Table 1. Characteristics of study subjects at baseline according to exposure variable (Continued)

Factor	All subjects	Family history of stomach cancer			Body mass index (kg/m^2)			
		Absent	Present in siblings only	Present in father or mother	<18.5	18.5≤ <23.0	23.0≤ <25.0	25.0≤
Histological type, n (%)								
Adenocarcinoma	976 (94.5)	713 (93.5)	83 (97.7)	180 (97.3)	74 (90.2)	421 (92.7)	226 (95.8)	255 (97.7)
Other	57 (5.5)	50 (6.5)	2 (2.3)	5 (2.7)	8 (9.8)	33 (7.3)	10 (4.2)	6 (2.3)
Curative resection, n (%)								
No	356 (34.5)	266 (34.9)	27 (31.8)	63 (34.1)	41 (50.0)	164 (36.1)	73 (30.9)	78 (29.9)
Yes	677 (65.5)	497 (65.1)	58 (68.2)	122 (65.9)	41 (50.0)	290 (63.9)	163 (69.)1	183 (70.1)
Family history of stomach cancer in first-degree relatives[2], n (%)								
No	763 (73.9)				58 (70.7)	342 (75.3)	174 (73.7)	189 (72.4)
Yes	270 (26.1)				24 (29.3)	112 (24.7)	62 (26.3)	72 (27.6)
Body mass index (kg/m^2), n (%)								
<18.5	82 (7.9)	58 (7.6)	10 (11.7)	14 (7.6)				
18.5≤ <23.0	454 (44.0)	342 (44.8)	35 (41.2)	77 (41.6)				
23.0≤ <25.0	236 (22.8)	174 (22.8)	18 (21.2)	44 (23.8)				
25.0≤	261 (25.3)	189 (24.8)	22 (25.9)	50 (27.0)				

[1]Household wife / Domestic help / Student / Others.
[2]First-degree relatives include siblings and parents.

Table 2. Hazard ratio of all-cause death and stomach cancer death according to family history of stomach cancer and BMI

	Number of subjects	Person-years	Number of death	Age, sex and stage-adjusted HR	95% CI	Multivariate-adjusted 1 HR	95% CI	Multivariate-adjusted 2 HR	95% CI
All cause of death									
Family history of stomach cancer									
Absent	763	4160.3	304	1.00 (reference)		1.00 (reference)[2]		1.00 (reference)[4]	
Present in first-degree relatives[3]	270	1482.7	99	1.06	0.84 - 1.33	1.05	0.83 - 1.33	1.05	0.83 - 1.33
in siblings only	85	491.0	28	0.93	0.63 - 1.37	0.89	0.60 - 1.32	0.89	0.60 - 1.32
in father or mother[5]	185	991.7	71	1.12	0.86 - 1.45	1.13	0.87 - 1.48	1.13	0.87 - 1.47
BMI (kg/m^2)									
<18.5	82	306.0	51	1.98	1.37 - 2.87	1.84	1.27 - 2.68	1.85	1.27 - 2.69
18.5≤ <23.0	454	2426.0	199	1.50	1.14 - 1.98	1.50	1.14 - 1.98	1.55	1.17 - 2.04
23.0≤ <25.0	236	1449.8	69	1.00 (reference)		1.00 (reference)[3]		1.00 (reference)[4]	
25.0≤	261	1461.2	84	1.22	0.88 - 1.69	1.28	0.93 - 1.77	1.33	0.96 - 1.84 p=0.0864
p for trend				0.002		0.01		0.01	
p for trend in BMI <25.0				0.0001		0.0004		0.0004	
Stomach cancer death									
Family history of stomach cancer									
Absent	763	4160.3	210	1.00 (reference)		1.00 (reference)[2]		1.00 (reference)[4]	
Present in first-degree relatives[3]	270	1482.7	69	1.13	0.86 - 1.48	1.15	0.87 - 1.53	1.15	0.87 - 1.52
in siblings only	85	491.0	20	1.17	0.74 - 1.86	1.09	0.68 - 1.77	1.10	0.68 - 1.78
in father or mother[5]	185	991.7	49	1.11	0.81 - 1.52	1.18	0.86 - 1.62	1.17	0.85 - 1.61
BMI (kg/m^2)									
<18.5	82	306.0	42	1.72	1.12 - 2.63	1.61	1.04 - 2.49	1.58	1.02 - 2.44
18.5≤ <23.0	454	2426.0	133	1.30	0.93 - 1.82	1.32	0.94 - 1.85	1.35	0.96 - 1.89

Table 2. Hazard ratio of all-cause death and stomach cancer death according to family history of stomach cancer and BMI (Continued)

	Number of subjects	Person-years	Number of death	Age, sex and stage-adjusted HR	95% CI	Multivariate-adjusted 1 HR	95% CI	Multivariate-adjusted 2 HR	95% CI	
23.0≤ <25.0	236	1449.8	47	1.00 (reference)		1.00 (reference)[3]		1.00 (reference)[4]		
25.0≤	261	1461.2	57	1.13	0.76 - 1.68	1.22	0.82 - 1.82	1.25	0.84 - 1.87	p=0.2677
p for trend				0.03		0.12		0.15		
p for trend in BMI <25.0				0.01		0.03		0.03		

Abbreviations: BMI, body mass index. HR, hazard ratio. CI, confidence interval.
[1]First-degree relatives include siblings and parents.
[2]Adjusted by age (continuous), sex, referral status (from screening, other), stage (I, II, III, IV, unknown), histological type (adeno, other), occupation (professional or office work, other), smoking (never, ever), alcohol drinking (never, ever), and BMI (<18.5, 18.5≤ <23, 23≤ <25.0, 25.0≤).
[3]Adjusted by age (continuous), sex, referral status (from screening, other), stage (I, II, III, IV, unknown), histological type (adeno, other), occupation (professional or office work, other), smoking (never, ever), alcohol drinking (never, ever), and family history of stomach cancer in first-degree relatives (no, yes).
[4]Additionally adjusted for curative resection (no, yes).
[5]Include both with and without history in siblings.

Table 3. Age-specific all-cause mortality rate according to family history of stomach cancer

	Family history of stomach cancer												Moratlity rate ratio in relation to family history	
	Absent				Present in siblings only				Present in father or mother					
Age at diagnosis (years)	Number of subjects	Person-years	Number of death	Mortality rate (per 1,000) (A)	Number of subjects	Person-years	Number of death	Mortality rate (per 1,000)	Number of subjects	Person-years	Number of death	Mortality rate (per 1,000)	Present in siblings only *vs.* absent	Present in father or mother *vs.* absent
30–39	19	115.9	5	43.1	0	0.0	0	0	0	0	0	0	0.00	0.00
40–49	60	391.6	17	43.4	0	0.0	0	0	13	77.1	4	51.9	0.00	1.20
50–59	144	831.2	41	49.3	11	57.7	3	52.0	42	221.8	16	72.1	1.05	1.46
60–69	221	1262.7	83	65.7	28	195.3	4	20.5	57	337.1	20	59.3	0.31	0.90
70–79	246	1296.3	108	83.3	39	206.9	15	72.5	61	299.2	25	83.6	0.87	1.00
80–	73	262.6	50	190.4	7	31.1	6	192.9	12	56.5	6	106.2	1.01	0.56
Total	763	4160.3	304	73.1	85	491.0	28	57.0	185	991.7	71	71.6	0.78	0.98

Table 4. Cause of death according to age group

	All age	Age category	
		<60 years	≥60 years
Number of deceased subjects (n)	403	86	317
Cause of death (n, (%))			
Vascular diseases	47 (11.7)	4 (4.6)	43 (13.6)
Pneumonia	25 (6.2)	1 (1.2)	24 (7.6)
Accident	6 (1.5)	0 (0.0)	6 (1.9)
Suicide	1 (0.3)	1 (1.2)	0 (0.0)
Stomach cancer	279 (69.2)	76 (88.3)	203 (64.0)
Cancer of other sites	30 (7.4)	3 (3.5)	27 (8.5)
Other	15 (3.7)	1 (1.2)	14 (4.4)

BMI groups in the analysis including adjustment for curative resection (BMI < 18.5, HR = 2.28, 95% CI: 1.48–3.53; BMI ≥ 25, HR = 1.61, 95% CI: 1.10–2.34). The risk pattern among these subjects is likely to be J-shaped (p for trend in all BMI categories = 0.02; p in BMI <25.0 = 0.0001). With regard to stomach cancer death among subjects aged 60 years and over, the risk patterns in relation to BMI were similar to those for all-cause death. However, the risk of stomach cancer death associated with higher BMI was not statistically significant (BMI ≥ 25, HR = 1.38, 95% CI: 0.85–2.22).

Although data are not shown in the tables, we also evaluated the risk of mortality among subjects who had undergone curative resection. In this evaluation, the association with family history became more evident among subjects aged under 60 years. Higher risk of all-cause death was observed among subjects under 60 years of age with a family history in first-degree relatives (HR = 3.71, 95% CI: 1.53–9.03) and with a parental history (HR = 3.89, 95% CI: 1.58–9.62), respectively. A significantly higher risk of stomach cancer death was also found among these subjects (family history in first-degree relatives, HR = 5.94; parental history, HR = 5.46). Among subjects aged 60 years and over, the J-shaped pattern in relation to BMI was unclear. Although a significantly higher risk of all-cause death was observed among lean subjects (BMI < 18.5, HR = 2.11, 95% CI: 1.05–4.25), the HR for the high BMI category was not significant.

Table 6 shows the risk of mortality associated with BMI in subjects with and without a parental history of stomach cancer. This mortality risk was evaluated according to age group. The risk patterns in subjects aged 60 years and over were similar between those with and without a parental history, although the statistical power might have been limited for subjects with a parental history. Conversely, the risk of mortality among subjects aged under 60 years showed patterns different from those in subjects aged 60 and over. Among subjects aged under 60 years without a parental history, the association of BMI with the risk of mortality was unity for both all-cause and stomach cancer death; conversely, an inverse association with BMI was observed among subjects with a parental history, although statistical analysis demonstrated only marginal significance (p for trend = 0.07 for all-cause death and p for trend = 0.06 for stomach cancer death).

Discussion

This prospective study of stomach cancer patients clarified the associations of family history of stomach cancer and BMI at diagnosis with mortality. Although there was no association between a family history in first-degree relatives and overall mortality, analysis according to age group found that a parental history of stomach cancer was associated with an increased risk of all-cause death among patients aged under 60 years at diagnosis. BMI was related to the risks of all-cause death and stomach cancer death in subjects aged 60 years and over, showing a J-shaped pattern. Furthermore, analysis according to the presence or absence of a parental history of stomach cancer found different risk patterns in relation to BMI between patients under 60 years of age and those aged 60 years and over.

In Japan, two prospective cohort studies have evaluated the risk of stomach cancer death in relation to family history of stomach cancer.[10,11] One of them showed that the association between a positive parental history and the risk of stomach cancer death was stronger in subjects aged 40–59 years at the baseline than in subjects aged 60–79 years.[11] This appears to support our present result for patients under 60 years of age. Conversely, studies from other regions have yielded different results. In studies from Taiwan and Korea, a family history of stomach cancer was associated with improved survival[12] or had no association with survival.[29] A study from Italy also suggested better survival.[30] These conflicting results may have been partly due to differences in study design, including selection of study subjects, definition of family history and selection of confounders. We interpret our result, that is, the adverse effect of a parental history, as follows. First, genetic factors may play an important role in the progression of both stomach cancer and other diseases among younger patients with a parental history.[9] The

Table 5. Hazard ratio of all-cause death and stomach cancer death according to family history of stomach cancer and BMI stratified by age group

	<60 years							≥60 years						
				Multivariate-adjusted 1		Multivariate-adjusted 2					Multivariate-adjusted 1		Multivariate-adjusted 2	
	Number of subjects	Person-years	Number of death	HR	95% CI	HR	95% CI	Number of subjects	Person-years	Number of death	HR	95% CI	HR	95% CI
All cause of death														
Family history of stomach cancer														
Absent	223	1338.7	63	1.00 (reference)[2]		1.00 (reference)[4]		540	2821.6	241	1.00 (reference)		1.00 (reference)	
Present in first-degree relatives[1]	66	356.6	23	1.73	0.99 - 3.00	1.61	0.93 - 2.78	204	1126.1	76	0.98	0.75 - 1.28	1.00	0.76 - 1.30
in siblings only	11	57.7	3	0.55	0.13 - 2.33	0.58	0.14 - 2.46	74	433.3	25	0.91	0.59 - 1.39	0.92	0.60 - 1.41
in father or mother[5]	55	298.9	20	2.05	1.17 - 3.59	1.86	1.06 - 3.26	130	692.8	51	1.02	0.75 - 1.40	1.04	0.76 - 1.42
BMI (kg/m^2)														
<18.5	21	101.3	11	0.74	0.29 - 1.87	0.72	0.29 - 1.80	61	204.7	40	2.23	1.45 - 3.45	2.28	1.48 - 3.53
18.5≤ <23.0	138	800.4	41	1.10	0.62 - 1.97	1.08	0.61 - 1.92	316	1625.6	158	1.69	1.22 - 2.35	1.75	1.26 - 2.43
23.0≤ <25.0	70	439.4	20	1.00 (reference)[3]		1.00 (reference)[4]		166	1010.4	49	1.00 (reference)		1.00 (reference)	
25.0≤	60	354.2	14	0.90	0.44 - 1.84	0.81	0.40 - 1.66	201	1107.0	70	1.52	1.04 - 2.21	1.61	1.10 - 2.34
p for trend				0.95		0.80				0.02		0.02		
p for trend in BMI <25.0				0.74		0.69				0.0001		0.0001		
Stomach cancer death														
Family history of stomach cancer														
Absent	223	1338.7	57	1.00 (reference)[2]		1.00 (reference)[4]		540	2821.6	153	1.00 (reference)		1.00 (reference)	
Present in first-degree relatives[1]	66	356.6	19	1.69	0.92 - 3.12	1.54	0.84 - 2.81	204	1126.1	50	1.21	0.80 - 1.57	1.15	0.82 - 1.60
in siblings only	11	57.7	3	0.75	0.17 - 3.31	0.84	0.19 - 3.80	74	433.3	17	1.21	0.71 - 2.05	1.23	0.72 - 2.08
in father or mother[5]	55	298.9	16	1.93	1.04 - 3.60	1.68	0.90 - 3.12	130	692.9	33	1.08	0.73 - 1.60	1.11	0.75 - 1.64
BMI (kg/m^2)														
<18.5	21	101.3	10	0.78	0.28 - 2.16	0.79	0.29 - 2.15	61	204.7	32	1.89	1.13 - 3.15	1.88	1.13 - 3.13
18.5≤ <23.0	138	800.4	37	1.29	0.67 - 2.47	1.28	0.67 - 2.43	316	1625.6	96	1.34	0.89 - 2.02	1.37	0.90 - 2.07

Table 5. Hazard ratio of all-cause death and stomach cancer death according to family history of stomach cancer and BMI stratified by age group (Continued)

	<60 years						≥60 years					
				Multivariate-adjusted 1		Multivariate-adjusted 2				Multivariate-adjusted 1		Multivariate-adjusted 2
	Number of subjects	Person-years	Number of death	HR	95% CI	HR	95% CI	Number of subjects	Person-years	Number of death	HR	95% CI	HR	95% CI
23.0≤ <25.0	70	439.4	16	1.00 (reference)[3]		1.00 (reference)[4]		166	1010.4	31	1.00 (reference)		1.00 (reference)	
25.0≤	60	354.2	13	1.06	0.49 - 2.29	0.92	0.42 - 2.02	201	1107.0	44	1.32	0.82 - 2.12	1.38	0.85 - 2.22
p for trend				0.99		0.74				0.15	0.19			
p for trend in BMI <25.0				0.85		0.89				0.01	0.01			

Abbreviations: BMI, body mass index. HR, hazard ratio. CI, confidence interval.
[1]First-degree relatives include siblings and parents.
[2]Adjusted by age (continuous), sex, referral status (from screening, other), stage (I, II, III, IV, unknown), histological type (adeno, other), occupation (professional or office work, other), smoking (never, ever), alcohol drinking (never, ever), and BMI (<18.5, 18.5≤ <23, 23≤ <25.0, 25.0≤).
[3]Adjusted by age (continuous), sex, referral status (from screening, other), stage (I, II, III, IV, unknown), histological type (adeno, other), occupation (professional or office work, other), smoking (never, ever), alcohol drinking (never, ever), and family history of stomach cancer in first-degree relatives (no, yes).
[4]Additionally adjusted for curative resection (no, yes).
[5]Include both with and without history in siblings.

significant HR for parental history among younger patients strongly suggests a role of genetic factors. Hereditary diffuse stomach cancer, which has an early onset and is suspected to be caused by E-cadherin germline mutations, is known to be an autosomal-dominant inherited form.[31] Some patients who died might have suffered from this type of cancer. Other germline mutations, for example in *p53*, may also contribute to the risk of death in relation of hereditary stomach cancer.[32] Besides, a number of low-penetrant alleles acting in combination may be related to the progression of stomach cancer.[9,33] These genetic mutations and polymorphic variants may also be associated with the development of other fatal diseases among younger patients with a parental history.[34,35] Even if curative resection is performed, the contribution of genetic susceptibilities remains unchanged. A higher risk of death associated with a parental history among younger patients who undergo curative resection may support the significant role of genetic factors. Second, patients with a parental history share some lifestyle-related factors with their parents, which may be associated with the risk of death, although this is speculative. For example, detailed analysis of our data demonstrated that patients aged under 60 years with a parental history had a lower consumption of green and yellow vegetable and fruit than those without a parental history. Such lifestyles may impact negatively on prognosis. Third, a parental history of stomach cancer is related to low socioeconomic status (SES), which may be responsible for higher risk of death. A positive family history could be a factor resulting from a shared environment.[36] The prevalence of subjects with a shared environment such as *H. pylori* infection is high in low-SES families.[36] Furthermore, SES may be passed from parents to their children. Younger patients with low SES may have lower access to cancer screening programs and hospitals, thus resulting in poorer prognosis.[37]

With regard to the impact of BMI, previous studies have evaluated the association of BMI with stomach cancer mortality in the general population.[13–15] A prospective study conducted in the USA demonstrated a significant positive association between BMI and stomach cancer mortality in males.[13] In a prospective study from China, an inverse association between BMI and stomach cancer mortality in males was observed within the lower BMI range.[15] A Japanese study has found no association between BMI and stomach cancer mortality.[14] Thus, previous studies of general populations have yielded inconsistent results. Similarly, evidence for the association between BMI and long-term prognosis in stomach cancer patients has also been inconsistent. Most studies have analyzed patients after gastrectomy.[18,22–24,38,39] Some of them showed that being overweight tended to have no effect on long-term survival,[18,23] whereas a recent large-scale study in Japan indicated beneficial effects of being overweight in terms of both overall and disease-specific survival.[22] Although some other studies have observed worse survival among subjects with lower BMI, the authors of those studies concluded that BMI was not an independent prognostic factor.[21,24]

Table 6. Hazard ratio of all-cause death and stomach cancer death according to BMI stratified by parental history[1]

	Without parental history of stomach cancer									With parental history of stomach cancer								
				Multivariate-adjusted 1[2]			Multivariate-adjusted 2[3]						Multivariate-adjusted 1[2]			Multivariate-adjusted 2[3]		
	Number of subjects	Person-years	Number of death	HR	95% CI		HR	95% CI		Number of subjects	Person-years	Number of death	HR	95% CI		HR	95% CI	
All cause of death																		
Age <60 years																		
BMI (kg/m^2)																		
<18.5	14	69.2	7	0.76	0.26	2.22	0.73	0.25	2.12	7	32.1	4	1.75	0.17	18.02	1.81	0.19	17.51
18.5≤ <23.0	113	665.4	31	1.03	0.52	2.03	1.04	0.53	2.04	25	135.0	10	0.92	0.11	7.65	1.14	0.14	9.15
23.0≤ <25.0	57	366.4	16	1.00 (reference)			1.00 (reference)			13	73.0	4	1.00 (reference)			1.00 (reference)		
25.0≤	50	295.5	12	1.02	0.45	2.28	0.90	0.40	2.03	10	58.7	2	0.27	0.02	3.32	0.27	0.03	2.80
p for trend					0.77			0.96						0.10			0.07	
p for trend in BMI <25.0					0.69			0.65						0.57			0.52	
Age ≥60 years																		
<18.5	54	178.8	36	2.49	1.55	3.99	2.54	1.58	4.07	7	25.9	4	2.64	0.62	11.19	2.83	0.65	12.34
18.5≤ <23.0	264	1354.3	134	1.76	1.23	2.52	1.83	1.28	2.63	52	271.3	24	1.10	0.46	2.63	1.16	0.48	2.79
23.0≤ <25.0	135	829.0	40	1.00 (reference)			1.00 (reference)			31	181.4	9	1.00 (reference)			1.00 (reference)		
25.0≤	161	892.8	56	1.56	1.03	2.37	1.67	1.10	2.53	40	214.2	14	1.23	0.48	3.14	1.38	0.53	3.57
p for trend			0.01			0.02			0.80				0.88					
p for trend in BMI <25.0			0.0001			0.0001			0.02				0.02					
Stomach cancer death																		
Age <60 years																		
BMI (kg/m^2)																		
<18.5	14	69.2	7	0.97	0.31	3.02	0.94	0.30	2.92	7	32.1	3	2.77	0.05	154.70	2.23	0.03	147.29
18.5≤ <23.0	113	665.4	29	1.27	0.59	2.74	1.32	0.61	2.83	25	135.1	8	0.73	0.02	27.59	0.62	0.02	25.91
23.0≤ <25.0	57	366.3	13	1.00 (reference)			1.00 (reference)		13	73.0	3	1.00 (reference)			1.00 (reference)			
25.0≤	50	295.5	11	1.22	0.50	2.96	1.05	0.43	2.58	10	58.7	2	0.19	0.01	7.35	0.15	0.01	6.86
p for trend					0.94			0.80						0.06			0.06	
p for trend in BMI <25.0					0.96			0.96						0.40			0.48	

Table 6. Hazard ratio of all-cause death and stomach cancer death according to BMI stratified by parental history[1] (Continued)

	Without parental history of stomach cancer								With parental history of stomach cancer							
				Multivariate-adjusted 1[2]			Multivariate-adjusted 2[3]					Multivariate-adjusted 1[2]			Multivariate-adjusted 2[3]	
	Number of subjects	Person-years	Number of death	HR	95% CI		HR	95% CI	Number of subjects	Person-years	Number of death	HR	95% CI		HR	95% CI
Age ≥60 years																
<18.5	54	178.8	29	2.09	1.20	- 3.64	2.07	1.19 - 3.60	7	25.9	3	3.80	0.53	- 27.26	4.93	0.63 - 38.65
18.5≤ <23.0	264	1354.3	80	1.35	0.86	- 2.11	1.39	0.89 - 2.19	52	271.3	16	0.89	0.25	- 3.11	0.94	0.27 - 3.35
23.0≤ <25.0	135	829.0	26	1.00 (reference)			1.00 (reference)		31	181.4	5	1.00 (reference)			1.00 (reference)	
25.0≤	161	892.8	35	1.33	0.79	- 2.24	1.41	0.84 - 2.39	40	214.2	9	0.77	0.19	- 3.09	0.88	0.21 - 3.66
p for trend				0.11			0.14					0.48			0.53	
p for trend in BMI <25.0				0.01			0.01					0.24			0.24	

Abbreviations: BMI, body mass index. HR, hazard ratio. CI, confidence interval.
[1]Parental history: history of stomach cancer in father or mother.
[2]Adjusted by age (continuous), sex, referral status (from screening, other), stage (I, II, III, IV, unknown), histological type (adeno, other), occupation (professional or office work, other), smoking (never, ever), and alcohol drinking (never, ever).
[3]Additionally adjusted for curative resection (no, yes).

However, most of the previous studies have used coarse categories such as dichotomous categories for classifying BMI, for example, BMI < 25.0 and ≥25[18,22–24]; therefore any linear association between BMI and prognosis has remained unclear. Additionally, although evaluation according to stage has been performed in some previous studies,[24,38,39] the modifiable effect of age on the association between BMI and mortality has never been considered. In the present study, the risk of mortality was evaluated according to younger and older age group. Separate evaluation was also performed for patients who underwent curative resection. We interpret our major finding, that is, the J-shaped pattern in relation to the risk for BMI, as follows, although this pattern was pronounced in older patients. First, subjects with a lower BMI, who tended to have advanced cancer as shown in Table 1, have a poor nutritional status due to impaired oral intake. Consequently, they may have a higher risk of all-cause or stomach cancer death. However, a higher risk of all-cause death associated with lower BMI was also observed among older patients who underwent curative resection. The adverse effect of poor nutritional status may last after curative treatment. The association of being underweight with a high risk of all-cause death has been observed in the elderly general population of our study area.[40] In contrast, the effect of high BMI on long-term survival may be complicated. Poorer surgical outcome has been reported among obese patients.[17–19] It is possible that postoperative complications among them might have adverse effects on prognosis. In addition, comorbidities among older obese patients may be linked to a higher risk of all-cause death. A high prevalence of comorbidities among elderly cancer patients has been observed for cancers at several sites.[41,42] A relationship between being overweight and comorbidities has also been indicated among patients with stomach cancer.[18,23] In the present study, the prevalence of some comorbidities among patients aged 60 years and over were large in the high BMI group (hypertension, 36.3% in the 25.0 ≤ group *vs.* 9.8% in the <18.5 group; diabetes mellitus, 13.9% in the 25.0 ≤ group *vs.* 8.2% in the <18.5 group).

Our analysis stratified by a parental history of stomach cancer revealed different risk patterns in relation to BMI between patients aged under 60 years and those aged 60 years and over, as shown in Table 6. There was a difference in the association with BMI between subjects under 60 years of age with and without a parental history. The inverse association with BMI observed among the younger subjects with a parental history of stomach cancer suggests that such a parental history may affect survival, perhaps through nutritional status. Some genetic factors inherited from the parents might accelerate not only disease progression but also cachexia.[43,44] Younger lean patients with a parental history of stomach cancer will need to be carefully followed.

The present study had both strengths and limitations. First, major strength was that a relatively large number of stomach cancer patients were included. Consequently, we

were able to evaluate the risk of mortality based on some stratified analysis. Another strength was that no subject was lost to follow-up. The MCCH cancer registry conducts active follow-up by accessing hospital visit records, resident registration cards and permanent domicile data. In cases of death occurring outside the hospital, information on the date and cause of death was obtained with permission from the Ministry of Justice. A further strength was that lifestyle factors such as occupation, smoking and alcohol drinking were controlled for in the analysis. Referral status (from screening, other) was also controlled. Previous studies had not considered the effects of these confounders.

A major limitation was that any family history of stomach cancer was self-reported; therefore, this information was never validated. However, since the questionnaire covering family history was given to each subject on the day of reservation for the first admission to the MCCH before any definite diagnosis or treatment, misclassifications for family history were not dependent upon all-cause or stomach cancer death, that is, they were nondifferential.[45] Therefore, any information bias due to self-reporting would likely have been minimal. Second, BMI at the baseline was also estimated based on self-reported weight and height. However, the self-reported current height and weight data were highly correlated with measured data, and therefore any possible bias was likely small. Third, the number of patients with a family history was limited; therefore, statistical power might have been insufficient in some subgroup analyses. Especially, the 95% CIs for several BMI groups were wide in the subjects aged under 60 with a parental history as shown in Table 6. The stratification by family history may have resulted in false-positive or false-negative results. To obtain reliable results with this stratification, subsequent recruitment of patients and follow-up will be required. Fourth, this study was performed at a single hospital in Miyagi Prefecture; therefore, the generalizability of our results to the Japanese population may be limited. The distribution of pathological stage presented in Table 1, which is an important prognostics factor, was relatively similar to the distribution in stomach cancer cases entered to the Miyagi Prefectural Cancer Registry.[46] However, it is unclear whether our subjects represent the population of stomach cancer patients in Japan. To validate our results and assess their generalizability, further studies in other regions are required.

In conclusion, this prospective study of stomach cancer patients has clarified the associations of a family history of stomach cancer and BMI at diagnosis with long-term prognosis. Although the association between a family history and mortality was unclear in the overall analysis, analysis according to age group found some differences in the risk of mortality associated with a family history and BMI between younger and older patients. A parental history of stomach cancer was significantly associated with an increased risk of all-cause death among patients under 60 years of age. BMI was related to all-cause and stomach cancer death among patients aged 60 years and over, showing a J-shaped pattern. Inherited factors may affect survival among younger patients with stomach cancer, whereas nutritional status may be a determinant of prognosis in older patients. In any strategy aimed at improving the survival of stomach cancer patients, the roles of family history and nutritional status must be considered.

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Original Research

International variation in management of screen-detected ductal carcinoma in situ of the breast

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KEYWORDS
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Abstract ***Background:*** Ductal carcinoma in situ (DCIS) incidence has grown with the implementation of screening and its detection varies across International Cancer Screening Network (ICSN) countries. The aim of this survey is to describe the management of screen-detected DCIS in ICSN countries and to evaluate the potential for treatment related morbidity.

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Overtreatment
Axillary staging
Cancer registration

Methods: We sought screen-detected DCIS data from the ICSN countries identified during 2004–2008. We adopted standardised data collection forms and analysis and explored DCIS diagnosis and treatment processes ranging from pre-operative diagnosis to type of surgery and radiotherapy.

Results: Twelve countries contributed data from a total of 15 screening programmes, all from Europe except the United States of America and Japan. Among women aged 50–69 years, 7,176,050 screening tests and 5324 screen-detected DCIS were reported. From 21% to 93% of DCIS had a pre-operative diagnosis (PO); 67–90% of DCIS received breast conservation surgery (BCS), and in 41–100% of the cases this was followed by radiotherapy; 6.4–59% received sentinel lymph node biopsy (SLNB) only and 0.8–49% axillary dissection (ALND) with 0.6% (range by programmes 0–8.1%) being node positive. Among BCS patients 35% received SLNB only and 4.8% received ALND. Starting in 2006, PO and SLNB use increased while ALND remained stable. SLNB and ALND were associated with larger size and higher grade DCIS lesions.

Conclusions: Variation in DCIS management among screened women is wide and includes lymph node surgery beyond what is currently recommended. This indicates the presence of varying levels of overtreatment and the potential for its reduction.

1. Introduction

Ductal carcinoma in situ (DCIS) has become a relatively common disease after the introduction of screening mammography, representing up to 20–25% of all incident breast malignancies in industrialised countries [1–4]. The natural history of screen-detected DCIS is not yet completely understood [5] and we are therefore in large part unable to distinguish different conditions that are likely to exist under the same label of DCIS [6,7].

Management guidelines increasingly take this uncertainty into account by trying both to provide adequate care and to avoid unnecessary treatment. For example, axillary lymph node dissection (ALND) is not recommended for women with DCIS [8–10]. The International Cancer Screening Network (ICSN) oversees organised programmes that include quality monitoring of the process of screening and care. The purpose of the report is to assess practice variation in the management of screen-detected DCIS and the potential morbidity associated with detection of DCIS among participants in the ICSN.

2. Patients and methods

A survey was launched within the ICSN. All of the screening settings covered were population-based, organised screening programmes, with the exception of Czech Republic, which at the time did not adopt personal invitations, and of the United States, whose data, provided by the Breast Cancer Surveillance Consortium, derived from opportunistic screening in well defined populations.

Selected characteristics of participating programmes were collated from the ICSN web site (http://appliedresearch.cancer.gov/icsn) and reported in Table 1. Attendance rates exceeded 60% in all programmes for which this information was available with the exceptions of Switzerland and Japan.

A previous paper [4] on DCIS detection reports in detail the design of this survey. In brief, we sought data from the 33 ICSN member countries regarding the pure DCIS cases they identified within their screened population between January 1, 2004 and December 31, 2008. We asked sites to complete, based on individual data records from their screening and clinical databases often obtained by linkage with population-based cancer registries, a structured questionnaire that summarised data on DCIS detection, diagnosis and treatment. The questionnaire was piloted in a regional screening programme before distribution. Internal data consistency was checked routinely and outlying data were verified with data providers. All data were stratified by calendar year and age in decades, both referred to the date of the screening test. The following data stratifications were also included in the questionnaire: type of breast surgery by DCIS size; nodal surgery by DCIS size; nodal surgery by nuclear grade; nodal surgery by type of breast surgery; and radiotherapy by type of breast surgery. As size by clinical imaging was often unavailable, all sites were asked to provide pathological size ($\leqslant$10 mm, 11–20 mm, >20 mm).

For the analysis of DCIS management process we selected a number of measures encompassing issues ranging from diagnosis to surgical and adjuvant treatment, namely: pre-operative diagnosis (PO); time from abnormal screen to surgery; use of breast conserving surgery (BCS) as definitive intervention; use of ALND and sentinel lymph nodes biopsy (SLNB); radiotherapy after BCS. Indicators were identified, following a systematic literature review, from two main sources [9,10], by selecting measures believed to be collectable retrospectively from participating screening programmes. A pre-operative diagnosis was defined as the presence

Table 1
International cancer screening network survey on the management of ductal carcinoma in situ (DCIS). Description of the screening programmes included in the analysis, number of reported tests and number of screen-detected DCIS.

Country/region	Year programme started	Target age group	Attendance rate (2010)	Data collection years	No. of reported tests (age 50–69)	No. of screen- detected DCIS (age 50–69)
Czech Republic	2002	45–69	Not available	2007–2008	699,726	359
Denmark Copenhagen	1991	50–69	73%	2004–2007	47,249	73
Denmark Fyn	1993	50–69		2004–2007	97,176	63
Finland	1987	50–69[a]	85%	2004–2007	862,908	361
Ireland	2000	50–64	Not available	2004–2008	331,854	393
Italy[b]	1990	50–69	61%	2006–2008	1,453,292	1,066
Japan[c]	2000	50–69	19%	2004–2008	106,898	72
Luxembourg	1992	50–69	64%	2006–2008	45,586	48
Netherlands	1990	50–74[d]	81%	2007	718,202	576
Norway	1996	50–69	76%	2004–2008	963,424	899
Spain Barcelona	2001	50–69	Not available	2004–2008	184,748	90
Spain Navarra	1989	45–69	87%	2004–2008	131,948	95
Spain Valencia	1992	45–69	Not available	2004–2008	739,829	422
Switzerland[e]	1999	50–69	48%	2004–2008	176,318	190
United States of America (USA)[f]	1991	40–74	67%	2004–2007	616,892	617
Total	–	–	–	2004–2008	7,176,050	5,324

[a] Targeted women aged 50–59 until 2006.
[b] Data from five regional programmes: Piemonte, Valle d'Aosta, Emilia Romagna, Toscana, and Lazio.
[c] Data from the Miyagi Prefecture, source The Miyagi Cancer Society.
[d] Targeted women aged 50–69 until 1999.
[e] Data from four Swiss regional programmes: Vaud, Valais and Fribourg (2004–2008), and Jura-Neuchâtel (2005–2008).
[f] Data from the Breast Screening Surveillance Consortium.

prior to open surgery of a definitive diagnosis of malignancy based on either fine needle aspiration cytology (FNAB) or core biopsy. Waiting time applied to patients with surgery as first treatment only. SLNB rates refer to patients who received this procedure as the only axillary procedure.

For all parameters, project documentation instructed sites to indicate the number of missing values. All analyses reported in this paper were restricted to ages 50–69, as this was the age range covered by most participating programmes, and in order to minimise confounding by age. As not all programmes were able to provide data for the entire time period, time trend analysis was restricted to the years 2004–2007.

All files provided by participating centres were included in a flat file and the resulting database analysed by using the R environment (v. 3.0.0). All measures were expressed as proportions, where the numerator was the number of cases managed as described in the measure definition and the denominator the number of eligible cases, after subtraction of missing values. The χ^2 test was used for studying differences between pairs of parameters or trends.

3. Results

Screening co-ordination centres in 12 countries volunteered to participate and contributed data from a total of 15 screening programmes, all from Europe except United States of America (USA) and Japan. Denmark and Spain provided separate regional data. In the age group 50–69 years 7,176,050 screening tests and 5324 screen-detected DCIS were reported, ranging from 48 from Luxembourg to 1066 from Italy (Table 1).

Results of process of care measures are illustrated in Table 2. Not all programmes were able to provide information for all items. In total, a pre-operative diagnosis was reported for 73% of the DCIS cases ranging from 21% to 93% across areas, surgical-waiting-time-within-60-days was 47% ranging from 25% to 85%, BCS was performed for 78% of cases ranging from 67% to 90%, radiotherapy (RT) after BCS for 66% of cases ranging from 41% to 100%, ALND for 7.9% ranging from 0.8% to 49%, and SLNB (with no ALND) for 35% ranging from 6.4% to 59%. Any nodal surgery was performed for 43% of all DCIS, ranging from 19% in The Netherlands to 63% in Ireland. Most centres reported to use more frequently SLNB only than ALND, with the exceptions of Japan, Luxembourg and the USA (Table 2).

Results for each indicator stratified by time period are shown in Table 3. Use of pre-operative diagnosis and SLNB increased over time. There was a slight decrease in the proportion of DCIS cases operated within 60 days of diagnosis.

Both ALND and SLNB were more frequent at mastectomy (Table 4) and in high grade and larger tumours

Table 2
Ductal carcinoma in situ (DCIS): process of care indicators and lymph node status by country/region, age 50–69. Results are expressed as proportion of cases with known information (PO = pre-operative diagnosis; BCS = breast conserving surgery; RT = radiotherapy; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy, NA = not available).

Area	No. DCIS	% PO	% missing	% surgery ⩽60 days	% missing	%BCS	% missing	% RT in BCS	% missing	% ALND	% SLNB only	% any nodal surgery	% missing	No. DCIS with ALND or SLNB	% N+	% N status missing
Czech Republic	359	81	0	53	17	NA	100	NA	NA	NA	NA	NA	100	NA	NA	100
Denmark Copenhagen	73	NA	100	25	8.2	NA	100	NA	NA	NA	NA	NA	100	NA	NA	100
Denmark Fyn	63	NA	100	60	4.8	NA	100	NA	NA	NA	NA	NA	100	NA	NA	100
Finland	361	60	0.3	NA	100	67	11	NA	100	11	31	42	0	151	2.3	12
Ireland	393	76	0	85	0.3	78	0	NA	100	3.3	59	63	0.3	245	0	0.8
Italy	1066	73	3.8	29	13	86	1.4	83	74	4.4	53	57	8.2	562	0.2	8.2
Japan	72	21	0	54	0	71	0	41	0	49	7.0	56	0	40	0	43
Luxembourg	48	77	0	50	4.2	75	2.1	NA	100	30	6.4	36	2.1	17	0	11
Netherlands	576	74	14	NA	100	70	43	NA	100	0.8	19	19	14	95	0	47
Norway	899	NA	100	55	3.2	72	0	73	25	7.3	43	51	0	454	0	0
Spain Barcelona	90	89	12	NA	100	78	0	78	17	7.5	51	59	11	47	8.1	35
Spain Navarra	95	93	0	30	1.1	90	1.1	100	0	1.1	38	39	0	37	0	0
Spain Valencia	422	63	22	50	4.0	84	5.9	53	60	14	24	38	7.3	147	1.4	17
Switzerland	190	76	0	65	3.2	86	0	54	0	2.6	23	25	0	48	4.2	0
United States of America (USA)	617	68	38	71	78	79	4.7	59	3.9	14	9.1	23	1.8	137	0	0
All Areas[a]	**5324**	**73**	**11**	**47**[b]	**5.7**	**78**	**7.4**	**66**[c]	**13**	**7.9**	**35**	**43**	**4.6**	**1980**	**0.6**	**27**

[a] Excluding countries for which information is not available.
[b] Excluding USA, in addition to countries for which information is not available, due to the high proportion of missing values.
[c] Excluding Italy and Valencia, in addition to countries for which information is not available, due to the high proportion of missing values.

Table 3
Ductal carcinoma in situ (DCIS): process of care indicators by time period, age 50–69. Cases reported for year 2008 and countries not reporting cases for the whole period 2004–2007 were excluded. Results are expressed as proportion of cases with known information.

	2004–2005			2006–2007			Total			
	No. of DCIS	% missing	Result%	No. of DCIS	% missing	Result%	No. of DCIS	% missing	Result%	*p*-value[c]
Pre-operative diagnosis[a]	977	20	**64**	914	13	**74**	1891	17	**69**	<0.001
Surgery within 60 days from abnormal screening test[b]	790	1.0	**62**	888	3.4	**56**	1678	2.3	**59**	0.01
Breast conservation surgery[c]	1316	4.6	**76**	1283	1.8	**77**	2599	3.2	**77**	0.74
Radiotherapy after breast conservation surgery[d]	678	9.0	**66**	597	16	**65**	1275	12	**66**	0.94
Axillary dissection [c]	1316	1.7	**11**	1283	1.2	**11**	2599	1.5	**11**	0.86
Sentinel Lymph Node Biopsy only[c]	1316	1.7	**26**	1283	1.2	**35**	2599	1.5	**31**	<0.001

[a] Including Finland, Ireland, Japan, Spain, Switzerland and United States of America (USA).
[b] Including Denmark, Ireland, Japan, Norway, Spain (excl. Barcelona), and Switzerland.
[c] Including Finland, Ireland, Japan, Norway, Spain, Switzerland and USA.
[d] Including Japan, Norway, Spain (excl. Valencia), Switzerland and USA.
[e] χ^2 test between 2004–2005 and 2006–2007.

(Table 4 and Figs. 1, 2). ALND and SLNB were performed in about 20% and more than 50% of mastectomies, respectively, and in 5% and 35% of BCS. Their usage approximately doubles from low to high nuclear grade and from small (⩽10 mm) to large (>20 mm) pathological size. Of cases with any type of nodal surgery (1980/4607or 43%), only 0.6% were node positive (range by programmes 0–8.1%, Table 2).

4. Discussion

We evaluated six measures of DCIS management across 15 active screening programmes in Europe, Japan and the USA. As reported by us elsewhere [4], age-standardised detection rates of DCIS varied from 0.41 to 1.38/1000 women. In this report we observed that pre-operative evaluation, surgical wait times, use of nodal surgery, and radiation therapy also varied substantially across programmes. The implications are that women with potentially detectable DCIS may experience very different morbidity depending upon where they are screened and seek care because both their likelihood of a diagnosis and how it is treated vary across countries. Despite this wide variation, practices overall seem to be moving towards the consensus recommendations on DCIS treatment except SLNB has increased over time also in low and intermediate grade and small DCIS treated with BCS.

Cytological or histological pre-operative diagnosis is recommended in order to limit the need for open surgical biopsies, to allow for surgical planning, and to avoid under or overtreatment. Our overall result of 73% (Table 2), though slightly increasing over time (Table 3), is short of the target of 90% suggested by some guidelines [9,10] and the range among programmes is very wide, with only two Spanish programmes coming close to or above the stated standard. Even though FNAB and core biopsy are both accepted modalities for preoperative diagnosis, the latter allows discriminating invasive from in situ lesions and, in most settings, it is likely to provide a higher proportion of preoperative diagnosis being more sensitive and specific [11]. However, this distinction is not available in our data. Centres with low level of preoperative diagnosis reported that, at the time under study, cases received exclusively or predominantly FNAB.

Women also face a wide variation in the range of waiting times for the definitive operation. Although it is recognised that two or three months delay from screening to treatment is not likely to affect prognosis (especially in the case of slowly growing lesions such as most DCIS), relatively long waiting times may cause anxiety and affect quality of life [12].

Using BCS for the surgical treatment of DCIS is usually considered good practice, even if it is recognised that patient preference plays a role [13]. The proportion

Table 4
Ductal carcinoma in situ (DCIS): surgery on the axilla by type of breast surgery and by grade and pathological size, age 50–69. Results are expressed as proportion of cases with known information. BCS = breast conserving surgery; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy).

Type of surgery[a]	No. of DCIS	% ALND	*p*-Value[d]	% SLNB only	*p*-Value[d]	% missing
BCS	2939	4.8	<0.001	35	<0.001	3.1
Mastectomy	892[c]	19		51		2.2
Total	3831	8.1		39		2.9
DCIS nuclear grade[b]	No. of DCIS	%ALND	*p*-Value[e]	%SLNB only	*p*-Value[e]	% missing
Low	793	4.7	<0.001	22	<0.001	3.2
Intermediate	1241	6.2		33		3.2
High	2059	11		45		1.8
Unknown	587	10		23		9.2
Total	4680	8.4		35		3.3
DCIS pathological size[b]	No. of DCIS	%ALND	*p*-Value[e]	%SLNB only	*p*-Value[e]	% missing
⩽10 mm	1442	6.6	<0.001	26	<0.001	2.7
11–20 mm	923	9.3		36		2.6
>20 mm or multicentric	1252	10		49		2.5
Unknown	1063	7.7		32		5.8
Total	4680	8.4		35		3.3

[a] Including Finland, Ireland, Italy, Japan, Luxembourg, Norway, Spain (excl. Valencia), Switzerland and United States of America (USA).
[b] Including Finland, Ireland, Italy, Norway, Spain, Switzerland and USA.
[c] 52 cases with type of surgery unknown included.
[d] χ^2 test.
[e] χ^2 test for trend.

of BCS in our series is high (78% overall) and relatively constant across programmes and time periods, with only one programme reporting slightly short of 70% and with three programmes exceeding 85%. BCS for DCIS not greater than 2 cm in pathological size is even more frequent (88% in 2190 cases of this size). In England, where a report on non-invasive breast cancers diagnosed within and outside the national breast cancer screening programme is periodically issued, the proportion of BCS in screen-detected cases in 2006–2007 is 71% [14], while 70% is the figure reported by a French survey for the period 2003–2004 [15]. Even lower was the proportion of BCS in the East Netherlands during 1999–2003: 55% [16]. In a population-based study in Southern Netherlands, which documented an increasing time trend, it was reported to be 68% in 2010 [17].

BCS is often complemented by radiotherapy [8,18], in order to lower the risk of local in situ or invasive recurrence. In our series radiotherapy is performed in 66% of BCS patients, with the lowest result being 41%. In United Kingdom during 2003–2006 53% of BCS received radiotherapy, with radiotherapy provision significantly related to tumour size and grade [14]. In France in 2003–2004 the corresponding figure was 89% [15]. In the East Netherlands during 1999–2003 [16] and in the Southern part of the country in 2010 [17] radiotherapy was performed respectively in 34% and in 89% of DCIS treated with BCS.

Management of the axilla is a subject of debate in DCIS, but there is consensus regarding the need to avoid ALND, considered unnecessary and a cause of frequent complications [8–10]. This survey documented that ALND takes place in 5% of women with DCIS as final diagnosis treated by BCS and in almost 20% of women treated by mastectomy. The use of SLNB was much more frequent and on the rise over time, with a large variation among programmes, so that in our series almost half of all cases had any type of nodal surgery. We were able to show that the recommendation [8,9,19–21] to limit SLNB to women undergoing mastectomies and/or those with large (where micro-invasion might be more easily overlooked) or high grade DCIS were clearly reflected in actual practice, although not fully followed since we observed one third of BCS patients and many small or low grade DCIS had SLNB only (Table 4 and Figs. 1, 2). Notably, the proportion of all DCIS cases associated with positive lymph nodes in this study was low (0.6%) and thus not likely to be influencing treatment management. These results add support to the limited value of nodal staging in women with screen-detected DCIS [22,23] and to recent guidelines [24] that further restrict the indication for SLNB in DCIS, suggesting that clinicians consider SLNB when mastectomy is planned, in case of clinically evident mass lesions suggestive of invasive cancer, and in very large size DCIS (>5 cm.) only.

Similarly to our observation, the correlation of the use of SLNB with DCIS size and grade has been reported in an analysis of US Seer data 1998–2002 [25], in France during 2003–2004 [15] and in Australia during 1995–2000 [26]. However, in Australia the use of nodal surgery was correlated with the size of the breast lesion but not with its grade.

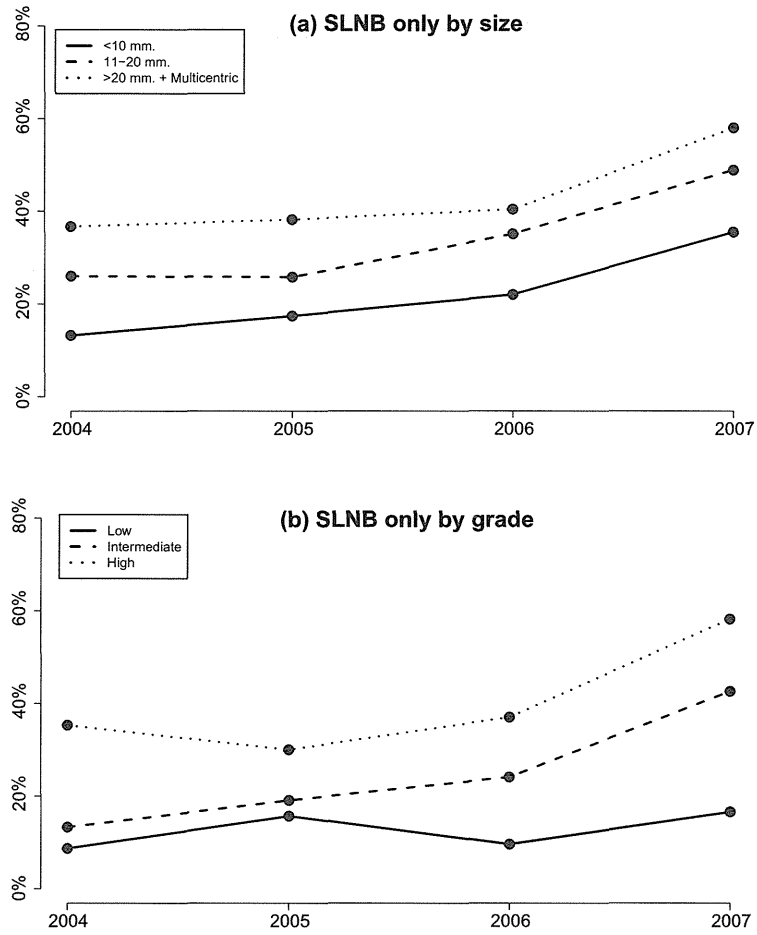

Fig. 1. Ductal carcinoma in situ: performance of sentinel lymph node biopsy (SLNB) only by pathological size and time period (a), and by nuclear grade and time period (b). Any type of breast surgery included. Cases reported for year 2008 and countries not reporting cases for the whole period 2004–2007 or lacking the stratification by size and grade were excluded from this analysis. Data are included for Finland, Ireland, Norway, Spain, Switzerland and United States of America (USA).

In England in 2006–2007 the use of SLNB in screen-detected non-invasive breast cancers having breast conserving surgery was 4.0% [14], a figure lower than in any of the programmes included in our survey. In France in 2003-2004 SLNB was performed in 21% of patients and the proportion of ALND was 10% [15]. In the East Netherlands during 1999–2003 any axillary staging procedure was performed in 25% of DCIS [16] while in Southern Netherlands use of SLNB was reported being 65% in 2010 [17]. In Italy the use of SLNB in screen-detected DCIS increased from 20% to slightly over 50% from 2001 to 2007 and then remained virtually stable through 2010 [27].

Limitations of this study are those specific to aggregate data surveys: limited detail in available data, possible use of different definitions of study parameters in the different sites, need to restrict overall data analyses to data stratifications being planned in advance. Not all programmes could contribute all required data and the number of missing values for some of the parameters was high. However, we minimised these limitations by providing strictly structured data collection forms, with several pre-specified stratification tables, detailed documentation on definitions used, and internal consistency checks. It must be also acknowledged that this paper provides a picture of DCIS management during 2004–2008, and practice is likely to have evolved since then, both in detection, with the gradual introduction of digital mammography [4], and in treatment. ICSN will consider updating these results seeking data from an even larger number of programmes.

This survey covered screen-detected DCIS cases only. Few countries have yet similar information available from the in situ carcinoma diagnosed at all ages outside organised screening programmes, which have been quantified as 51% of all cases in Southern Netherlands [17], 43% in Finland [28], and 38% in United Kingdom [14]. Projects conducted in co-operation between clinical Centres and population Cancer Registries [17] could cover this gap.

This study is, to our knowledge, the first large (more than 5000 cases) international survey of DCIS

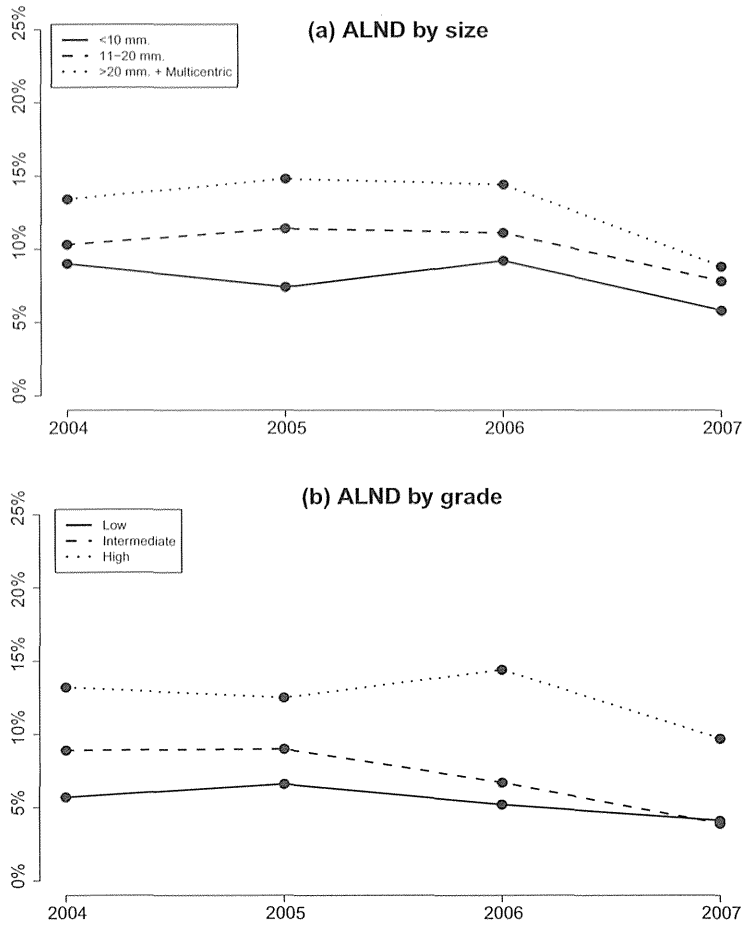

Fig. 2. Ductal carcinoma in situ: axillary lymph node dissection (ALND) by pathological size and time period (a), and by nuclear grade and time period (b). Any type of breast surgery included. Cases reported for year 2008 and countries not reporting cases for the whole period 2004–2007 or lacking the stratification by size and grade were excluded from this analysis. Data are included for Finland, Ireland, Norway, Spain, Switzerland and United States of America (USA).

management practices. We found wide variation in clinical management for all of the parameters studied. While awaiting progress from research enabling to differentiate indolent lesions amenable of follow up only from those at high risk of subsequent invasive cancer [29–31], efforts should be made to optimise diagnostic assessment and management of screen-detected cases to mitigate overdiagnosis and overtreatment [32]. Specifically, we found that axillary surgery, although used more often in high grade and large size lesions, showed an increasing time trend and was performed, with large variation between centres, beyond what is recommended by guidelines. This indicates the presence of varying levels of overtreatment and the potential for the reduction of treatment-related morbidity. In fact, although less frequently harmful than ALND, SLNB is not exempt from complications. According to the update of the SLNB American Society of Clinical Oncology Clinical Practice Guidelines [24], which includes a literature review of adverse events, important morbidity of node surgery includes lymphoedema, infections, seroma and neurologic complications. These were found to be more frequent in patients receiving ALND as opposed to SLNB only, but they are still not negligible even in the latter. For example, in the ALMANAC trial [33] at 12 months after operation lymphoedema occurred in 5% of patients having received SLNB only versus 13% of patients having received ALND, and sensory loss 11% and 31% respectively.

Specialised multidisciplinary care for breast cancer has proved to improve process of care [34] and decrease mortality [35]. Screening programmes should link to specialised clinical Units and Cancer Registries and jointly set up or expand multidisciplinary teams in charge of quality assurance of diagnosis and treatment of screen-detected lesions, including DCIS, so to assure that current guidelines are applied and opportunities for research in the heterogeneity of these lesions are taken.

Conflict of interest statement

None declared.

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