Tracking cancer occurrence in the 5 years after referral for suspected head and neck cancer

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ABSTRACT

Objectives

Very little is known about those who receive a negative (benign) result after referral for suspected cancer, including their risk for future cancer. This service evaluation aimed to track the occurrence of cancer (of any type) in the 5 years after an appointment for suspected head and neck cancer (HNC) and compare to those referred to hospital for routine ear nose and throat reasons.

Materials & Methods:

Patient identifiers of referrals to one hospital Trust with either a) suspected HNC cancer on a two week wait (TWW) pathway, or b) routine ear, nose & throat problems, were linked with the National Cancer Registry data to determine the occurrence, site and stage of subsequent cancer.

Results:

10,314 patients were referred between 2009 and 2011. Cancer occurrence in the 5 years after their appointment for those who had initially received a negative diagnosis, was 4.0% for those referred via TWW and 2.1% for those routinely referred. Lung cancer was the most common subsequent cancer site in the TWW group. Those in higher age groups, those with previous cancer, and those referred via the TWW pathway were significantly more likely be diagnosed with subsequent cancer.

Conclusion:

Given the increased risk of subsequent cancer, it could be beneficial to improve the service provision (e.g. advice on screening attendance, ways to reduce risk, advice on timely help-seeking for symptoms of cancer) at the point of a negative diagnosis on the TWW pathway, especially in older patients and those with a previous diagnosis of cancer.

KEY WORDS

Head and Neck Cancer; Early diagnosis; Teachable moment; Two week wait; Suspected cancer; Referral; Diagnostic accuracy;

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INTRODUCTION

There are 363,000 new cases of cancer in the UK each year [1]. Half of these are diagnosed at an advanced stage when prognosis is poor and treatment costs are high [1], [2], [3]. For instance, when diagnosed at an early stage (small and localised), 1-year survival rates are higher than 90% for colorectal cancer and cancers of the bladder and kidney. In contrast, when diagnosed at an advanced stage, 1-year survival is less than 50% (colorectal cancer: 45%; bladder: 37%; kidney: 39%) [4]. For lung cancer, the difference is even greater (85% 1-year survival for early stage cancer, versus 17% 1-year survival for advanced stage cancer [4]). The higher proportion of cancers at an advanced stage at diagnosis has been posited as one of the reasons why the UK has worse cancer outcomes compared to other high-income countries [5]. To save lives and reduce treatment costs it is vital to develop initiatives to encourage diagnosis of cancer at an earlier stage.

One initiative to reduce time to diagnosis is dedicated urgent referral pathways for those with symptoms suspicious of cancer, with a pledge for patients to receive specialist opinion or access to diagnostic tests within two weeks of referral by a general practitioner or other healthcare professional. In England, over 2 million people are referred with suspected cancer each year via this two week wait (TWW) pathway [6]. The majority (93%) of these will not be found to have a diagnosis of cancer at that time [7]. This has led to some debate about the value of the two week wait pathway, given the burden on services and low conversion rate (e.g. low proportion of all TWW referrals resulting in a diagnosis of cancer). This is particularly the case in head and neck cancer (HNC) where the positive predictive value of TWW referrals resulting in a diagnosis is lower than 4% [8]. The TWW pathway for HNC has been reported to be 'overused', leading to funding strains and issues with capacity, with consultants spending more time with those without cancer rather than patients with HNC [8], [9]. This has led clinicians to argue that for HNC, the TWW system may be an inefficient use of clinicians time and not an effective way to detect patients with cancer [8], [9], [10].

Rather than dismiss the TWW system, the use of which is associated with a favourable prognosis [12], perhaps this could be used an opportunity to intervene to ensure early diagnosis of subsequent cancer. A previous benign diagnosis is one of the predictors of delay in presentation of cancer symptoms, whereby those previously experiencing a symptom that

turned out to be benign are more likely to delay seeking help for subsequent symptoms [13], [14]. This is thought to occur because of over-reassurance from the previous 'all-clear' result leading to subsequent symptoms being interpreted as benign and concern about appearing hypochondriacal or uncertain about the appropriate next actions [13]. Similarly, it has been suggested that the temporal nature of negative screening results should be stressed to patients [15]. Further, it has been claimed that referral for suspected cancer could be a ‘teachable moment’ whereby people may be more responsive and receptive to health information [16], [17]. Thus, there may be an opportunity to intervene at this time, offering preventative advice, encouragement to attend at future screening, and support for prompt presentation should they develop potentially malignant symptoms in the future.

However, very little is known about the group who receive a negative (benign) result after referral for suspected cancer, including their risk for future cancer. The current study aimed to analyse longitudinal data regarding subsequent cancer following an initial negative (benign) result after referral for suspected HNC at one NHS trust, to investigate the potential for early diagnosis initiatives in this setting.

The main objective of this analysis was to identify the occurrence of cancer (of any type) in the 5 years following receipt of a negative (benign) result after referral for suspected HNC and compare this to occurrence of cancer in those referred for routine (i.e. non-urgent, no suspicion of cancer) reasons. A secondary objective was to determine the stage of cancer in those diagnosed with of cancer in the 5 years following receipt of a negative (benign) result after referral for suspected HNC to estimate the need for early diagnosis initiatives.

MATERIALS AND METHODS

Study design: A local cohort study linking Public Health England's (PHE) National Cancer Registration data with hospital referral data from a department within Guy's & St Thomas' (GSTT) NHS Foundation Trust.

Participants: All patients referred on the TWW pathway to GSTT in between January 2009 and December 2011 with suspected HNC and those referred to the general ENT clinics in the same department over the same duration for routine (non-urgent) care, were identified by the direct care team using routinely collected referral data.

Procedure:

The appointment date, date of birth (converted to age at appointment), NHS number, post code (converted to level of deprivation using the Indices of Multiple Deprivation [18]) and gender were recorded and each patient was assigned a pseudonym. Using a secure transfer system, the Direct Care team sent an encrypted file to PHE listing patient identifiers (NHS numbers, date of birth) and pseudonyms. Patient identifiers were then removed from the direct care team's dataset. PHE returned pseudonyms with the requested data items (see below) to the direct care team using the secure transfer system. Data was matched to the direct care team's dataset using the pseudonyms.

To provide a basic description of the cancers that occurred, the following information was requested from the PHE Cancer Registration Service: site (ICD-10 code), stage at diagnosis, whether screen detected (whether or not the tumour was identified by the cancer bowel or breast cancer screening programme); and when diagnosis occurred (date of diagnosis) for each occurrence of cancer. Data was shared under GSTT Caldicott Guardian's approval. Data in the full period of the Cancer Registration Service (1985-2016) was requested in order to identify occurrence of cancer in the 5 years after referral and to control for previous history of cancer, as this is a known predictor of subsequent cancer.

Analysis

Chi square tests were used to compare the occurrence of cancer in the 5 years following a negative diagnosis between those referred with suspected cancer via the TWW pathway and those referred for routine care. Descriptive statistics were used to report the site, time between appointment and diagnosis, stage and vital status of those with a diagnosis of cancer within the first 5 years after their appointment. If patients experienced more than one diagnosis of cancer post appointment, only the first diagnosis was included in the analysis.

Single and multivariable Cox Proportional Hazards regression was used determine which factors were associated with an occurrence of cancer following receipt of a negative result. Patients who had not been diagnosed with cancer were censored on 31/12/2016. For all analysis statistical significance was defined as $p<0.05$.

RESULTS

Some patients had been referred to the department more than once during between 2009 and 2011. The first referral of those patients who had been referred more than once (duplicate cases) was retained in the dataset and subsequent referrals were removed from analyses.

Between 2009 and 2011 there were 2754 patients referred with suspected HNC on the Two Week Wait (TWW) pathway and 7859 patients referred to the general ENT out-patients' clinics. Cancer data was not available for 57 routinely referred patients due to missing NHS numbers and as such they were excluded from analyses. On the TWW pathway, 206 (7.5%) patients were diagnosed with cancer within 6 months of their appointment. For routine referrals, 36 (<0.5%) patients were diagnosed with cancer within 6 months of their appointment. These 242 patients with a diagnosis of (any) cancer occurring in within 6 months of referral were also excluded from analyses, under the assumption that this was diagnosed as a result of the referral. All remaining patients were deemed to have a negative (benign) diagnosis and were the focus of this service evaluation.

Sample Characteristics

2548 (92.5%) TWW patients and 7766 (99.5%) routinely referred patients were not diagnosed with cancer within the first 6 months following their appointment and thus were deemed to have a negative (benign) diagnosis.

For both TWW and routine referrals with a negative diagnosis, patients were most often aged 35-64years, female, and living in more deprived areas (see **Table 1**). Six percent of those referred on the TWW pathway had previously received a cancer diagnosis whereas 3% of those referred routinely had previously had cancer.

Cancer occurrence

Cancer occurrence in the 5 years post appointment for those who had initially received a negative diagnosis was 4.0% for those initially referred via TWW and 2.1% for those routinely referred to ENT ($p<0.0001$). The rate for those referred via TWW was higher than the London incidence [19] whereas the rate for those routinely referred to ENT was lower than the London incidence (see **Table 2**).

Table 1. Characteristics of patients with initial negative (benign) diagnosis

	TWW Referral	Routine Referral

		(n=2548)		(n=7766)	
		n	%	n	%
Age at appointment (years)	**0-17**	3	0.1	111	1.4
	18-34	400	15.7	2178	28.0
	35-64	1490	58.5	4130	53.2
	65-74	387	15.2	755	9.7
	75+	268	10.5	592	7.6
Gender	**Male**	1132	44.4	3521	45.3
	Female	1416	55.6	4244	54.6
	Missing	0	0.0	1	0.01
Index of Multiple Deprivation Decile	**1 (most deprived)**	150	5.9	456	5.9
	2	677	26.6	1991	25.6
	3	558	21.9	1572	20.2
	4	358	14.1	1103	14.2
	5	326	12.8	994	12.8
	6	184	7.2	552	7.1
	7	97	3.8	408	5.3
	8	89	3.5	289	3.7
	9	56	2.2	244	3.1
	10 (least deprived)	39	1.5	106	1.4
	Missing	14	0.5	51	0.7
Any cancer diagnoses prior to appointment	**Yes**	154	6.0	254	3.3
	No	2394	94.0	7512	96.7
Any cancer diagnoses in 5yrs following appointment [a]	**Yes**	103	4.0	162	2.1
	No	2445	96.0	7604	97.9

[a] If non-melanoma skin cancers are discounted, proportion of cancer cases in TWW group = 3.6%; Routine referral group = 1.8%

Table 2. Comparisons of estimated incidence

	Incidence per 100,000			
	London 2011	**London 2017**	**TWW referral**	**Routine referral**
Male	553.0	625.7	955.0 (95% CI: 751.7-1213.4)	455.8 (95% CI: 375.4-553.4)
Female	489.3	509.4	682.4 (95% CI: 529.8-878.8)	409.9 (95% CI: 340.4 -493.8)

Table 3 outlines the timing of the first diagnosis of cancer following an initial negative diagnosis and indicates cancer occurrences were spread over the 5 years following the appointment for both the TWW group and those routinely referred. Using all cases and adjusting for censoring, average (median) time between appointment and diagnosis of cancer was 6.2yrs (range=0.52-8.0yrs) for those initially referred via TWW, and 6.4yrs (range=0.53-8.0yrs) for those referred via a routine outpatient clinic.

Table 3. Timing of cancer diagnosis after initial negative diagnosis

	TWW Referral (n=103)		**Routine Referral (n=162)**	
	n	%	n	%
6-12 months after appointment	18	17.5	24	14.8

1-2 years after appointment	19	18.4	40	24.7
2-3 years after appointment	21	20.4	36	22.2
3-4 years after appointment	17	16.5	36	22.2
4-5 years after appointment[b]	28	27.2	26	16.0

[b] An additional 75 patients developed cancer 5-8 years following the appointment (24 in TWW group, 51 in routine referral group).

Figure 1 summarises the type of cancer for those diagnosed after an initial negative diagnosis. The most common types of subsequent cancer were lung, prostate and non-melanoma skin cancer. 8% of cases were head and neck cancer, (TWW referral: N=9, 9%; Routine referral: N=11, 7%). In the UK there are national screening programmes for breast, cervical and colorectal cancer. Of the 50 patients who were diagnosed with these cancers, 8 (TWW referral: N=5, 33%; Routine referral: N=3, 9%) were screen-detected.

***** Insert Figure 1 about here*****

Regarding stage of cancer, there was a lot of missing data, with no information on stage for 118 (45%) of patients. In the remaining 147 patients (56 referred on TWW pathway; 91 referred routinely) where data was available, 26 patients (46%) of those initially referred on the TWW pathway were diagnosed with advanced cancer and 35 patients (38%) of those initially referred for routine care were diagnosed with advanced cancer. This must be regarded with caution given the scarcity of data.

Factors associated with diagnosis of cancer following initial negative (benign) diagnosis

The single variable analysis results are shown in **Table 4** and show that those aged over 65, those who had a previous cancer diagnosis and those referred via the TWW pathway were significantly more likely to be diagnosed with cancer following an initial negative diagnosis. Neither gender or level of deprivation were associated with risk of subsequent cancer.

The results of the multivariable analysis (see **Table 4**) gave similar results to the single variable analysis. Patients were more likely to be diagnosed with a cancer as they got older, although only those aged over 75 were significant. Those who had a previous cancer diagnosis and those who were referred via the TWW pathway were also significantly more likely to be diagnosed with a cancer.

Of the 2548 on the TWW pathway who had an initial benign diagnosis, 88 (3.5%) were 65 years or older and had had a previous cancer. Of these 88, 22 (25%) developed a subsequent cancer.

Table 4. Factors associated with subsequent cancer after initial negative diagnosis

		Developed subsequent cancer		No subsequent cancer		Single Variable Cox Regression			Multivariable Cox Regression		
		n	%	n	%	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Age at appointment (years)	**0-17**	1	0.9	113	99.1	1.00	Reference	-	1.00	Reference	-
	18-34	10	0.4	2168	99.6	0.44	0.06-3.46	0.437	0.42	0.05-3.25	0.403
	35-64	152	2.7	5468	97.3	3.14	0.44-22.43	0.254	2.67	0.37-19.12	0.328
	65-74	**93**	**8.1**	**1049**	**91.9**	**9.68**	**1.35-69.47**	**0.024**	7.16	0.99-51.57	0.051
	75+	**84**	**9.8**	**776**	**90.2**	**11.83**	**1.65-84.99**	**0.014**	**8.47**	**1.18-61.08**	**0.034**
Gender	**Male**	169	3.6	4484	96.4	1.00.	Reference	-	1.00	Reference	-
	Female	171	3.0	5489	97.0	0.83	0.67-1.03	0.085	0.83	0.67-1.03	0.087
Index of Multiple Deprivation Decile	**1 (most deprived)**	17	2.8	589	97.2	1.00	Reference	-	1.00	Reference	-
	2	58	2.2	2610	97.8	1.17	0.70-1.97	0.549	1.11	0.66-1.87	0.691
	3	68	3.2	2062	96.8	1.14	0.67-1.93	0.639	1.10	0.64-1.87	0.732
	4	55	3.8	1406	96.2	1.35	0.78-2.33	0.277	1.35	0.78-2.32	0.282
	5	44	3.3	1276	96.7	1.19	0.68-2.08	0.545	1.15	0.66-2.01	0.630
	6	30	4.1	706	95.9	1.46	0.81-2.65	0.212	1.31	0.72-2.37	0.379
	7	14	2.8	491	97.2	0.99	0.49-2.01	0.975	0.85	0.42-1.73	0.649
	8	9	2.4	369	97.6	0.85	0.38-1.90	0.689	0.71	0.31-1.59	0.400
	9	8	2.7	292	97.3	0.94	0.41-2.18	0.885	0.94	0.40-2.18	0.882
	10 (least deprived)	6	4.1	139	95.9	1.49	0.59-3.79	0.397	1.16	0.45-2.94	0.761
Any cancer diagnoses prior to appointment	**No**	277	2.8	9629	97.2	1.00	Reference	-	1.00	Reference	-
	Yes	**63**	**15.4**	**345**	**84.6**	**5.84**	**4.44-7.68**	**<0.001**	**3.20**	**2.41-4.26**	**<0.001**
Type of referral	**Routine**	213	2.7	7553	97.3	1.00	Reference	-	1.00	Reference	-
	TWW	**127**	**5.0**	**2421**	**95.0**	**1.87**	**1.50-2.32**	**<0.001**	**1.40**	**1.12-1.75**	**0.003**

DISCUSSION

This analysis set out to investigate the occurrence of any type of cancer in the 5 years following referral for suspected HNC, particularly in those who initially receive a negative result. This is the first analysis to report this follow-up data, not just for referrals for suspected HNC, but for any suspected cancer pathway. As reported elsewhere [20], the majority of patients referred on the TWW pathway were not diagnosed with cancer. However, the novel finding is that those referred on the TWW pathway may be at higher risk of developing cancer in the 5 years following their appointment, even if initially no cancer is found and a substantial proportion of these may be diagnosed at an advanced stage. Of those referred with suspected HNC, 7.5% were diagnosed with cancer within in the first 6 months. Of those who had initially received a negative diagnosis, cancer occurrence in the 5 years post appointment for was 4.0%. Given the current scale of TWW referrals in the UK this has implications for service provision, to ensure those who are initially discharged with benign conditions receive appropriate advice, follow-up, and safety netting, to ensure any subsequent cancers are diagnosed in a timely manner and at an early stage. The results of the current study indicate that this is particularly the case for those who are at higher risk of cancer in general (i.e. those over 65 and/or have experienced a previous cancer). Given that previous benign diagnosis is one of the predictors of delay in presentation of cancer symptoms [13], [14], guidance as to when to seek help seems paramount. It has previously been suggested that referral for suspected cancer could be a 'teachable moment' where patients may be more receptive to health advice such as advice and assistance to stop smoking [16]. Use of referral for suspected cancer as a teachable moment for prevention or early diagnosis of subsequent cancer will require consultation with service users and providers to formulate an acceptable and feasible approach.

This study has also provided information on the type of cancer diagnosed after an initial negative diagnosis. Not surprisingly, the four most common cancer types in the UK (lung, breast, prostate, colorectal [21]) are among the most common cancer diagnoses. There were some differences in subsequent cancer type between those referred on TWW pathway and those referred for routine care, with lung cancer being more common in those referred on the TWW pathway, and prostate, colorectal and skin cancers being more common in those referred on for routine care. Without further investigation the reason for these differences is unknown. However, occurrence of lung cancer might be expected given the common risk factors with HNC and lung cancer being a common site for second primary cancers.

There are a number of limitations to this study that should be considered. Firstly, one objective of this study was to determine the stage of cancer in those diagnosed with of cancer following receipt of a negative (benign) result after referral for suspected HNC. However 45% of patients had missing data with regard to stage of cancer and thus conclusions regarding this objective are currently unreliable. The issue of incomplete stage data within the UK Cancer Registry is not new. Using complete case indicators (i.e. calculating the proportion with advanced stage disease based only on those cases with data on stage) may introduce bias and under-estimate advanced stage diagnosis [22], [23], whereas presuming those with missing data have advanced stage disease is likely to over-estimate the occurance of advanced stage disease [23]. There are continuing improvements in stage completion in the cancer registries and thus future research will be able to provide more accurate data on this issue. Secondly, this analysis reports on data for just one service for for referral for just one cancer type and thus may not be generalisable to other centres or other cancers. Analysis of large datasets such as the Clinical Practice Research Datalink [24], could offer insight and could be used to determine which suspected cancer referral pathways may be most suitable for additional intervention at the time of negative diagnosis. Thirdly, this study reports on patients referred with suspected cancer between 2009 and 2011 to allow follow up for 5 years from available cancer registry data. In 2015 UK referral guidelines for HNC were changed [25]. This may mean the profile of those currently referred on the TWW pathway for suspected HNC could be different to those referred on the pathway prior to 2015. Under the new referral guidelines, symptoms with positive predictive value of 3% or higher were included (as opposed to 5% or higher in the previous guidelines) thus increasing the number of patients who meet the criteria for referral. This has led to a decrease in the proportion of head and neck cancers detected [8] but is unknown if risk of subsequent cancers would also be lower. Validating the current findings with a sample of patients referred via the 2015 UK referral guidelines is an important next step. Fourthly, the available dataset did not include mortatility data and as such regression analyses included those who may not have been alive, potentially affecting risk estimates. Finally, the absence of data on general risk factors for cancer weakens the conclusions that can be drawn from the analysis. For instance, smoking is a common risk factor across cancers. An unbalanced proportion of smokers in the 2 groups could justify the different rate of new cancer occurrence. Accordingly, the finding that the TWW group conveys a higher risk of new cancer development could be lost when smoke is included in the multivariate analysis. Future studies should determine if this (or presence of other general risk factors) is the reason for the higher incidence of subsequent cancer in the TWW group and could be a target for interventions if so.

Whilst being mindful of the above limitations, this study gives the first indication that there may be increased risk of subsequent cancer in those referred on the TWW, regardless of their initial diagnosis. This suggests it may be beneficial to improve the service provision (e.g. provision of advice on screening attendance, ways to reduce risk, advice on timely help-seeking for symptoms of cancer) and ensure appropriate safety netting is in place at the point of a negative diagnosis on the TWW pathway for suspected HNC, especially in older patients and those with a previous diagnosis of cancer.

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Figure 1. Sites of cancer