A Case of a Young Woman with Tuberculous Peritonitis Diagnosed Owing to High Value of ADA

Kammei RAI[1], Etuko KURIMOTO[1], Nobuchika KUSANO[1], Norio KOIDE[1] & Kenji NISHII[2]
[1]Department of General Internal Medicine, Okayama University Hospital
[2]Faculty of Internal Medicine, Okayama Health Promoting Foundation Hospital

A 26-year-old woman visited the first hospital due to ascites in August 2003, She had continual abdominal pain diagnosed as Irritable bowel disease after a gastrointestinal and colon fiberscopy was performed. Chest-abdominal CT scan revealed normal chest, massive ascites and swollen ovary. To rule out malignancy, surgical biopsy was performed, which brought no significant findings. We focused on the high value of Adenosin deaminase (ADA) in ascites and strongly suspected tuberculotic peritonitis. Consequently, pathologist confirmed the existence of bacterial bodies stained by acid-fast stain after our consultation. Compared with the poor diagnostic accuracy of surgical biopsy, the value of ADA in ascites has a very high sensitivity and specificity. Considering the high risk of being infertile, to begin diagnostic medication of tuberculotic peritonitis is an acceptable choice for young women with a high value of ADA in the ascites.

〔J.J.A. Inf. D. 78 : 916～922, 2004〕

神奈川県における外科治療の施設間格差の現状について

宮松 篤* 岡本 直幸 今村 由香

1. はじめに

医療資源の整備を進める上で、治療成績の施設間格差の問題が指摘されている。今回、治療成績の施設間格差の現状を明らかにするため、神奈川県地域がん登録から得られた情報をもとに、施設規模（手術件数）と術後生存率の関係、および病院規模（病床数）と手術件数の関係を検討した。

2. 対象

神奈川県地域がん登録によると、1991 年から 1994 年の 4 年間に診断された胃がんは 11,412 例、乳がんは 5,618 例、および肺がんは 6,656 例であった。そのうち、手術施行日の記載のあった、胃がん 7,280 例（63.8%）、女性乳がん 4,310 例（76.7%）、および肺がん 1,573 例（23.6%）を対象とした。なお、DCO 症例、重複がんの第 2 がん以降、および県外で手術を受けた症例は対象から除外した。

3. 方法

各施設の登録手術件数を施設規模として集計し、一般病院群を手術件数により 3-5 群に分類し、特定機能病院群（大学病院・専門病院）を対照として、術後生存率を比較した。また、登録の得られた施設の病床数と手術件数の関係を検討した。また、乳がんにおいては術後、放射線療法や化学療法の併用が行われることが多いことより、選択された治療内容についての検討を行った。患者の追跡は 2000 年末までとした。

4. 結果

胃がん、乳がん、肺がんともに、一般病院群での治療成績は、特定機能病院群と比較すると、登録手術件数がより少ない施設群で、成績の低下が観察された。病床数と手術件数の関係では、病床数が多い施設でも、必ずしも手術件数の登録が多いとは限らないことが観察された（図 1-3）。乳がんの治療内容では、特定機能病院群（大学病院群・専門病院群）と比較して、一般病院群では手術のみの治療が選択される頻度が高かった（表 1）。

5. 考察

今回検討した胃がん、乳がんは、肺がんに比べ手術率が高く、外科手術が治療の第一選択となることが多い。そのため、技術レベルの均一化が進んでいることが推測され、肺がんに比べ施設間格差は少ないことが想像された。しかし検討結果を見ると、胃がん、乳がん症例において手術数の少ない施設での治療成績の低下が目立った。

国内外での報告によると、治療成績の施設間格差に影響する原因として、症例集積による技術レベルの偏りに加え、施設群間の進行度分布の偏りを指摘する報告が見られる。一方、地域がん登録を基にした国内の報告では、地域によっては、病院規模（病床数）別の進行度分布の偏りは目立たないとする報告もみられる。

*神奈川県立がんセンター臨床研究所研究 3 科（疫学）
〒241-0815 横浜市旭区中尾 1-1-2

今回の検討では、とくに胃がん、乳がんにおいて、施設規模による治療成績の格差が目立った。神奈川県地域がん登録では、進行度情報の収集は行っておらず、今回、進行度分布の偏りを検討することはできなかったが、乳がんにおいて治療内容を検討した結果、一般病院群では化学療法や放射線療法など、手術以外の治療が併用された症例の割合は、特定機能病院群と比較して低かった。神奈川県内の施設でも施設間での進行度分布の偏りが目立たないとすると、乳がんにおける治療成績の施設間格差の原因として、選択する治療内容（施設の治療機能）が一定の影響を及ぼしている可能性が推測された。

6. まとめ

神奈川県地域がん登録を用いて、外科手術の治療成績における施設間格差について検討した。国内外での報告と同様に手術件数と治療成績の間に、関連が観察された。

施設間格差の原因として、技術集積や、施設群間の進行度割合の偏りが指摘されているが、乳がん治療においては、手術以外の治療内容（施設の治療機能）も一定の影響を及ぼしている可能性が推測された。

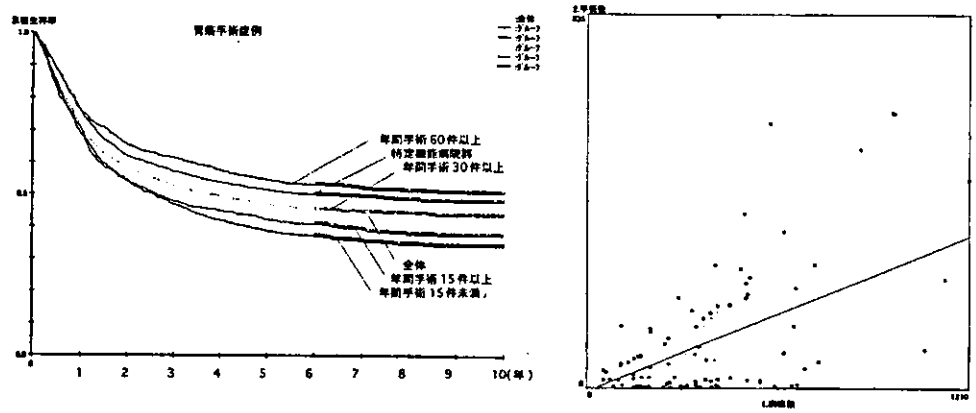


図1. 手術件数と術後生存率・病床数と手術件数（胃がん）

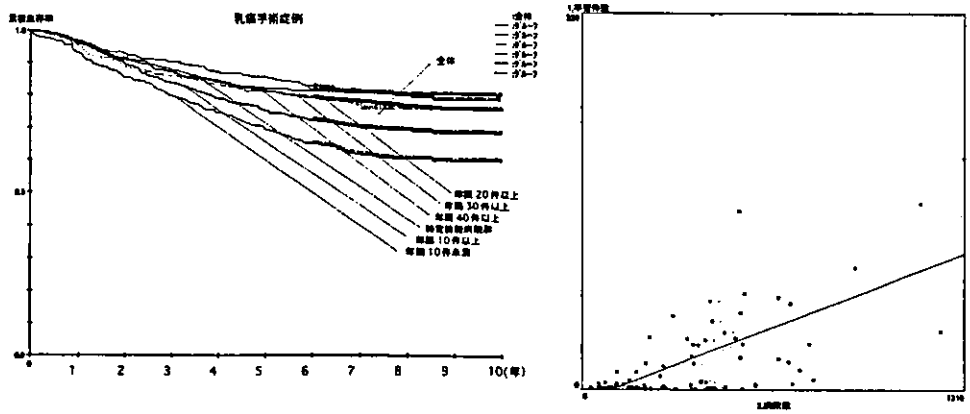


図2. 手術件数と術後生存率・病床数と手術件数（乳がん）

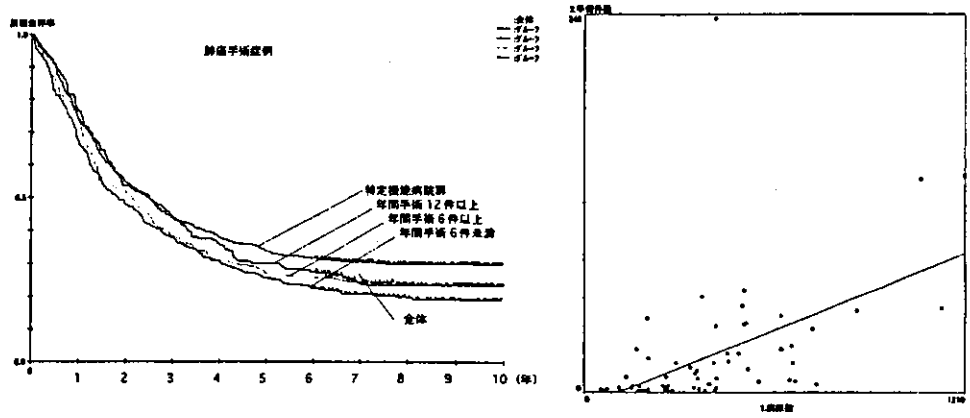


図 3. 手術件数と術後生存率・病床数と手術件数（肺がん）

表 1. 施設規模別各治療の割合（%）

	大学病院群	専門病院群	一般病院群	全体
手術のみ	43.6	48.9	55.8	51.2
手術以外の治療の併用	56.4	51.1	44.2	48.8
(手術＋放射線)	(5.6)	(3.2)	(2.4)	(3.3)
(手術＋化学療法)	(40.3)	(43.8)	(35.9)	(38.6)
(手術＋放射線＋化学療法)	(10.5)	(4.1)	(5.9)	(6.9)

表　題

著者名

醫學のあゆみ 別刷

第　巻・第　号：　　年　月　日号

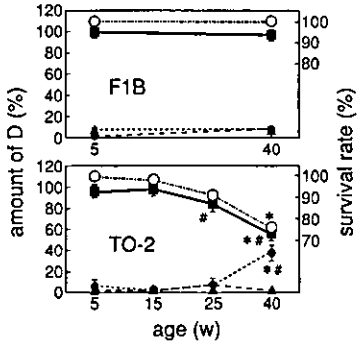


図 2 動物の生存率(○)とジストロフィン(■),またはその分解産物,60 kDa バンド量(●)との関係[6]

正常ハムスター(F1B)に比較して DCM 動物(TO-2)ではジストロフィン量の減少は生存率の低下と一致していた.この両者の変化は 60 kDa 量の増加と一致していたが,160 kDa バンド(▲)とはまったく関係しなかった.

の細胞内浸潤が認められたことから,先天性,後天性,急性および慢性を問わず,心不全一般に共通した病態であった[6].実に興味あることに原因不明のヒト DCM 症例の末期に心移植用に取り出した心筋も,ハムスターと同様の断片化が認められ,共通した病態を示した[6].以上の結果から心筋細胞で選択的にジストロフィンが断裂(disrupt)して,筋ジストロフィー様の病変が重症心不全を引き起こすという作業仮説をたてた(図 3).

なお,上記の TO-2 系ハムスターに無害で長期発現可能な rAAV ベクターを用い,*in vivo* で δ-SG 遺伝子を発現させると,上記の細胞膜の透過性,ジストロフィンの translocation,心機能と生命予後も改善して rescue され,心不全の発症が予防された[3].今後は患者が心不全の重症化後に治療を求める現状を考慮して,*ex vivo* で遺伝子を正常化した心筋細胞を移植する治療を展開する予定である.近未来で実現可能な遺伝子,再生医療に熱意のある若手の参画を期待する.

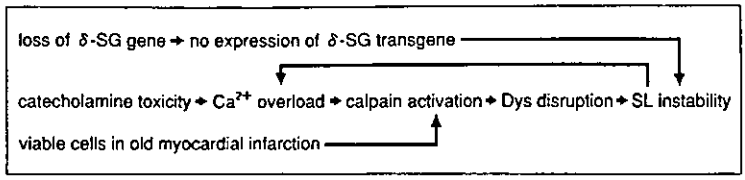


図 3 数種の原因によるジストロフィンの崩壊と心不全の重症化機構[6]

謝辞:本研究は,文部科学省,厚生労働省,三菱財団および車両財団より研究支援を受けてなされた.

1) Sakamoto, A. et al.: *Proc. Natl. Sci. Acad. USA*, **94**: 13873-13878, 1997.
2) Tsubata, S. et al.: *J. Clin. Invest.*, **106**: 655-662, 2000.
3) Kawada, T. et al.: *Proc. Natl. Acad. Sci. USA*, **99**: 901-906, 2002.
4) Xi, H.: *J. Cardiovasc. Pharamcol.*, **36**(Suppl. 2): S25-S29, 2000.
5) Yoshida, H. et al.: *Cardiovasc. Res.*, **59**: 419-427, 2003.
6) Toyo-oka T. et al.: *Proc. Natl. Acad. Sci. USA*, **101**: 7381-7385, 2004.

豊岡照彦／Teruhiko TOYOOKA
東京大学大学院医学系研究科器官病態内科学

消化器外科学

がん専門施設における胃癌生存率の格差

Differences of stomach cancer survival rates among the cancer-oriented hospitals in Japan

生存率は治療や疾病対策の有効性評価の指標のひとつとして各分野で用いられている.しかし,生存率には多くの交絡因子(ステージ,治療方法など)が含まれており,また,生死確認の追跡調査の不完全性に大きく影響を受けるため,算出された数値を安易に受け止めて施設間格差を問うことは危険である.比較を可能とするためには追跡調査を完全に実施し,交絡因子を補正した生存率を算定する必要があろう.

本稿では,わが国のがん専門診療施設で構成される全国がん(成人病)センター協議会[1](通称,全がん協)加盟施設で,毎年収集されている"がんの個別データ"を用い[2],生存率の施設間格差を問う場合の交絡因子の影響について検討した結果を紹介したい.

資料の収集と解析の方法

全がん協加盟 29 施設〔平成 15 年(2003)4 月 1 日現在〕の協力を得て収集された"1996 年に初発で入院治療を行ったがん患者"(ICD-10 コード番号が C00～C96)の個別データ(性別,年齢,来院理由,診断時指示,症例区分,診断結果,告知状況,原発部位,cTNM,pTNM,臨床病期,病理病期,臨床進行度,治療内容,組織診断,手術,放射線治療,化学療法,免疫療法,生存期間,生死状況)[3]のうち,胃癌(C16)の資料を用いた.データクリーニング作業を行い,14 歳以下の小児がん患者,95 歳以上のがん患者,生存期間が無記載あるいは 3,000 日以上(診断年が 1996 年以前と推測される)のデータ,上皮内がんおよびステージ 0 のデータは集計対象から除外した.また,生存期間が 5 年(1,825 日)未満の症例はセンソードデータ(打ち切り)として計算を行った.生存率の算定はカプラン-マイヤー法で行い,相対生存率算定のためのコホート生存率は国立がんセンター算出のデータを用いた[4].交絡因子の影響に関する解析には SPSS10.0 の Cox の

表 1　胃癌の施設別，施設群別の 5 年実測・相対生存率とステージ別割合

施設番号	胃癌例数	5年生存率 実測	5年生存率 相対	消息判明率	ステージ I	ステージ II	ステージ III	ステージ IV	ステージ不明
1	271	0.7343	0.8067	100.0	51.3	4.1	10.0	8.1	26.6
2	465	0.7226	0.7906	100.0	47.1	5.2	7.3	8.8	31.6
3	235	0.6723	0.7478	100.0	19.6	3.8	5.1	0.9	70.6
4	188	0.6628	0.7221	62.3	56.9	3.7	9.6	20.7	9.0
5	196	0.6580	0.7296	97.6	60.7	5.1	13.8	12.2	8.2
6	148	0.6418	0.6858	98.9	56.8	12.2	14.9	14.2	2.0
7	136	0.6194	0.6831	97.6	59.6	5.1	11.0	17.6	6.6
8	136	0.6092	0.6683	92.3	18.4	8.1	3.7	4.4	65.4
9	246	0.6000	0.6581	98.6	32.1	2.8	6.9	8.5	49.6
10	185	0.5946	0.6570	98.1	53.5	4.9	10.3	22.2	9.2
11	157	0.5730	0.6155	92.0	42.7	7.0	15.9	25.5	8.9
12	379	0.5714	0.7306	98.4	—	—	—	—	100.0
13	63	0.5710	0.6414	100.0	47.6	17.5	11.1	22.2	1.6
14	58	0.5344	0.5857	100.0	43.1	10.3	19.0	24.1	3.4
15	121	0.5289	0.5761	100.0	51.2	9.9	5.8	24.8	8.3
16	50	0.4759	0.5530	68.2	48.0	4.0	14.0	30.0	4.0
17	132	0.4544	0.5061	94.5	50.0	11.4	15.9	13.6	9.1
18	106	0.4528	0.5246	100.0	30.2	5.7	7.5	28.3	28.3
19	104	0.4327	0.4821	100.0	1.0	16.3	41.3	39.4	1.9
A 群*	2,009	0.6092	0.6674	94.5	38.8	4.6	7.8	12.6	36.2
B 群*	498	0.6305	0.6996	100.0	45.4	6.8	10.6	16.1	21.1
C 群*	383	0.6606	0.7235	99.6	33.9	7.1	8.9	6.0	44.1
D 群*	300	0.5799	0.6438	98.2	40.0	9.0	23.3	21.7	6.0
E 群*	188	0.5716	0.6344	87.0	26.3	7.0	6.5	11.3	48.9
合計	3,376	0.6142	0.6757	95.8	38.7	5.7	9.6	13.1	32.9

*：再掲—A 群(2,4,7,9,10,11,12,15,17)，B 群(1,13,14,18)，C 群(3,6)，D 群(5,19)，E 群(8,16)．

比例ハザードモデルを用いた．

生存率の施設間格差

収集された胃癌のデータは 19 施設から 3,376 件であった．平均の消息判明率は 95.8%(62.3〜100.0%)で，5 年生存率は実測で 0.6142(SE＝0.00020)，相対で 0.6757(SE＝0.00022)と計算された．表 1 に施設別の 5 年実測生存率の高い順に，5 年相対生存率，消息判明率およびステージ別割合を併記して示した．また，各施設の診療形態別に，がんセンター群(A)，総合病院併設がんセンター群(B)，成人病センター群(C)，総合病院併設成人病センター群(D)，総合病院群(E)の 5 群に分け，同様の指標を再掲している．施設別の実測生存率をみると，もっとも高い 0.7343 からもっとも低い 0.4327 まで分布しており，その差は 30 ポイントにも及んでおり，施設群別でみると C 群 0.6606 でもっとも高く，E 群 0.5716 でもっとも低く，やはり両者には約 9 ポイントの差がみられる．

以上の結果より，胃癌の 5 年生存率には施設間格差の存在が示唆されるが，併記したステージの分布をみると，生存率の上位施設は下位施設と比較し，ステージIVの割合が少ないと思われる．このように，算出された生存率だけをみると大きな差の存在が示唆されるが，表 1 に示しているステージ割合にみられるように，生存率の数値の裏にはいくつもの交絡因子が大きな影響を与えていることを看過することはできない．

そこで，施設群別のデータを用い，①性別，②年齢，③検診由来の有無，④臨床病期(ステージ)，⑤手術の有無，⑥化学療法の有無，の 6 つの交絡因子について比例ハザードモデルを用いて検討を行った(表 2)．がんセンター群を基準の 1 として他の施設群のハザード比を求めた．6 つの交絡因子のいずれも補正を行わなかった場合，C 群のオッズ比が 0.810($p<0.05$)と有意に低く，E 群では 1.237(有意差なし)となった．性別，年齢をそれぞれ補正した場合はオッズ比の大きな変化はなかったが，検診由来で補正すると C 群の有意差が消え，D 群 1.234($p<0.05$)，E 群 1.253($p<0.05$)と有意に高いオッズ比が観察された．しかし，性別，年齢，検診由来の 3 つの因子を同時に補正すると，いずれのオッズ比も有意な値を示さなかった．また，臨床病期(ステージ)や手術・化学療法の有無を含めて検討すると，B 群のオッズ比(1.340，$p<0.05$)のみ，有意に高い

表 2　比例ハザードモデルによる交絡因子の補正後の施設群別オッズ比

交絡因子						A．がんセンター群	B．総合病院併設がんセンター群	C．成人病センター群	D．総合病院併設成人病センター群	E．総合病院群
性別	年齢	検診由来	臨床病期	手術	化学療法					
—	—	—	—	—	—	1.000	0.992	0.810*	1.171	1.237
○	—	—	—	—	—	1.000	0.991	0.804*	1.181	1.239
—	○	—	—	—	—	1.000	0.973	0.812*	1.119	1.170
—	—	○	—	—	—	1.000	1.002	0.851	1.234*	1.253*
○	○	—	—	—	—	1.000	0.974	0.807*	1.129	1.172
○	○	○	—	—	—	1.000	0.983	0.842	1.187	1.187
○	○	○	○	—	—	1.000	1.130	1.101	0.856	0.981
○	○	○	—	○	—	1.000	1.118	1.151	0.925	1.096
○	○	○	—	—	○	1.000	1.293*	1.157	0.920	1.083
○	○	○	○	○	—	1.000	1.135	1.136	0.999	1.184
○	○	○	○	○	○	1.000	1.340*	1.135	0.961	1.109

○：補正，—：補正なし，*：$p<0.05$.

値であった．

生存率の施設間格差を問うために

単純な生存率の比較によっては，施設間格差を表すことには限界がある．比較のためには，第1に集計の対象となる患者の背景を一致させること(今回の報告では入院患者のみ)，第2に追跡調査の完全度を表す消息判明率を上げること[5]，第3に本報告で検討した交絡因子を配慮することが不可欠である．今後，標準化した生存率算定方法の構築が望まれる．

1) http://www.zengankyo.ncc.go.jp/index.html
2) 岡本直幸・他：がん治療の専門施設における主要がんの相対生存率．がんの臨床，42：1183-1188，1996.
3) 岡本直幸：全がん協加盟施設における主要がんの進行度別5年相対生存率．厚生労働省がん研究助成金「地域がん専門診療施設のソフト面の整備拡充に関する研究」平成15年度報告書，2004，pp.17-24.
4) http://www.ncc.go.jp/jp/ncca/cohort01.html
5) 木下洋子・他：がん専門施設における生存率計測の標準化．がんの臨床，46：1197-1203，2000.

岡本直幸／Naoyuki OKAMOTO
神奈川県立がんセンター臨床研究所研究第三科(疫学)

形成外科学

脊髄損傷の治療方法の開発

Development of new treatments for spinal cord injury

哺乳類の中枢神経系は一度損傷を受けると再生しないと，19世紀初頭にCajalが報告して以来長く信じられてきた[1]．近年，動物の脊髄損傷部に胎児脊髄移植を行うことで，再生しないと考えられてきた脊髄神経も再生を獲得できることが示された[2]．その後，BDNF，GDNF，NT-3などの栄養因子の投与，軸索伸長阻害因子の抑制，損傷脊髄神経の細胞死を抑制する抗体治療や，ES細胞・神経幹細胞などの細胞移植治療により，動物の脊髄再生が促される報告が多数なされてきた[3]．著者らも臨床応用を目標にし，倫理的にも医学的にも問題が少ないと考えられる手法により脊髄損傷の治療法を探索してきたので，その現況について以下に述べる．

人工マトリックスアルギン酸による脊髄神経の再生

アルギン酸は，海藻の一種である褐藻類から抽出される多糖類である．そのアルギン酸を中枢神経再生用マトリックスとして共有結合アルギン酸スポンジを作製し，約2カ月で吸収されるように調整したものを用いた．脊髄をTh6〜8のレベルで切除し，生じた2 mmのギャップにアルギン酸を埋植した．数週間後，ギャップ内に多数の再生軸索を認めた．また，神経根から侵入したと考えられる末梢の組織であるSchwann細胞がアルギン酸内の再生軸索に髄鞘を形成している所見を電子顕微鏡で確認した．さらに細胞内電位測定により，上行性，下行性の再生軸索がシナプスを形成していることを証明した．HRPのトレーシングでは，再生軸索はギャップを越え反対側の脊髄端に侵入していることが証明された．アルギン酸が軸索再生のよい環境を提供できる人工マトリックスである可能性を示唆した[4,5]．

Int. J. Cancer: **112,** 722–725 (2004)

Publication of the International Union Against Cancer

SHORT REPORT

PROSPECTIVE STUDY OF TRANSFUSION HISTORY AND THYROID CANCER INCIDENCE AMONG FEMALES IN JAPAN

Yoshihisa FUJINO[1,2,*], Akiko TAMAKOSHI[3], Yoshiharu HOSHIYAMA[4], Haruo MIKAMI[5], Naoyuki OKAMOTO[6], Yoshiyuki OHNO[7], Takesumi YOSHIMURA[1] and the Japan Collaborative Cohort Study Group[8]

[1]*Department of Clinical Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan*
[2]*Department of Epidemiology, Statistics and Public Health, University of Wales College of Medicine, United Kingdom*
[3]*Department of Preventive Medicine/Biostatistics and Medical Decision Making, Field of Social Life Science, Program in Health and Community Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*
[4]*Department of Public Health, Showa University School of Medicine, Japan*
[5]*Head Division of Epidemiology, Chiba Cancer Center Research Institute, Chiba, Japan*
[6]*Department of Epidemiology, Research Institute, Kanagawa Cancer Center, Yokohama, Japan*
[7]*Labour Welfare Corporation Asahi Rosai Hospital, Asahi, Japan*
[8]*See Acknowledgements*

A link between hepatitis C virus (HCV) infection and thyroid cancer was recently reported in a series of case-control studies in southern Italy. A prospective study could reinforce these findings. However, cohort studies that began before 1990 rarely assessed serological HCV infection. In addition, thyroid cancer is rare and generally has a good prognosis. Therefore, incidence outcome data are required, rather than mortality data, to evaluate the risk of thyroid cancer. Blood transfusion history might be a possible substitute measure to evaluate the cancer risks associated with HCV infection because blood transfusions were the major HCV transmission route in Japan until 1992. The purpose of our study was therefore to examine the association between transfusion history and thyroid cancer. A baseline survey of members of the JACC Study was conducted from 1988 until 1990, which involved 110,792 participants from 45 areas throughout Japan. Data were collected from a total of 37,983 women with no history of cancer at the baseline (337,906 person-years) and 79 cases of thyroid cancer were identified among this group. A history of blood transfusion marginally increased the risk of thyroid cancer [risk ratio (RR) = 1.77, 95% confidence interval (CI) = 0.95–3.30], and a history of transfusion and/or liver disease significantly increased the thyroid cancer risk (RR = 1.84, 95% CI = 1.07–3.16). These results indirectly support an association between HCV and thyroid cancer. In addition, our data reveal an association between blood transfusion and thyroid cancer, which might be facilitated by transfusion-associated immunomodulation.

Key words: *thyroid cancer; blood transfusion; hepatitis C virus; immunomodulation; Japanese population*

Infection with the hepatitis C virus (HCV) is a strong risk factor for liver cancer[1] and several studies have reported associations between HCV and other cancers, including non-Hodgkin lymphoma and multiple myeloma.[2,3] In addition, a novel link between HCV and thyroid cancer was recently reported in a series of case-control studies in southern Italy.[4–6] For example, Montella *et al.*[4] carried out a hospital-based study in an area of southern Italy with a high prevalence of HCV (up to 12.6%) among the general population. Their study group comprised 106 female patients who had been histologically diagnosed with thyroid cancer and 116 controls who were hospitalised without any history of cancer. The odds ratio (OR) for the relationship between serological HCV-positive status and thyroid cancer among females was 4.0 [95% confidence interval (CI) = 1.1–8.8].

A prospective study could confirm the association between HCV and thyroid cancer. However, cohort studies that began before 1990 rarely assessed serological HCV infection, as the virus was only identified in 1988. In addition, thyroid cancer is relatively rare and generally has a good prognosis. Therefore, incidence rather than mortality data are required to evaluate the thyroid cancer risk associated with HCV infection.

Blood transfusion history might be a possible alternative measure for evaluating the cancer risks associated with HCV infection. Several studies have revealed an association between transfusion history and liver cancer, which might be explained by the proposed link between transfusion history and HCV infection. Blood transfusions were the major transmission route for HCV in Japan before 1992.[7] The purpose of our study was therefore to examine the association between blood transfusion history and thyroid cancer.

MATERIAL AND METHODS

The JACC study

The details of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study), sponsored by the Ministry of Education, Science, Sports and Culture of Japan, have been described previously.[8–13] Briefly, this cohort study involved a total of 110,792 subjects (46,465 male and 64,327 female) who were aged 40–79 years at recruitment. Subjects were enrolled between 1988 and 1990 on the basis of participation in general health check-ups that were periodically provided by the 45 municipalities involved.

The vital status of each participant was checked annually using data held at each regional research centre, with permission from the Ministry of Public Management, Home Affairs, Post and Telecommunications, to review the population register sheets. The incidence of cancer was ascertained in 24 study areas (with a total of 65,184 subjects) and coded according to the tenth revision of the International Classification of Disease (ICD-10) and the second edition of the International Classification of Diseases for Oncology (ICD-O). The analysis in the present study also included follow-up data collected before 1999.

Grant sponsor: Ministry of Education, Science, Sports and Culture of Japan; Grant numbers: 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 12218237

*Correspondence to: Department of Clinical Epidemiology, IIES, UOEH 1-1, Iseigaoka, Yahatanishi-ku, Kitakyushu, 807-8555, Japan. Fax: +81-93-603-0158. E-mail: zenq@med.uoeh-u.ac.jp

Received 28 November 2003; Accepted after revision 19 April 2004

DOI 10.1002/ijc.20440
Published online 30 June 2004 in Wiley InterScience (www.interscience.wiley.com).

The informed consent procedures were approved by the Ethics Committee of Medical Care and Research, University of Occupational and Environmental Health, Kitakyushu, Japan, and the Ethical Board of the Nagoya University School of Medicine, Japan.

Data retrieval for analysis

In order to identify the appropriate data for our analysis, we first restricted the subjects to those who lived in the study areas for which cancer incidence was ascertained. We then further restricted the data to include only those participants who provided information concerning their age and sex, and who lacked a previous history of cancer. Our final dataset comprised data from 37,983 women (a total of 379,135 person-years) and thyroid cancer cases were identified among this group using code C73 of the ICD10. Of a total of 79 thyroid cancer cases, 4 individuals died during the follow-up period: 2 as a result of thyroid cancer, 1 as a result of lung cancer and 1 as a result of ovarian cancer. The crude incidence for thyroid cancer in females was 20.8 per 100,000 person-years, whereas the crude estimated thyroid cancer incidence in Japan, based on data obtained from 12 population-based cancer registries between 1986 and 1997, was 7–11 per 100,000.[14] The older age of the JACC cohort at study entry (40–79 years) may explain the higher incidence in this population.

History of blood transfusion and liver disease

Participants with a history of blood transfusion were identified at the baseline by a positive response to a question about previous transfusions (n = 3,504). Information was also obtained about certain other diseases, including hepatitis and liver cirrhosis: respondents indicated on a checklist those diseases with which they had been diagnosed either currently or previously.

Statistical analysis

The Cox proportional hazards model was used to estimate the age-adjusted risk ratio (RR) of a history of blood transfusion for thyroid cancer incidence. The risk of thyroid cancer following liver disease was also estimated. Subjects were divided into 3 groups: individuals with neither a history of transfusion nor of liver disease; individuals with a history of transfusion and/or liver disease; and individuals who had no transfusion history but whose history of liver disease was unknown, or who had no history of liver disease but whose transfusion history was unknown. All calculations were performed using the SAS statistical software package.[15]

RESULTS

As shown in Table I, the prevalence of history of liver disease among subjects with a history of blood transfusion (11.5%) was twice that of those without a history of transfusion (5.3%; p <0.001 derived from chi-squared test).

Table II shows that a history of transfusion was associated with an increased risk of thyroid cancer, although this relationship was not statistically significant (RR = 1.77, 95% CI = 0.95–3.30). No increase in the risk of thyroid cancer was associated with a history of liver disease. However, subjects with a history of transfusion and/or liver disease had a significantly increased risk of thyroid cancer compared with those with neither a history of transfusion nor liver disease (RR = 1.84, 95% CI = 1.07–3.16). When the thyroid cancer data were restricted to only the 59 cases of papillary adenocarcinoma using the ICD-O classification, the results were similar although the risk was higher (RR = 1.96, 95% CI = 1.06–3.63). In addition, after the exclusion of subjects who died as a result of liver cancer, in order to avoid competing risk, the results remained similar (RR = 1.85, 95% CI = 1.08–3.18).

The RRs for liver cancer mortality were also estimated. The risk of a transfusion history for liver cancer was 3.84 (95% CI = 2.34–6.31) and the risk of liver disease for liver cancer was 25.9 (95% CI = 15.8–42.3).

TABLE I – BASELINE CHARACTERISTICS BY HISTORY OF TRANSFUSION

	Transfusion history		
	No n = 29,169	Yes n = 3,504	Unknown n = 5,310
Mean age (SD)	55.5 (10.1)	58.6 (9.9)	61.8 (9.5)
History of liver disease (%)[1]			
No	89.4	75.8	49.3
Yes	5.3	11.5	5.7
Unknown	5.3	12.7	45.0
Number of deaths due to liver cancer	49	23	7
Number of incidences of thyroid cancer	58	12	9

[1] p value derived from chi-squared test <0.001.

DISCUSSION

Our study revealed a marginal association between blood transfusion history and thyroid cancer among females in Japan. Two possible underlying pathways for this association are discussed below.

The first possible mechanism is the transmission of HCV. Chronic HCV infections have been linked with various autoimmune disorders, including autoimmune thyroid diseases and autoimmune hepatitis.[2,3,16,17] Autoimmune thyroiditis is thought to be a preneoplastic condition for thyroid carcinoma[18] and the oncogenetic potential of HCV might partly be explained by modulating effects of the host immune system.[6,19] In addition, autoimmune hepatitis is also associated with thyroiditis: according to a nationwide survey in Japan, chronic thyroiditis was seen in 12% of all cases of autoimmune hepatitis.[20,21]

Transfusion history was used as a proxy for HCV infection in our study, as blood transfusions have been an important transmission route for HCV in Japan. Like Italy, Japan has a high prevalence of HCV, with most cases being present in older individuals. The screening of donated blood for anti-HCV antibodies by the Japanese Red Cross commenced in 1989 with a first-generation ELISA, and the process was improved in 1992 when a second-generation assay was adopted. One previous study estimated that 33% of all HCV infections were acquired through blood transfusions.[22]

An HCV transmission rate of approximately 7–18% following blood transfusion has been reported in Japan.[7,23] Among blood donors with a history of transfusion, 7.4% were found to be positive for anti-HCV antibodies, whereas the anti-HCV-positive rate was only approximately 1.0% among more than 10 million blood donations screened throughout Japan.[7] In addition, the present study showed that individuals with a history of transfusion had higher rates of liver disease and an increased risk of liver cancer. These results also support the hypothesis that transfusion history is a reasonable proxy for HCV infection, as more than 80% of all liver cancer patients in Japan have antibodies to HCV.[24]

The second possible mechanism underlying the association between blood transfusion history and thyroid cancer is based on the hypothesis that blood transfusion-induced immunomodulation promotes the carcinogenic progression from thyroiditis to cancer. Allogeneic blood transfusions induce clinically significant immunosuppression in recipients; this clinical syndrome is referred to as transfusion-associated immunomodulation and its effects have been shown to increase the rate of cancer recurrence.[25]

In our study, a history of liver disease alone did not increase the risk of thyroid cancer. Although liver disease could be a proxy for HCV, other factors, such as HBV and alcohol consumption, are also associated with liver disease, which might lead to a weak association between a history of liver disease and thyroid cancer if the proposed association between HCV and thyroid cancer is genuine. However, when these categories were combined, subjects with a history of transfusion and/or liver disease had a higher risk

TABLE II - THE RISK OF HISTORY OF TRANSFUSION AND LIVER DISEASES FOR THYROID CANCER

	n	Person-years	Thyroid cancer	RR	95% CI	
History of transfusion						
No	29,169	291,920	58	Reference		
Yes	3,504	34,287	12	1.77	0.95	3.30
Unknown	5,310	52,928	9	0.91	0.45	1.84
History of liver disease						
No	31,363	315,766	64	Reference		
Yes	2,257	21,590	6	1.39	0.60	3.21
Unknown	4,363	41,780	9	1.13	0.55	2.30
Transfusion and liver disease						
Neither transfusion nor liver disease	26,088	262,190	50	Reference		
Transfusion and/or liver disease	5,357	52,061	18	1.84	1.07	3.16
Other[1]	6,538	64,885	11	0.95	0.49	1.84

[1]Subjects who did not have a transfusion history and whose history of liver disease was unknown, or subjects who did not have liver disease and whose transfusion history was unknown.

of thyroid cancer compared with those with no history of either. We propose that the combined category of individuals with a history of liver disease and transfusion captured more HCV-positive subjects, even if the sensitivity of HCV detection was relatively low. In addition, an HCV-negative reference group, comprising individuals with a history of neither transfusion nor liver disease, might have been more inclusive than only those with no history of transfusion, as blood transfusion is not the exclusive route of HCV transmission.[22]

A potential limitation of our study is that the participants reported their own blood transfusion history. However, a previous report[26] calculated the sensitivity and specificity of self-reported transfusion histories as 93% and 78%, respectively. In addition, misclassification would tend to weaken any association between a history of transfusion and thyroid cancer; therefore, the actual risk might be greater than that reported here.

This prospective cohort study indirectly supports the association between HCV and thyroid cancer suggested by a recent series of case-control studies in southern Italy. In addition, our results raise a new hypothesis: the association between blood transfusions and thyroid cancer is facilitated by transfusion-associated immunomodulation. Detailed epidemiological studies will be necessary to further examine the interactions between thyroid cancer, HCV and blood transfusion, including immunomodulation effects.

ACKNOWLEDGEMENTS

Japan Collaborative Cohort Study Group: The present investigators involved in the JACC study and their affiliations are as follows: Dr. Y. Ohno (the present chairman of the Monbusho ECC), Dr. A. Tamakoshi (Secretary General of the Monbusho ECC) and Dr. H. Toyoshima, Nagoya University Graduate School of Medicine; Dr. M. Mori, Sapporo Medical University School of Medicine; Dr. Y. Motohashi, Akita University School of Medicine; Dr. S. Hisamichi, Tohoku University Graduate School of Medicine; Dr. Y. Nakamura, Jichi Medical School; Dr. T. Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. H. Mikami, Chiba Cancer Center; Dr. S. Hashimoto, School of Health Sciences and Nursing, University of Tokyo; Dr. Y. Inaba, Juntendo University School of Medicine; Dr. H. Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Y. Hoshiyama, Showa University School of Medicine; Dr. H. Suzuki, Niigata University School of Medicine; Dr. H. Shimizu, Gifu University School of Medicine; Dr. S. Tokudome, Nagoya City University Medical School; Dr. Y. Ito, Fujita Health University School of Health Sciences; Dr. A. Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. T. Kawamura, Kyoto University Center for Student Health; Dr. Y. Watanabe, Kyoto Prefectural University of Medicine, Research Institute for Neurological Diseases and Geriatrics; Dr. M. Nakao, Kyoto Prefectural University of Medicine; Dr. T. Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. T. Hashimoto, Wakayama Medical University; Dr. T. Nose, Tottori University Faculty of Medicine; Dr. N. Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. T. Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. K. Fukuda, Kurume University School of Medicine; Dr. T. Kitagawa, Cancer Institute of Japanese Foundation for Cancer Research; Dr. T. Kuroki, Institute of Molecular Oncology, Showa University; Dr. N. Okamoto, Kanagawa Cancer Center; Dr. T. Ishibashi, Asama General Hospital; Dr. H. Shio, Shiga Medical Center and Dr. K. Tajima, Aichi Cancer Center Research Institute. The former investigators involved in the JACC study and their affiliations are as follows: Dr. K. Aoki, Aichi Cancer Center; Dr. S. Tominaga, Aichi Cancer Center Research Institute; Dr. S. Anzai, Dr. T. Kawaguchi, Dr. K. Nakamura and Dr. M. Masaki, Showa University School of Medicine; Dr. S. Kanamori, Dr. M. Morimoto and Dr. S. Yoshimura, Shiga Medical Center for Adults; Dr. S. Kamiyama, Dr. Y. Takizawa and Dr. N. Hachiya, Akita University School of Medicine; Dr. K. Kawai, Dr. S. Nakagawa and Dr. H. Watanabe, Kyoto Prefectural University of Medicine; Dr. M. Kurihara, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Y. Komachi, Institute of Community Medicine, University of Tsukuba; Dr. R. Sasaki, Aichi Medical University; Dr. M. Sugita, Toho University School of Medicine; Dr. I. Sugimura, Asahikawa Kosei Hospital; Dr. T. Tanaka, Chigasaki Public Health Center; Dr. T. Hirohata, Kyushu University School of Medicine; Dr. I. Fujimoto, Center for Adult Diseases, Osaka; Dr. M. Matsuzaki, Chigasaki Public Health and Welfare Center; Dr. H. Miyake, Sapporo Medical University School of Medicine; Dr. M. Murata, Chiba Cancer Center; Dr. S. Morio, Kanagawa Cancer Center; Dr. H. Yanagawa, Jichi Medical School and Dr. S. Watanabe, Tokyo University of Agriculture.

REFERENCES

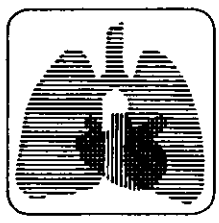
1. London WT. Liver cancer. In: Schottenfeld D, Fraumeni JF, eds. Cancer epidemiology and prevention, 2nd ed. New York: Oxford University Press, 1996. 772–93.
2. Obermayer-Straub P, Manns MP. Hepatitis C and D, retroviruses and autoimmune manifestations. J Autoimmun 2001;16:275–85.
3. Manns MP, Rambusch EG. Autoimmunity and extrahepatic manifestations in hepatitis C virus infection. J Hepatol 1999;31:39–42.
4. Montella M, Crispo A, Pezzullo L, Izzo F, Fabbrocini G, Ronga D, Tamburini M. Is hepatitis C virus infection associated with thyroid cancer?: a case-control study. Int J Cancer 2000;87:611–2.
5. Montella M, Crispo A, de Bellis G, Izzo F, Frigeri F, Ronga D, Spada O, Mettvier V, Tamburini M, Cuomo O. HCV and cancer: a case-control study in a high-endemic area. Liver 2001; 21:335–41.
6. Montella M, Pezzullo L, Crispo A, Izzo F, Amore A, Marone U, Tamburini M, Ronga D, Chiofalo MG, Chiappetta G, Mozzillo N.

Risk of thyroid cancer and high prevalence of hepatitis C virus. Oncol Rep 2003;10:133–6.
7. Yamaguchi K, Kiyokawa H, Machida J, Obayashi A, Nojiri N, Ueda S, Takatsuki K. Seroepidemiology of hepatitis C virus infection in Japan and HCV infection in haemodialysis patients. FEMS Microbiol Rev 1994;14:253–8.
8. Yatsuya H, Toyoshima H, Mizoue T, Kondo T, Tamakoshi K, Hori Y, Tokui N, Hoshiyama Y, Kikuchi S, Sakata K, Hayakawa N, Tamakoshi A, et al. Family history and the risk of stomach cancer death in Japan: differences by age and gender. Int J Cancer 2002;97:688–94.
9. Hoshiyama Y, Kawaguchi T, Miura Y, Mizoue T, Tokui N, Yatsuya H, Sakata K, Kondo T, Kikuchi S, Toyoshima H, Hayakawa N, Tamakoshi A, et al. A prospective study of stomach cancer death in relation to green tea consumption in Japan. Br J Cancer 2002;87:309–13.
10. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, Kurosawa M, Ohno Y, Yatsuya H, Toyoshima H, Mizoue T, Kondo T, et al. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk—family history and the risk of stomach cancer death in Japan: differences by age and gender. Int J Cancer 2002;99:742–6.
11. Ohno Y, Tamakoshi A. Japan collaborative cohort study for evaluation of cancer risk sponsored by monbusho (JACC study). J Epidemiol 2001;11:144–50.
12. Ando M, Wakai K, Seki N, Tamakoshi A, Suzuki K, Ito Y, Nishino Y, Kondo T, Watanabe Y, Ozasa K, Ohno Y, Lin Y, et al. Attributable and absolute risk of lung cancer death by smoking status: findings from the Japan Collaborative Cohort Study. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk-family history and the risk of stomach cancer death in Japan: differences by age and gender. Int J Cancer 2003;105:249–54.
13. Fujino Y, Tamakoshi A, Ohno Y, Mizoue T, Tokui N, Yoshimura T. Prospective study of educational background and stomach cancer in Japan. Prev Med 2002;35:121–7.
14. The Research Group for Population-Based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1998: estimates based on data from 12 population-based cancer registries. Jpn J Clin Oncol 2003;33:241–5.
15. SAS Institute Inc. SAS/STAT User's Guide, Release 6.03. Cary, North Carolina: SAS Institute Inc., 1988.
16. Lunel F, Cacoub P. Treatment of autoimmune and extrahepatic manifestations of hepatitis C virus infection. J Hepatol 1999;31:210–6.
17. Ganne-Carrie N, Medini A, Coderc E, Seror O, Christidis C, Grimbert S, Trinchet JC, Beaugrand M. Latent autoimmune thyroiditis in untreated patients with HCV chronic hepatitis: a case-control study. J Autoimmun 2000;14:189–93.
18. Okayasu I, Fujiwara M, Hara Y, Tanaka Y, Rose NR. Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma: a study of surgical cases among Japanese, and white and African Americans. Cancer 1995;76:2312–8.
19. Ferri C, La Civita L, Zignego AL, Pasero G. Viruses and cancers: possible role of hepatitis C virus. Eur J Clin Invest 1997;27:711–8.
20. Onji M, Nonaka T, Horiike N, Moriwaki H, Muto Y, Ohta Y. Present status of autoimmune hepatitis in Japan. Gastroenterol Jpn 1993;28:134–8.
21. Zeniya M. Thyroid disease in autoimmune liver diseases. Nippon Rinsho 1999;57:1882–7.
22. Shimoyama R, Sekiguchi S, Suga M, Sakamoto S, Yachi A. The epidemiology and infection route of asymptomatic HCV carriers detected through blood donations. Gastroenterol Jpn 1993;28:1–5.
23. Watanabe J, Minegishi K, Mitsumori T, Ishifuji M, Oguchi T, Ueda M, Tokunaga E, Tanaka E, Kiyosawa K, Furuta S. Prevalence of anti-HCV antibody in blood donors in the Tokyo area. Vox Sang 1990;59:86–8.
24. Nishioka K, Watanabe J, Furuta S, Tanaka E, Iino S, Suzuki H, Tsuji T, Yano M, Kuo G, Choo QL. A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. Cancer 1991;67:429–33.
25. Blajchman MA. Immunomodulation and blood transfusion. Am J Ther 2002;9:389–95.
26. Sandhu JS, Campbell PM, Preiksaitis JK, Carriere KC, Hessel PA. Validation of self-reported transfusion histories in renal dialysis patients. Can J Public Health 1999;90:201–4.

The Natural History of Radiographically Occult Bronchogenic Squamous Cell Carcinoma*

A Retrospective Study of Overdiagnosis Bias

Masami Sato, MD, FCCP; Yasuki Saito, MD; Chiaki Endo, MD; Akira Sakurada, MD; David Feller-Kopman, MD; Armin Ernst, MD, FCCP; and Takashi Kondo, MD



Vol. 126, p. 108-113
July 2004 Issue

Reprinted from CHEST

The Natural History of Radiographically Occult Bronchogenic Squamous Cell Carcinoma*

A Retrospective Study of Overdiagnosis Bias

Masami Sato, MD, FCCP; Yasuki Saito, MD; Chiaki Endo, MD; Akira Sakurada, MD; David Feller-Kopman, MD; Armin Ernst, MD, FCCP; and Takashi Kondo, MD

Objective: **An *overdiagnosis bias* occurs with the diagnosis of a disease that does not produce signs or symptoms before the patient dies from other causes. We sought to determine whether overdiagnosis bias is a factor when screening for squamous cell carcinoma of the lung.**
Design: **Retrospective study of the Miyagi Population-Based Lung Cancer Screening Registry for high-risk patients who were seen between January 1, 1982 (when sputum cytology tests were added for men with long smoking histories), and December 31, 1996.**
Setting: **Miyagi Prefecture, Japan.**
Patients: **A total of 251 patients (all men) who had sputum cytology test results that were positive for squamous cell carcinoma but had normal radiograph findings, 44 of whom declined cancer treatment (mean age, 70 years) and 207 of whom were treated with resection within 12 weeks of diagnosis (mean age, 65.5 year).**
End Points: **Five-year and 10-year survival rates from primary lung cancer in both groups as of August 15, 2001.**
Results: **Among the 44 untreated patients, 15 (34%) remained asymptomatic. The survival rate due to primary lung cancer death in the untreated group was 53.2% at 5 years and 33.5% at 10 years. The survival rate among treated patients was 96.7% at 5 years and 94.9% at 10 years. Of the 125 treated patients who died, 14 (11.2%) died from primary lung cancer.**
Conclusion: **Given that the two thirds of the untreated patients with squamous cell carcinoma of the bronchus died from lung cancer within 10 years, overdiagnosis bias does not appear to be a factor in screening for this disease. Thus, we recommend that patients with radiographically occult squamous cell carcinoma of the bronchus undergo tumor treatment after localization.**
(CHEST 2004; 126:108–113)

Key words: early detection; lead-time bias; lung cancer; mass screening; overdiagnosis bias; sputum cytology; squamous cell carcinoma; tumor localization

Abbreviation: CI = confidence interval

The concept of overdiagnosis, as formulated after the Mayo Lung Project,[1–6] is based on the fact that many patients with slow-growing cancers will likely die of other causes before the cancer produces clinical signs and symptoms. In such cancers, screening programs for the early diagnosis of cancer will produce an *overdiagnosis bias* by diagnosing patients with a cancer that may not need to be treated.

Screening for lung cancer has been thought to be

*From the Department of Thoracic Surgery (Drs. Sato, Endo, Sakurada, and Kondo), Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Japan; the Department of Thoracic Surgery (Dr. Saito), National Sendai Hospital, Sendai, Japan; and the Division of Interventional Pulmonology (Drs. Feller-Kopman and Ernst), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.
The results of this study were presented at the 10th World Conference on Lung Cancer, Vancouver, BC, Canada, August 14, 2003.
This study was partly supported by grants-in-aid from the Ministry of Education, Science, Sports, and Culture of the Japanese Government.

Manuscript received March 24, 2003; revision accepted January 22, 2004.

Correspondence to: Masami Sato, MD, Department of Thoracic Surgery, Institute of Development, Aging, and Cancer, Tohoku University, 4–1 Seiryo-machi, Aoba-Ku, Sendai 980-8575, Japan; e-mail: m-sato@idac.tohoku.ac.jp

ineffective, and overdiagnosis bias has been used to explain the disappointing results of mass screening programs.[7–14] However, in the late 1990s, the Mayo Lung Project was reevaluated,[9,10,13–17] and some authors have suggested[15,16] the possible usefulness of chest radiography for lung cancer screening.

Knowing the natural course of a disease in untreated patients can be helpful in determining the presence of overdiagnosis bias. Sobue et al[18] reported the course of nonsurgically treated, clinical stage I lung cancer detected by radiography. Including their report, most studies[19,20] have dealt with adenocarcinoma diagnosed from an abnormal shadow on a radiograph. To our knowledge, however, the natural course of radiographically negative squamous cell carcinoma of the lung has not been described. Patients who have cytologic evidence of lung cancer but have normal chest radiographs are thought to be in the early stages of cancer. The introduction of autofluorescence bronchoscopy has made it easy to detect many intraepithelial lesions.[21,22] However, it is not known whether these lesions should be treated or not. Clarifying the natural history of this type of lung cancer could help to determine whether a latent or nonprogressive form of squamous cell carcinoma exists and, in turn, whether this cancer is subject to overdiagnosis bias.

In the United States, lung cancer screening tests are generally administered only to persons with good cardiopulmonary function who can undergo surgical treatment. Japan, however, has a 50-year history of screening for tuberculosis with chest radiography. Everyone is screened because some people remain worried about tuberculosis. As a result, some people with poor cardiopulmonary function in whom cancer is detected may decline cancer treatment. Others may mistake sputum cytology, which became part of the screening program in 1982, as a screening test for tuberculosis and thus may also decline treatment for lung cancer if it is diagnosed. We took advantage of this unique situation, in which patients with cytologic evidence of squamous cell carcinoma and normal chest radiograph findings remain untreated, to study the natural history of squamous cell carcinoma. We herein report the results of a retrospective study of a cancer screening registry in which we compared the survival of cancer patients with cytologic evidence of squamous cell carcinoma and normal chest radiograph findings, who did and did not undergo tumor resection.

Patients and Methods

We reviewed the registry of the Miyagi Population-Based Lung Cancer Screening Program, which is a database of people from Miyagi Prefecture who were screened with radiography, originally for tuberculosis and later for lung cancer. In 1982, the registry added sputum cytology as a new screening method for the early detection of lung cancer.[23] Men with a Brinkman index[24] of ≥ 600 were candidates for screening.

All patients with abnormal sputum cytology test results were examined at the Department of Thoracic Surgery, Tohoku University Hospital, where they underwent CT scans of the chest and bronchoscopy. When patients had abnormal radiographic findings, they were referred to other hospitals.

Records dated between January 1, 1982, and December 31, 1996, were studied to identify patients in whom sputum cytology test results were positive for squamous cell carcinoma of the lung and in whom the findings of miniature (*ie*, 100 mm × 100 mm) posteroanterior chest radiographs were normal. These patients constituted two groups, namely, those who chose not to receive treatment for cancer and those who underwent tumor resection (Table 1). Patients receiving radiotherapy or photodynamic therapy were excluded.

Willing patients in the untreated group underwent a chest radiograph and sputum cytology test every 4 months, chest CT scans every 6 months, and bronchoscopic examinations every 12 months. The cause of death for patients who died before August 15, 2001, also was obtained from the registry. Death from primary lung cancer was defined as a tumor in the lung that was accompanied by clinical complications, such as obstructive pneumonia, hemoptysis, or brain metastasis. When the registry did not list the patient's cause of death, we used the cause of death identified by the patient's personal physician. The end points of this study were the 5-year and 10-year survival rates from primary lung cancer in both groups.

Statistical Analysis

Kaplan-Meier curves were plotted for both treated patients (*ie*, those who underwent resection) and untreated patients using a statistical software package (StatView; SAS Institute; Cary, NC).

Results

We identified 251 patients (all men) with positive sputum cytology test results and normal radiograph findings (Table 1). Of these patients, 44 did not receive treatment for cancer (*ie*, *untreated patients*). The mean (± SD) age was 70 ± 8.2 years (age range,

Table 1—*Background of Patients*

Variables	Natural Course Cases (n = 44)	Resected Cases (n = 207)*
Gender	All male	All male
Age		
Mean/SD	70/8.2	65.5/6.5
Minimum–maximum	53–86	51–81
Brinkman index†		
Mean/SD	1,065/381	1,053/442
Minimum–maximum	500–2,400‡	400–3,420

*Two patients who died within 30 days after operation were excluded.

†Brinkman index[24]: (No. of cigarettes per day) × (No. of years subject has smoked).

‡In 10 patients, we could not obtain information about the smoking history.

53 to 86 years). In this group, 27 patients had tumors that were localized by bronchoscopic examination, but they nevertheless declined treatment, 13 patients declined bronchoscopic examinations, and 4 patients had disease that could not be localized, even after intensive examinations,[21,23,25,26] including bronchoscopy, CT scans of the chest, and inspections by otorhinolaryngologists. These last 17 patients were eventually confirmed as having lung cancer at a mean of 49 months after the initial examination (range, 4.6 to 160 months).

Although the smoking histories of 10 untreated patients were not available, the 34 remaining patients each had a history of smoking. The mean Brinkman index[24] (*ie*, the number of cigarettes smoked per day times the number of years of smoking) was 1,065 (range, 500 to 2,400).

We also identified 207 patients who underwent pulmonary resection shortly after learning the results of the sputum cytology test (*ie, treated patients*). The mean age was 65.5 years (SD, 6.5 years) [age range, 51 to 81 years]. The mean Brinkman index was 1,053 (range, 400 to 3,420).

The overall survival rates of the 44 untreated patients were 53.2% at 5 years and 33.5% at 10 years (Fig 1). Among the 44 untreated patients, 15 (34%) remained asymptomatic. Nine of the 15, however, died due to the following conditions: cardiovascular disease (4 patients); extrapulmonary malignancy (2 patients); emphysema (1 patient); and unknown causes (2 patients).

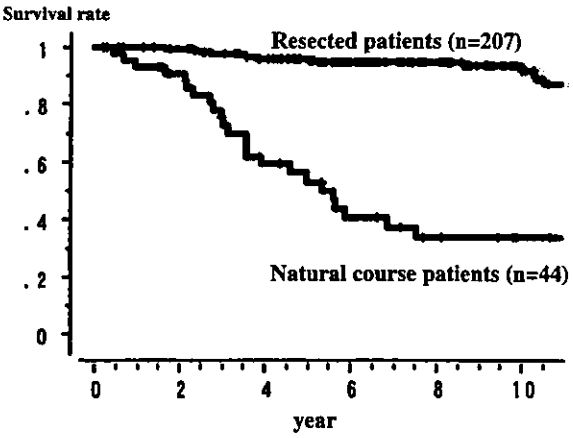


FIGURE 1. Survival curves of natural course patients and of patients who underwent resection. The lower curve represents the survival curve of 44 patients with sputum cytology results that were positive for squamous cell carcinoma of the bronchus but with normal chest radiograph findings, who chose not to be treated for cancer. The upper curve represents 207 patients with sputum cytology positive for squamous cell carcinoma of the bronchus but with normal chest radiograph findings, who underwent tumor resection.

The survival rates based on death from primary lung cancer in the 207 treated patients were 96.7% at 5 years and 94.9% at 10 years (Fig 1). None of these patients had abnormal radiographic findings at the time of treatment.

Of the 207 surgically treated patients, 125 (60%) died within 10 years (from primary lung cancer, 14 [11%]; from metachronous secondary lung cancer, 28 [22%]) [Table 2]. Thus, among treated patients who died, the rate of lung cancer death, including the first primary and metachronous second primary lung cancer, was 33.6% (42 of 125 patients).

We also analyzed data from 19 additional patients with radiographically occult lung cancer, identified as described, who initially declined treatment but who eventually sought treatment for cancer. When cancer cells were present in the sputum anytime during the follow-up period, or when chest radiographs showed abnormalities, we recommended bronchoscopic examination to the patients. At the time of treatment, all 19 patients had lung cancer, as diagnosed bronchoscopically, but chest radiograph findings were still normal in 10 patients and abnormal in 9 patients.

In the 10 patients with normal radiograph findings, there were no lung cancer deaths. However, patients who had abnormal shadows at the time of treatment had worse prognoses (Fig 2).

DISCUSSION

Overdiagnosis bias is often discussed in the field of mass cancer screening. The concept is easily understood, and many authors have used it when discussing their data. However, this bias is difficult to evaluate. One common approach is to analyze autopsy data to determine retrospectively the incidence of undiagnosed cancer. However, this method yields only the prevalence of cancer at the time of autopsy and does not include much information concerning the development of the disease. Drlicek and

Table 2—*Causes of Death in Patients With Roentgenographically Occult Squamous Cell Carcinoma Who Underwent Resection (n = 125)*

Cause of Death	Patients (n = 125) No.	%
Primary lung cancer	14	11.2
Second primary lung cancer	28	22.4
Extrapulmonary malignancy	23	18.4
Others	59	47.2
Unknown	1	0.8

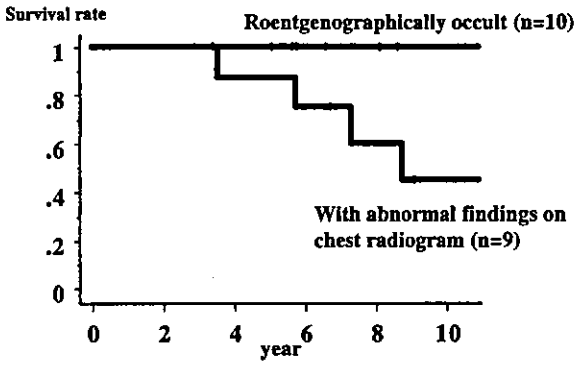


FIGURE 2. Survival curves of patients who received treatment later and radiographic findings at the time of therapy.

Bodenteich[27] examined a large number of autopsy reports from three hospitals and reported an overall incidence of undiagnosed lung cancer of 7.8% (67 of 859 patients). He also reported the incidence of clinically undiagnosed lung cancer for each of the three hospitals. The incidence of undiagnosed cancer in the hospital having a pulmonary department was 3.4%, which was the lowest among the three hospitals.

Another way of evaluating overdiagnosis bias is to observe patients who have received a diagnosis of cancer but who have not received treatment. Ethical issues do not allow a prospective study of such patients. Since 1982, we have been conducting lung cancer screening tests with both miniature chest radiographs and sputum cytology among high-risk individuals whose Brinkman index is ≥ 600.[23] Between 1982 and 1996, we detected 282 cases of bronchogenic squamous cell carcinoma with sputum cytology tests in patients with normal chest radiograph findings, 251 of whom had undergone resection or had declined treatment. (The latter 251 patients were included in the present analysis. The remaining 31 excluded patients consisted of 15 patients who received radiotherapy and 16 patients who were treated with photodynamic therapy.) Although almost all the patients were asymptomatic, most chose to undergo treatment. Among them, however, were 44 patients reported here who declined further examination or treatment and 19 patients who eventually sought treatment when the diagnosis was confirmed. We analyzed the natural course of the disease in these patients because we could observe, retrospectively, the biological behavior of the cancer.

We also analyzed the survival curves of the occult lung cancer patients who underwent complete resection. A few of these patients died from a recurrence of resected cancer, although their resected tumors were small. This result indicates that some of these patients had an extremely high malignant potential, despite the cancer being at an early stage at the time of surgery. It also suggests that overdiagnosis bias is not applicable in all cases of radiographically occult, bronchogenic squamous cell carcinoma.

All the untreated patients had cancer cells in their sputum, but all had normal chest radiograph findings. Two thirds of the patients died from lung cancer within 10 years. This finding indicates that overdiagnosis bias is not a major factor in such patients. We speculate that a long lead-time bias is a key factor in understanding the natural course as well as the clinical course in this group. In cases in which tumors could not be localized but showed positive cytology results, some tumors in the otorhinolaryngeal region were detected during the follow-up period. In this study, however, we focused on the natural course of radiographically occult bronchogenic squamous cell carcinoma. Thus, the data of patients with tumors in the otorhinolaryngeal region are not included in this report. Similarly, regarding the treatment group, we chose patients who had undergone pulmonary resection from among those who received various kinds of treatment, because pulmonary resection is believed to be the most curative.

To our knowledge, no one has described the natural course of patients with radiographically occult, bronchogenic squamous cell carcinoma. Sobue et al[18] described the course of stage I lung cancer. The 5-year survival rate was 14.3% for the screening-detected group and 3.7% for the symptom-detected group.[18] Because the patients of Sobue et al[18] had abnormal shadows on their radiographs, the difference between the 5-year survival rate of their patients and ours is also understandable in terms of lead-time bias. Nou,[19] reporting on the natural course of bronchial carcinoma, found a 5-year survival rate of 7.5% in cases of squamous cell carcinoma detected by radiography. He did not document cancer stage distributions, however.

Motohiro et al[20] examined the prognosis of non-surgically treated clinical stage I lung cancer patients and reported a 5-year survival rate of about 20%. Interestingly, he also found that the survival rate continued to decrease after 5 years. Although his cases were detected by radiography, we believe they support our results. In an early report of the Mayo Lung Project, Woolner et al[4] described a case in which positive sputum findings preceded the development of a radiographic abnormality.

In addition to the Mayo Lung Project, two other famous randomized trials, the Johns Hopkins Study[28,29] and the Memorial Sloan-Kettering study,[30,31] also have addressed this issue. Based on the

results of the Sloan-Kettering study, Melamed et al[32] concluded that the squamous cell carcinomas detected by cytologic examination alone are very slow growing and tend to remain localized until detected by radiography. This conclusion may be based on the fact that survival and mortality rates in their study were the same between the screened and control groups. Thus, we tried to observe the treatment results of the patients who received treatment later. The 9 patients who had abnormal radiographic shadows at the time of their delayed treatment had a worse prognosis than did the 10 patients with normal radiograph findings.

Finally, three randomized controlled trials in the United States in the late 1970s and early 1980s reported that screening with sputum cytology did not reduce deaths from lung cancer. The Johns Hopkins Study[28,29] and the Memorial Sloan-Kettering study[30,31] examined the effectiveness of sputum cytology screening in combination with radiographic screening compared with that of radiographic screening alone. There were 2.7 lung cancer deaths per person-year in both the screened and the control group in the Memorial Sloan-Kettering study,[30,31] and 3.4 per person-year in the screened group and 3.8 per person-year in the control group in the Johns Hopkins Study.[28,29]

Sagawa et al,[33] however, reported on the efficacy of lung cancer screening conducted in the 1990s. He reported four case-control studies in Japan, three of which revealed statistically significant reductions in lung cancer deaths among screened patients. The odds ratios in each study were 0.54 (95% confidence interval [CI], 0.41 to 0.73) in Miyagi Prefecture, 0.40 (95% CI, 0.27 to 0.59) in Niigata Prefecture, 0.59 (95% CI, 0.46 to 0.74) in Okayama Prefecture, and 0.68 (95% CI, 0.44 to 1.05) in Gunma Prefecture. In the three studies showing significant reductions, high-risk persons (*ie*, smokers) were screened with annual chest radiographs and sputum cytology tests, and nonsmokers were screened with an annual chest radiograph. In the one prefecture in which screening did not yield a significant reduction in lung cancer deaths, only annual radiographs were used.

Limitations of the Study

Our study was retrospective and nonrandomized, so the groups were not necessarily equivalent at baseline. For example, the age distributions were slightly different between the two groups. Patients who underwent resection likely had a will to survive and a strong interest in their health, whereas those who declined treatment may not have. Our study cannot exclude such biases. Our study nevertheless offers some important information on the natural course of radiographically occult squamous cell carcinoma of the bronchus.

Conclusion

In conclusion, although some investigators believe that cancer patients with normal radiograph findings have slow-growing tumors, two thirds of the patients with such tumors in our study died from primary lung cancer within 10 years. This result suggests that overdiagnosis bias is not a factor in the course of squamous cell carcinoma of the bronchus in patients with normal chest radiograph findings. We recommend that these patients be treated after the tumor is localized.

ACKNOWLEDGMENT: We thank Drs. Yoshitaka Tsubono, Ichiro Tsuji, and Zen'ichi Nishino, and the Miyagi Cancer Registry for their help.

References

1 Woolner LB, Fontana RS, Cortese DA, et al. Roentgenographically occult lung cancer: pathologic findings and frequency of multicentricity during a 10-year period. Mayo Clin Proc 1984; 59:453–466
2 Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic Study. Am Rev Respir Dis 1984; 130:561–565
3 Fontana RS. The Mayo Lung Project: a perspective. Cancer 2000; 89:2352–2355
4 Woolner LB, Fontana RS, Sanderson DR, et al. Mayo Lung Project: evaluation of lung cancer screening through December 1979. Mayo Clin Proc 1981; 56:544–555
5 Sanderson D, Fontana R. Results of the Mayo Lung Project: an interim report. Recent Results Cancer Res 1982; 82:179–186
6 Fontana RS, Sanderson DR, Woolner LB, et al. Screening for lung cancer: a critique of the Mayo Lung Project. Cancer 1991; 67:1155–1164
7 Dammas S, Patz EF, Goodman PC. Identification of small lung nodules at autopsy: implications for lung cancer screening and overdiagnosis bias. Lung Cancer 2001; 33:11–16
8 Hakama M, Holli K, Visakorpi T, et al. Low biological aggressiveness of screen-detected lung cancers may indicate over-diagnosis. Int J Cancer 1996; 66:6–10
9 Sugarbaker DJ, Strauss GM. Extent of surgery and survival in early lung carcinoma: implications for overdiagnosis in stage IA non-small cell lung cancer. Cancer 2000; 89(suppl):2432–2437
10 Strauss GM, Gleason RE, Sugarbaker DJ. Screening for lung cancer re-examined: a reinterpretation of the Mayo Lung Project randomized trial on lung cancer screening. Chest 1993; 103(suppl):337S–341S
11 Eddy D. Screening for lung cancer. Ann Intern Med 1989; 111:232–237
12 Fontana RS. Screening for lung cancer: recent experience in the United States. In: Hansen HH, ed. Lung cancer: basic and clinical aspects. Boston, MA: Martinus Nijhoff, 1989; 91–111

13 Straus GM, Gleason RE, Sugarbaker DJ. Screening for lung cancer: another look, a different view. Chest 1997; 111:754–768
14 Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000; 92:1308–1316
15 Flehinger BJ, Kimmel M, Polyak T, et al. Screening for lung cancer: the Mayo Lung Project revisited. Cancer 1993; 72:1573–1580
16 Strauss GM, Gleason RE, Sugarbaker DJ. Chest x-ray screening improves outcome in lung cancer, a reappraisal of randomized trials on lung cancer screening. Chest 1995; 107: 270S–279S
17 Marcus PM, Prorok P. Reanalysis of the Mayo Lung Project data: the impact of confounding and effect modification. J Med Screen 1999; 6:47–49
18 Sobue T, Suzuki T, Matuda M, et al. Survival for clinical stage I lung cancer not surgically treated. Cancer 1992; 69:685–692
19 Nou E. The natural five-year course in bronchial carcinoma: epidemiologic results. Cancer 1984; 53:2211–2216
20 Motohiro A, Ueda H, Komatsu H, et al. Prognosis of non-surgically treated, clinical stage I lung cancer patients in Japan. Lung Cancer 2002; 36:65–69
21 Sato M, Saito Y, Nagamoto N, et al. Diagnostic value of differential brushing of all branches of the bronchi in patients with sputum positive or suspected positive for lung cancer. Acta Cytol 1993; 37:879–883
22 Lam S, MacAulay C, Hung J, et al. Detection of dysplasia and carcinoma *in situ* with a lung imaging fluorescence endoscope devise. J Thorac Cardiovasc Surg 1993; 105:1035–1040
23 Nakada T, Sato M, Saito Y, et al. Detection of early lung cancer: results of radiologic and cytologic screening in the Miyagi Program. Tohoku J Exp Med 1987; 152: 173–185
24 Brinkman GL, Coates EB. The effect of bronchitis, smoking, and occupation on ventilation. Am Rev Respir Dis 1963; 87:684–693
25 Sato M, Sakurada A, Sagawa M, et al. Diagnostic results before and after introduction of autofluorescence bronchoscopy in patients suspected of having lung cancer detected by sputum cytology in lung cancer mass screening. Lung Cancer 2001; 32:247–253
26 Sato M, Saito Y, Usuda K, et al. Occult lung cancer beyond bronchoscopic visibility in sputum-cytology positive patients. Lung Cancer 1998; 20:17–24
27 Drlicek M, Bodenteich A. Identification of lung cancer by autopsy: an indicator for clinical underdiagnosis. Lung Cancer 2002; 35:217
28 Tockman MS. Survival and mortality from lung cancer in a screened population: the Johns Hopkins Study. Chest 1989; 96(suppl):324–325
29 Johns Hopkins Medical Institutions. Final report: lung cancer control, detection and therapy, phase II, NCI-PHS; contract No. N01-CN-4537, December 31,1984. Bethesda, MD: National Cancer Institute, 1984
30 Flehinger BJ, Melamed MR, Zaman MB, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. Am Rev Respir Dis 1984; 130:555–560
31 National Lung Program, Memorial Sloan-Kettering Cancer Center. Final report and data summary, December 31, 1984. Bethesda, MD: National Cancer Institute, 1984
32 Melamed MR, Flehinger BJ, Zaman MB, et al. Screening for early lung cancer: results of the Memorial Sloan-Kettering study in New York. Chest, 1983; 86:44–53
33 Sagawa M, Nakayama T, Tsukada H, et al. The efficacy of lung cancer screening conducted in 1990s: four case-control studies in Japan. Lung Cancer 2003; 41:29–36

ELSEVIER

Ann Anat 186 (2004): 337–347
http://www.elsevier.de

ANNALS OF ANATOMY

Comparative histology of lymph nodes from aged animals and humans with special reference to the proportional areas of the nodal cortex and sinus

Izumi Taniguchi[1], Akira Sakurada[2], Gen Murakami[3], Daisuke Suzuki[3], Masami Sato[2], Gen-iku Kohama[1]

[1]Department of Oral Surgery, Sapporo Medical University School of Medicine, Sapporo, Japan, [2]Department of Thoracic Surgery, Tohoku University Institute of Development, Aging and Cancer, Sendai, Japan, [3]Department of Anatomy, Sapporo Medical University School of Medicine, South 1, West 17, Chuo-ku, Sapporo, 060-8556 Japan

Summary. Lymph nodes are composed of a lymphocyte-rich area or cortex (subdivided into the superficial and deep cortex and the medullary cord) and another, macrophage-rich area (incorporating the subcapsular and medullary sinuses). We measured the proportional area of the cortex in lymph nodes from aged experimental mammals (rats, guinea pigs, dogs and rabbits) and elderly Japanese humans. The cervical, axillary and inguinal nodes were generally richer in cortex tissue than the pulmonary regional and mesenteric nodes. Histological heterogeneity and medullary sinus dominance were much more evident in the human nodes than in those from animals, except for the guinea pig thoracic node. Human pulmonary regional nodes were characterized by a large medullary sinus; in guinea pigs, these nodes had a similar histology but the T lymphocyte-containing areas were smaller and thinner than in humans. The paraaortic node was well developed in humans and dogs, but not in other animals tested. These species- and region-specific histological differences may influence the evaluation of experimental animal models of lymph node function, such as those recently identified for research into sentinel nodes.

Key words: Lymph nodes – Cortex area – Proportional area – Aging – Sentinel node

Correspondence to: Daisuke Suzuki, PhD.
E-mail: daisuke@sapmed.ac.jp

Introduction

Age-dependent morphological alterations have been reported in lymphatic cell components (Rópolo et al. 2001), the general histology of lymph nodes (van der Valk and Meijer 1997) and even the gross anatomy of the lymphatics (Bourgeois 2002). Using mice, Hoshi et al. (2001) described region-specific differences in the postnatal development of lymph nodes. Very recently, our group demonstrated that abdominal nodes from elderly humans have a specific histological architecture that differs from the usual textbook descriptions (Sato et al. 2003). Briefly, the normal polar, laminar configuration, comprising the subcapsular sinus, superficial cortex, deep cortex, medullary sinus and hilus, is often or usually lost in human visceral nodes. These potentially age-dependent and region-specific morphological variations may warrant consideration in studies of lymph node histology as well as in routine clinical medicine, for example, in research into sentinel nodes (Veronesi et al. 1997; Faries et al. 2000). This is especially important as the sentinel node procedure has been expanded to encompass many primary sites for neoplasms (Kitagawa et al. 2000) and is often performed in elderly patients.

When making such considerations, it is important to focus on the histological architectural features that are critically connected to the nodal immune response. In lymph nodes, various critical cell-cell interactions seem to occur between cortical and sinusoidal components such as T lymphocytes and sinus macrophages (Delemarre et al. 1990a, b; van Rooijen 1991; Geijtenbeek et al. 2002), T

0940-9602/04/186/04–337 $30.00/0