Future cancer risk after urgent suspected cancer referral in England when cancer is not found: a national cohort study

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Summary

Background Following referral for investigation of urgent suspected cancer within the English National Health Service referral system, 7% of referred individuals are diagnosed with cancer. This study aimed to investigate the risk of cancer occurrence within 1–5 years of finding no cancer following an urgent suspected cancer referral.

Methods This national cohort study used urgent suspected cancer referral data for England from the Cancer Waiting Times dataset and linked it with cancer diagnosis data from the National Cancer Registration dataset. Data were extracted for the eight most commonly referred to urgent suspected cancer referral pathways (breast, gynaecological, head and neck, lower and upper gastrointestinal, lung, skin, and urological) for the period April 1, 2013, to March 31, 2014, with 5-year follow-up for individuals with no cancer diagnosis within 1 year of referral. The primary objective was to investigate the occurrence and type of subsequent cancer in years 1–5 following an urgent suspected cancer referral when no cancer was initially found, both overall and for each of the eight referral pathways. The numbers of subsequent cancers were compared with expected cancer incidence in years 1–5 following referral, using standardised incidence ratios (SIRs) based on matched age-gender distributions of expected cancer incidence in England for the same time period. The analysis was repeated, stratifying by referral group, and by calculating the absolute and expected rate of all cancers and of the same individual cancer as the initial referral.

Findings Among 1·18 million referrals without a cancer diagnosis in years 0–1, there were 63 112 subsequent cancers diagnosed 1–5 years post-referral, giving an absolute rate of 1338 (95% CI 1327–1348) cancers per 100 000 referrals per year (1038 [1027–1050] in females, 1888 [1867–1909] in males), compared with an expected rate of 1054 (1045–1064) cancers per 100 000 referrals per year (SIR 1·27 [95% CI 1·26–1·28]). The absolute rate of any subsequent cancer diagnosis 1–5 years after referral was lowest following suspected breast cancer referral (746 [728–763] cancers per 100 000 referrals per year) and highest following suspected urological (2110 [2070–2150]) or lung cancer (1835 [1767–1906]) referral. For diagnosis of the same cancer as the initial referral pathway, the highest absolute rates were for the urological and lung pathways (1011 [984–1039] and 638 [598–680] cancers per 100 000 referrals per year, respectively). The highest relative risks of subsequent diagnosis of the same cancer as the initial referral pathway were for the head and neck pathway (SIR 3·49 [95% CI 3·22–3·78]) and lung pathway (3·00 [2·82–3·20]).

Interpretation Cancer risk was higher than expected in the 5 years following an urgent suspected cancer referral. The potential for targeted interventions, such as proactive monitoring, safety-netting, and cancer awareness or risk reduction initiatives should be investigated.

Funding Cancer Research UK.

Introduction

Urgent suspected cancer referral pathways from primary care are used to facilitate prompt investigation and potentially early diagnosis of cancer. In England, there are separate pathways and referral guidelines for different anatomical sites.[1] National Health Service (NHS) England waiting time targets have stipulated that patients suspected of having cancer be seen by a specialist within 2 weeks, or more recently (as of October, 2021), that diagnostic evaluation be completed (ie, patients should have cancer ruled out or receive a diagnosis) within 28 days of referral.[2]

The number of patients referred on urgent suspected cancer referral pathways has increased markedly in the last 13 years.[3] In 2009–10, just over 900 000 patients were referred, whereas by 2022–23, this had increased to over 2·9 million.[4] The urgent suspected cancer referral pathway is now the most common route to cancer diagnosis in England, with a corresponding decline in diagnoses via emergency presentation.[5] Primary care practices using urgent suspected cancer referral pathways more frequently have better cancer outcomes; patients from practices with a higher number of urgent suspected cancer referrals have better survival rates and lower odds of advanced-stage disease compared with practices with lower numbers of urgent suspected cancer referrals.[6,7] With the exception of cancer screening, urgent suspected cancer referral pathways are the route to diagnosis with the highest proportion of early-stage cancer diagnoses

Research in context

Evidence before this study

In England, over 2·9 million patients were referred on urgent suspected cancer pathways in 2022–23. Cancer is not found in the vast majority (over 90%) of urgent suspected cancer referrals, yet the subsequent cancer risk for these individuals is unknown. We searched PubMed for relevant articles published from database inception to June 6, 2023, using the search terms "urgent referral OR two-week wait" AND "subsequent cancer", with no language restrictions. This is an under-researched area and there were only two papers published that reported occurrence of cancer more than 1 year after an urgent suspected cancer referral when cancer had not been found. One paper followed up 1200 patients between 12 months and 58 months (median 35 months) following referral to one rapid access clinic with symptoms suspicious of colorectal cancer and found no subsequent cases of colorectal cancer. The second paper tracked occurrence of any cancer in the 5 years following negative diagnosis (defined as no cancer diagnosis within 6 months of referral) after urgent referral to one hospital for suspected head and neck cancer. That study found that 4% of patients were diagnosed with cancer in the following 5 years, which was a higher proportion than that for routine referrals to the same department (2%). These studies were based on single institutions and only focused on single urgent suspected cancer referral pathways.

Added value of this study

In this study we used national data (Cancer Waiting Times and linked National Cancer Registration data) to provide insight across England and across the eight most common urgent suspected cancer referral pathways (breast, gynaecological, head and neck, lower and upper gastrointestinal, lung, skin, and urological). To our knowledge, this the first study to comprehensively investigate risk and type of subsequent cancer in years 1–5 for those referrals when no cancer was found in years 0–1. Our study expands previous research and indicates that although the majority of people referred with suspected cancer do not have cancer diagnosed at that time, these individuals have an increased risk for a subsequent cancer diagnosis compared with people of similar age and sex.

Implications of all the available evidence

Our findings highlight a potential unmet need for individuals following urgent suspected cancer referral. Given the high numbers of people passing through the urgent suspected cancer referral pathways, this increased risk is not insubstantial. Investigation into the potential for targeted interventions, such as proactive monitoring, safety-netting, and cancer awareness or risk reduction initiatives might be warranted.

(stages 1 and 2). For example, in 2018, 52% of cancers diagnosed through urgent suspected cancer referral were early-stage cancers, compared with 16% diagnosed through emergency presentation and 45% through non-urgent general practitioner (GP) referral.[5]

In 2015, guidelines from the National Institute for Health and Care Excellence published urgent referral criteria for suspected cancer based on symptoms and signs with a cancer risk (or positive predictive value) of 3% or more. Although referrals have been increasing by approximately 10% year-on-year,[3] the conversion rate (or proportion of referrals resulting in diagnosis of cancer) has dropped from 10% to around 6% (ie, six in 100 referred patients are diagnosed with cancer).[8] This figure varies between referral pathways; for instance, for the brain or CNS referral pathway approximately 1% of patients are diagnosed with cancer, whereas for the haematological pathway approximately 20% are diagnosed with cancer following an urgent suspected cancer referral.[9,10] Concern has been raised about the increased numbers of referrals and the burden it places on the health-care system,[11] yet the proportion of early-stage cancers diagnosed through the urgent suspected cancer referrals route continues to increase.[5]

Little is known about what happens to patients after discharge from an urgent suspected cancer referral pathway when cancer is not found. It is possible that they are still at risk of being diagnosed with cancer in the future due to common risk factors such as diet, smoking, and alcohol use or missed diagnoses. A criticism of urgent suspected cancer pathways is that they are focused on one anatomical site. Thus, if cancer is not found through one pathway, the patient requires further referral to a second pathway (either internally within secondary care or via primary care) if cancer is still suspected. In Denmark, one in 16 patients on urgent suspected cancer pathways are re-referred within 6 months to another organ-specific urgent suspected cancer pathway, with 4% of those re-referred then diagnosed with cancer, compared with 0·3% of those who are not re-referred.[12] A clinical service evaluation in England found that alongside risk factors of increasing age and previous cancer diagnosis, those referred via the head and neck urgent suspected cancer pathway were at twice the risk of being diagnosed with cancer in the following 5 years (4%) compared with routine referrals to the same department (2%).[13] However, beyond this initial pilot work in one institution, the occurrence of cancer after urgent suspected cancer has not been investigated in England. We aimed to investigate the risk of future cancer in the 1–5 years following an urgent suspected cancer referral when no cancer was found across the eight most commonly referred to urgent suspected cancer pathways, using national data for England.

Methods

Study design and data sources

We conducted a national cohort study linking data from the Cancer Waiting Times dataset[4] (the system used in

England to monitor cancer waiting times targets) and the National Cancer Registration dataset[14] (the registry maintaining details of all cancers diagnosed each year across England). Cancer Waiting Times data were extracted (with no age restrictions, although there is a separate suspected children's cancer referral type for individuals younger than 16 years at the time of referral that was not included in this study) for the eight most commonly suspected cancer types (breast, gynaecological, head and neck, lower and upper gastrointestinal, lung, skin, and urological [excluding testicular but including prostate]) in England, with a "decision to refer" date (or, where null, "referral request received" date) between April 1, 2013, and March 31, 2014.

Data for this study were collected and analysed under the National Disease Registries Directions 2021, made in accordance with sections 254(1) and 254(6) of the 2012 Health and Social Care Act. Further ethical approval for this study was not required per the definition of research according to the UK Policy Framework for Health and Social Care Research.

Procedures

The retrospective Cancer Waiting Times data included suspected cancer referral type, gender (from electronic medical records; obtained as person-stated gender as registered in primary care), age at referral, ethnic group (from electronic medical records), deprivation quintile at referral (based on residential postcode and the Index of Multiple Deprivation[15]), and number of previous urgent suspected cancer referrals (for the same eight referral types, from Jan 1, 2009, onwards). These data were linked to National Cancer Registration data to identify any cancers (International Classification of Diseases 10th Revision [ICD-10] codes C00–C97 and D05) diagnosed in the 5 years following referral, with the data including the interval from first referral to diagnosis, cancer type (ICD-10), stage at diagnosis (grouped as either early [0, 1, 2, or Binet A or B]; or advanced [3, 4, or Binet C][16]), route to diagnosis, and number of previous cancers (from 1995 onwards, as cancer registration data pre-1995 are limited and not routinely linked to other cancer registration data in England).

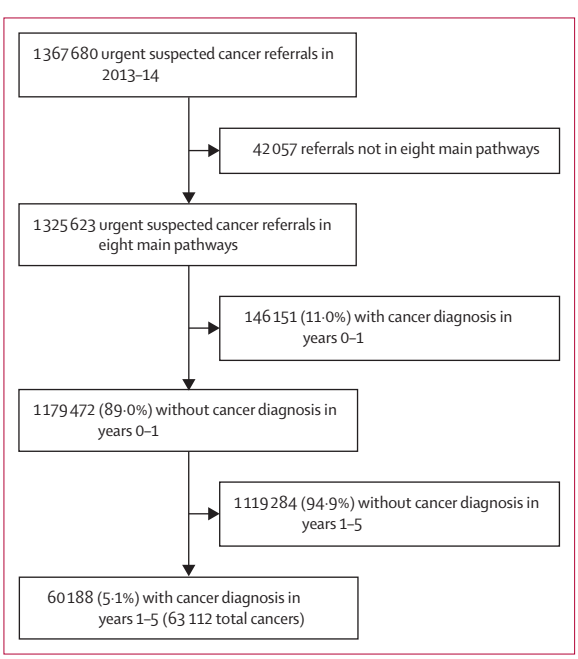

Figure 1: **Study cohort**

Outcomes

The primary aim was to investigate the occurrence and type of subsequent cancer in the 1–5 years following an urgent suspected cancer referral when no cancer was initially found, both overall and for each main referral pathway. Secondary aims were to investigate the patient characteristics, stage, and route to diagnosis of subsequent cancers.

Statistical analysis

Subsequent cancers were defined as cancers occurring in years 1–5 (months 13–60) for individuals who were referred with no cancer diagnosis within 1 year (months 0–12) of the initial referral. Allowing 1 year for initial cancer diagnosis limits misinterpretation of future risk from circumstances in which multiple urgent suspected cancer referrals might occur for the same symptom episode. The numbers, type, and stage of subsequent cancers diagnosed were documented for each year period from 1 year to 5 years after initial referral, stratified by referral pathway. Subsequent cancers are presented as rates per 100 000 referrals per year, with 95% CIs calculated using Byar's method;[17] these rates can include more than one subsequent diagnosis following a given referral. The rates presented do not account for deaths or those lost to follow-up during the follow-up period.

Indirect standardised incidence ratios (SIRs),[18] and associated 95% CIs (Byar's method), were calculated by comparing the number of cancers observed in the cohort with those expected in England in the same time period studied, based on the age-gender distribution of the cohort and cancer incidence rates in England by 5-year age groups (0–4 years to ≥90 years) and gender. Using the same methodology, absolute rates, expected rates, and SIRs stratified by referral group and interval from referral to diagnosis were calculated for all new cancer diagnoses, and for the same cancer type as the initial referral pathway.

To visualise the most common types of subsequent cancers, heatmaps were generated of subsequent cancer type frequencies by each urgent suspected cancer referral pathway as a whole and by gender, highlighting the cancer types constituting more than 10% or more than 20% of the subsequent cancers. Patient and cancer characteristics (ie, gender, age, level of deprivation, stage at diagnosis, and route to diagnosis) of subsequent

cancers were compared with those of the initial urgent suspected cancer referrals and from published National Cancer Registration data (England).

The main analysis included diagnoses of invasive cancers (ICD-10 codes C00–C97 and C45–C97) and excluded non-melanoma skin cancer (ICD-10 code C44) and carcinoma in situ of breast (ICD-10 code D05). A sensitivity analysis repeated all analysis including non-melanoma skin cancer and carcinoma in situ of breast. The main analysis used referrals as the denominator for rates of future cancer diagnoses; an additional sensitivity analysis used a patient denominator. All analyses were conducted using Stata version 17.0.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

There were 1·33 million urgent suspected cancer referrals across the eight most commonly referred to cancer pathways from April 1, 2013, to March 31, 2014 (97% of all 1·37 million urgent suspected cancer referrals; figure 1). 146 151 (11%) of the 1·33 million referrals concluded in a diagnosis of cancer in the year following referral. For the 1·18 million referrals not found to have

	Years 1–2		Years 2–3		Years 3–4		Years 4–5		Years 1–5 combined	
	n	Rate*	n	Rate*	n	Rate*	n	Rate*	n	Rate*
Breast (n=231 463)	1678	725 (691–760)	1669	721 (687–757)	1763	762 (727–798)	1794	775 (740–812)	6904	746 (728–763)
Gynaecological (n=113 828)	1206	1059 (1001–1121)	1155	1015 (957–1075)	1097	964 (908–1022)	1077	946 (890–1004)	4535	996 (967–1025)
Head and neck (n=116 242)	1595	1372 (1306–1441)	1538	1323 (1258–1391)	1466	1261 (1197–1327)	1484	1277 (1213–1343)	6083	1308 (1276–1342)
Lower gastrointestinal (n=189 760)	3138	1654 (1596–1713)	2904	1530 (1475–1587)	2731	1439 (1386–1494)	2749	1449 (1395–1504)	11 522	1518 (1490–1546)
Lung (n=37 185)	804	2162 (2015–2317)	697	1874 1738–2019)	618	1662 (1533–1798)	611	1643 (1515–1779)	2730	1835 (1767–1906)
Skin (n=236 102)	3386	1434 (1386–1483)	3221	1364 (1318–1412)	3168	1342 (1295–1389)	3094	1310 (1265–1357)	12 869	1363 (1339–1386)
Upper gastrointestinal (n=126 654)	2094	1653 (1583–1726)	1915	1512 (1445–1581)	1884	1488 (1421–1556)	1755	1386 (1322–1452)	7648	1510 (1476–1544)
Urological (n=128 238)	3352	2614 (2526–2704)	2638	2057 (1979–2137)	2527	1971 (1894–2049)	2304	1797 (1724–1872)	10 821	2110 (2070–2150)
All pathways (n=1 179 472)	17 253	1463 (1441–1485)	15 737	1334 (1313–1355)	15 254	1293 (1273–1314)	14 868	1261 (1240–1281)	63 112	1338 (1327–1348)

The first column shows the number of patients in each referral pathway for whom no cancer was diagnosed in years 0–1 following the urgent suspected cancer referral. The other columns show subsequent cancer diagnoses in years 1–5 post–referral. *n per 100 000 referrals per year (95% CI).

Table 1: **Subsequent cancers in years 1–5 after urgent suspected cancer referral**

	Observed cases	Expected cases	Absolute cancer rate*	Expected cancer rate*	Standardised incidence ratio (95% CI)
Years 1–5 combined					
All pathways	63 112	49 739	1338 (1327–1348)	1054 (1045–1064)	1·27 (1·26–1·28)
Breast	6904	5328	746 (728–763)	575 (560–591)	1·30 (1·27–1·33)
Gynaecological	4535	3667	996 (967–1025)	805 (780–832)	1·24 (1·20–1·27)
Head and neck	6083	4619	1308 (1276–1342)	993 (965–1022)	1·32 (1·28–1·35)
Lower gastrointestinal	11 522	10 245	1518 (1490–1546)	1350 (1324–1376)	1·13 (1·10–1·15)
Lung	2730	2022	1835 (1767–1906)	1359 (1301–1420)	1·35 (1·30–1·40)
Skin	12 869	10 047	1363 (1339–1386)	1064 (1043–1085)	1·28 (1·26–1·30)
Upper gastrointestinal	7648	6563	1510 (1476–1544)	1295 (1264–1327)	1·17 (1·14–1·19)
Urological	10 821	7248	2110 (2070–2150)	1413 (1381–1446)	1·49 (1·47–1·52)
Years 1–2					
All pathways	17 253	12 933	1463 (1441–1485)	1097 (1078–1116)	1·33 (1·31–1·35)
Years 2–3					
All pathways	15 737	12 591	1334 (1313–1355)	1068 (1049–1086)	1·25 (1·23–1·27)
Years 3–4					
All pathways	15 254	12 385	1293 (1273–1314)	1050 (1032–1069)	1·23 (1·21–1·25)
Years 4–5					
All pathways	14 868	11 829	1261 (1240–1281)	1003 (985–1021)	1·26 (1·24–1·28)

*n per 100 000 referrals per year (95% CI).

Table 2: **Standardised incidence ratios for risk of any subsequent cancer in years 1–5 after urgent suspected cancer referral**

cancer in the first year, 60 188 patients were diagnosed with 63 112 cancers 1–5 years post-referral, giving an absolute rate of 1338 (95% CI 1327–1348) new cancers diagnosed per 100 000 referrals per year (table 1). The occurrence of subsequent cancer remained relatively stable over time, but was highest in years 1–2 across all referral pathways (table 1). The largest numbers of subsequent cancers were diagnosed after referral through the skin, lower gastrointestinal, and urological urgent suspected cancer pathways (table 1). These referral pathways also had some of the highest absolute rates of subsequent cancers, along with the lung and upper gastrointestinal referral pathways (table 1).

See Online for appendix

SIRs for any subsequent cancer are presented in table 2. The absolute cancer rate in years 1–5 was higher than would be expected for rates in England (SIR 1·27 [95% CI 1·26–1·28]). The highest risk was in years 1–2 and the lowest was in years 3–4 (table 2). Although there was an increased risk of future cancer in years 1–5 following all urgent suspected cancer referral pathways compared with expected rates in England, there was variation between individual pathways. The pathways with the highest SIRs were the urological, lung, and head and neck referral pathways; those with the lowest SIRs were the gastrointestinal pathways (table 2).

Figure 2 is a heatmap of the types of the 63 122 subsequent cancers by referral pathway (reported by gender in appendix pp 2–3). Across all referral pathways, lung cancer consistently comprised a substantial proportion of the subsequent cancers (ranging from 9·8% to 34·8%; 9872 [15·6%] of 63 122 overall). Other frequently occurring cancers across most referral pathways included urological cancers in males, breast cancers in females, and lower gastrointestinal cancers regardless of gender (figure 2; appendix pp 2–3). Breast and gynaecological cancers made up around half of cancers occurring when no cancer was found in the first year after referral on the gynaecological pathway, and a similar proportion following referral on the breast referral pathway.

For three referral pathways (breast, lung, and urological), the most frequent cancer type diagnosed in years 1–5 after a referral was the same as the initial referral pathway (figure 2). The urological and lung pathways had the highest absolute rate of the same cancer diagnosis as the initial referral pathway (table 3).

Type of subsequent cancer

10–19%
≥20%

Referral pathway with no cancer found in years 0–1 and subsequent cancer diagnosis in years 1–5	Breast	Gynaecological	Head and neck	Lower gastrointestinal	Lung	Skin	Upper gastrointestinal	Urological	Other
Breast (n=6904)	2745 (39·8%)	636 (9·2%)	265 (3·8%)	627 (9·1%)	737 (10·7%)	323 (4·7%)	372 (5·4%)	437 (6·3%)	762 (11·0%)
Gynaecological (n=4535)	1401 (30·9%)	900 (19·8%)	168 (3·7%)	460 (10·1%)	446 (9·8%)	171 (3·8%)	298 (6·6%)	206 (4·5%)	485 (10·7%)
Head and neck (n=6083)	776 (12·8%)	245 (4·0%)	626 (10·3%)	642 (10·6%)	1098 (18·1%)	238 (3·9%)	562 (9·2%)	1079 (17·7%)	817 (13·4%)
Lower gastrointestinal (n=11 522)	1429 (12·4%)	484 (4·2%)	422 (3·7%)	1302 (11·3%)	2045 (17·7%)	407 (3·5%)	1327 (11·5%)	2360 (20·5%)	1746 (15·2%)
Lung (n=2730)	209 (7·7%)	75 (2·7%)	117 (4·3%)	240 (8·8%)	949 (34·8%)	70 (2·6%)	257 (9·4%)	475 (17·4%)	338 (12·4%)
Skin (n=12 869)	1451 (11·3%)	473 (3·7%)	486 (3·8%)	1603 (12·5%)	1839 (14·3%)	1063 (8·3%)	1192 (9·3%)	2896 (22·5%)	1866 (14·5%)
Upper gastrointestinal (n=7648)	958 (12·5%)	311 (4·1%)	310 (4·1%)	986 (12·9%)	1447 (18·9%)	274 (3·6%)	907 (11·9%)	1382 (18·1%)	1073 (14·0%)
Urological (n=10 821)	465 (4·3%)	215 (2·0%)	259 (2·4%)	992 (9·2%)	1311 (12·1%)	320 (3·0%)	886 (8·2%)	5186 (47·9%)	1187 (11·0%)
Total (n=63 112)	9434 (14·9%)	3339 (5·3%)	2653 (4·2%)	6852 (10·9%)	9872 (15·6%)	2866 (4·5%)	5801 (9·2%)	14 021 (22·2%)	8274 (13·1%)

Figure 2: **Heat map of types of subsequent cancers in years 1–5 by referral pathway**

	Observed cases	Expected cases	Absolute cancer rate*	Expected cancer rate*	Standardised incidence ratio (95% CI)
Breast	2745	1716	296 (285–308)	185 (177–194)	1·60 (1·54–1·66)
Gynaecological	900	448	198 (185–211)	98 (89–108)	2·01 (1·88–2·15)
Head and neck	626	179	135 (124–146)	39 (33–45)	3·49 (3·22–3·78)
Lower gastrointestinal	1302	1384	172 (162–181)	182 (173–192)	0·94 (0·89–0·99)
Lung	949	316	638 (598–680)	212 (190–237)	3·00 (2·82–3·20)
Skin	1063	405	113 (106–120)	43 (39–47)	2·62 (2·47–2·79)
Upper gastrointestinal	907	673	179 (168–191)	133 (123–143)	1·35 (1·26–1·44)
Urological	5186	2190	1011 (984–1039)	427 (409–445)	2·37 (2·30–2·43)

The first column shows the urgent suspected cancer referral pathway. *n per 100 000 referrals per year (95% CI).

Table 3: **Standardised incidence ratios for risk of same cancer diagnoses as the initial referral pathway in years 1–5**

For the same cancer diagnosis as the initial referral pathway, the lowest SIR for years 1–5 was for the lower gastrointestinal pathway and the highest SIRs were for the head and neck and lung pathways (table 3).

Demographic characteristics of referrals without a cancer diagnosis in years 0–1 post-referral and those with subsequent cancer diagnosis in years 1–5 are shown in table 4. The absolute rate of subsequent cancers was higher in males than females, in those with White ethnicity than other ethnicities, and in older adults than younger adults and children or adolescents. Higher absolute cancer rates were also found in those with a previous history of cancer versus no previous history and previous urgent suspected cancer referral versus no referral, although most referred patients and most patients with a subsequent cancer diagnosis had no previous history of cancer and no previous urgent suspected cancer referral (table 4). Rate of subsequent cancers did not appear to differ by Index of Multiple Deprivation quintile. Distribution in number of subsequent cancer diagnoses in years 1–5 by gender and level of economic deprivation was similar to national cancer registrations, but subsequent cancers were more common in those aged 60–79 years in this cohort (appendix p 4).

As with cancer registrations in England, subsequent cancers were most commonly diagnosed by urgent suspected cancer referral pathways, followed by non-urgent GP referral and emergency presentation (table 4) although proportions did differ (appendix p 4). Of 50 137 diagnosed cancers with available staging information, 20 933 (42%) were diagnosed at an advanced stage (table 4), which is a higher proportion than that seen for cancer registrations in England (52%, appendix p 4). This proportion varied by type of subsequent cancer, with high proportions of upper gastrointestinal, lung, lower gastrointestinal, and head and neck cancers being diagnosed at an advanced stage compared with the other four cancers (appendix p 5).

A sensitivity analysis including non-melanoma skin cancer and carcinoma in situ of breast (in years 0–5) demonstrated similar patterns of cancer rates as the main analyses, with higher rates of cancer diagnoses in years 1–5 than would be expected on the basis of incidence rates in England. The absolute cancer rate was higher for each urgent suspected cancer referral pathway (particularly the skin pathway) and overall (1970 [95% CI 1957–1983] cancers per 100 000 referrals per year), although the SIR was similar (1·30 [95% CI 1·30–1·31]; appendix pp 6–9). Analyses at the individual patient level demonstrated little change in absolute cancer rates compared with the primary analyses that used referrals as the denominator (appendix p 10).

Discussion

When no cancer was found in the first year after an urgent suspected cancer referral, there were 1338 (95% CI 1327–1348) subsequent diagnoses of cancer

	Urgent suspected cancer referrals with no cancer found in years 0–1 (n=1 179 472)	Subsequent cancer diagnoses in years 1–5 (n=63 112)	Absolute cancer rate*
Gender			
Female	763 842 (64·8%)	31 725 (50·3%)	1038 (1027–1050)
Male	415 630 (35·2%)	31 387 (49·7%)	1888 (1867–1909)
Age group at referral, years			
<50	351 623 (29·8%)	4739 (7·5%)	337 (327–347)
50–59	218 682 (18·5%)	7824 (12·4%)	894 (875–914)
60–69	241 559 (20·5%)	16 921 (26·8%)	1751 (1725–1778)
70–79	214 900 (18·2%)	20 209 (32·0%)	2351 (2319–2384)
≥80	152 708 (12·9%)	13 419 (21·3%)	2197 (2160–2234)
Ethnicity			
Asian	50 248 (4·3%)	1538 (2·4%)	765 (727–804)
Black	27 171 (2·3%)	986 (1·6%)	907 (851–966)
Mixed and other	13 185 (1·1%)	324 (0·5%)	614 (549–685)
Unknown	34 374 (2·9%)	705 (1·1%)	513 (476–552)
White	1 054 494 (89·4%)	59 559 (94·4%)	1412 (1401–1423)
Index of Multiple Deprivation quintile (at referral)			
1 (most deprived)	218 695 (18·5%)	11 336 (18·0%)	1296 (1272–1320)
2	228 822 (19·4%)	11 806 (18·7%)	1290 (1267–1313)
3	242 628 (20·6%)	13 188 (20·9%)	1359 (1336–1382)
4	246 579 (20·9%)	13 409 (21·2%)	1360 (1337–1383)
5 (least deprived)	242 748 (20·6%)	13 373 (21·2%)	1377 (1354–1401)
Number of previous cancers before referral			
0	1 082 030 (91·7%)	55 983 (88·7%)	1293 (1283–1304)
1	90 402 (7·7%)	6539 (10·4%)	1808 (1765–1853)
2	6582 (0·6%)	534 (0·8%)	2028 (1860–2208)
≥3	458 (<0·1%)	56 (0·1%)	3057 (2309–3970)
Number of previous urgent suspected cancer referrals for eight main referral pathways in 5 years before referral			
0	897 616 (76·1%)	45 099 (71·5%)	1256 (1245–1268)
1	220 764 (18·7%)	13 842 (21·9%)	1568 (1542–1594)
2	47 500 (4·0%)	3239 (5·1%)	1705 (1647–1764)
≥3	13 592 (1·2%)	932 (1·5%)	1714 (1606–1828)
Stage at diagnosis			
Early	NA	29 204 (46·3%)	NA
Advanced	NA	20 933 (33·2%)	NA
Unable to stage	NA	4132 (6·5%)	NA
Unknown	NA	8843 (14·0%)	NA
Route to diagnosis†			
Death certificate only	NA	55 (0·1%)	NA
Emergency presentation	NA	11 735 (18·6%)	NA
Non-urgent GP referral	NA	17 662 (28·0%)	NA
Inpatient elective	NA	859 (1·4%)	NA
Other outpatient	NA	5802 (9·2%)	NA
Screening	NA	3047 (4·8%)	NA
Urgent suspected cancer referral	NA	21 966 (34·8%)	NA
Unknown	NA	1986 (3·1%)	NA

GP=general practitioner. NA=not applicable. *n per 100 000 referrals per year (95% CI). †Definitions are provided in CancerData: Routes to Diagnosis.[19]

Table 4: **Characteristics of patients with urgent suspected cancer referrals and subsequent cancers**

per 100 000 referrals per year in the following 1–5 years, many with advanced-stage disease. This absolute rate of cancer is not high, but it is higher than expected for people of similar age and gender, and represents a substantial number of cancers given the size of the urgent suspected cancer referral cohort. The highest observed absolute rates of cancer incidence were after urological, lung, skin, and lower and upper gastrointestinal urgent suspected cancer referral pathways. The SIRs were highest for urological, lung, and head and neck pathways, and lowest for upper and lower gastrointestinal pathways, indicating that the seemingly high absolute rates for gastrointestinal referrals are in line with what would be expected for the age and gender of patients referred on the gastrointestinal pathways. The types of subsequent cancers diagnosed broadly reflects the cancers most commonly diagnosed in England, with urological (including prostate), lung, breast, and lower gastrointestinal cancers the most common.[20] The characteristics of patients with subsequent cancers are generally similar to those for overall cancer incidence in England. In line with national cancer incidence data, high proportions of subsequent upper gastrointestinal, lung, lower gastrointestinal, and head and neck cancers were diagnosed at an advanced stage. Yet, overall, subsequent cancers were more likely to be diagnosed at an early stage (58%) compared with all cancers registered in England (52%). Compared with the national registrations, a higher proportion of the subsequent cancers in this cohort were diagnosed following non-urgent GP referral (28% compared with 21%) and fewer diagnosed via urgent suspected cancer referral (35% compared with 40%).

There was relative stability of cancer occurrence over time, between 1–2 years and 4–5 years after referral. Put together, these patterns indicate that most of these cancers might be due to higher cancer risk in these patients rather than due to being missed cancers, or might be due to patients entering follow-on investigation and treatment pathways leading to future monitoring and detection of disease. Although further studies would be required, this increased risk of cancer might be explained by common risk factors. For example, family history, smoking, and alcohol consumption have known associations with some of the cancers shown here to have the highest relative risks in this population, and urgent suspected cancer referrals might be more common in patients with a smoking history or family history of cancer. These findings support and extend previous exploratory work on the risk of cancer after urgent suspected head and neck cancer referral[13] and sustained risk of breast cancer after previous false-positive screening results.[21] Sensitivity analyses revealed similar patterns of cancer rates whether including or excluding non-melanoma skin cancer and carcinoma in situ of breast, although skin cancers became the largest proportion of subsequent cancers, demonstrating the substantial burden of these diagnoses.

Urgent suspected cancer pathways are often criticised for having a low conversion rate, yet the current analysis indicates that the frequency of any invasive cancer in years 0–5 after referral is 15·6% (146 151 [11·0%] of 1 325 623 in the first year and 60 188 [4·5%] in years 1–5). While acknowledging that most new cancers will occur in individuals who did not have a previous urgent suspected cancer referral, there might be scope to investigate the potential for targeted interventions for older patients who are referred but not initially diagnosed with cancer, through active monitoring or tailored support to facilitate the prevention or early-stage detection of cancers at the same or other anatomical sites. For instance, they could be offered support on when or how to seek help for ongoing or new symptoms, targeted to the cancers at greatest risk of a subsequent diagnosis following the urgent suspected cancer referral in question, or assistance to take part in cancer screening programmes. There are of course challenges with these initiatives. For instance, the upper ages of screening initiatives in England are 64 years (cervical), 70 years (breast), and 74 years (bowel and lung), although self-referral beyond these age limits is possible. Preventive advice, for instance tackling tobacco use, alcohol consumption, and obesity could be of value given the common risk factors across multiple conditions and should not be ruled out because of advancing age.[22]

Many subsequent diagnoses were found for the same cancer as the initial referral pathway. It was the most common subsequent cancer for three pathways (breast, lung, and urological), with the highest SIRs for two of these (lung and urological), along with the head and neck and skin pathways. Across all referral pathways, lung cancer consistently comprised a substantial proportion of the subsequent cancers and could offer an initial focus for interventions, possibly linking these patients at potential high risk to the developing lung cancer screening programmes.[23]

The findings reinforce suggestions from behavioural science that individuals who have undergone urgent referral for suspected cancer might be a key group to target as they could be more responsive and receptive to health information,[24] and the event of an urgent suspected cancer referral offers the opportunity to reach those who might not be reached by cancer awareness campaigns.[25] There is mounting evidence that patients who have previously experienced a symptom that turned out to be benign on investigation, often delay seeking help for subsequent symptoms.[26] This could be because of over-reassurance from the previous "all-clear" result leading to subsequent symptoms being interpreted as benign, concern about appearing hypochondriacal, not wanting to further bother the doctor, or uncertainty about the appropriate next actions.[26]

Although 40% of subsequent cancers in this study were diagnosed via either urgent suspected cancer referral pathways or screening, many subsequent cancers were diagnosed via non-urgent GP referral (28%) or emergency presentation (19%), a known predictor of poorer outcomes.[27] There could therefore be benefit in alerting primary care physicians to the potential risk of future cancer following urgent suspected cancer referral and that suspicion of cancer might still be warranted even when cancer is not found initially. Even if the excess risk is not detectable at a practice level, it is clear that ruling out cancer via an urgent suspected cancer referral does not mean a reduced risk of cancer, and practitioners should remain vigilant. Future work could investigate the rate and timing of subsequent urgent suspected cancer referrals and whether more proactive primary care can contribute to an increased rate of early subsequent cancer diagnoses. The current findings also offer scope for reassuring patients. For instance, following a lower gastrointestinal urgent suspected cancer referral when no cancer is found, the rates of lower gastrointestinal cancer in years 1–5 are lower than would be otherwise expected.[28]

The benefit of providing additional support to this patient group is yet to be quantified and should be offset against potential risks (eg, concern or medicalisation by over-interpretation of risks and use of invasive investigations or monitoring) as well as costs to the health-care service. Any changes to practice need to be achievable and implementable within health-care settings such as the NHS, and acceptable to patients so that messages are supportive, framed to facilitate behaviour change, and do not cause anxiety. Our recent work indicates that health-care professionals are supportive of providing additional support after urgent suspected cancer referral, yet have concerns as to whether it is possible due to limited time and resources and current focus of the urgent suspected cancer pathways being to either rule out or diagnose cancer within 28 days.[29] This reflects barriers for implementation of more general risk reduction initiatives to encourage health behaviour change, such as the Making Every Contact Count scheme that encourages NHS staff to deliver healthy lifestyle messages as part of routine practice.[30] Future work could focus on piloting initiatives, finding practical solutions to health system challenges, and involving patients to develop appropriate and acceptable messaging and support. Longer term follow-up, survival analysis, and investigation of the cost-effectiveness of potential change to practice would also add value.

There are many strengths of this research. To our knowledge, this is the first study to use national data to calculate cancer rates in years 1–5 subsequent to urgent suspected cancer referral in England, and includes comparisons across the eight main referral pathways. Furthermore, we used SIRs to compare cancer risk after urgent suspected cancer with that expected for the English population of similar age and gender. The value of this work is strengthened from its use of national cohort data with linked datasets but there are also limitations that should be considered. The clinical context of urgent suspected cancer referrals is specific to England, and triage, cancer investigations, and screening programmes have changed since the cohort was referred in 2013–14. For example, the national guidelines for recognition and referral of cancer[1] were updated in 2015, lowering the symptomatic risk threshold for referral, and rapid diagnostic clinics and community diagnostics centres for non-specific symptoms have been launched alongside the site-specific urgent suspected cancer pathways. Furthermore, faecal immunochemical testing has been introduced for symptomatic individuals with possible bowel cancer, prostate cancer diagnosis has improved over time with MRI, and NHS Lung Health Checks[23] have begun. These developments might mean that the results presented here are out of date, and the profile of those currently referred on the urgent suspected cancer pathways and the proportions who are subsequently diagnosed with cancer could be different to those reported here. Validating the current findings with a sample of recently referred individuals is an important next step once sufficient follow-up data are available. The generalisability to other health systems is unknown as there is variation in urgent suspected cancer referral pathways between high-income countries. For instance, primary care physicians in Australia have direct access to a wide range of specialist investigations, and while some countries (eg, Denmark) have similar urgent suspected cancer pathways to England with defined referral criteria and thresholds, others do not. Future work should include confounders other than age and gender, and also account for survivorship bias and the competing risk of death from non-cancer causes within the study period, which was not possible with the data used here. Key confounders include major risk factors such as tobacco use, BMI, and alcohol intake. As national cancer datasets do not include this information, future studies would have to collect primary data and follow up patients in a longitudinal manner. Conclusions regarding proportions of cancers that were advanced-stage should be made with some caution as some cancers are not able to be staged and for others stage is not known. We used complete case indicators (ie, calculating the proportion with advanced-stage disease based only on those cases with data on stage) which, although recommended, probably still displays some bias and might underestimate the numbers of advanced-stage diagnoses.[31,32]

The majority of individuals referred through urgent suspected cancer pathways in England do not have cancer diagnosed at the conclusion of their referral. Although the excess risk of subsequent cancer is not large, given the size of our assessed cohort who were passing through the urgent suspected cancer referral pathways, the absolute number is substantial, with over

63 000 subsequent cancers in the 1–5 years after urgent suspected cancer referral in this cohort. There is scope to further investigate the potential to develop interventions to support these individuals with the aim of preventing and diagnosing subsequent cancers.

Contributors

SES is the Principal Investigator for the project. SES, CG, BDN, TR, DS, and JW conceptualised and designed the study. CG and TR directly accessed and verified the underlying data reported in the manuscript. All authors interpreted the data, and reviewed and revised the manuscript. SES, CG, and TR conducted the analyses and drafted the initial manuscript. DS is a patient and public representative. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SES has received grant support from the National Institute of Health Research (NIHR) and Cancer Research UK for research outside of the current study. JW has received grant support from Breast Cancer Now, GRAIL Bio UK, NHS England, and the Department of Health and Social Care for research outside of the current study. AP has received grant support from Cancer Research UK and Wellcome LEAP for research outside of the current study, is on the Board of Directors for Maggie's Cancer Charity, and is a Trustee of The Richard Dimbleby Cancer Fund Charity. TR has received support from the NIHR, Royal Marsden Partners, and GRAIL Bio UK for research outside of the current study and has an honorary contract with the National Disease Registration Service, NHS England for data analysis. BDN has received grant support from Cancer Research UK, GRAIL Bio UK, and the NIHR outside of the current study and is a member of the independent data monitoring and ethics committee for the CaDET study. BDN and TR receive honoraria for medical education content for the Royal College of General Practitioners. All other authors declare no competing interests.

Data sharing

Study data, including a data dictionary, may be made available on request to accredited researchers with the correct legal permissions by submitting a request to the Data Access Request Service of NHS England (https://digital.nhs.uk/services/data-access-request-service-dars).

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