharynx (ICD-10: C12.0-C13.9) and Oesophagus (ICD-10: C15.0-C15.9).

In each center, controls were frequency-matched to cases by age (5-year groups) and sex. In the UK centres, population controls were randomly selected from the same community medical practice list as the corresponding cases. Specifically, for each case, a total of 10 controls were selected, matched by age and sex. Potential controls were approached in random order one at a time until one agreed to participate [22]. In all other centres hospital admitted controls for a wide spectrum of medical conditions were ascertained [23]. None of these patients had malignant tumours or diseases associated with alcohol consumption or smoking. In the hospital based centres subjects from rural or remote areas were included, but this variable was not provided for analysis.

A structured questionnaire was used and blood samples were taken to analyse risk factors and genetic susceptibility on cancer outcome in UADT. Data were pooled, controlled and managed at the International Agency for Research on Cancer (IARC), Lyon.

A standardized questionnaire was applied by a face-to-face interview to cases and controls to obtain information on demographic details, physical constitution and occupational history. Past and present smoking and alcohol consumption, diet, and medical factors were assessed in detail.

A detailed occupational history was recorded by year of beginning and end, job title and branch of industry for each occupational period held at least three years on the basis of performed tasks and industry. In every centre job descriptions and titles were coded blindly to case/control status in respect to the *International Standard Classification of Occupations* [ISCO] version from 1968 [24].

The recruitment period of controls and incident cases for the French study took place between 1987 and 1992 and for all other participating centres between 2002 and 2005. A case-control ratio of at least 1:1 was aspired. All included subjects were Caucasian.

Detailed information about the study population and the study design is described elsewhere [23].

Assessment of Social Prestige

All occupational biographies were checked for plausibility (e.g. correct order of starting and ending years of jobs, duration of education and work biographies). Incomplete job histories were discarded from the analysis dataset. The study sample comprised 1796 cases and 1585 controls after exclusion of 55 cases and 76 controls due to incomplete job biographies or other explaining variables.

To compare different job titles from different countries the *ISCO* was utilized. ISCO-codes were connected with SIOPS-values using a matrix for each job period. After restriction to the first three ISCO digits 267 different job titles were derived. SP was grouped in three categories each spanning over an equal number of occupations.

For periods with two parallel jobs the maximum value of SP of both jobs was taken. Occupations in a family context, honorary working and subsistent farming were excluded. The duration of a job period was calculated by subtracting year of start from year of end plus 0.5.

SP was analysed at different time points: SP value of first job or value for job held at age of at least 18, last occupation, maximum and time-weighted average mean of all occupations. Time weighted average of SP was defined as the sum of the products of SP of the jobs held and the duration of this job divided through the total time employed. SP was categorised in tertiles (H=high, M=medium, H=high) with the highest category as reference. The maximum SIOPS score was assessed for each 10-year age interval between the age of 21 and 60. For the age groups 20 years and below as well as 60 years and older analyses were done without age constraint.

Transitions were analysed by grouping SIOPS values into three classes based on the three categories as mentioned above. Transitions between these categories were analysed for first job to last job and first job to job with maximum SIOPS value. Nine socioeconomic trajectories were analysed: (1) H→H, (2) H→M, (3) H→L, (4) M→ H, (5) M→M, (6) M→L, (7) L→H, (8) L→M and (9) L→L.

Statistical Analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (95%-CIs) were calculated with logistic regression models which included the following variables: age (9 categories: <40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75+ years) dummy variables for each study centre, smoking status (never, former and current smoking) and alcohol intake (never, former and current drinking). Lifetime tobacco consumption was classified in 5 categories (0, >0-<20, 20-<40, 40-<60 and 60+ pack-years). Alcohol intake was classified in 5 categories of drinks per day (<1, 1-2, 3-4, 5+, unknown). The total consumption per week was summed up for all fruit and vegetable variables to get a total fruit or vegetable consumption/week variable. Frequency of fruit and vegetable consumption was categorised by country specific tertiles as low, medium and high [25]. The highest level of SP was chosen as the reference category.

ORs were estimated by unconditional logistic regression analysis, using the PROC LOGISTIC function of the SAS software package, Version 8.2. The logistic regression model 1 included age and study centre (OR_1). The logistic regression model 2 included variables smoking status (never, former, current) and cumulative consumption of tobacco, alcohol status (never, former, current) and daily alcohol intake, 2 variables for fruit and vegetable intake frequency in addition to variables in model 1 (OR_2). Differences between cases and controls in categorical variables were tested by a χ^2-statistic. Analyses were also done by stratification for site of UADT (oesophagus, hypopharynx and larynx, oral cavity and oropharynx).

Results

The size of the study population and the ratio of cases to controls varied between countries. The mean age differed only marginally between cases and controls. Cases of UADT were born between 1901 and 1985, controls between 1902 and 1983. Mean age and standard deviation at time of interview for cases was 59.2±9.6 (median: 59), for controls 59.3±10.7 (median: 59) years (Table 1). More than 80% of tumour cases were diagnosed with tumours of the larynx and hypopharynx (N=785; 43.7%) or oral cavity and oropharynx (N=760; 42.3%). Tumours of the oesophagus (N=169; 9.4%) were less frequent. For 82 cases (4.6%) it was not possible to assess the site of origin within the UADT (data not shown).

Consumption of tobacco and alcohol ever was more frequent in cases than in controls. About 50% of cases had accumulated 40 pack-years or more or drunk at least three drinks a day, as compared to 20% of controls. Almost half of the cases were classified as low fruit or vegetables consumers (data not shown).

Table 1: Age distribution of study population in accordance to study centre and case control status

	Analysed study population						
	Cases			Controls			
Country (Centre)	N	%	Age	N	%	Age	
			Mean (Range)			Mean (Range)	Ca/Co-Ratio
Czech. Republic (Prague)	158	8.8	57.5 (35-76)	148	9.3	59.5 (37-78)	1.07
Germany (Bremen)	225	12.5	58.2 (42-77)	255	16.1	58.4 (37-81)	0.88
Greece (Athens)	192	10.7	61.2 (18-82)	136	8.6	62.0 (29-96)	1.41
Italy (Aviano)	120	6.7	61.0 (40-71)	118	7.4	60.9 (41-80)	1.02
Italy (Padova)	108	6.0	61.4 (40-78)	93	5.9	60.8 (26-79)	1.16
Italy (Turin)	115	6.4	60.7 (28-78)	141	8.9	59.2 (32-79)	0.82
Ireland (Dublin)	29	1.6	59.4 (43-85)	5	0.3	51.4 (25-68)	5.80
Norway (Oslo)	119	6.6	60.6 (37-80)	106	6.7	59.6 (26-80)	1.12
UK (Glasgow)	59	3.3	58.8 (41-79)	44	2.8	62.8 (45-81)	1.34
UK (Manchester)	104	5.8	58.7 (34-80)	116	7.3	59.7 (36-78)	0.90
UK (Newcastle)	71	4.0	61.4 (40-80)	87	5.5	61.4 (41-90)	0.82
Spain (Barcelona)	163	9.1	59.4 (36-95)	95	6.0	61.2 (20-96)	1.72
Croatia (Zagreb)	45	2.5	54.9 (32-72)	36	2.3	59.0 (34-83)	1.25
INSERM (France)	288	16.0	55.3 (22-89)	205	12.9	54.1 (25-88)	1.40
							1.13
Total	1796		58.9 (18-95)	1585		59.3 (20-96)	

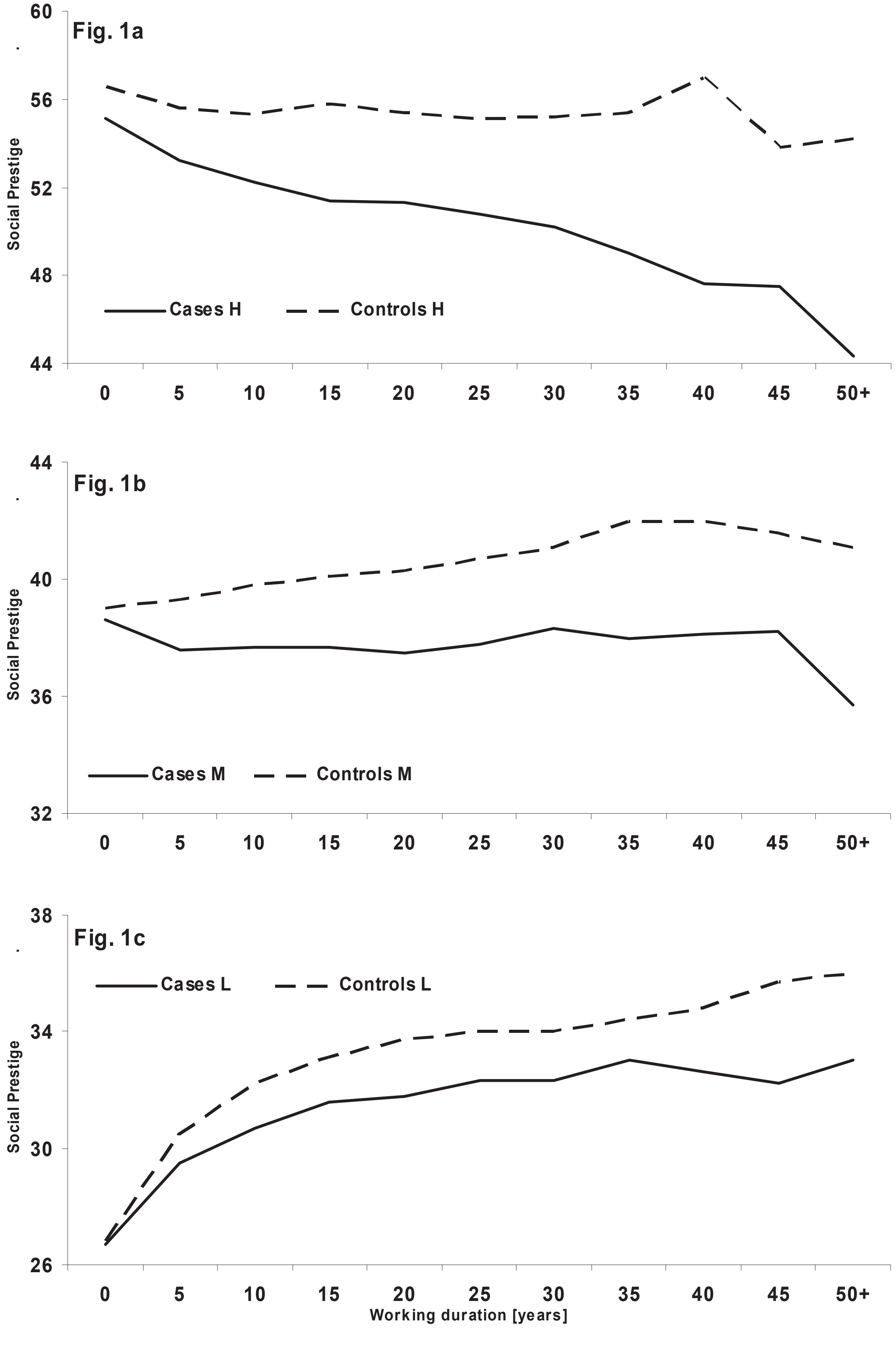
Occupational characteristics

The number of economically active periods including military services varied between 1 and 12 job periods for cases and 1 and 13 job periods for controls. 90% of cases and controls had less than 6 job periods with a median of 2 for cases and 3 for controls (mean values for cases=2.8; controls=2.9). The mean values for duration of work at time of interview were 35.2 years for cases and 35.6 years for controls, excluding economically inactive periods (unemployment, imprisonment, house husband, disease).

Social prestige of occupations

Risk estimates of the time-weighted average of SIOPS for the all UADT and for the different subsites are presented in Table 2. Similar associations were observed for the SP of the job held longest, the maximum SP during working life and the SP of the last occupation, while for the SP of the first job held no association was observed (not shown).

Over the life course cases showed a lower SP than controls while the distance of SP values between cases and controls increased regardless of the level at which they started their careers (Figures 1a-c). The mean SP value for all occupations for cases was 36 and 39 for controls. The median value of SP was two points and one point lower than the mean in cases and controls, respectively. In general, upward trends were seen among controls, regardless of the starting level, while cases decreased when starting from the high category and seemed to have no upward trend when starting in category M. Cases starting in the L category showed a slower rise of SP than controls in this category.



Figures 1a; 1b; 1c: Development of mean value of social prestige for cases and controls following their occupational biography, grouped in respect of their first occupational prestige into high (H, fig. 1a), medium (M, fig. 1b) and low (L, fig. 1c). Only cases and controls which were economically active were considered. Number of cases declined continuously in respect of age and economically inactive periods from 1796 to 189, number of controls from 1585 to 220 subjects. Number of cases starting in category H, M and L were 266, 791 and 739, number of controls 304, 695 and 586.

Table 2: Distribution of cases and controls for achieved time weighted SIOPS values for whole study population and for entities of UADT.

	Time weighted Average					
	complete study[‡]					
		Cases		Controls		
SIOPS	N	%	N	%	OR_1 [95%-CI]	OR_2 [95%-CI]
H	345	19.21	474	29.91	1[†]	1[†]
M	730	40.65	652	41.14	1.50 [1.25-1.78]	1.08 [0.88-1.31]
L	721	40.14	459	28.96	2.04 [1.70-2.45]	1.28 [1.04-1.56]
	Oral cavity and oropharynx[‡]					
		Cases		Controls		
	N	%	N	%	OR_1 [95%-CI]	OR_2 [95%-CI]
H	151	38.55	474	29.91	1[†]	1[†]
M	316	41.58	652	41.14	1.43 [1.14-1.80]	1.04 [0.81-1.33]
L	293	19.87	459	28.96	1.81 [1.43-2.30]	1.15 [0.89-1.50]
	Hypopharynx and larynx[‡]					
		Cases		Controls		
	N	%	N	%	OR_1 [95%-CI]	OR_2 [95%-CI]
H	146	40.51	474	29.91	1[†]	1[†]
M	321	40.89	652	41.14	1.57 [1.25-1.98]	1.10 [0.85-1.43]
L	318	18.60	459	28.96	2.13 [1.69-2.70]	1.24 [0.95-1.62]
	Oesophagus[‡]					
	Cases		Controls			
	N	%	N	%	OR_1 [95%-CI]	OR_2 [95%-CI]
H	31	18.34	474	29.91	1[†]	1[†]
M	60	35.50	652	41.14	1.56 [0.98-2.48]	1.24 [0.77-1.99]
L	78	46.15	459	28.96	2.84 [1.81-4.47]	2.02 [1.26-3.23]

[†]Reference. OR_1: adjusted for age and study centre, OR_2: adjusted for age, study centre, smoking status, cumulative tobacco consumption, alcohol drinking status, alcohol drinking frequency, fruit and vegetable intake frequency.
[*]Categories chosen for an equal frequency of occupations within scaling points. Number of occupations of the social prestige categories L=14-33, M=34-45 and H=46-78 were 87, 88 and 91. [‡]Cochran-Armitage Trend Test<0.001.

Cases had more downward than upward transitions in their career than controls ($p<0.0005$). While 22.5% of the cases moved downward 19.8% of controls had this trend. Vice versa, upward transitions were more frequent in controls (32.2%) than in cases (26.0%). In 478 cases (26.6%) and 413 controls (26.1%) up- and downward mobility was balanced.

Table 3 displays the risk estimates in relation to transitions of SP. The highest risks were observed for the change H→L from the first occupation to the occupation with the maximum SP thereafter (OR_2 1.71 [95%-CI: 0.75-3.87]) while no risk elevations were observed for the downward transition M→L (OR_2=1.08 [95%-CI: 0.75-1.54]) and only a modest elevation was seen for L→L (OR_2=1.24 [95%-CI: 0.95-1.61]) (reference H→H).

The transition H→L (first to last occupation) resulted in an OR_2 of 1.58 [95%-CI: 0.85-2.94] while the corresponding transition H→M resulted in an OR_2 of 1.51 [95%-CI: 0.84-2.72]. An elevated risk was observed in all men who descended from a higher to a lower class. The risks were similar for M→L (OR_2=1.28 [95%-CI: 0.95-1.73]) and M→M

(OR_2=1.33 [95%-CI: 1.02-1.73]) and slightly weaker for L→L (OR_2=1.24 [95%-CI: 0.96-1.62]).

The risk was elevated for at least 21% for class stability in all these analyses. Furthermore, upward transitions were associated with no or a reduction in risk of UADT.

The maximum difference in SP observed in occupational biographies of study subjects varied between +51 and -41 points. Increased risk estimates were also found in subjects who never changed their job, regardless of whether the first occupation was classified as H, M or L (data not shown).

Table 3: Distributions and risk estimates with 95%-confidence intervals of transition in SP for first occupation to occupation with maximum value achieved at any time, first occupation to social status prestige at last occupation and for maximum value occupation to last occupation for cases and controls.

First occupation to occupation with maximum prestige						
	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
	N	%	N	%		
H→H	215	11.97	267	16.85	1†	1†
H→M	31	1.73	25	1.58	1.53 [0.87-2.67]	1.11 [0.60-2.05]
H→L	20	1.11	12	0.76	2.00 [0.95-4.19]	1.71 [0.75-3.87]
M→H	175	9.74	230	14.51	1.01 [0.77-1.32]	1.01 [0.75-1.37]
M→M	496	27.62	374	23.60	1.70 [1.36-2.13]	1.26 [0.98-1.62]
M→L	120	6.68	91	5.74	1.68 [1.21-2.33]	1.08 [0.75-1.54]
L→H	105	5.85	134	8.45	1.01 [0.74-1.39]	0.76 [0.54-1.08]
L→M	222	12.36	184	11.61	1.56 [1.19-2.04]	0.98 [0.73-1.32]
L→L	412	22.94	268	16.91	1.93 [1.52-2.33]	1.24 [0.95-1.61]
Change of SP from first occupation to last occupation						
H→H	194	10.80	256	16.15	1†	1†
H→M	37	2.06	26	1.64	1.89 [1.10-3.22]	1.51 [0.84-2.72]
H→L	35	1.95	22	1.39	2.12 [1.20-3.73]	1.58 [0.85-2.94]
M→H	125	6.96	192	12.11	0.93 [0.69-1.24]	0.97 [0.70-1.34]
M→M	425	23.66	330	20.82	1.76 [1.39-2.23]	1.33 [1.02-1.73]
M→L	241	13.42	173	10.91	1.95 [1.48-2.56]	1.28 [0.95-1.73]
L→H	80	4.45	96	6.06	1.14 [0.80-1.63]	0.88 [0.60-1.30]
L→M	142	7.91	128	8.08	1.52 [1.12-2.06]	0.91 [0.64-1.27]
L→L	517	28.79	362	22.84	1.94 [1.54-2.45]	1.24 [0.96-1.62]

†Reference. OR_1: adjusted for age and study centre, OR_2: adjusted for age, study centre, smoking status, cumulative tobacco consumption, alcohol drinking status, alcohol drinking frequency, fruit and vegetable intake frequency. * Categories chosen for an equal frequency of occupations within scaling points L=14-33, M=34-45, H= 46-78.

Table 4: Distributions and risk estimates within 95%-confidence intervals for maximal social prestige achieved in 10-year intervals of age for cases and controls.

	Age 21-30					
	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
SP	N	%	N	%		
H	399	22.43	489	31.29	1[†]	1[†]
M	825	46.37	688	44.02	1.49 [1.26-1.76]	1.13 [0.94-1.36]
L	555	31.20	386	24.70	1.75 [1.46-2.11]	1.18 [0.96-1.45]
total	1779		1563			
	Age 31-40					
	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
SP	N	%	N	%		
H	418	23.55	551	35.16	1[†]	1[†]
M	712	40.11	570	36.38	1.64 [1.39-1.95]	1.26 [1.04-1.52]
L	645	36.34	446	28.46	1.90 [1.60-2.27]	1.32 [1.09-1.61]
total	1775		1567			
	Age 41-50					
	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
SP	N	%	N	%		
H	428	25.07	543	36.30	1[†]	1[†]
M	626	36.67	508	33.36	1.57 [1.32-1.86]	1.16 [0.96-1.41]
L	653	38.25	445	29.75	1.85 [1.55-2.21]	1.24 [1.01-1.50]
total	1707		1496			
	Age 51-60					
	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
SP	N	%	N	%		
H	331	26.12	428	37.19	1[†]	1[†]
M	427	33.70	383	33.28	1.41 [1.16-1.72]	1.11 [0.89-1.39]
L	509	40.17	340	29.54	1.90 [1.55-2.32]	1.28 [1.02-1.60]
total	1267		1151			
	Age >60					
	Cases		Controls		OR_1 [95%-CI]	OR_2 [95%-CI]
SP	N	%	N	%		
H	93	25.91	189	48.09	1[†]	1[†]
M	97	27.02	100	25.45	1.95 [1.34-2.85]	1.43 [0.95-2.16]
L	169	47.08	104	26.46	3.39 [2.37-4.86]	2.62 [1.78-3.86]
total	359		393			

[†]Reference. OR_1: adjusted for age and study centre, OR_2: adjusted for age, study centre, smoking status, cumulative tobacco consumption, alcohol drinking status, alcohol drinking frequency, fruit and vegetable intake frequency. Total indicates the number of 1796 cases and 1858 controls which were economically active for at least one year within the specific 10-year interval and considered for analyses. [*]Categories chosen for an equal frequency of occupations within scaling points L=14-33, M=34-45, H= 46-78.

Risk development at different points of age

Figure 2 shows that the difference of mean SP values between cases and controls increased continuously with increasing age. For class M and L cases and controls showed a continuous increase of SP until the age of 50. While the SP values continue to rise until the age of 60 in controls, it remains more or less stable in cases and drops down after the age of 60. Table 4 displays the corresponding risk estimates relative to the highest SP category by 10 year age groups which reflect these curves, especially for OR_1. Further adjustment reduces the risk estimates substantially but the elevated risk remains, predominantly in the older age groups.

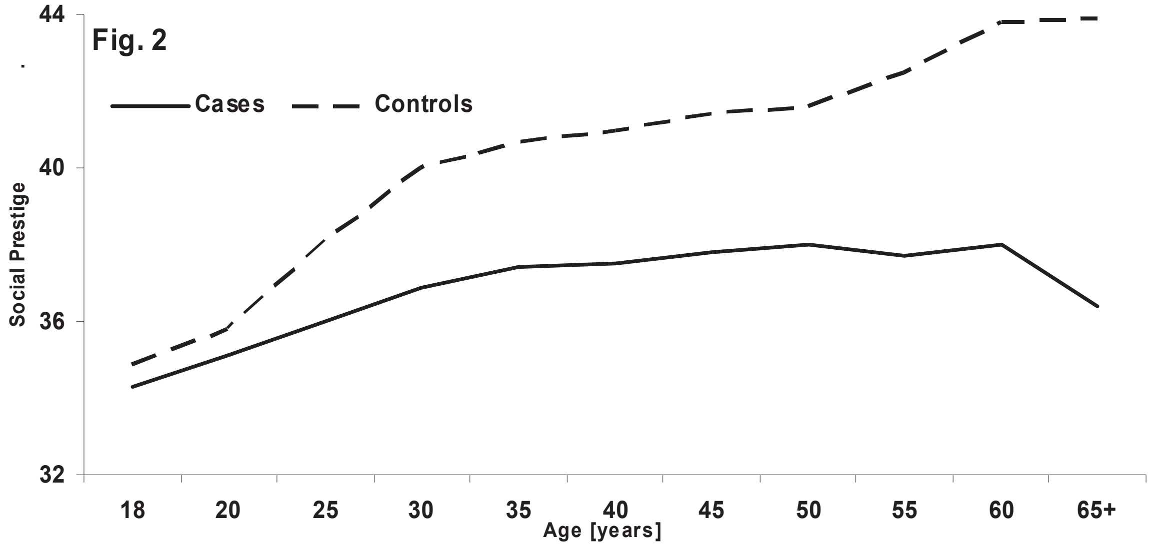


Figure 2: Development of mean value of social prestige for cases and controls according to age. Number of cases from 18 to 65+ were 1318, 1444, 1688, 1746, 1741, 1702, 1585, 1337, 971, 518, 183 and number of controls 1078, 1224, 1453, 1533, 1531, 1496, 1400, 1209, 907, 520, 212.

Discussion

These analyses of 1796 cases and 1585 controls aimed to identify the effect of occupational prestige differences on the risk of developing UADT. A negative relationship between occupational prestige and downward trajectories of SP during lifetime and the risk of UADT was seen. This corroborates findings by Menvielle and co-workers who found an increased risk for UADT cancers for transitions from white collar jobs to blue collar jobs [15]. However, in contrast to this study, these results were not adjusted for main risk factors. The adjustment for alcohol and tobacco consumption attenuated the effect of SP on the risk of UADT tumours substantially. Further adjustment for frequency of fruit and vegetable intake had only a small attenuating effect. Nevertheless, after controlling for alcohol/ tobacco consumption and for the frequency of fruit and vegetable intake a relevant effect of SP persisted.

Residual confounding in aspects of alcohol and tobacco consumption should be a minor problem in this study. Every change in tobacco and alcohol consumption pattern was an integral part of the interview. The questionnaire used in the INSERM study differed from all other questionnaires of the pooled study with respect to fruit and vegetable items. A sensitivity analysis excluding the INSERM data did not alter the risk estimates.

In this study hospital controls with diseases related to smoking and alcohol consumption were excluded. Alcohol and tobacco consumption of controls in this study were comparable to those in other case control studies [5,14,26-29]. Since interviewers were not always blinded to the case-control status of a study subject, an information bias can not be ruled out, especially regarding behaviours that are socially desirable like non-smoking and low alcohol consumption. In the case of an underreporting of smoking by cases this might lead to an overestimation of the effect of SP on the risk of UADT tumours even after adjustment. On the other hand, hospital based case-control studies considering education, social status and SP as risk factors are prone to an underestimation of effects because hospitalization is more frequent in lower social classes [30].

Galobardes [31] pointed out that childhood social status has an influence on later health outcomes. This may be mediated through school education that determines later employment opportunities via different pathways [32,33]. This study did not include information on parental social class. Parental SES influence childhood socioeconomic prospects including social and economic resources particularly education which affects adult SES [34]. However, occupational status may be considered as a factor with an effect that lasts continuously and having more influence on health outcomes than education.

Educational and occupational opportunities may differ by economic system and over time. No differences were found when data from the two study centres of former socialist states Croatia and Czech Republic were analysed separately (data not shown). In addition, there was no difference observed by leaving French subjects (recruitment period: 1987-1992) from analysis. Different willingness to be interviewed can be a possible element of bias for SP. In view of a 68% participation rate in this study such an effect may be small.

The strength of this study is the measure SP on the basis of full detailed life history of occupations. This information was obtained by in-person interviews; no surrogate interviews were taken. In addition, the study participants were not aware of the SP analysis. Performed tasks and occupations are reported accurately even if the interviewer is aware of the case-control status [35].

SIOPS can be measured exactly through the occupational title and allows a much more differentiated ranking of job titles than the traditional classification into manual and non-manual workers. A further advantage is its unambiguous hierarchical order. Differences can be expressed in terms of exact numerical values, but periods of unemployment and illness cannot be ranked by this scale. Non-consideration of such periods may lead to an underestimation of any SP differences [36].

The strongest negative association between SP and tumour risk was observed for tumours of the oesophagus, while for tumours of the hypopharynx and larynx the associations were weak. The strongest risk was observed for transition from high to low SP while reduced risk was observed for low to high transitions, although this was based on a small number of observations.

Pre-diagnostic health problems of cases could influence the most recent SP transition by reducing the chance to change into higher positions and increasing the chance for downward transitions. However, this is not a plausible explanation of the results since only occupations with a duration of at least three years were solicited in the ARCAGE-questionnaire and an increased risk for maximum SP at age 21-30 to age 51-60, i.e. long before the disease was diagnosed was also observed.

Alcohol abuse may have an independent and direct effect on transitions of SP. Different studies show consequences of high alcohol consumption and binge drinking, including economic loss due to time off work because of alcohol-related illness or injury, unemployment, disruption of family and social relationships, emotional problems and impact on perceived health [37-42]. Patterns of alcohol consumption differ by social class, e.g. members of higher social classes tend to drink more frequently, while members of lower classes tend to drink more heavily [40,41,43].

Smoking and alcohol behaviours seem to explain most of the risks associated with socioeconomic mobility [44]. However, the main finding in this study is the association between downward transitions of SP and UADT tumours which is attenuated but not eliminated after adjustment for alcohol and tobacco consumption and fruit and vegetable intake frequency. Despite different methods used to assess social inequality, the findings of our study are consistent with previous studies [11,15,27,45,46]. A particular causal mechanism by which SP acts on the development of UADT cancers remains to be elucidated. The complexities of occupational circumstances and how they interact with other causal factors associated with social status is not entirely clear and can not be disentangled completely in such an analysis.

The pathway from social factors to biological change in the aetiology of cancer is not entirely clear, but emerging hypotheses include the ‘biological ageing’ effects resulting from pour socioeconomic circumstances [47]. The biological ageing hypothesis basically proposes that poor people age faster due to the social and physical environments to which they are exposed, such that poor people die younger, but from the same conditions as their richer counterparts. There may also be a genetic role within this socioeconomic –biological ageing- cancer aetiological pathway, perhaps mediated by shortened telomeres [48-51].

However, research of the psychosocial mechanisms through which inequality may act, focuses on investigating the biologically plausible pathways between inequalities through loss of social capital and the resulting psycho-physiological stresses it brings. Neuroendocrine responses, including the chronic secretion of stress-response hormones, and in particular the inability to cope or recover from this, may have an impact on the immune system, especially in relation to the cardiovascular system [52]. Most of the evidence on this is related to cardiovascular disease and less regarding cancer aetiology. However, it is possible to see a potential link in that the immune system, and a chronic inflammation in particular, have been implicated in the aetiology of cancer [53].

A further potential strand to the psychosocial explanation comes from the work by Everson and colleagues (1996). In their Finish longitudinal study they found men with high self-rated feelings of “hopelessness”, which correlated with low socioeconomic status, were at increased cardiovascular and cancer risk. This suggests a possible association with mental health conditions.

The psychosocial mechanisms may help elucidate the physiological pathway leading from downward socioeconomic mobility to UADT cancer risk observed over and above the behavioural risk factors. Specifically, these results may have some parallels in the research of psychosocial effects of work stress although as yet there is only empirical evidence in relation to coronary heart disease, musculoskeletal disorders, and mental illness [52]. The lower intake of fruit and vegetables observed among cases compared to controls might be a further hint for a psychosocial impact, since persons with low awareness or with low family connectedness are found to consume less often fruit and vegetables [54-56].

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3 Hinführung Methodendiskussion

In vier Manuskripten werden auf Basis von Fragebogendaten unterschiedliche Verfahren angewandt, um das Risiko auf verschiedene Krebslokalisationen zu untersuchen. Den vorgenommenen Expositionseinstufungen liegen die Berufsbiografie betreffende persönliche Angaben der Studienteilnehmer zugrunde. Die untersuchten Expositionen sind von unterschiedlicher Qualität. Expositionen gegenüber Pestiziden, also stoffliche Expositionen, stellen Situationen dar, die an einen Arbeitsprozess gebunden sind, während die Einstufung des sozialen Status anhand des Berufs eine Situation beschreibt, die auch außerhalb des Berufslebens wirkt. Jede Studie benutzt eine unterschiedliche Methode der Einstufung der Pestizidexposition bzw. des sozialen Status basierend auf Fragebogenangaben. In den vorgelegten Manuskripten wurden für das Thema sozialer Status/Faktoren grundsätzlich andere Herangehensweisen der Schichteinstufung genutzt als die Expositionseinstufung, wie sie für Pestizide eingesetzt wurde.

Diskussionen die die Einzelartikel betreffen oder dort geführt wurden, werden hier nicht erneut aufgegriffen. Vielmehr sollen allgemeine Betrachtungen, die die Methodik der Expositionseinstufung betreffen, angestellt werden.

3.1 Diskussion der Methoden

Alle Einstufungen von Pestizidexpositionen und Sozialschichtfaktoren dieser Dissertation beruhen ausschließlich auf Interviewangaben der Studienteilnehmer. Es besteht eine Reihe von Vorteilen, Selbstangaben aus Interviews zur Einstufung von Expositionen zu nutzen. Fragebögen sind ein erprobtes und aussagefähiges Werkzeug, das auf jeden Studienteilnehmer angewendet werden kann (McGuire et al. 1998). Mit dieser Methode besteht die Möglichkeit, auch zurückliegende Expositionen über eine Zeitspanne von mehreren Jahren bis Jahrzehnten zu erfassen. Diese Methode ist vergleichsweise kostengünstig, benötigt keine invasiven Methoden und stellt somit keine zusätzliche Belastung der Studienteilnehmer dar. Die Verlässlichkeit der Angaben hängt mit der Qualität und dem Niveau der gesammelten Information, d.h. der Formulierung der gestellten Fragen und der Schulung der Interviewer, zusammen. Ebenfalls ist durch die direkte Auswertung von Selbstangaben der Studienteilnehmer keine kosten- und zeitintensive Einstufung durch Experten nötig. Es stellen sich durch die Auswertung der durch Interviews gewonnenen Informationen keine zusätzlichen ethischen Bedenken, wie sie bei der Gewinnung von biologischem Material vorhanden sein könnten. Eine Gewinnung von biologischem Material ist zudem mit einem zusätzlichen Einsatz and

Gerätschaften, Personal und damit zusammenhängendem logistischen Aufwand verbunden (Teschke et al. 2002).

3.1.1 Diskussion: Soziale Faktoren

Bei der Auswertung des sozialen Status ist es in epidemiologischen Studien ein Anliegen, die Aspekte der sozialen Schicht zu identifizieren, die eng mit dem gesundheitlichen Zustand in Beziehung stehen (Berkman & Macintyre 1997).

Obwohl Bildung und berufliche Stellung im allgemeinen korrelieren, haben einige Studien gezeigt, das sie einen unabhängigen Effekt auf Mortalität und Morbidität haben (Davey Smith et al. 1998; Bosma et al. 1994; Wohlfarth 1997), was die Vermutung nahe legt, das der Gebrauch einer Variable für sozialen Status alleine nicht alle Dimensionen der sozialen Position erfasst. Darüber hinaus wurde die Wichtigkeit der Entwicklung weiterer Indikatoren herausgestellt, die andere soziale Gesichtspunkte berücksichtigen, wie die Einbindung in ein soziales Netzwerk, Einkommen und Wohlstand (Oakes et al. 2003; Coleman 1990; Liberatos et al. 1988).

In den vorgelegten Manuskripten wurde auf vorhandene Skalen, die den sozialen Status bestimmen, zurückgegriffen. Den Skalen ist gemeinsam, dass sie international anerkannt und validiert sind (Ganzeboom & Treiman 1996; Wolf 1995). Es wurden das Sozialschicht-Schema nach Erikson und Mitarbeitern (EGP) (1983) und die Einstufung des sozioökonomischen Status anhand der International Scale of Socio-Ecconomic Index (ISEI) (Ganzeboom et al. 1992) in dem Manuskript „Social factors and testicular cancer" (Kapitel 2.3), sowie das soziale Prestige anhand der Standardized International Occupational Prestige Scale (SIOPS) (Treiman 1977) in „Life course social mobility and risk of upper aerodigestive tract cancer in men" (Kapitel 2.4) angewendet. Alle diese Einstufungen basieren auf dem Vorhandensein von Berufsbezeichnungen und –titeln, die gemäß ISCO in der Version von 1968 (ILO 1968) kodiert wurden. Die in den Arbeiten verwendeten Skalen SIOPS, ISEI und EGP eignen sich durch ihre Etablierung auf die ISCO-68 Kodierung für Sekundäranalysen (Wolf 1995). Analog einer Expositionsmatrix werden EGP, ISEI und SIOPS mit den Kodierungen des Berufs verknüpft.

Angaben zur Berufsbiografie von Studienteilnehmern gelten als Variable mit einer hohen Validität und Reliabilität. In verschiedenen Studien wurde die Selbstangabe des Berufs mit externen Vergleichsdaten, wie Pensionskassen-, Gewerkschafts- und Firmendaten untersucht. Dabei zeigte sich eine 70-90%ige Übereinstimmung zwischen Selbstangabe und externer Quelle (Teschke et al. 2002).

Die Kodierung der Berufe anhand des ISCO-68 ist ein Standardverfahren. Die Überführung der Berufsangaben in den ISCO-Kode ist mit einem hohen zeitlichen Aufwand verbunden. Die Verwendung des ISCO-68 bei der Erstellung eines Index für die Einstufung der Sozialschicht entsprechend SIOPS bzw. ISEI ist in mehrerer Hinsicht sinnvoll. Die Kodierung der Berufe anhand der Berufsbezeichnung, Beschreibungen der Tätigkeit, der hergestellten Produkte sowie der Branche, in der der beschäftigende Betrieb angesiedelt ist, ist intern und extern vergleichbar. Diese Berufskodierung ist weithin akzeptiert, verlässlich und anhand der Freitextangaben durch unabhängige Kodierer überprüfbar (Geis & Hoffmeyer-Zlotnik 2001). In den vorliegenden Manuskripten wurden die ersten drei Ziffern des ISCO-Code angewendet. Mit den ersten drei Ziffern werden die Berufsgattungen, d.h. die ausgeübte Tätigkeit, zusammengefasst. Die Beschränkung auf die ersten drei Ziffern erhöht zudem die Reliabilität und Validität der Kodierung (Maaz et al. 2009).

Beruf ist eine anerkannte Grundlage für die Messung des sozialen Status, wenn auch als Grundlage der Messung weniger stabil wie Bildung. Gerade diese Eigenschaft war in dem Manuskript zur sozialen Mobilität (Kapitel 2.4) von Bedeutung. Im Manuskript zu sozialen Status (Kapitel 2.3) wurde durch die Auswertung verschiedener Parameter, wie Beruf mit dem höchsten Status oder Beruf in dem am längsten gearbeitet wurde, ein stabiles Merkmal definiert. Die Auswertung der sozialen Mobilität erschien für diese Arbeit ungeeignet, da aufgrund des niedrigen Durchschnittsalters für einen Anteil von mehr als 40% der Fälle und Kontrollen die Berufsbiografie nur zwei oder weniger Berufsphasen beobachtet wurden.

Auf weitere Informationen die sich aus dem Beruf ergeben, wie der hierarchische Status innerhalb einer Berufsgruppe, konnte und musste nicht zurückgegriffen werden. Da Berufstitel häufig Informationen zum Status als Selbständigen oder als Vorgesetzten enthalten, ist der Informationsverlust zwischen der vollständigen (die diesen Status zusätzlich erhebt) und der einfachen (die diesen Status nicht erhebt) Methode der Generierung der Klasse gering. Eine Studie der EGP-ähnlichen britischen *National Statistics Socio-Economic Classification*-Scale zeigte, dass verglichen mit der vollständigen Methode, die einfache Methode 98% der Individuen in die richtige Klasse einstuft (Rose et al. 2005).

Die Klassifizierungssysteme SIOPS und ISEI sind intervallskaliert. Ein Merkmal der Variablen ISEI und SIOPS ist die Verstetigung der Variablen beruflicher sozialer Status bzw. Prestige. Aufgrund der Zuordnung von gleichen Zahlenwerten zu unterschiedlichen Berufen kommt es zu einem Informationsverlust in Bezug auf die berufliche Tätigkeit. Eine Vermischung von beruflichen Expositionen und sozialen Status ist somit vorgegeben. Mit den in diesen Studien angewandten Methoden kann der Hypothese, dass sozial und ökonomisch benachteiligte Gruppen höheren beruflichen Expositionen ausgesetzt sind, nicht nachgegangen werden (Quinn et al. 2007).

Obwohl die Variablen soziales Prestige und sozialer Status statistisch mit $\rho=0.74$ eine hohe Korrelation aufweisen (Wolf 1995), sind die zugrunde liegenden sozialwissenschaftlichen Konzepte sehr unterschiedlich. Der mit ISEI gemessene sozioökonomische Status wird von den Autoren definiert als eine Variable, die den indirekten Einfluss auf das Einkommen maximiert und den direkten Einfluss minimiert. Ausgehend von der Überlegung, dass jede berufliche Tätigkeit (direkter Einfluss auf das Einkommen) eine bestimmte Bildung (indirekter Einfluss auf das Einkommen) erfordert und entsprechend mit einem Arbeitseinkommen entlohnt wird (Ganzeboom et al. 1992). Im Gegensatz dazu misst die Variable SIOPS das Ansehen, dass sich mit einem Beruf verbindet (Treiman 1977). Beide Skalensysteme sind in der Weise miteinander korreliert, dass Berufe, die eine hohe Bildung voraussetzen, allgemein höher angesehen und entlohnt werden, als Berufe, die einen niedrigen Bildungsanspruch haben (Ganzeboom et al. 1991).

Die Unterschiede der Variablen *Soziales Prestige* und *Sozialer Status* in ihren Konzepten lassen sich auch allgemeiner erschließen. Der Begriff *Status* wird auf Attribute einer einzelnen Person bezogen. Status ist eine *Stellung, die von einer Person aufgrund Rasse, Bildung, Geschlecht, Einkommen u. a. in der Gesellschaft eingenommen wird*.[2] Prestige ist im Gegensatz dazu das *[positive] Ansehen, die Geltung*[2] und beschreibt eine Stellung, die einer Person von außen zugewiesen wird. Beide Variablen haben zwar die gleiche Struktur, beinhalten jedoch andere Ansätze und Aussagen. Der Prestige-Status ist eine Sonderform des Status, der Beziehungen zu anderen Schichtpositionen herstellt, und sich dadurch für die Analyse der sozialen Mobilität anbietet (Hoffmeyer-Zlotnik & Geis 2003).

Die durch EGP gemessene berufliche Position ist in ihrer Definition anders geartet als die verwendeten Indizes SIOPS und ISEI. Das EGP-Schema bestimmt die Position innerhalb

[2] Der Duden in 10 Bänden Band 5. Das Fremdwörterbuch, 4., neu bearbeitete und erweiterte Auflage; Herausgegeben vom Wissenschaftlichen Rat der Dudenredaktion: Prof. Dr. Günther Drosdowski, Dr. Rudolf Köster, Dr. Wolfgang Müller, Dr. Werner Scholze-Stubenrecht

einer Ordnung der Berufe, und kann durch ihre Genese ebenfalls zu internationalen Vergleichen herangezogen werden. Das EGP-System verwendet originär 11 Klassen, die streng genommen keine Hierarchie, sondern eine Verortung in einem beruflichen System sind. Die Zuordnung in die Schichten erfolgte in der ursprünglichen Fassung selbst nach dem Prinzip der intergenerationellen sozialen Mobilität, d.h. es war gefordert berufliche Schichten zu definieren, in die vorwiegend ein- oder ausgewandert wird, bzw. Schichten, die sich als stabil erweisen. Als Grundlage diente der Beruf des Vaters verglichen mit dem Beruf des Sohnes (Erikson et al. 1983). Dieses System zeigt im Gegensatz zu ISEI und SIOPS Unterschiede in der sozialen Mobilität, d.h. für die Wahrscheinlichkeit aus einer oder in eine anderen Kategorie zu wechseln, auf (Ganzeboom et al. 1989, Ganzeboom et al. 1992). Dem EGP-Schema liegt auch ein Zugang zu materiellen Ressourcen der unterschiedlichen Berufsgruppen zugrunde. Für dieses Schema konnte in verschiedenen Arbeiten eine hohe Konstruktvalidität, d.h. die Fähigkeit in abhängigen Variablen Variationen vorherzusagen, gezeigt werden (Kunst 1996, Sacker et al. 2000).

3.1.2 Limitierungen: Soziale Faktoren

Die Einteilungen in eine soziale Schicht wurde in den vorliegenden Manuskripten im Rahmen von Sekundäranalysen, ähnlich einer Job-Exposure-Matrix (JEM) vorgenommen. In dieser Beziehung wären auch die Limitierungen die sich aus einer JEM ergeben für die vorliegenden Arbeiten zu nennen.

Durch die Anwendung dieser Skalensysteme werden auch deren Nachteile aufgezeigt. Sie können der Veränderung der Sozialstruktur nur bedingt folgen. Waren beispielsweise in Deutschland vor 200 Jahren noch 3/4 der Bevölkerung mittelbar in der Landwirtschaft beschäftigt, so waren es vor dem Jahr 2000 weniger als 3% (Kuhnen 1997). Andere Berufe erleben einen gegenteiligen Trend oder werden neu kreiert um den Anforderungen der Industrie gerecht zu werden. Eine Einstufung solcher Berufe in ein bestehendes Skalensystem ist unter Umständen problematisch und fehlerbehaftet.

Die verwendeten Systeme, die zur Einstufung in eine soziale Schicht dienten, waren dadurch anwendbar, dass die Berufshistorie der Studienteilnehmer zu dem Zeitpunkt der Entwicklung dieser Systeme ablief. In neueren Studien wird auf andere Systeme der Einstufung ausgewichen werden müssen, um den Bedingungen des Arbeitsmarkts angepasst zu sein und interpretierbare Ergebnisse zu liefern. Dabei sind Fragen, die die interne Konstitution der Studienteilnehmer erfassen, von existenzieller Bedeutung, um den

Zusammenhang von sozialen Status und stofflicher Exposition auf die Entstehung von Erkrankungen zu klären.

Durch Arbeitsmarktlagen können veränderte Bedingungen herrschen die den Einstufungen nicht entsprechen. Beispielsweise wurde in der Vergangenheit Berufen mit niedrigem Prestige, wie etwa Abfallentsorgungsarbeiter, durch Ausgleichszahlungen ein vergleichsweise hoher ökonomischer Status durch hohes Einkommen verliehen, um überhaupt einen Anreiz zu schaffen, diese Arbeit anzunehmen. Umgekehrt werden Berufe mit einem hohen sozialen Prestige durch Zeitarbeitsverträge mit dem Problem der Arbeitsplatzunsicherheit konfrontiert. Gerade für Arbeitsplatzunsicherheit konnte gezeigt werden, dass diese einen eigenständigen Risikofaktor für Gesundheitsbeeinträchtigungen darstellt (Bethge et al. 2008).

Eine wesentliche Schwäche der Einstufung der sozialen Schicht aufgrund beruflicher Tätigkeit ist, dass ökonomisch inaktive Phasen nicht eingruppiert werden können. Dadurch werden sie vor allem Frauen mit zu erwartenden Berufsauszeiten nicht gerecht.

Branchenspezifische Unterschiede werden durch diese Skalen nicht abgebildet. Gerade dies kann sich jedoch in der Entlohnung von Arbeit auswirken. Es kann in der vorgestellten Studie Kapitel 2.3 nicht berücksichtigt werden, wenn derselbe Beruf in verschiedenen Branchen tarifvertraglich unterschiedlich hoch entlohnt wird. Ebenfalls werden außertarifliche Entlohnungssysteme und Arbeitsverhältnisse, sowie Zuschläge durch Akkordarbeit oder Erfolgsprämien in diesem System nicht berücksichtigt, die erhebliche Auswirkungen auf das verfügbare Einkommen haben können.

Die verwendeten Systeme beruhen auf einer unterschiedlichen Anzahl von Umfrage- bzw. Erhebungsergebnissen. Den Werten ISEI und SIOPS kann somit für unterschiedliche Berufe ein unterschiedlich großer Fehler zugrunde liegen. Die Gefahr einer möglichen Fehlklassifikation bei der Zuweisung einer dieser Werte zu einem Individuum ist gegeben.

Wenn der soziale Status ein potenzieller Risikofaktor für Hodentumoren sein sollte, stellt sich die Frage, ob mit der Verwendung des ISEI der Teilaspekt ausgewertet wurde, der einen Risikofaktor für diese Tumorlokalisation darstellt, da hier die ökonomische Situation des Individuums gemessen wird. Gerade die zusätzliche Auswertung mit der Variable EGP könnte ein Hinweis darauf sein, dass Faktoren, weiter entfernt von ökonomischen Verhältnissen, wie Wohnlage in ländlichen Umgebungen und berufliche Expositionen, eine Rolle bei der Entstehung von Hodentumoren spielen.

Es gibt eine Anzahl von Indizes und Konzepten, die den sozialen Status anhand der Berufe in ein Schema einordnen. Die zugrunde liegenden sozialtheoretischen Modelle sind primär darauf ausgerichtet, Ungleichheit in sozialen Handlungen zu analysieren und zu erklären (Wolf 1995). Bei der Auswahl der Skalen für die vorgelegten Manuskripte war entscheidend, dass sie einen internationalen Vergleich erlauben. Zudem war die Auswahl beschränkt auf solche Skalen, die sich auf der Grundlage ISCO-68 anwenden lassen. Nur die in den Manuskripten verwendeten Systeme konnten diese Kriterien erfüllen. Eine Einschränkung der Messsysteme der sozialen Schicht ist ihr Alter. Wenn sie auch als stabile Systeme zur Einstufung herangezogen werden können und bei den ausgewerteten Studien der Beginn der Berufsbiografie meist weit vor dem Jahr 1990 liegt, ist die Problematik, das sich die soziale Struktur im Laufe der Zeit, insbesondere in den letzten 20 Jahren, mit der Ablösung des Industriemodells hin zur Dienstleistungsökonomie, stark verändert hat. Dies trifft insbesondere auf SIOPS zu, deren Datengrundlage Erhebungen aus den Jahren 1949 bis 1968 sind (Treiman 1977).

3.1.3 Diskussion: Pestizidexpositionen

Die Genauigkeit einer Expositionseinstufung zeigt hohe Variabilität in Abhängigkeit der Methode. Eine getreue Einstufung von Pestizidexpositionen durchzuführen hieße, dass Wissen und Expertise aus mehreren wissenschaftlichen Disziplinen wie Toxikologie, Agronomie, Geografie, Chemie und Biologie zusammengeführt werden (Worgan & Rozario 1995). Aus dieser Sicht wären genauere Informationen, wie z.B. Wirkstoffklasse oder Namen der verwendeten Pestizide, Bodenverhältnisse usw. aus Sicht der Expositionseinstufung wünschenswert, sind in Fall-Kontrollstudien jedoch nicht erfassbar.

In den beiden vorgelegten Studien werden berufliche Expositionen gegenüber einer Reihe von Stoffen und chemischen Verbindungen aus unterschiedlichsten Berufsfeldern abgefragt die relevant für die untersuchte Tumorlokalisation sein können. Pestizide machen dabei nur einen Bruchteil der Expositionen von Interesse aus. Fragen zu Pestizidexpositionen waren meist in der geschlossenen Form gestellt, so dass die Expositionen einheitlich ausgewertet werden konnten. Das Verwenden von strukturierten (geschlossenen) Fragebögen hat zudem den Vorteil eine höhere Sensitivität zu erreichen als offene Fragebögen (Joffe 1992). Durch den Aufbau der Fragebogenmodule in berufsbezogene Einheiten wird die Verlässlichkeit der Angaben erhöht, da Exposition von Interesse gezielt erfragt werden können (Stewart et al. 1996, Stewart et al. 1998).

Die Expositionseinstufung von Pestiziden musste sich im Kontext des Designs der Studien am Dosis-Wirkungskonzept und der Unterscheidung der in den Studien vorhandenen Angaben zu Applikationstechniken, zum Selbstausbringen der Pestizide und Verwendung von persönlichen Schutzmaßnahmen orientieren, um homogene Expositionsgruppen zu erhalten. Aufgrund der Anzahl der Exponierten konnte in Kapitel 2.1 diese Auflösung und Analyse in Bezug auf die Angabe der Methode des Pestizideinsatzes erfolgen, was im Manuskript Kapitel 2.2 aufgrund der geringen Anzahl Exponierter nicht möglich war.

In den ausgewerteten Studien konnte durch die zusätzlichen Angaben im Hauptfragebogen eine gute Annäherung an die Arbeitsumstände der Pestizid exponierten Studienteilnehmer gewonnen werden, was insbesondere bei fehlenden Werten in den berufsspezifischen Fragebögen hilfreich war. So wurden in beiden Studien land- und forstwirtschaftliche Tätigkeiten bzw. Tätigkeiten, die womöglich mit dem Ausbringen der Pestizide verbunden sind, als Surrogat für mögliche Expositionen ausgewertet. Die Intensität der Exposition konnte nur in Manuskript Kapitel 2.1 untersucht werden. Diese Auswertungen beruhen auf quantitativen Angaben wie der durchschnittlichen Anzahl der Tage pro Jahr, an denen Pestizide eingesetzt wurden und qualitativen Daten (wie Hauptgruppe des Pestizids und Methode der Ausbringung). Besonders die quantitativen Daten sind durch fehlende Werte in dieser Studie mit Unsicherheiten verknüpft.

In der RARECAN-Studie (Kapitel 2.1) waren die Angaben zu der Häufigkeit des Pestizideinsatzes teilweise nicht vorhanden. In einer Studie wurde gezeigt, dass die Anwendung von Pestiziden gut erinnert wird (Hoppin et al. 2002). Daher können die fehlenden Angaben möglicherweise auf einen Artefakt, der durch Interviewanweisungen bzw. durch mangelnde Interviewerschulung bedingt ist, zurückgeführt werden, da es sich bei den Interviews, bei denen diese Angaben fehlen, beinahe ausschließlich um Telefoninterviews eines Studienzentrums handelt. Ein möglicher Zusammenhang von Bildungsstatus und fehlenden Werten wurde nicht untersucht.

3.1.4 Limitierungen

Die Häufigkeit beruflicher Expositionen gegenüber bestimmten Stoffen ist in bevölkerungsbezogenen Fall-Kontrollstudien erwartungsgemäß niedrig. Eine Vielzahl von Chemikalien wird unter dem Begriff Pestizide summiert. Durch ihren explorativen Charakter der Studien erfassen die vorgelegten Manuskripte Pestizdexpositionen aus unterschiedlichen Arbeitsbereichen, was eine Unschärfe in der Aussagefähigkeit der Ergebnisse zur Folge hat.

Epidemiologische Studien, wie auch die in den Kapiteln 2.1 und 2.2, nutzen häufig Surrogatvariablen für die Exposition, wie angebaute Früchte oder Größe der bebauten Fläche, um die Auswirkung von Pestiziden auf die Gesundheit zu untersuchen. Diese Herangehensweise zeitigt häufig nur vage Ergebnisse und ist schwierig zu überprüfen (Fait & Maroni 1995).

Eine weitere Einschränkung liegt in der großen Anzahl der auf dem Markt verfügbaren Wirkstoffklassen die über den Zeitraum der Berufsbiografie zurückverfolgt werden müssten. Da eine Anzahl von Pestizidprodukten regional beschränkt ist, ist eine Eingruppierung erschwert. Ein weiteres Problem besteht in der Bewertung nicht gängiger, sowie vom Markt genommener Wirkstoffe hinsichtlich ihres gesundheitsgefährdendes Potentials. Ob eine Expositionseinstufung und anschließende Auswertung, die diese Probleme berücksichtigt, sinnvoll wäre, ist fraglich. Joffe (1992) konnte in einer Studie zeigen, dass die Sensitivität zunimmt, also die Angabe falsch positiver niedriger wird, je generalisierter eine Substanz abgefragt wird.

Pestizidexpositionen wurden unabhängig vom Zeitpunkt und der Häufigkeit der Exposition, der Anzahl und Klassen der verwendeten Pestizide und den eingesetzten Techniken in Gruppen zusammengefasst. Dies kann zu einer fehlerhaften Schätzung der Exposition führen, da sich die Expositionsbedingungen und Wirkstoffe im lauf der Zeit verändern. Zudem kann die Variabilität der Expositionen durch die Methoden des Einsatzes und der eingesetzten möglichen Schutzvorkehrungen unterschiedlich sein kann.

Zudem muss in Erwägung gezogen werden, dass die Möglichkeiten und Informationen, die zur Verfügung standen, durch das Konzept einer bevölkerungsbezogenen Fall-Kontrollstudie bzw. durch eine in einer Kohorte von Werksangehörigen in der KFZ-Industrie konzipierten Fall-Kontrollstudie beschränkt sind. Angaben von Studienteilnehmern in Fall-Kontrollstudien sind retrospektiv und immer mit dem Verdacht des *recall bias* behaftet. Zudem haben die geführten Interviews hohe Anforderungen an die teils in fortgeschrittenen Alter stehenden Studienteilnehmer gestellt, da eine Reihe von möglicherweise Jahre zurückliegenden Expositionen und Umstände der Exposition erfragt wurden. Für die Fälle ist noch die gleichzeitige Belastung durch ihre Erkrankung zum Zeitpunkt des Interviews zu bedenken. Für Berufe in landwirtschaftlichen Bereichen besteht zudem eine hohe Variabilität in der Dauer und Häufigkeit innerhalb einer einzelnen Tätigkeit, was die Genauigkeit der Selbstangaben weiter einschränkt.

Angaben von Studienteilnehmern zur Häufigkeit von Pestizidanwendungen sind als durchschnittlich verbrachte Expositionstage pro Jahr und Anbaufrucht bzw. Tiergattung im Datensatz hinterlegt. Die Verwendung dieser Angabe als Surrogat für eine Extremexposition muss unter dem Vorbehalt einer möglichen weiten Streuung stattfinden. Als weiteres Expositionsmaß wurde die kumulierte Anzahl von Tagen über den gesamten Expositionszeitraum erfasst (Manuskript Kapitel 2.1). Die Verwendung dieses Maßes mag verlässlich sein, konnte in einer Studie zur Räuchermittel-Exposition, die die Anzahl der Jahre bzw. Tage unter Exposition aus Selbstangaben mit denen von Firmendaten verglich, eine relativ hohe Korrelation beider Informationsquellen festgestellt werden (Calvert et al. 1997).

Der Algorithmus zur Quantifizierung der Expositionsdosis wie der von Dosemeci konnte in dem Manuskript Kapitel 2.1 angewendet werden. Dieser Algorithmus, der anhand einer Studie zu Expositionen im Agrarbereich entwickelt wurde (Dosemeci et al. 2002) kann dann Verwendung finden, wenn die dafür erforderlichen Variablen bei der Abfrage der Exposition erfasst wurden. Diese Variablen sind in beiden Studien (HTS/RARECAN) dem Einstufungskatalog von Dosemeci sehr ähnlich, so dass dieser Algorithmus technisch gesehen angewendet werden kann. Dieser Algorithmus konnte jedoch aufgrund der niedrigen Anzahl Pestizidexponierter in der HTS-Studie (Kapitel 2.2) nicht angewandt werden. Auf der Basis von jemals-niemals-Einstufungen und der Auswertung von Zeitintervallen für die Gesamtheit der durch landwirtschaftliche Tätigkeiten potenziell Exponierten waren die Möglichkeiten der Expositionseinstufungen in dieser Studie ausgeschöpft.

Auch in epidemiologischen Studien muss der Effekt des Messfehlers der zugrunde liegenden Parameter der Exposition und der Suszeptibiltät der Studienteilnehmer auf die Schätzung des Risikos bedacht werden. Bei dem Vergleich von Selbstangaben mit Konzentrationen von Pestizidmetaboliten in Körperflüssigkeiten (Urin oder Blut) findet sich häufig nur eine geringe Übereinstimmung (Chester 1995). Mögliche Erklärungen für diese Unterschiede zwischen bioanalytischen Messverfahren und Selbstangaben ergeben sich, neben Ungenauigkeiten in den Selbstangaben, durch mögliche interindividuelle Unterschiede im Metabolismus und aus unterschiedlichen Absorptionsraten. Daher wird gefordert, zusätzliche Determinanten der Genauigkeit der Selbstangaben von beruflicher und Umwelt verursachten Expositionen zu untersuchen (Perry et al. 2006; Marquart et al. 2003). Einige Pestizide bestehen aus einer Anzahl von Substanzen, die sich gegenseitig in ihrer Wirkung beeinflussen können, was eventuelle Monitoringergebnisse verzerrt. Für eine Anzahl von Pestiziden gibt es noch keine verlässlichen oder ausreichend geprüften Biomarker, so dass die Biomonitoring-Ergebnisse selbst mit Unsicherheiten verbunden bleiben. Bei kritischer Betrachtung muss festgestellt werden, dass Pestizidexpositionen hochvariabel sind und unterschiedliche Routinen im Umgang mit Pestiziden bei gleichen Tätigkeiten zu unterschiedlich hohen Belastungen führen (Perry et al. 2006; Marquart et al. 2003).

3.2 Schlussfolgerung

In dieser Arbeit werden zwei grundlegend verschiedene Expositionsklassen an drei Tumorlokalisationen anhand von Fragebogendaten untersucht. Eine abschließende inhaltliche Gesamtbewertung ließe sich daher nur konstruieren.

Die methodischen Möglichkeiten retrospektive Studien auszuwerten werden immer vielfältiger. Die den vorgelegten Manuskripten zugrunde liegenden Daten wurden unter der Prämisse der bestmöglichen anwendbaren Expositionseinstufung ausgewertet.

Die Verbesserung von retrospektiven Expositionseinstufungen wird immer eine Herausforderung in der Epidemiologie sein. Epidemiologische Forschung stellt sich der Frage, warum Krankheiten in bestimmten Populationen auftreten. Epidemiologie ist eine Handlungswissenschaft und bedient sich an Konzepten und Methoden aus anderen Wissenschaften. Nur das Verständnis und die Zusammenziehung dieser Konzepte zur Erklärung von Krankheitsursachen kann eine Ziel führende Schlussfolgerung ergeben, um der Aufgabe gerecht zu werden, Fragen zur Ätiologie und Möglichkeiten zur Prävention von Erkrankungen zu beantworten.

Für die Einstufung von Pestiziden sind andere/weitere Konzepte notwendig als sie in den Manuskripten Kapitel 2.1 und 2.2 angewendet werden konnten. Die Einstufung von stofflichen Expositionen bei retrospektiven populationsbasierten Studien ist häufig mit dem Problem behaftet, dass meist nur eine kleine Anzahl von Personen exponiert ist, es durch die Anfälligkeit gegenüber Reporting-Bias oder Missklassifikation von Expositionen zu Verzerrungen der Ergebnisse kommen kann, und dies die Studienergebnisse ernsthaft zu beeinträchtigen vermag. Des Weiteren werden in den Auswertungen der hier durchgeführten Studien primär landwirtschaftliche Tätigkeiten mit Pestizidexpositionen assoziiert. Jedoch sind auch in anderen Berufsgruppen Expositionen gegenüber Pestiziden vorhanden, werden aber häufig nicht als solche wahrgenommen (Blair & Zahm 1993) und können schon daher zu Missklassifikationen führen.

Gesundheitsbeeinträchtigende Auswirkungen von Pestiziden können nicht allein anhand von Dosis-Wirkungsbeziehungen dargestellt werden, werden nur die Hauptklassen von Pestiziden (Fungizide, Herbizide, Insektizide) zusammengefasst. Eine Dosis-Wirkungsbeziehung ist nur dann sinnvoll für Pestizide darzustellen, wenn der vermuteten Wirkung ein gleichwertiger Prozess im Sinn eines biochemischen Reaktionsschemas im Organismus zugrunde liegt. Dies kann geleistet werden, wenn die Notwendigkeit erkannt wird, auch in Studien mit einer geringen Anzahl an Exponierten Biomarker einzusetzen, um die Effektivität der epidemiologischen Studien zu erhöhen (Fait & Maroni 1995).

Durchgeführte Studien sind immer auch ein Spiegel der Zeit. Fragestellungen werden aufgrund von Auffälligkeiten in der Gesellschaft aufgeworfen und in wissenschaftlichen Kollektiven nach einem Denkstil interpretiert (Fleck 1935/1999), was dadurch befördert wird, dass Daten keine objektiven Instanzen sind. Sie sind vieldeutig - interpretativ flexibel - und mit verschiedenen, auch untereinander widersprüchlichen Theorien kompatibel (Heintz 2000). Die Initiierung von Skalensystemen zur Kategorisierung des sozialen Status in den Sozialwissenschaften und deren Verwendung in epidemiologischen Studien ist ein Beispiel für einen Denkstil. Dabei muss bei kritischer Betrachtung auch erkannt werden, dass den Veränderungen der Bedingungen der Arbeitswelt in retrospektiven Studien nur mit Mühe Rechnung getragen werden kann, da es die Datenlage nicht erlaubt, Modelle aus sich selbst heraus entwickeln zu können.

Risiken bei Expositionen mit einer niedrigen Prävalenz, wie in den Studien zu Pestiziden zu sehen, können nur bedingt in einer populatonsbasierten Fall-Kontrollstudie oder industriebasierten Fall-Kontrollstudie mit einem anderen Fokus aufgedeckt werden. Hier sind Studien notwendig, die auf diese spezifische Exposition fokussiert sind, und dabei gleichzeitig die Möglichkeit geben, genügend Freiraum für eine Modellierung der Daten zu bieten.

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4 Zusammenfassung

Die Identifikation von Krebs verursachenden Expositionen in der Arbeitswelt ist ein Gebiet der Epidemiologie. Dazu werden etablierte Methoden aus anderen Wissenschaftsgebieten integriert. Es wurden die Themen soziale Faktoren und Pestizidexpositionen bearbeitet. Alle Auswertungen basieren auf Fragebogendaten aus Fall-Kontrollstudien. In den Artikeln wurde versucht, das optimale Verfahren zur Einstufung anhand der Anzahl der Exponierten anzuwenden. Alle Risikoschätzer basieren auf logistischer Regression. Potenzielle Confounder wurden in den Modellen berücksichtigt.

In Manuskript 2.1 wurde die Assoziation zwischen beruflichen Pestizidexpositionen und Tumoren der extrahepatischen Gallenwege bei Männern in einer multizentrischen Fall-Kontrollstudie untersucht. Expositionen wurden in Bezug auf Zeit, Gebrauch persönlicher Schutzmaßnahmen und Applikationsmethode quantifiziert. Ein publizierter Algorithmus wurde zur Bewertung der Expositionsintensität verwendet. Wenige nichtsignifikant erhöhte Risiken wurden festgestellt, die jeweils auf einer niedrigen Anzahl von Exponierten beruhten. Die Hypothese, dass berufliche Pestizidexpositionen ein Risiko für Tumoren der extrahepatischen Gallenwege bei Männern ist, lässt sich nicht ausschließen.

Daten einer in eine Industriekohorte eingebetteten Fall-Kontrollstudie wurden in Manuskript 2.2 ausgewertet, um der Hypothese nachzugehen, dass Pestizidexpositionen und Tätigkeiten in landwirtschaftlichen Berufsfeldern die erhöhte Inzidenz von Keimzelltumoren in dieser Kohorte erklären kann. Es haben 5.3% der Fälle und 6.3% der Kontrollen jemals einem landwirtschaftlichen Beruf ausgeübt. Expositionen gegenüber Pestiziden, Dünge- und Desinfektionsmitteln ergaben keine erhöhten Risiken. Forstarbeit und mit der Verarbeitung von Holz verbundene Expositionen zeigten nichtsignifikant erhöhte Risiken. Es konnten keine Schlüsse über die Assoziation von landwirtschaftlichen Tätigkeiten und Expositionen und Keimzelltumor-risiko gezogen werden.

In Manuskript 2.3 werden unterschiedliche berufliche Sozialindikatoren verwendet, um die Assoziation mit Hodentumoren zu untersuchen. Ebenfalls werden Schulbildung und der Ausbildungsstatus untersucht. Ein erhöhtes Risiko konnte nur für Beschäftigungen in landwirtschaftlichen Bereichen anhand des Schemas aufgedeckt werden, das Tätigkeiten ordinal schichtet. Diese Studie legt die Schlussfolgerung nahe, dass soziale Faktoren kein Risikofaktor für Hodentumore sind. Das aufgedeckte erhöhte Risiko für Tätigkeiten im landwirtschaftlichen Bereich kann auf stofflichen Expositionen beruhen.

Studie 2.4 untersucht die Assoziation der sozialen Mobilität und Tumoren der oberen Luft- und Speisewege anhand der Berufsbiographie. Das Berufspretige wurde anhand des Standard International Occupational Prestige Scale (SIOPS) untersucht. Die SIOPS-Werte wurden in Hoch (H), Mittel (M) und Niedrig (L) kategorisiert. Wechsel zwischen den Kategorien während der Berufsbiografie und der zeitgewichtete Mittelwert wurden analysiert. Die niedrigste Kategorie im Vergleich zur Höchsten ergab für den zeitgewichteten Mittelwert ein signifikant erhöhtes Risiko. Eine Abwärtsmobilität von H zu L (H→L), sowie Schichtstabilität (M→M und L→L) ergaben erhöhte Risiken im Vergleich zu H→H. Die Assoziation zwischen sozialem Prestige und UADT kann nicht vollständig mit confundierenden Variablen erklärt werden. Abwärtsmobilität könnte ein unabhängiger Risikofaktor sein.

Verbesserte Verfahren der Einstufung von Expositionen sind bei der Auswertung von epidemiologischen Studien eine ständige Herausforderung. Die Bereitschaft, neue Ansätze zu übernehmen, muss gerade im Bereich *sozialer Status* vorhanden sein.